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Anesthesia for Cesarean Delivery

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Cesarean Delivery in the United States

Childbirth is the most common reason for admission to a hospital in the United States (US),[1] and cesarean deliveries are one of the most commonly performed surgeries. There has been an increase in the rate of cesarean deliveries, and this has become an issue of increasing public health concern. In a study by investigators from the Consortium on Safe Labor, data from 228,668 deliveries were weighted to represent a national sample and the overall cesarean delivery rate was 30.5%.[2] This rate has been increasing since the mid-1990s, and while the cause of this increase is multifactorial, one important contributor was a sharp decrease in the number of women who attempted a trial of labor after cesarean delivery (TOLAC).[3] Professional guidelines by the American Society of Anesthesiologists (ASA) and American College of Gynecologists state the need for "immediate availability" of anesthesia and surgical personnel, limiting the number of hospitals that provide TOLAC services. Other important contributors to the increasing cesarean delivery rate include increasing rates of obesity, multiple gestation, and advanced maternal age.[2] Projections estimate a continued increase in the cesarean delivery rate over time. Therefore, attention to the anesthetic management of these patients will continue to be of increasing importance.

Role of anesthesia in preventing of cesarean delivery

The incidence of breech presentation is approximately 3-5%, and cesarean delivery is usually recommended over vaginal delivery when the fetus is in a breech presentation.[4] External cephalic versions (ECV) are often performed in an attempt to avoid cesarean delivery. The use of neuraxial anesthesia may increase the success of external cephalic versions, and thus have a role in decreasing the overall cesarean delivery rate. The impact of anesthetic dosing (7.5 mg intrathecal bupivacaine) compared to no anesthesia or systemic opioids is profound (87% success rate in the anesthetic group compared to 58% in the control group, P= 0.012*)*.[5] A meta-analysis of all of the randomized controlled trials evaluating neuraxial compared to no anesthesia (or systemic analgesia) for external cephalic version identified a possible dose-response relationship between the density of the block and ECV success.[6] Four studies that used analgesic dosing found no difference in the success of versions, while anesthetic dosing was associated with an increased success rate.[6] The proposed mechanism for the higher success rates is possibly through improved muscle relaxation and improved maternal comfort during the procedure.[7] However, to date, one randomized controlled dose finding study has been conducted. Women undergoing an external cephalic version were randomized to combined spinal-epidural analgesia with either analgesic or anesthetic dosing (2.5, 5, 7.5, 10 mg bupivacaine with 15 mcg fentanyl).[8] No differences in the version success rate or in subsequent cesarean delivery rates were identified.

Anesthetic management for routine cesarean deliveries

While the specific management of any case should be decided on an individual basis, the typical sequence of events for providing anesthesia for cesarean deliveries is as follows:

1. Preoperative assessment and consent
2. Aspiration prophylaxis
3. Placement of monitors
4. Administration of antibiotics
5. Patient positioning
6. Anesthetic options for surgical anesthesia
7. Fluid co-loading
8. Management of hypotension
9. Administration of uterotonics
10. Postoperative analgesia planning

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1. *Preoperative assessment:*
A thorough preoperative assessment should be performed for all cases. The Practice Guidelines for Obstetrical Anesthesia from the ASA state that specific attention should be given to relevant obstetric issues that may complicate the surgery (e.g., obesity, hypertensive disorders of pregnancy, and number of previous cesarean deliveries).[9] Physical examination should include an examination of the back if neuraxial anesthesia is planned.[9] If the patient has been laboring, or a significant interval of time has elapsed since the original preoperative evaluation, reassessment of the airway should be performed, as studies have shown that there may be changes in the class of the airway as pregnancy/labor progresses.[10] The decision to obtain routine laboratory analysis prior to a cesarean delivery remains controversial. Routine laboratory analysis is not necessary for all patients; however, in high-risk patients, such as those patients who have symptoms or medical conditions that may be consistent with coagulation disorders, a platelet count and/or coagulation studies should be obtained.

A sample of the patient's blood should be sent to the blood bank for all cesarean deliveries. The decision to type and screen or type and cross match blood should be made based on the likelihood of requiring a blood transfusion.

Consent:
Patients should be informed of the risks and benefits of the anesthetic planned for the procedure. While there are no specific guidelines as to what information needs to be communicated, generally the most common risks should be discussed. For neuraxial anesthesia these should include infection, bleeding, risk of postdural puncture headache, hypotension, and patchy/failed block requiring conversion to general anesthesia.

2. *Aspiration prophylaxis:*
The American Society of Anesthesiologists recommends withholding clear liquids for 2 hours prior to elective cesarean deliveries and withholding solids for 6-8 hours, depending on the fat content of the meal.[9] Controversy has recently arisen around whether laboring women should be allowed to eat light meals during labor. A Cochrane review evaluating oral intake in labor found no difference in labor or neonatal outcomes when low-risk patients were allowed liquid/solid intake,[11] and concluded that low-risk patients should be allowed to eat/drink, yet none of the studies included in the meta-analysis were powered to assess maternal aspiration as a primary outcome. The ASA Practice Guidelines for Obstetrical Anesthesia state that solid foods should be avoided during labor.[12]

Prior to cesarean delivery, pharmacologic aspiration prophylaxis should be given. Three classes of drugs are routinely used: non-particulate antacids, H_2-receptor antagonists, and dopamine antagonists. Of the three, in an emergency cesarean delivery, the most important to administer is the non-particulate antacid as it has the fastest onset and decreases gastric acidity.

3. *Monitors:*
As for all surgical procedures, ASA standard monitors are required. Invasive hemodynamic monitoring is not required for routine cesarean deliveries, but should be considered on a case-by-case basis for high-risk deliveries or patients with cardiopulmonary disease. The American College of Obstetrics and Gynecology states that fetal heart rate should be documented prior to surgery.

4. *Antibiotics:*
The American College of Obstetrics and Gynecology recommends that antibiotic prophylaxis be administered within 60 minutes of the start of a cesarean delivery.[13] Antibiotic administration should not be delayed until after umbilical cord clamping as several randomized controlled trials have demonstrated that there is a decrease in endometritis and/or wound infection when antibiotics are administered prior to incision, as opposed to umbilical cord clamping, with no increased adverse events for the mother or the fetus. In the event of an emergency cesarean delivery, antibiotics should be administered as soon as they are available. A study published in 2016 evaluated the impact of the addition of azithromycin to standard antibiotics for surgical site infection for cesarean deliveries after labor or ruptured membranes.[14] The addition of 500 mg azithromycin reduced the incidence of the composite outcome of endometritis, wound infection, and other infections (relative risk: 0.51, 95% confidence interval: 0.38 – 0.68).

5. *Patient positioning:*

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Left uterine displacement (a minimum of 15-degree leftward tilt) should be utilized to prevent aorto-caval compression syndrome. After delivery of the infant, the left tilt may be removed. However, given the increased use of co-loading and phenylephrine infusions, this practice was recently questioned. A randomized controlled study (n=100) compared the effect of left uterine displacement versus supine position on neonatal acid-base status.[15] There was no difference in umbilical artery base excess between the two groups.

6. *Anesthetic options for surgical anesthesia:*

Neuraxial anesthesia (spinal, epidural, or combined spinal-epidural anesthesia) remains the most common type of anesthesia used for cesarean delivery.[16] Alternatives to neuraxial anesthesia include general anesthesia and local-infiltration anesthesia. The type of anesthesia selected for cesarean deliveries needs to be tailored to the patient situation. To a certain extent, the anesthetic plan is determined by the urgency of the cesarean delivery.

Neuraxial anesthesia:

The majority of cesarean deliveries are performed using neuraxial anesthesia, with the most common anesthetic being a single-shot spinal. A T4-T6 dermatomal level should be established prior to commencement of the surgery, otherwise the patient may experience breakthrough pain and require supplemental opioids, or conversion to general anesthesia. The assessment of sensory level should be to touch/pinprick as the discrepancy between cold and touch may exceed two dermatomes.[17]

Common regimens for spinal anesthesia include a local anesthetic agent with a short acting opioid. The addition of the opioid allows for a reduction in the local anesthetic dose, thus decreasing the incidence of hypotension and other local anesthetic-related side effects. For patients without clinical contraindications, morphine is often added for postoperative analgesia. In patients in whom the duration of surgery is anticipated to exceed the duration of the spinal, epinephrine may be added to the spinal, or alternatively, an epidural or combined spinal-epidural technique may be chosen.

Epidural anesthesia may be chosen for the initiation of anesthesia (de-novo placement), or used in laboring women with an in-dwelling epidural catheter.

Choice of local anesthetic in patients with in-dwelling labor epidural catheters:

The clinical situation will influence the decision for what local anesthetic is used. In emergency cesarean deliveries, (those in which there is an immediate threat to the life of the mother or fetus), 3% chloroprocaine is the most expeditious choice.[18] In the absence of fetal compromise, or when there is fetal compromise that responds to therapy, a slower-onset local anesthetic such as 2% lidocaine may be chosen. The advantage of lidocaine over chloroprocaine is that it appears that chloroprocaine interferes with the efficacy of epidural morphine.[19] The mechanism of this interaction is not completely understood.

General anesthesia

General anesthesia is required in emergency situations where there is insufficient time for placement of neuraxial anesthesia, or when patients have contraindications to neuraxial anesthesia. A rapid sequence intubation is indicated for parturients undergoing cesarean delivery, as all patients undergoing general anesthesia are considered full stomachs. General anesthesia is associated with a shorter decision-to-incision interval when compared to neuraxial anesthesia. The trade-off is increased neonatal depression, lower Apgar scores, and an increased likelihood of postpartum hemorrhage.[20]

The following is a common approach to general anesthesia.[21] Induction and intubation should occur after surgical site antisepsis and confirmation that the surgical team is prepared to proceed with surgery. The patient should initially be ventilated with 100% oxygen and 1 MAC of a potent inhalational agent. Following delivery of the infant, nitrous oxide may be added, and the concentration of volatile agent should be reduced in order to mitigate the effect of the volatile agent on uterine tone. Benzodiazepines and opioids may now also be administered. As the risk of hemorrhage is increased with general anesthesia,[22] the dose of oxytocin administered after delivery should be increased.[23,24] Other actions should include decompression of the stomach with an orogastric tube and temperature monitoring. Patients should be extubated awake and monitored in the post-anesthetic recovery unit.[25]

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Local-only anesthesia:
In situations where anesthesiologists are not readily available, a cesarean delivery may be preformed under local anesthesia. Lidocaine (0.5%) is used to sequentially anesthetize the skin, subcutaneous tissues, fascia, and peritoneum. The obstetrician should make a vertical abdominal incision and not exteriorize the uterus.

7. *Fluid co-loading:*
Hypotension is the most common complication of spinal anesthesia following cesarean delivery.[26] Side effects of hypotension could include nausea/vomiting, loss of consciousness, maternal cardiac arrest, and decreased uteroplacental perfusion resulting in neonatal acidosis. Current evidence suggests that crystalloid preloads are ineffective at preventing hypotension and instead co-loading should be performed to reduce hypotension and vasopressor requirements.[27] Colloids may possibly be more effective than crystalloids when given as a co-load;[28] however consideration to the side effects of colloid should be given (pruritus, coagulation abnormalities, and severe allergic reactions).

8. *Management of hypotension:*
Phenylephrine and ephedrine are the two most commonly used vasopressors for treatment of hypotension in cesarean deliveries. Higher doses of vasopressors are required for treatment of hypotension in pregnant women compared to non-pregnant women due to the physiologic dependence on the sympathetic nervous system and down-regulation of adrenergic receptors.

Phenylephrine is the preferred vasopressor in obstetrics as ephedrine crosses the placenta which results in in fetal tachycardia and possible neonatal acidosis.[29] The ED_{90} for bolus administration phenylephrine following spinal anesthesia has been shown to be 150 mcg (95% CI: 98-222 mcg).[30] A suggested starting dose for ephedrine would be 10 mg. Current evidence does not support the use of a fixed-rate phenylephrine infusion;[31] however, if an infusion is to be used, clinicians should start with lower doses (25-50 mcg/min), as these doses are associated with less reactive hypertension.

9. *Administration of uterotonic agents:*
Oxytocin is considered the first-line agent for prevention of postpartum hemorrhage following cesarean delivery. The optimal dose and route of delivery are not established. Recent evidence suggests that adequate uterine tone can be achieved with bolus doses as low as 0.5-3 IU.[23] Bolus administration of oxytocin has been associated with many undesirable cardiovascular side effects, such as hypotension, tachycardia, and electrocardiogram changes that may be suggestive of myocardial ischemia.[32] Many institutions have therefore transitioned to the use of oxytocin infusions following umbilical cord clamping at cesarean delivery. The ED_{90} for oxytocin delivered as an infusion has been estimated to be 0.4 IU/min using an up-down sequential allocation with a biased-coin design.[24] There does not appear to be a benefit from administration of a bolus of oxytocin prior to initiation of an oxytocin infusion.[33] Higher doses of oxytocin may be necessary after prolonged labor with oxytocin induction/augmentation, as animal evidence suggests that there is receptor desensitization with increasing doses of oxytocin.[34]Although transient hypotension is common after the bolus administration of oxytocin, EKG changes, particularly ST-segment depression, are concerning side effects.[35] While the electrocardiogram changes are likely not reflective of myocardial ischemia,[35] it is prudent to use the lowest effective dose of oxytocin in order to avoid possible iatrogenic injury.

Postpartum hemorrhage is one of the leading causes of maternal mortality worldwide. Mortality from hemorrhage in part is due to difficulty recognizing the amount of blood lost,[36] and delay in initiating treatment for the hemorrhage. In the setting of postpartum hemorrhage due to atony, additional uterotonic agents may be necessary. In addition to oxytocin, the two most commonly used classes of agents are ergot alkaloids and 15-methyl prostaglandin $F_{2\alpha}$.

10. *Postoperative analgesia management:*
There are two components to postoperative pain, the somatic (incisional) and visceral (uterine) pain. Options for postoperative analgesia are described below.

Neuraxial opioids:

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Neuraxial morphine is the gold standard for achieving postoperative analgesia due to its ability to treat visceral and somatic pain. Spinally administered morphine acts primarily at the mu receptors in the spinal cord, whereas epidurally-administered morphine acts through spinal and supraspinal opioid receptors.[37] The duration of action of neuraxially administered morphine is between 12-24 hours. An extended-release epidural morphine has been developed; however, the increased monitoring requirements (48-hours) and the pharmacologic interaction with epidural local anesthetics limit its clinical use.[38] Patients who receive neuraxial opioids should receive scheduled parenteral non-steroidal anti-inflammatory agents (NSAIDs) postoperatively for treatment of visceral pain.

Parenteral Analgesia:
Intravenous narcotics and NSAIDs should be administered to patients who do not receive neuraxial opioids.

Transversus abdominis plane blockade:
The transversus abdominis plane (TAP) block is an adjuvant analgesic technique for post-cesarean delivery analgesia. Local anesthetic is deposited in the fascial plane between the transversus abdominis and the internal oblique. Several nerves lie in the transversus abdominis plane: the lower thoracic nerves (T7-T11), the subcostal nerve, and the two branches of the first lumbar nerve (the iliohypogastric and ilioinguinal nerves). While intrathecal morphine is the most efficacious technique for providing postoperative analgesia due to its ability to provide somatic as well as visceral analgesia, TAP blocks should be considered for women who undergo general anesthesia for cesarean delivery, for women who did not receive neuraxial morphine, and for those who experience breakthrough incisional pain despite having received neuraxial morphine.[39]

Complications of anesthesia:
Aspiration:
Aspiration is one of the feared complications of general anesthesia. While the incidence is decreasing, aspiration prophylaxis should be taken in all parturients undergoing cesarean delivery, even if under regional anesthesia, because of the risk of intraoperative conversion to general anesthesia.

Difficult Intubation:
Due to the physiologic changes of pregnancy (increased capillary engorgement with resultant decreased internal tracheal diameter), there is the potential for increased difficulty with intubation in pregnant patients.

Awareness:
The incidence of awareness following general anesthesia in the obstetric patient population is low, with current estimates of 0.1-0.2%.[40]

High spinal:
If a patient experiences a high spinal, it is important to assist with ventilation or intubate, maintain left uterine displacement, and treat hypotension until the level recedes.

Local anesthetic systemic toxicity:
Local anesthetic systemic toxicity (LAST) may occur in following the initiation of epidural anesthesia or with transversus abdominis plane blockade. Providers should be aware of the signs and symptoms of LAST and treatment algorithms.[41]

Neonatal depression:
Infants delivered under general anesthesia have a higher incidence of fetal acidemia and lower 1-minute Apgar scores than those delivered under neuraxial anesthesia.[20] With prolonged uterine incision-to-delivery intervals (>3-minutes), there is a higher incidence of acidosis and neonatal depression.[42]

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Management of Ambulatory Patients with Sleep Apnea: Application of Society of Anesthesia and Sleep Medicine Guidelines

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Obstructive sleep apnea (OSA) syndrome is the most common type of sleep-disordered breathing and is characterized by recurrent apnea, hypopnea, or both lasting 10 seconds or longer during sleep despite ongoing efforts to breathe. Patients with OSA have increased depression of pharyngeal muscle tone during sleep, resulting in a recurrent pattern of partial or complete upper airway obstruction with impaired respiration.[1] The prevalence of mild OSA is 1 in 4 males and 1 in 10 females,[2,3] whereas moderate OSA occurs in 1 in 9 males and 1 in 20 females.[4,5] A significant number of OSA patients are undiagnosed when they come for elective surgery.[6] Approximately 10% to 20% of surgical patients, of whom 80% had not been previously diagnosed with OSA, were found to be at high risk for OSA based on preoperative screening.[7,8] An increase in the prevalence of OSA owing to the obesity epidemic as well as a greater number of operations performed as ambulatory procedures pose a practical challenge to the anesthesiologist. The suitability of ambulatory surgery in OSA patients remains controversial because of concerns for increased perioperative complications, including death, following discharge. The effects of residual anesthetics, sedatives, and opioids on upper airway muscle tone and ventilator responsiveness, along with postoperative supine positioning, may worsen OSA in the early postoperative period. At present, evidence related to the safety of ambulatory surgery for OSA patients is limited. The American Society of Anesthesiologists (ASA)[9,10] and the Society for Ambulatory Anesthesia (SAMBA)[11] have published guidelines that emphasize the importance of proper patient selection and management of OSA patients for ambulatory surgery. In 2016, the Society of Anesthesia and Sleep Medicine (SASM) published guidelines on preoperative screening and assessment of patients with OSA.[12] In this Refresher Course, we review the current postoperative morbidity and mortality associated with OSA and screening tools to detect it, and we describe application of the SASM guidelines and best perioperative practices for ambulatory surgical patients with suspected or known OSA.

RISK FACTORS AND PATHOPHYSIOLOGY Patients are predisposed to OSA by various pathophysiological, demographic, and lifestyle factors.[13] These include anatomical abnormalities that may cause mechanical changes in the airway lumen (*e.g.*, craniofacial deformities, retrognathia, macroglossia), connective tissue diseases (*e.g.*, Marfan syndrome), endocrine diseases (*e.g.*, hypothyroidism, Cushing disease), male gender, neck circumference greater than 40 cm, age above 50 years, and lifestyle factors including alcohol consumption and smoking. The prevalence of OSA may be up to 78% in morbidly obese patients scheduled for bariatric surgery.[14] Obesity causes enlargement of soft tissue structures around the airway as well as narrowing of the pharyngeal airway. Lung volumes are markedly reduced by an increase in the abdominal fat mass. Reduction of lung volume may decrease longitudinal traction forces on the trachea and pharyngeal wall tension, which causes narrowing of the airway. Visceral obesity is common in subjects with OSA.

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OSA is associated with various comorbidities such as myocardial ischemia, heart failure, hypertension, arrhythmias, metabolic syndrome, cerebrovascular disease, insulin resistance, gastroesophageal reflux, and obesity. Sympathetic activation is increased by apneic episodes, which prevent the normal nocturnal decline in blood pressure. Sleep apnea associated with obesity leads to increased sympathetic tone, hypertension, left ventricular hypertrophy, chronic hypoxemia, and exaggerated swings in intrathoracic pressure during obstructive episodes. OSA also causes an increase in cavity size and wall thickness of the right ventricle. OSA is one of the common reasons for resistance hypertension.[15] Though OSA is not a component of metabolic syndrome (central obesity, hypertension, hyperlipidemia, and insulin resistance), experimental and clinical evidence demonstrates the relationship between OSA and cardiometabolic syndrome.[16] Anesthetic agents, including sedative-hypnotics, opioids, and muscle relaxants, exaggerate OSA-related airway instability and worsen the apnea. Surgical stress response during the postoperative period significantly changes sleep architecture.[17] These sequelae warrant a thorough understanding of the pathophysiology of OSA and the effects of anesthetics on patients with the disorder.

Obesity hypoventilation syndrome (OHS) consists of the triad of obesity, daytime hypoventilation, and sleep-disordered breathing without an alternative neuromuscular, mechanical, or metabolic cause of hypoventilation.[18,19] OHS, which is often undiagnosed, has a prevalence of 10% to 20% in obese patients with OSA and 0.15% to 0.3% among the general adult population. Compared to eucapneic obese patients, OHS patients present with blunted central respiratory drive, severe upper airway obstruction, restrictive chest physiology, pulmonary hypertension, and increased mortality risk.[20] Compared with OSA patients, patients with OHS have a higher risk of perioperative complications including postoperative respiratory failure, postoperative heart failure, prolonged intubation, postoperative intensive care unit (ICU) transfer, and longer ICU and hospital stay.[21] Patients with OHS are generally not suitable candidates for operations at ambulatory surgical centers.

DIAGNOSTIC CRITERIA FOR OSA The gold standard for the diagnosis of OSA is the polysomnography or sleep study.[13] The apnea-hypopnea index (AHI), defined as the average number of abnormal breathing events per hour of sleep, is used to diagnose and assess the severity of OSA. Diagnostic criteria for OSA by the American Academy of Sleep Medicine require either an AHI of 15 or above or AHI of 5 or higher with symptoms, such as daytime sleepiness, loud snoring, or observed obstruction during sleep.[22] OSA severity is considered mild for AHI of 5 to 15, moderate for AHI of 15 to 30, and severe for AHI above 30.[22]

PERIOPERATIVE COMPLICATIONS IN OSA PATIENTS UNDERGOING SURGERY A systematic review by the SASM task force on preoperative preparation of patients with sleep-disordered breathing identified 52 studies that reported on the association of OSA with selected perioperative outcomes for operations under general or neuraxial anesthesia.[23] In total, the included studies reported on 413,576 OSA patients (diagnosed by ICD-9 coding, polysomnography, chart or clinical diagnoses, and screening questionnaires) and 8,557,044 control (non-OSA) patients.[23] The majority of the studies reported worse outcomes among patients with OSA compared to the control group.[23] In another recent meta-analysis, OSA patients had 33.3% higher odds of major adverse cardiac or cerebrovascular events up to 30 days after cardiac surgery and 18.1% higher odds of newly documented postoperative atrial

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fibrillation vs. non-OSA patients.[24] Regarding mortality, studies reported a lower death rate in the OSA group and one study reported increased deaths among OSA patients. The lower mortality rate might result from better monitoring and management of diagnosed OSA patients, a protective effect of ischemic preconditioning, and the obesity paradox (obesity is protective and associated with increased survival) in OSA patients. The only study reporting a higher death rate was a population-based database study that found an association between a diagnosis of OSA and increased mortality in patients undergoing revision knee or hip arthroplasties.[25]

OSA Patients Undergoing Ambulatory Surgery Recent outcome studies on postoperative inpatients have clearly demonstrated serious cardiac and pulmonary complications in OSA patients, but evidence is limited regarding postoperative outcome in OSA patients undergoing ambulatory surgery. The systematic review conducted by SAMBA evaluated five prospective and two retrospective studies with various ambulatory surgical procedures including general surgery, orthopedic surgery, laparoscopic bariatric surgery, and upper airway surgery.[11] In that review, the postoperative outcomes of 1,491 patients with diagnosed or high-risk for OSA and 2,036 patients who were low-risk for OSA were compared with 2,095 non-OSA patients.[11] None of the included studies reported the need for a surgical airway, hypoxic brain injury, longer time to discharge, unanticipated hospital admission, death, or other clinically significant adverse outcomes. The systematic review also showed that OSA patients had a higher incidence of postoperative hypoxemia, but there was no increase in the need for ventilatory assistance or reintubation.[11] In a prospective cohort study, those patients with greater probability for OSA experienced more attempts at laryngoscopy, difficult laryngoscopic grade, and fiberoptic intubation.[8] Also, the use of intraoperative ephedrine, metoprolol, and labetalol was greater in OSA patients, but there was no difference in unanticipated hospital admissions.[8] A recent study on 404 ambulatory head and neck procedures in OSA patients showed no increase in either complications or readmissions.[26] A historical cohort study of 77,809 ambulatory surgical procedures did not identify any clinically significant increase in the rate of unplanned admissions related to a prior diagnosis of OSA in 674 OSA patients.[27] A recent systematic review and meta-analysis of the safety of conscious sedation for gastrointestinal endoscopy did not find a difference in cardiopulmonary complications in patients with OSA.[28] However, a recent retrospective review of the legal literature on perioperative complications in OSA reported on 2 patients undergoing minor ambulatory procedures who received intraoperative opioids.[29] Both patients had hypoxic arrests and required emergent transfer to hospital with 1 patient dying and the other suffering anoxic brain injury. The lack of increased postoperative complications in some of these studies may be attributable to careful selection of OSA patients for ambulatory surgery, use of continuous positive airway pressure (CPAP), and minimal use of opioids.

PREOPERATIVE CONSIDERATIONS

Preoperative Assessment for OSA Routine preoperative screening for OSA in patients presenting for surgery may identify the majority of OSA patients and may provide opportunities for heightened awareness and potential risk reduction by implementing appropriate preoperative, intraoperative, and postoperative interventions.[12] Although the ultimate goal is to minimize the risk of postoperative complications as much as feasible by ensuring that every patient with *suspected* OSA is identified, clearly such an approach will result in a challenging logistical, economic, and clinical burden for healthcare providers.[12] Hence, a balance has to be struck

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between the desire to minimize postoperative complications and the responsible use of resources. The realistic goal is to stratify those at particular risk, and suggest methods to prevent or treat problems, without creating undue economic burden on the healthcare system.[12]

Screening tools such as STOP-Bang,[30-33] the perioperative sleep apnea prediction (P-SAP) score,[34] the Berlin questionnaire,[35] and the ASA Checklist[35] can be used as preoperative screening tools to identify patients with suspected OSA.[12] These tools have been validated in the surgical population. The STOP-Bang questionnaire was initially developed for the surgical population but has been validated in various patient populations.[36] Patients with a STOP-Bang score of 0 to 2 are considered at low risk, 3 to 4 at intermediate risk, and 5 to 8 at high risk for OSA.[37-39] The STOP-Bang questionnaire has the highest methodological validity and accuracy in predicting a diagnosis of OSA.[40,41] The addition of a serum bicarbonate level 28 mmol/L or higher to a STOP-Bang score of 3 or above increases the specificity for a preoperative diagnosis of OSA.[42] For obese or morbidly obese patients, a STOP-Bang score of 4 or greater can be used as a cut-off to define patients as higher risk of OSA[43] The STOP-Bang score can be used to risk stratify patients who are at high risk for OSA.[44] High-risk OSA patients (STOP-Bang score ≥3) had a longer hospital stay and almost 4-fold higher risk of postoperative complications compared with low-risk OSA patients.[44]

Also, the oxygen desaturation index (ODI) from a high-resolution oximeter is sensitive and specific to identify undiagnosed sleep-disordered breathing in surgical patients.[45] ODI is a good predictor of AHI. An ODI of 10 or higher has demonstrated a high sensitivity (93%) and reasonable specificity (75%) to detect moderate and severe OSA. Patients with preoperative mean overnight oxygen saturation below 93% or ODI higher than 29 events per hour were recently shown to be at higher risk for postoperative complications.[46]

SASM guidelines indicate that additional evaluation for preoperative cardiopulmonary optimization should be considered in patients with a high probability of having OSA *and* in whom there is indication of uncontrolled systemic conditions or additional problems with ventilation or gas exchange. These conditions include, but may not be limited to: (1) hypoventilation syndromes, (2) severe pulmonary hypertension, and (3) resting hypoxemia not attributable to other cardiopulmonary disease.[12]

Best Preoperative Practices in Patients Who Are Diagnosed with OSA, Are Nonadherent with Prescribed Therapy, or Have a High Pretest Probability for OSA Because OSA remains undiagnosed in the majority of patients presenting for surgery, many will be identified as having a high probability for OSA for 1st time during the preoperative screening process or on the day of surgery.[12] In addition, many with an established diagnosis of OSA either refuse to use, or are poorly adherent with, their prescribed therapy. The optimal benefit of CPAP may require 4 to 6 weeks of treatment for upper airway edema to decrease.[47] There are limited data to suggest that preoperative PAP therapy in the form of CPAP, autotitrated positive airway pressure (APAP), or bilevel positive airway pressure (BPAP) may improve perioperative outcomes.[48-51] The limited benefit of CPAP in surgical patients was shown in a recent meta-analysis.[48] A diagnosis of OSA and the use of CPAP were associated with a reduction in postoperative complications, especially cardiac arrest and shock.[50] Another study found that OSA patients treated with CPAP have fewer cardiorespiratory complications than those without CPAP therapy.[51] All this evidence gives preliminary confirmation that patients with OSA may safely undergo ambulatory surgery if they are cautiously selected and receive focused perioperative care

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Patient Selection for Ambulatory Surgery In 2006 and 2014, the ASA published practice guidelines on the perioperative management of OSA patients[9,10] based on the severity of sleep apnea, invasiveness of the procedure, type of anesthesia, and the need for postoperative opioids. Using a systematic review of recent evidence, SAMBA published a consensus statement on the preoperative selection of patients with OSA for ambulatory surgery.[11] According to SAMBA guidelines, patients who have a diagnosis of OSA, are compliant with CPAP, have optimized comorbid conditions, and have minimal postoperative opioid requirements can be considered for ambulatory surgery.[11] However, patients who are noncompliant with CPAP may not be appropriate for ambulatory surgery. At the same time, patients with a presumed diagnosis of OSA, based on the screening tool, and optimized comorbid conditions may be considered for ambulatory surgery if postoperative pain relief can be managed predominantly with nonopioid analgesic techniques. In contrast to the ASA OSA guidelines, laparoscopic upper abdominal surgeries such as gastric banding may be safely performed on a day surgery basis provided the perioperative precautions are followed. Because of limited evidence, no guidance was provided for OSA patients undergoing upper airway surgery. A recent systematic review on selection of obese patients for ambulatory surgery showed that the literature lacks enough information to make recommendations regarding the selection of these patients and whether there is a cut-off of body mass index (BMI) for ambulatory surgery.[52] Super-obese patients with BMI greater than 50 kg/m^2 are at increased risk for perioperative complications, while patients with lower BMI do not present any elevated risk as long as comorbidities are optimized before surgery.[52]

INTRAOPERATIVE MANAGEMENT Monitored anesthesia care with local or regional anesthesia techniques should be considered where appropriate.[53] Intraoperative capnography should be utilized to monitor ventilation to avoid oversedation during monitored anesthesia care.[13] Difficult intubation equipment should be available in anticipation of difficulty intubating a patient with OSA. Preoperative sedatives should be avoided.[53] Recently, gabapentin was shown to be associated with increased risk for respiratory depression among patients undergoing major laparoscopic procedures. The dose of perioperative opioids should be reduced if gabapentin is administered.[54] Application of CPAP during bag and mask ventilation may be helpful to minimize upper airway obstruction during induction and immediately after extubation.[55] Short-acting agents such as propofol, desflurane, or sevoflurane and remifentanil should be utilized to ensure rapid recovery.[56] Nonopioid analgesic agents such as nonsteroidal antiinflammatory drugs (NSAIDs) and local anesthesia infiltration should be administered to reduce postoperative opioid requirements. At the end of surgery, adequate reversal of neuromuscular blockade should be confirmed, and the patient should be extubated in the semiupright position when fully awake and recovered.[56]

POSTOPERATIVE DISPOSITION AND UNPLANNED ADMISSION AFTER AMBULATORY SURGERY The majority of cases of opioid-induced respiratory depression have been reported within 24 hours, mostly within the first 6 hours postoperatively.[57] Up to 50% of patients who died within 24 hours postoperatively from critical respiratory events had OSA.[58] In a closed claims analysis, OSA or suspected OSA was present in 24% of the patients with respiratory depression.[59] A significant association of postoperative opioid-induced respiratory depression exists in patients with underlying cardiac or pulmonary disease.[58,60] Among patients

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with postoperative opioid-induced respiratory depression, 34% had preexisting cardiac disease and 25% had pulmonary disease.[60]

Patients with diagnosed or suspected OSA who are receiving general anesthesia should have extended monitoring after they have met the modified Aldrete criteria for discharge.[10] Recurrent respiratory events (episodes of apnea ≥10 sec, bradypnea <8 breaths/min, pain–sedation mismatch, or repeated oxygen desaturation <90%) in the postanesthesia care unit are an indication for continuous postoperative monitoring.[61] OSA patients with recurrent respiratory events have an increased risk of postoperative respiratory complications.[61] These patients may require postoperative PAP therapy with monitoring.[12]

Ambulatory surgical centers that handle OSA patients should have the ability to manage postoperative complications related to OSA and an agreement with an appropriate inpatient facility. Postoperative complications may result from an imbalance between enhanced pain processes and increased sensitivity to anesthetics, opioids, or both in patients with some specific OSA phenotypes.[62,63] In a recent systematic review of 60 deaths or near-deaths in surgical patients with OSA, 81% of the patients reported to be on opioid therapy were receiving relatively small doses of opioids with a morphine equivalent daily dose less than 10 mg; only 20% received a relatively higher dosage of opioids.[64] Further analysis of the dosage of intravenous opioids showed a clear dose–response pattern in the death or near-death group, *i.e.*, increased odds of death or near-death with increasing opioid doses (OR of 1.0, 1.5, and 3.0 respectively at opioid doses of <10 mg, 10–25 mg, and >25 mg; P for trend <0.005).[64]

Postoperative disturbance of sleep-disordered breathing may occur in the first postoperative nights at home.[17,65] The use of opioids in unmonitored settings by patients with OSA increases the risk of complications. The anesthesiologist and surgeon should agree on postoperative analgesic medication, and patients should be advised to use acetaminophen, NSAIDs, and cyclo-oxygenase type 2 inhibitors rather than opioids. To reduce the risk of postoperative respiratory depression, the dose of opioids prescribed for discharge should be reduced if the patient was already taking gabapentinoids prior to surgery.[54] Patients should be educated to sleep in a semiupright position and to apply their PAP devices when sleeping, even during the daytime. It is necessary to educate surgeons, patients, and patients' families regarding the need for increased vigilance after discharge home. Brief information in the form of pamphlets can be given to patients to educate them about OSA.[66] At present, there are practice variations in the way anesthesiologists manage patients with OSA.[67] Depending on the facilities and the types of surgery, it is essential that each ambulatory surgical facility establish an individualized policy and protocol for the management of surgical ambulatory patients with OSA.[68] More studies are needed to determine the optimal approach to the perioperative management of ambulatory surgical patients with OSA.

CONCLUSION In recent years, there is a better understanding about the effect of anesthetics and opioids on postoperative sleep architecture in OSA patients. Careful selection of patients for ambulatory surgery using specific protocols and risk mitigation strategies are imperative to avoid cancellations and complications. Educating patients and the healthcare team will improve the perioperative outcome. With appropriate screening, careful patient selection, limited use of opioids, and algorithm-based management, the majority of ambulatory surgical procedures may be done safely in patients with OSA.

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Summary of recommendations from the SASM Guidelines:[1]

- OSA patients undergoing procedures under anesthesia are at increased risk for perioperative complications compared with patients without the disease diagnosis. Identifying patients at high risk for OSA before surgery for targeted perioperative precautions and interventions may help to reduce perioperative patient complications.
- Screening tools help to risk stratify patients with suspected OSA with reasonable accuracy. Practice groups should consider making OSA screening part of standard preanesthetic evaluation.
- There is insufficient evidence in the current literature to support canceling or delaying surgery for a formal diagnosis (laboratory or home polysomnography) in patients with suspected OSA, unless there is evidence of an associated significant or uncontrolled systemic disease or additional problems with ventilation or gas exchange.
- The patient and the health care team should be aware that both diagnosed OSA (whether treated, partially treated, or untreated) and suspected OSA may be associated with increased postoperative morbidity.
- If available, consideration should be given to obtaining the results of the sleep study and, where applicable, the patient's recommended positive airway pressure (PAP) setting before surgery.
- If resources allow, facilities should consider having PAP equipment for perioperative use or have patients bring their own PAP equipment with them to the surgical facility.
- Additional evaluation to allow preoperative cardiopulmonary optimization should be considered in patients with diagnosed, partially treated/untreated, and suspected OSA where there is indication of an associated significant or uncontrolled systemic disease or additional problems with ventilation or gas exchange such as: (i) hypoventilation syndromes, (ii) severe pulmonary hypertension, and (iii) resting hypoxemia in the absence of other cardiopulmonary disease.
- Where management of comorbid conditions has been optimized, patients with diagnosed, partially treated/untreated OSA, or suspected OSA may proceed to surgery provided strategies for mitigation of postoperative complications are implemented.
- The risks and benefits of the decision to proceed with surgery or delay surgery should include consultation and discussion with the surgeon and the patient.
- The use of PAP therapy in previously undiagnosed but suspected OSA patients should be considered case by case. Because of the lack of evidence from randomized controlled trials, we cannot recommend its routine use.
- Continued use of PAP therapy at previously prescribed settings is recommended during periods of sleep while hospitalized, both preoperatively and postoperatively. Adjustments may need to be made to the settings to account for perioperative changes such as facial swelling, upper airway edema, fluid shifts, pharmacotherapy, and respiratory function.

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Enhanced Recovery Strategy - Principles and Practice

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Enhanced recovery After Surgery (ERAS) are multimodal perioperative care pathways designed to attenuate the stress response during the patients' journey through a surgical procedure, facilitate the maintenance of preoperative bodily compositions and optimize organ function, and in doing so achieve early recovery. ERAS integrate a range of perioperative interventions to maintain physiologic function and facilitate postoperative recovery.[1]

There are several elements of ERAS that are new and specific to this approach, bringing together 2 best practices: 1) organization of care and 2) clinical management, while making sure that patients receive evidence-based care. In the 2000s, ERAS pathways in colorectal surgery were applied throughout Europe. Since then, ERAS pathways have been adopted worldwide, and pathways and guidelines have been published for other major surgical procedures because the principles of ERAS apply to all patients undergoing major surgery.

Successful implementation of ERAS pathways requires collaboration between surgery, anesthesia, perioperative nursing to provide optimal perioperative care as well as having the support of hospital administration. Anesthesiologists play a vital role in facilitating recovery because they routinely manage some of the key elements of ERAS (i.e., preoperative assessment and patient education, perioperative fluid management, short acting anesthetic agents, optimal multimodal analgesia, prevention of postoperative nausea and vomiting (PONV) and other opioid related side effects as well as close monitoring during surgery.[1]

In this presentation, I will focus on the principles and practice of enhanced recovery as well as discussing the various elements under the purview of the anesthesiologists that are critical for the success of an enhanced recovery program.

Preoperative Nutrition

Sub-optimal nutritional status is a strong independent predictor of poor postoperative outcomes.[2] Malnourished surgical patients have significantly higher postoperative mortality, morbidity, length of stay (LOS), readmission rates, and increased hospital costs. [3-5] It is estimated that 24-65% of patients undergoing surgery are at nutrition risk. [3 6-8] Additionally, recent prospective observational data indicate undernourished patients OR patients at risk of malnutrition are twice as likely to be readmitted within 30 days following elective colorectal surgery.[9] As defined by the National Surgical Quality Improvement Program (NSQIP), malnutrition is among the few modifiable preoperative risk factors associated with poor surgical outcomes, including mortality, in surgical patients. [10 11] Further, appropriate perioperative nutritional therapy has been shown to specifically improve perioperative outcomes in GI/oncologic surgery, where the greatest risk of baseline malnutrition risk (~65%) occurs. [3 6 12] In surgical patients overall, perioperative nutrition interventions can improve surgical outcomes and reduce infectious morbidity and mortality.[13]

Postoperative nutritional support is vital in maintaining nutritional status during the catabolic postoperative period and underscored by evidence for early and sustained feeding following surgery as part of ERP protocols.[14-16] In fact, the advancement of oral intake has been identified as an independent determinant of early recovery following colorectal surgery.[17] Recent data on the role of nutrition delivery in the perioperative period has demonstrated in patients undergoing oncologic surgery in an ERP, delivery of nutrition on the first postoperative day is an independent predictor of postoperative survival at 5 years.[18]

Unfortunately, recent evidence reveals significant deficiencies in nutritional screening and intervention in U.S. colorectal and oncologic surgical patients with only ~ 1 in 5 hospitals currently utilizing a formal nutrition screening process.[19] This is surprising as 83% of U.S. surgeons believe existing data support preoperative nutrition optimization to reduce perioperative complications.[19] However only ~20% of U.S. GI/Oncologic surgery patients receive any nutritional supplements in the pre-operative or post-operative setting.[19] A recent Perioperative Quality Initiative (POQI) consensus guidelines recommended that the use of Perioperative Nutrition Scoring (PONS) system[20] that determines the presence of nutrition risk based on a patient's body mass index (BMI), recent changes in weight, reported recent decrease in dietary intake, and preoperative albumin level. In addition, the PONS includes evaluation of preoperative albumin level, as this is a predictor of postoperative complications, including

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morbidity/mortality.[17-19 21 22] (Figure 1). The POQI consensus guidelines recommendations on perioperative nutrition is presented in Figure 2.

Figure 1. Perioperative Nutrition Scores

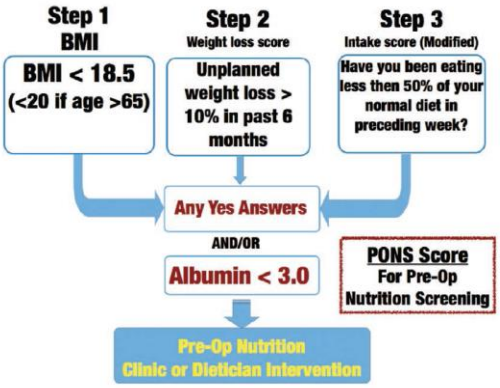
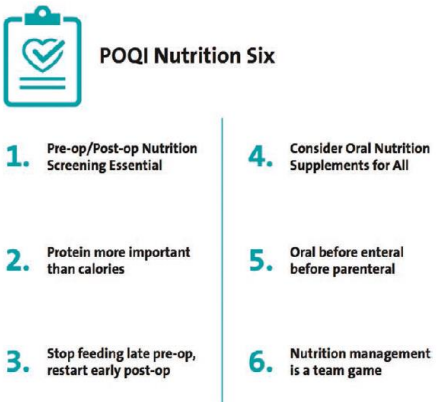


Figure 2. Recommendations on perioperative nutrition



Management of Postoperative Pain

Rationale for multimodal analgesia

The ideal analgesic regimen would provide effective pain relief, reduce opioid related side effects and surgical stress response and improve clinical outcome e.g. morbidity, mortality and hospital stay. The concept of multimodal analgesia was introduced to achieve these goals by combining various analgesic techniques and different classes of drugs to improve postoperative outcome.[23] However, available data are conflicting and do not necessarily resulted in improved outcome and concomitant reduction in adverse effects of opioids.[24-26] The failure to improve clinical outcome may be due to inappropriate combination and dosing of analgesics. Apart from adequate analgesia, postoperative morbidity and hospital stay depend on other factors such as initiation of early nutrition, mobilization and comprehensive rehabilitation program.[27] It is prudent to attenuate postoperative pain as effectively as possible during the intraoperative period and initiating effective analgesic therapy in the early phase of perioperative period.

The effectiveness of individual analgesics is enhanced by the additive or synergistic effect of two or more drugs acting by different mechanisms. For example, the synergism between alpha-adrenergic and opioid systems has been demonstrated.[28] Similarly, combination of acetaminophen and non-steroidal anti-inflammatory drugs provides additive analgesic effect in mild to moderate acute pain.[29] The addition of COX-2 inhibitors or NSAIDs reduces opioid requirements by 20-30% with the reduction of opioid related side effects and better analgesia. Similarly, ketamine has been shown to reduce the pain scores and lower analgesic requirement when added to a multimodal epidural analgesia.[30] Adding ketamine in patient controlled epidural analgesia along with morphine, bupivacaine and epinephrine has been demonstrated to result in enhanced analgesic effect. Chia et al.[31] showed that the mean visual analogue score in the ketamine group during movement and cough were lower than the control group. The cumulative total analgesic consumption in the ketamine group was lower by 30% than the control group 24 h following surgery. In another study, it was demonstrated that the combination of intraoperative ketamine and epidural analgesia may confer a long-term benefit in reducing incidence of chronic pain.[32]
Pharmacological Options

Peripheral Nerve Blocks (PNB)

Appropriate nerve blocks depending on the site of surgery are useful in providing short to intermediate-term pain relief after surgery. Direct visualization of neural tissue with ultrasound technology and the utility of stimulating catheters has made placement of indwelling catheters safer and more accurate. Continuous infusion of local anesthetics through a peripheral nerve catheter is becoming increasingly popular in both hospital and ambulatory setting to achieve prolonged analgesia.[33 34] For example, continuous femoral nerve block has been shown to reduce duration of hospital stay and the frequency of serious complications. [35] Similarly, several other studies have demonstrated the benefits of PNB including reduced length of stay and costs, [36] decreased incidence of PONV [37] and lower rates of unexpected hospital admissions after ambulatory surgery. [35 36 38] Systemic agents co-administered

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during PNB such as opioids and clonidine have been found to enhance intraoperative and postoperative analgesia. Two systematic reviews of 15 studies that used opioids as adjuvant, six reported a statistically significant benefit in analgesia. Of the six studies that evaluated clonidine, [39] five found improvement in analgesia.

A successful ERAS pain management strategy takes into considerations factors that include optimizing patient comfort, fastest functional recovery with fewest side effects. (Figure 3) A treatment algorithm is shown in Figure 4.[40 41]

Figure 3.

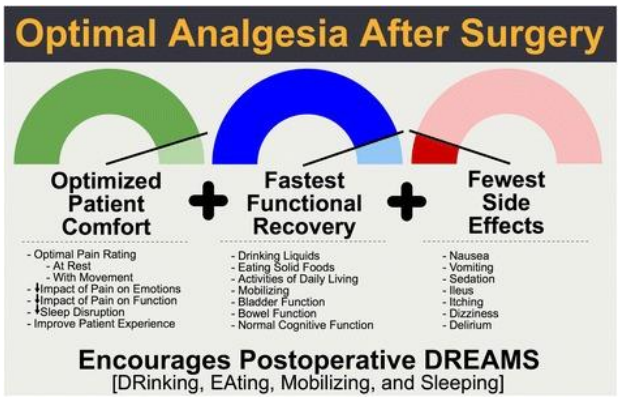
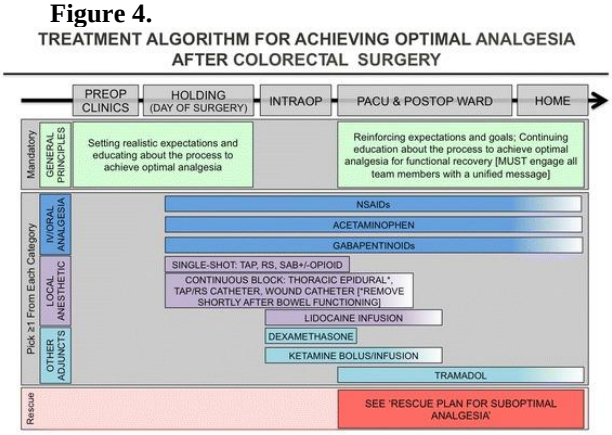


Figure 4.



Management of PONV

Risk factors for PONV

Identification of patients at high risk for PONV enables targeting prophylaxis to those who will benefit most from it. Patient, anesthesia, and surgery related risk factors have been identified. Anesthesia related risk factors include the use of volatile agents [42], nitrous oxide[43], opioids[42 44] and high doses of neostigmine (>2.5 mg) for the reversal of neuromuscular blockade.[45] Patient related factors include female gender[44 46], history of PONV or motion sickness [44 46 47], and non-smoking status.[44 46] High levels of anxiety and postoperative pain, especially of pelvic or visceral origin, may also be associated with a higher incidence of PONV.[48-50] A number of PONV risk scoring systems have been developed. Apfel et al developed a simplified risk score consisting of four predictors: female gender, history of motion sickness or PONV, non-smoking status and the use of opioids for postoperative analgesia.[44]

Combination Antiemetic Therapy

There are at least four major receptor systems involved in the etiology of PONV. The concept of combination antiemetic therapy was first introduced in 1988 in chemotherapy induced nausea and vomiting.[51] Its success prompted similar research in the field of PONV. Over 100 randomized controlled trials have been published comparing the relative efficacy of combination versus single agent antiemetic prophylaxis. Most of these studies suggested better efficacies against PONV can be achieved by the use of two or more antiemetics acting at different receptors compared with monotherapy.[52-54] The choice of combination is not critical. In a meta-analysis, Habib et al. found no statistically significant difference in the incidence PONV when a 5-HT_3 receptor antagonist was combined with either droperidol or dexamethasone. Both combination regimens provided significantly better PONV prophylaxis compared with 5-HT_3 receptor antagonists alone.[55]. In a large prospective study using a multifactorial design, Apfel et al. evaluated 3 antiemetic interventions (ondansetron 4 mg, droperidol 1.25 mg, dexamethasone 4 mg) and 3 anesthetic interventions (TIVA with propofol, omitting nitrous oxide, and substituting remifentanil for fentanyl) for the prophylaxis of PONV. The data suggest that antiemetics with different mechanisms of action have additive rather than synergistic effects on the incidence of PONV.

Recommended strategy for PONV prophylaxis

The management strategy for PONV has been summarized by a recent SAMBA sponsored PONV consensus guidelines.[56] First, the risk of PONV should be estimated for each patient. For patients at moderate to high risk for PONV, regional anesthesia should be considered. If this is not possible or contraindicated and a general anesthetic is used, strategies to minimize the baseline risk of PONV should be adopted, e.g. minimize the use of opioids, avoid high dose neuromuscular reversal drugs and the use of propofol maintained anesthesia. Second, the use of

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combination antiemetic therapy and more appropriately a multimodal approach in high-risk patients is recommended. However, the best available combination and the optimum doses of antiemetic agents when used in combination are yet to be established. Ondansetron should be considered in any prophylactic regimen as it is now generic and hence has a low acquisition cost.

Perioperative Fluid Management

The underlying principles guiding fluid management in any setting are to maintain central euvolemia, i.e., avoid excess and deficiency. In other words, maintain a full circulation to allow normal optimal cellular perfusion whilst avoiding any peripheral or interstitial edema, and associated increase in body weight. Episodes of hypovolemia, if undetected can lead to hypoperfusion and organ dysfunction, with associated adverse outcomes. Importantly, and perhaps not as readily acknowledged, excess fluid administration can result in tissue edema and adverse outcomes. Whilst both these processes can be extreme, more commonly they are subtle with the splanchnic circulation particularly at risk.

A recent Perioperative Quality Initiative (POQI) consensus group provided the following recommendations regarding perioperative fluid management in the context of an enhanced recovery protocol.[57]

Preoperative

1. We recommend unrestricted access to clear fluids for oral intake up to two hours before the induction of anesthesia to maintain hydration while minimizing the risk of aspiration.
2. We recommend that the clear fluid used to maintain oral hydration contain at least 45g of carbohydrate to improve insulin sensitivity (except in Type-I diabetics, due to their insulin deficiency state). We suggest that complex carbohydrate (e.g. maltodextrin) be used when available.
3. We recommend that clinicians avoid administration of intravenous fluids to replace preoperative “fluid losses” in patients who received iso-osmotic bowel preparation provided there was unrestricted intake of clear fluids for up to two hours before the induction of anesthesia. There is no evidence that iso-osmotic mechanical bowel preparation leads to adverse effects on preoperative volume status.
4. We recommend against the use of hyper-osmotic or hypo-osmotic bowel preparations prior to surgery since there is no benefit relative to iso-osmotic bowel preparation and there may be adverse effects on preoperative volume status.

Intraoperative and Postoperative

1. We recommend the application of a hemodynamic framework to guide clinical decision-making during surgery. We have developed such a framework and suggest that the use of intraoperative goal-directed fluid therapy (GDFT) is likely to be safe in the majority of patients undergoing major colorectal surgery. GDFT has little risk and the use of advanced hemodynamic monitoring equipment may enhance clinical decision-making when compared with the use of conventional monitors. (Figure 5)
2. We suggest that the advanced hemodynamic monitoring equipment used to guide clinical decision-making intraoperatively be selected based on a combination of surgical, patient and institutional factors since such monitoring can minimize both hypovolemia (by promoting therapy in volume responders) and hypervolemia (by restricting therapy in non-responders). (Figure 6)
3. We recommend that, in isolation, intraoperative oliguria should not trigger fluid therapy, as low urine output is a normal physiologic response during surgery and anesthesia. We also recommend that intraoperative oliguria be investigated and that absolute (as opposed to relative) hypovolemia be ruled out.
4. We recommend that intraoperative and postoperative anuria warrant immediate attention since anuria is pathological.
5. We recommend that fluid management strategies focus on: first, identifying if there is a clinical problem that can be solved by fluid therapy, and then identifying what fluid and how much is appropriate. Rather than treating every instance of abnormal hemodynamic values (displayed by conventional or advanced monitors), clinicians must establish causation based on available information about the patient and clinical context.
6. We recommend that therapy attempt to reverse the most likely cause of a hemodynamic derangement. Absolute hypovolemia may or may not be responsible for observed hemodynamic abnormalities. For instance, stroke volume variation above 13% soon after the induction of anesthesia and with the institution of mechanical ventilation should prompt consideration of vasodilation (relative hypovolemia) rather than as the cause of fluid

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responsiveness. The patient may hence require vasoconstrictors rather bolus fluid therapy provided clear fluids have been consumed preoperatively and iso-osmotic bowel preparation has been used.

7. We recommend the use of buffered isotonic crystalloids for the treatment of hypovolemia in patients undergoing colorectal surgical procedures. We acknowledge that the restrictions on use of starch solutions are based on extrapolations from the critical care literature.
8. We suggest that patients tolerating fluids orally after surgery be given unrestricted access to such fluids, as this increases patient satisfaction and as it is likely that intravenous fluid administration offer no added benefit.
9. We suggest that the hemodynamic framework utilized intraoperatively be extended into the post-operative period, to the extent possible, in situations where patients might benefit from such postoperative monitoring (high-risk patients, or those with significant blood loss or complications during surgery).

Figure 5. Guidelines for Goal-Directed Fluid Therapy.

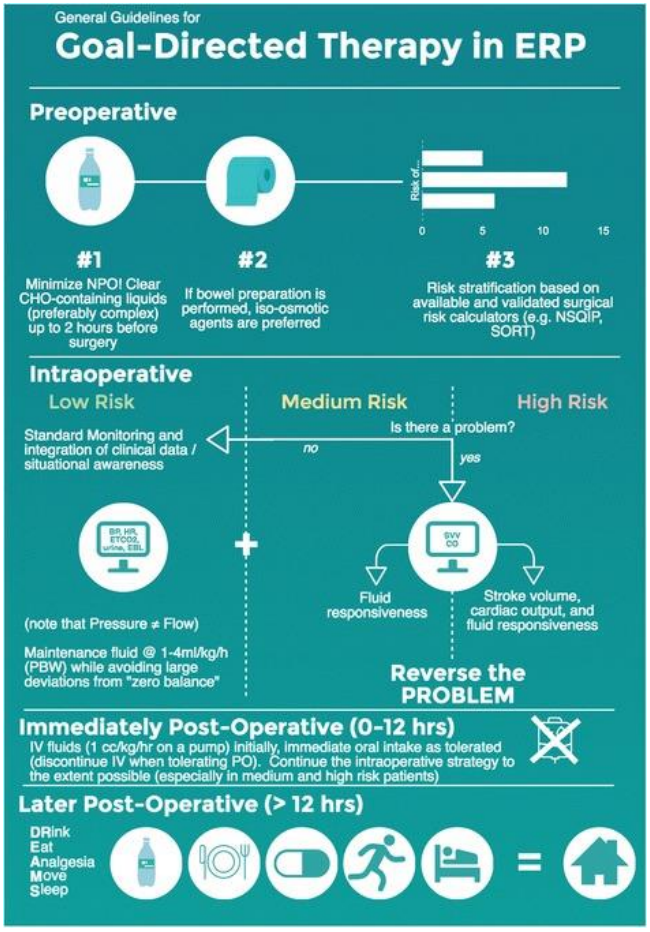
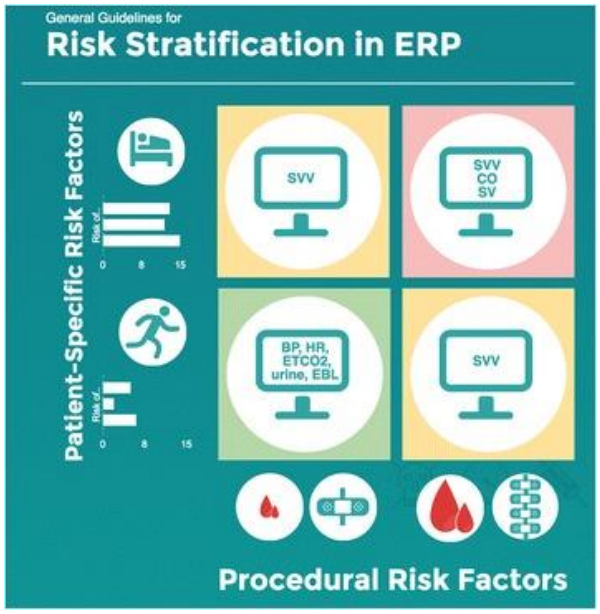


Figure 6. Risk Stratification for using advance hemodynamic device.



In summary, enhanced recovery is the cornerstone for reducing hospital length of stay, reducing postoperative complications and potentially increase patient satisfaction. Many successful enhanced recovery programs have been shown to increase quality and reduce cost, thereby increase value of healthcare delivery. Enhanced Recovery will likely become standard of care in the near future and should be embraced by patients, surgeons, anesthesiologists, hospital administrators, medical insurance payers and governments alike.

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Complications in Pediatric Anesthesia – How to Stay Out of Trouble!

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Emergency Agitation

Emergence agitation (EA) is a well documented phenomenon occurring in children and adults in the immediate postoperative period.[1]

Emergence agitation is defined as a dissociated state of consciousness in which the child is inconsolable, irritable, uncompromising or uncooperative, typically thrashing, crying, moaning, or incoherent.[2-4] Additionally paranoid ideation has been observed in combination with these emergence behaviors.[4] Characteristically these children do not recognize or identify familiar and known objects or people. Parents who witness this state claim the behavior is unusual and uncustomary for the child. Although generally self limiting (5-15 min) EA can be severe and may result in physical harm to the child and particularly the site of surgery.[3,5]

Emergence agitation is not a new phenomenon; it has been reported after the introduction of every new anesthetic including most inhalational agents and intravenous agents including midazolam, remifentanil and propofol.[6] Other drugs known to be associated with EA include 1) atropine or scopolamine, 2) ketamine, 3) droperidol, 4) barbiturates and possibly, 5) benzodiazepines.

The incidence of emergence agitation in all postoperative patients is 5.3% with a more frequent incidence in children (12-13%).[7] The incidence of emergence agitation after halothane, isoflurane, sevoflurane and desflurane ranges from 2-55%.[8-12]

It has been postulated that this phenomenon has become more acutely noticed with the increased use of agents such as sevoflurane and desflurane that have a rapid emergence profile due to their low blood gas solubility profile. It was thought that rapid emergence with lack of adequate pain control before emergence contributed or was the cause of this problem. This has been supported by Davis noting that ketorolac administration decreased the incidence of emergence agitation three to fourfold after myringotomy with either halothane or sevoflurane anesthesia.[13] Several studies have documented a reduction in EA with the administration of fentanyl 2.5 ug/kg intraoperatively or 2.0 ug/kg fentanyl administered intranasally, 1 ug/kg in each nostril after the induction of anesthesia.[14-18]

However, other studies have noted emergence agitation in children after sevoflurane anesthesia despite effective regional blocks to prevent postoperative pain.[12] These studies demonstrated that agitation occurred more frequently in preschool age children, 1 to 5 years of age, lasted 5-15 minutes in the recovery room and often resolved spontaneously.[12,19,20]

Studies that have also called into question whether adequate pain management is the cause of EA include sevoflurane vs halothane administration in patients undergoing MRI (no surgery) where the incidence of EA was 33% in sevoflurane treated patients versus 0% in halothane treated children.[21] But in patients undergoing MRI with sevoflurane anesthesia those that had a dose of intravenous fentanyl 1 ug/kg, 10 minutes before discontinuation of the anesthetic had an incidence of emergence agitation of 12% versus 56% in the placebo group.[22] An unanswered question was although discharge time was similar in both groups did the administration of fentanyl cause a slower awakening time?

In addition, studies have also called into question pain and rapid emergence as a cause for EA, since in these studies pain was well controlled and patients still exhibited signs of EA.[23,24] Murray demonstrated that preemptive oxycodone reduced post anesthesia agitation for children who received halothane but not for those who received sevoflurane.[25]

It must recognized in these studies it may be difficult to differentiate pain related agitation from other sources. Although pain cannot be entirely excluded as a contributing factor for EA the data does suggest the influence of another mechanism. Consideration of pain as a potential factor for agitation is important particularly in children undergoing short surgical procedures for which peak effect of analgesias may be delayed until they are well awake.

Other anesthetic techniques have been associated with decreased incidence of EA. Preschool children receiving a propofol versus sevoflurane anesthetic had a 38% incidence of EA with sevoflurane versus 0% with propofol. However, sevoflurane still provided a shorter PACU stay than propofol.[24] This was also confirmed by Cohen who had an incidence of 23.1% of patients with EA who received sevoflurane versus 3.7% with propofol.[23]

Another agent clonidine given intravenously at a dose of 2 ug/kg after induction of anesthesia in 40 male children age 2-7 years undergoing circumcision decreased emergence agitation to 2 patients in the clonidine group

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compared with 16 patients in the placebo group, being severe in 6 patients. Pain control was a penile nerve block before surgery.[26]

What about premedication in relation to EA - does it make it better or worse? Preoperative administration of midazolam has reduced the incidence of EA as compared with placebo[27] as has clonidine[28] however, this may be due to slower awakening rather than anxiety.

Oral premedication with the midazolam syrup 0.2 mg/kg had an incidence of emergence agitation that was seen in 47% of patients as compared to 81% who received a saline placebo.[29] In addition the midazolam premedication did not prolong the PACU stay. Sevoflurane has been reported at high concentrations to potentiate and at low concentrations to block gamma-aminobutyric acid A ($GABA_A$) receptor mediated inhibitory postsynaptic currents ($IPSC_s$).[30] Whether the biphasic effects of sevoflurane on $GABA_A$ receptor mediated $IPSC_s$ contribute to sevoflurane-induced EA remains unclear. Evidence that induction of sevoflurane anesthesia with propofol results in calmer recovery results in calmer recovery[31] does support that potentiation of $GABA_A$ receptor - mediated $IPSC_s$ may improve the recovery quality of sevoflurane. It is postulated that benzodiazepines such as midazolam potentiate the inhibitory effects of $GABA_A$ receptors[32] and therefore could be promising agents for improving the recovery quality of sevoflurane anesthesia. This study also confirmed that children younger than five years of age are more likely to have EA after sevoflurane anesthesia.[33] Ben-Ari et al indicated that the $GABA_A$ receptor could be excitatory rather than inhibitory in the early postnatal period[34] with the development of excitatory inputs the $GABA_A$ receptor becomes inhibitory as the child ages.[34] This development in the $GABA_A$ receptor is due to a switch from high to low chloride content in the neurons.[35] Developmental differences in the neurotransmitters and neuromodulators may account for the age-related differences. One study found children who received midazolam experienced EA more frequently than those who did not and observed the agitation lasted longer.[30]

Although Kain et al[36] demonstrated a decreased incidence of maladaptive behaviors at postoperative weeks after midazolam there was no difference in EA between children who received midazolam and those who did not. Furthermore, benzodiazepines themselves have been associated with paradoxical reactions and agitation that have been reversed with flumazenil.[37]

Therefore, other causes of emergence agitation must be searched for. It may be due to misperception of environmental stimuli with paranoid ideation,[4] differing CNS effects[4,14,38] sympathetic activation or some type of psychomotor effect.[14] It is known that the EEG pattern with sevoflurane differs from that of patients anesthetized with halothane.[39]

Although we may not know the cause of emergence agitation a recent prospective cohort study of emergence agitation in the pediatric post anesthesia care unit may give us the most insight into patients at risk for this phenomenon.[40]

Five hundred twenty-one children age 3-7 years who were undergoing general anesthesia for elective outpatient procedures were included. Ninety-six (18%) had emergence agitation. The agitation lasted up to 45 minutes in some cases with mean of 14 minutes. Fifty-two percent of children with agitation required pharmacologic intervention with prolonged post anesthesia care unit stay of 16 minutes over non-agitation children. Ten factors were associated with EA including 1) younger age (4.8 vs 5.9 years), 2) no previous surgery, 3) poor adaptability, 4) ophthalmology and 5) otorhinolaryngology procedures, 6) sevoflurane, 7) isoflurane, 8) sevoflurane/isoflurane, 9) analgesics and 10) short time to awakening. Of these otorhinolaryngology procedures, time to awakening and isoflurane were shown to be independent risk factors. Emergence agitation was associated with 5 adverse events, increased bleeding from surgical site (1) pulling out a surgical drain or an IV (2) increased pain at the operative site and minor injury of a nurse.

Interestingly enough children who received a combination of sevoflurane and isoflurane for induction and maintenance were twice as likely to have EA compared with any other anesthetic regimen.

Almost all children (98%) who had EA received intraoperative analgesics as compared with 86% of nonagitated children. There was no difference in the duration of anesthesia in the two groups but time to awakening was shorter in the EA group 14 $\pm$ 14 min versus 26 $\pm$ 23 min.

Why the increased incidence in otorhinolaryngology procedures? Eckenhoff et al[41] and Bastron and Moyers[42] speculate a "sense of suffication" may contribute to EA in patients undergoing head and neck procedures but there is no scientific data to support this.

As far as premedication with preoperative midazolam there was similar incidence in EA in those who received midazolam as those who did not (15% versus 19% respectively).

Temperament of the child with low adaptability has also been associated with sedation failure.[43] Kain has demonstrated children who were not enrolled in day care, those with no sibling and those who were very impulsive

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were at a greater risk for developing negative behavior changes such as separation anxiety, nightmares and bedwetting at two or more weeks after surgery.[44] More study definitely needs to be done in this area of temperament and emergence outcomes.

Diagnosis of emergency agitation can be made by using the Pediatric Anesthesia Emergence Delirium PAED) Scale 0-20. Scores greater than 10 or 12 were thought to have been diagnosed as having EA.[45] A risk scale for emergence agitation has been developed for children that includes four predictors, age (younger children), operative procedures (strabismus surgery, tonsillectomy), preoperative behavior score (shouting or screaming, tearful and/or withdrawn but compliant with induction), and anesthesia time (over 2 hours). This risk scale ranged from 1 to 23 points and a score of 11 was predictive. This can be used to predict EA and allow for prophylactic treatment.[46]

Treatment of emergence agitation can include opioids, midazolam, propofol and flumazenil. Propofol (0.5 mg/kg IV) or midazolam (0.02 mg/kg IV) have both been used successfully in treating EA in children.[14] When deciding on a therapy remember the occasional child may have a paradoxical reaction to midazolam, characterized by agitation combativeness or inability to be consoled. If the reaction is suspected consider the use of flumazenil 0.01 mg/kg IV, (max 0.2 mg/dose) at 1-2 min intervals to a maximum dose of 1 mg. In children greater than 12 years of age, give 0.2 mg/dose at 1-2 min intervals up to a total dose of 1 mg.

Dexmedetomidine has been shown to decrease the incidence of EA. Intravenous doses ranging between 0.3-1 ug/kg have been effective.[47-49] More recently a rapid IV bolus of dexmedetomidine 0.5 ug/kg given 5 min before the end of surgery has been effective in prophylactic prevention of EA but also may be used as treatment postoperatively.[50]

It is important to remember that several life threatening considerations (eg. hypoxia, severe hypercarbia, hypotension, hypoglycemia, increased intracranial pressure) may also result in disorientation and altered mental status. These entities must be diagnosed and treated promptly. Bladder distention may also yield a similar clinical picture.

Laryngospasm

Laryngospasm is a frequent occurrence during the administration of anesthesia to pediatric patients. The incidence is 8.7/1000 patients in a total population and 17.4/1000 in patients ages 0-9 years[51], with the age group 1-3 months having the greatest incidence - more than 3 times the rate in any other age group. Although laryngospasm has been seen as a self limiting complication - 5/1000 laryngospasm patients have a cardiac arrest.[51] Other complications include bronchospasm, hypoxia, gastric aspiration, arrhythmias, and delayed recovery. In addition, pulmonary edema has been reported as a significant complication.[52]

Etiology

Laryngospasm occurs as a response to glottic or subglottic mucosal stimulation and continues long after the stimulus is gone. Risk factors include younger age, NG tube or oral airway placement, endoscopy or esophagoscopy, upper respiratory infections or volatile anesthetics (induction with isoflurane and desflurane).

Two areas have recently come into focus as relative to the risk of development of laryngospasm. First of 15,183 children in a day surgery unit who had general anesthesia, those who developed laryngospasm were 2.05 times more likely to have an active upper respiratory infection. They were also more likely to be younger and be undergoing airway surgery.[53] Anesthetizing a child with a URI may have a higher incidence of complications if the patient requires intubation. Bronchospasm has been shown to be higher in intubated patients.[54,55] In children with a URI, LMA use instead of intubation has shown that laryngospasm was equal in both groups but the incidence of mild bronchospasm was higher in the intubated group. Therefore the LMA may be a suitable alternative if the decision is made to proceed with anesthesia in a child with a URI.[56] However, with LMA use, children with the presence of any 2 risk factors (cold < 2 weeks, wheezing < 12 months, wheezing at exercise, nocturnal dry cough, eczema, passive smoking, family history of hay fever/asthma/eczema) benefited from an IV induction with propofol rather than an inhalation induction with sevoflurane in decreasing respiratory adverse events.[57]

Secondly, children exposed to environmental tobacco smoke (ETS) were studied. Of those exposed to ETS, 9.4% developed laryngospasm whereas those without domestic ETS exposure, only 0.9% developed laryngospasm. All occurred on emergence from general anesthesia. The risk for laryngospasm is greater if the source of passive smoke is from the caretaker.[58,59]

Management

Laryngospasm may present as complete or incomplete airway obstruction. If incomplete airway obstruction is present sounds should be present - eg. grunts, expiratory squeaks. Complete or incomplete airway obstruction should have initial treatment with jaw thrust and chin lift. The middle finger of each hand should be placed in the "laryngospasm" notch. It is behind the lobule of the pinna of each ear. It is bounded anteriorly by the

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ascending ramus of the mandible adjacent to the condyle, posteriorly by the mastoid process of the temporal bone and cephalad by the base of the skull. Press firmly inward toward the base of the skull with both fingers at the same time lifting the mandible at the right angle to the plane of the body (jaw thrust or forward displacement of the mandible). This will convert laryngospasm within one or two breaths to laryngeal stridor and then to unobstructed respirations.[60] This should include administration of 100% O_2 with gentle positive pressure. It must be remembered that incomplete airway obstruction may rapidly become complete.

Complete airway obstruction shares many of the signs of incomplete airway obstruction - tracheal tug, retractions of the chest wall and marked abdominal respiration, but there is no sound present. Positive pressure will not "break" laryngospasm in the presence of complete airway obstruction.[61] It may worsen it by forcing supraglottic tissues downward into the glottic opening. High pressure generated by the flush valve may dilute anesthetic gases, and lead to a lighter level of anesthesia. It may also force gas down the esophagus into the stomach making ventilation more difficult. If IV access is present succinylcholine 1.5 mg/kg with atropine 0.02 mg/kg can be given. If no IV access is present IM succinylcholine 4 mg/kg is recommended to be given in the deltoid muscle. Intralingual atropine and succinylcholine can cause ventricular arrhythmias in patients anesthetized with halothane.[62] If laryngospasm is sustained and the child is extremely hypoxic it may be necessary to intubate without muscle relaxants. If these measures have not proved successful in securing the airway cricothyrotomy or emergency tracheostomy may be required.

Prevention

Mucosal stimulation and tracheal suctioning should only be done when the patient is deeply anesthetized. The effect of lidocaine is controversial. Intravenous lidocaine 2 mg/kg given one minute before extubation may attenuate or prevent laryngospasm. However Leicht[63] has suggested that IV lidocaine does not prevent laryngospasm if the patients are extubated after they begin to swallow. To benefit from lidocaine, patients must be extubated before swallowing begins.

Anesthesia-Related Cardiac Arrest

The etiology of cardiac arrest in the pediatric patient has changed over the past 20 years as practice has evolved in the care of these patients. The Pediatric Closed Claims Study in 1993 showed respiratory events were the most common category accounting for 43% of claims with inadequate ventilation seen in half of the respiratory events. The typical profile in this category of inadequate ventilation was healthy, non-obese children breathing halothane spontaneously whose arrest was preceded by hypotension or bradycardia. These children were difficult to resuscitate successfully, 70% died and 30% had permanent central nervous system impairment. Pulse oximetry was used in 7% of the Closed Claim cases and capnometry in 5%.[64] Recently the Pediatric Perioperative Cardiac Arrest (POCA) Registry has provided some new data. Out of 1,089,200 anesthetics, there were 150 cardiac arrests which were deemed anesthesia related (1.4/10,000).[65] Several points are relevant in analysis of this data.

First, an increased incidence of cardiovascular causes (32%) have differed from the Pediatric Closed Claims Study in 1993 where only 13% were from cardiovascular causes. This may have some basis in the fact that using chest compression was necessary as entry criteria for the POCA Registry or the fact that the use of pulse oximetry in 98% and capnography in 86% of cases may be more effective in preventing respiratory than cardiovascular incidents before arrests occur. Most of the cardiac arrests (82%) occurred during induction or maintenance of anesthesia. Bradycardia (54%), hypotension (49%), abnormality of SpO_2 (46%) or inability to measure blood pressure (25%) were the most common antecedent events. Twenty-one percent of arrests occurred during emergency surgery.

Second, infants are at increased risk. Infants <1-year accounted for 55% of the anesthesia related cardiac arrests. Several pediatric studies have confirmed that infants <1-year have the highest anesthetic risk and that mortality is inversely proportional to age with the highest risk in the <1 month of age group. This may be notably related to a higher ASA Physical Status (PS) Classification with underlying patient disease (particularly congenital heart disease) but also to cardiovascular depression by inhalational agents. In infants <30 days of age the MAC of halothane is .87%, as compared with children 1-6 months of age - MAC of 1.08. With isoflurane, the MAC for preterm infants (<32 weeks) is 1.28, 32-37 weeks is 1.41, and for term (0-1 month) 1.60, with 1-6 months being 1.87. Only sevoflurane appears to be different with the MAC being constant at 3.2-3.3% for neonates and infants less than one month, decreasing to 3% at 1-6 months, and 2.5-2.8% for 7 months - 12 years.[66]

Recent studies show sevoflurane may be less of a myocardial depressant and have less potential for producing bradycardia than halothane in infants.[67] Sevoflurane may also be safer for use in children with congenital heart disease. In comparison with children receiving halothane, the halothane treated patients experienced twice as

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many episodes of severe hypotension as those who received sevoflurane. Recurrences of hypotension occurred despite increased vasopressor use in the halothane as compared to the sevoflurane treated patients. Risk of hypotension was increased in children less than one year of age compared with older children and patients with preoperative cyanosis had a higher incidence of developing severe desaturation with halothane. Thus, sevoflurane may have hemodynamic advantages over halothane in infants and children with congenital heart disease.[68]

Third, 33% of all anesthesia-related cardiac arrests occurred in previously healthy ASA PS 1 and 2 patients - mostly medication-related errors (64%). Fifty percent of the arrests caused by halothane cardiovascular depression were seen at inspired concentrations of 2% or less with the median age being 6 months. Controlled ventilation may accelerate the rise in halothane concentration compounded by prolonged exposure due to difficult intravenous access. Four cases of arrest occurred following probable intravascular injection of local anesthetics. These occurred during combined halothane and caudal anesthesia with injection of 0.25% bupivacaine with 1/200,000 epinephrine despite negative test dose and aspiration. They occurred when both needles and catheters were used to deliver the medication. All had ventricular arrhythmias but were successfully resuscitated without injury.

Mortality rate in ASA PS 3-5 patients was 37% compared to 4% in ASA PS 1-2 patients. ASA PS 3-5 was the strongest predictor of mortality followed by emergency status. Overall the mortality rate in all arrests was 26%.[65]

Since publication of the initial series 397 additional cases have been submitted to the POCA Registry and 49% of these arrests were related to anesthetic causes. In the data from 1998-2004, the profile has changed again. Medication related causes have declined from 37% to 18% of the total due to the decline of cases of cardiovascular depression from inhaled agents, possibly due to the change from halothane to sevoflurane use. Respiratory causes have increased from 20% to 27% the most frequent etiology being laryngospasm. Cardiovascular causes of arrest increased from 32 to 41%. Hypovolemia (often from hemorrhage in spine fusion or craniectomy/craniotomy), the metabolic consequences of massive transfusion (usually hyperkalemia) or hyperkalemia from succinylcholine use were the most frequent known cause of arrest in this category. The exact cause of arrest could not be determined in some cases in the cardiovascular category – frequently these were children with congenital heart disease and an ASA physical status 3-5. Equipment problems (mainly complications from central venous catheter placement) have stayed fairly constant as a cause of arrest in pediatric patients being 7% in 1994-97 and 5% in the 1998-2004 data.

The demographic profile since 1998 has also changed, the percentage of ASA physical status 1 and 2 decreased from 33% to 25% and the percentage of patients less than 1 year of age decreased from 56 to 38%. This may be due to a decreased incidence in the number of arrests reported due to inhalational agents. These arrests were more likely to occur in ASA physical status one or two patients who were less than 1 year of age. The mortality rate in the two time periods hasn't changed, being 26 and 28% respectively.[69]

Another study evaluating the data in 92,881 patients from a tertiary care referral center between 1998-2005 indicated the incidence of anesthesia-related cardiac arrest was 0.65/10,000 anesthetics (less than the original POCA data). Both cardiac arrest incidence and mortality were highest among neonates (0-30 days of life) undergoing cardiac procedures. Most patients who experienced perioperative cardiac arrest (88%) had underlying congenital heart disease.[70]

In another report, the frequency of anesthesia-related cardiac arrests in patients with congenital heart disease undergoing cardiac surgery was 27.1/10,000 anesthetics with no mortality. Cardiac arrest was highest in the neonates.[71] In a Brazilian tertiary care hospital with 53,718 anesthetics over a 9 year period the incidence of anesthesia-related cardiac arrest was 3.35/10,000 and anesthesia-related deaths 0.56/10,000. Major causes of cardiac arrest were airway management and medication administration errors. Major risk factors were neonates and children <1 yr (prematurity and congenital heart disease were also factors) and emergency surgery.[72] A final study from an academic pediatric medical center looking at 105,436 procedures (except cardiac catheterization) over a 5-year period reported an incidence of 2.67/10,000 cases. Risk factors included ASA physical status $\geq$3 and children less than 1 year of age. Those providers that spent $\leq$40% of time in the OR also indicated a risk factor.[73]

STRATEGIES TO PREVENT CARDIAC ARREST IN THE PEDIATRIC PATIENTS:

1. Newer inhalational agents and improved monitoring may have already made a difference
2. Use of local anesthetics such as ropivacaine with less potential for toxicity
3. Regional techniques that include aspiration for blood, test dose and incremental not bolus injection
4. Limiting succinylcholine use to rapid securing of the airway and treatment of laryngospasm
5. Adequate intravenous lines and keeping up with intraoperative blood loss
6. Prevention of hyperkalemia with limited succinylcholine use and during transfusions (beware of old irradiated blood)

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7. Early treatment of laryngospasm with the understanding that having an IV in place can be helpful
8. Safer techniques for CVP placement – such as use of 2D US/Doppler
9. Put high risk children in experienced hands

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Perioperative Management of Thoracoabdominal Endovascular Aortic Repairs

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Introduction:
Endovascular aortic repair was pioneered by Parodi et al in the early 1990s.[1] As a result of immense development in endoluminal technologies and techniques, thoracic endovascular aortic repair (TEVAR) has now become established as a less invasive option for the management of thoracoabdominal aortic diseases compared to conventional open surgical repair (OSR). TEVAR has reduced morbidity and mortality compared to OSR and is especially better suited for patients with complex aortic pathologies who might otherwise be deemed high risk or unfit for an open repair.

In a large meta-analysis of TEVAR versus open repair for descending thoracic aortic disease, the authors reported on 5888 patients from 42 articles, 38 of which were comparative studies and 4 from registry data.[2] Overall, TEVAR patients were older with more comorbidities than the open surgical patients. All-cause mortality at 30-days, paraplegia or paraparesis, transfusions, reoperation for bleeding, renal dysfunction, pneumonia, and cardiac, neurologic, respiratory complications were significantly reduced with TEVAR compared to open surgery. Moreover, TEVAR was associated with reduced length of hospital stay, length of stay in the ICU as well as procedure time compared to open repair.

Technological Advances:
Improvements in endovascular devices, reduction in delivery sheath size, improved conformability, tapered grafts, and a wider range of sizes have improved TEVAR applicability and outcomes. Contrast-enhanced computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) with 3-dimensional (3D) reformatting helps delineate patient-specific anatomy and, thereby, determination of the most appropriate approach towards management of the aortic pathology such as the use of staged or hybrid approach, customized fenestrated or branched stent grafts as well as the most appropriate site for vascular access. Hybrid procedures and the evolution of fenestrated and branched grafts have facilitated the management of various thoracic aortic pathologies such as thoracoabdominal aortic aneurysm (TAAA), aortic arch aneurysm, aortic dissection, and ruptured descending thoracic aortic aneurysms (DTAA). Fenestrated endografts, which have holes (fenestrations) to accommodate the visceral arteries, are typically custom designed to fit the specific anatomy of the individual patient. Branched grafts come with pre-attached side-arm grafts sutured to the basic stent graft for deployment into the important arterial branches.

In the past decade, a number of endograft devices have become available for commercial use for the treatment of various thoracic aortic pathologies. The Gore TAG thoracic endoprosthesis (Gore & Associates) has been in commercial use since 2005 in the United States for the treatment of DTAAs. The Zenith TX2 TAA endovascular graft (Cook Inc, Bloomington, IN) and the Talent Thoracic Stent Graft System (Medtronic Vascular, Santa Rosa, CA) were approved for the treatment of DTAA and penetrating atherosclerotic aortic disease in 2008.[3] More recently, FDA approved the Valiant Captivia thoracic stent graft (Medtronic Inc, Minneapolis, MN) and the redesigned Conformable GORE TAG device (Gore & Associates) for the treatment of isolated lesions (excluding dissections) of the descending segment of the thoracic aorta. The Zenith Alpha thoracic endovascular graft (Cook Medical) received FDA approval for commercial use in 2015. This device, which offers a 2- to 4-F reduction in sheath size, is indicated for aortic aneurysm, penetrating aortic ulcer, and traumatic transection. Bolton Medical's Relay Pro system, which offers reduced sheath size as well as the mechanical advantage in the deployment system, is currently under investigation for treatment of Type B dissections.

Indications for TEVAR:
Descending Thoracic Aortic Aneurysms (DTAA): The incidence of thoracic aortic aneurysms is reported to be approximately 10.4 per 100,000 person-years.[4] The prevalence of descending aortic aneurysms seems to have tripled over the past two decades.[5] This could be related to the aging population, improved diagnostic capabilities or an actual increase in the incidence. The descending thoracic aorta grows quite slowly, on average at approximately a rate of 0.19 cm per year.[5] The annual risk of rupture, dissection, or death is 14.1% in patients with aneurysms greater

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than 6 cm, compared with 6.5% for aneurysms between 5 and 6 cm in diameter.[4] The Society of Thoracic Surgeons (STS) recommends TEVAR for DTAAs when the aortic diameter is greater than 5.5 cm (Class IIa recommendation, level of evidence B, when the patient has significant comorbidity; Class IIb recommendation, level of evidence C, when the patient has no significant comorbidity).[6] The STS advises against TEVAR when the aortic diameter is less than 5.5 cm (Class III recommendation, level of evidence C).

In a prospective, nonrandomized, multicenter trial that compared 140 patients who underwent endograft exclusion with 94 historical patients treated with OSR, TEVAR patients had a significant reduction in perioperative mortality (2.1% vs 11.7%), respiratory failure (4% vs 20%), renal insufficiency (1% vs 13%), spinal cord ischemia (SCI) (3% vs 14%), mean length of stay in the intensive care unit (2.6 ± 14.6 vs 5.2 ± 7.2 days), and overall hospital stay (7.4 ± 17.7 vs 14.4 ± 12.8 days). There was no difference in overall mortality at 2 years, however, there was a 9% incidence of endoleaks associated with TEVAR versus OSR.[7]

Ruptured Descending Thoracic Aortic Aneurysms (rDTAA): Ruptured DTAAs (rDTAAs), which occurs in 3.5 per 100,000 person-years, carry a 100% mortality when left untreated. Compared to OSR, TEVAR has been shown to have a lower risk of 30-day mortality, myocardial infarction, stroke and paraplegia. In a meta-analysis that compared outcomes after OSR versus TEVAR for rDTAAs, the 30-day mortality was 36% versus 19% respectively. The rates of myocardial infarction (11.1% vs 3.5%), stroke (10.2% vs 4.1%), and paraplegia (5.5% vs 3.1%) were higher for OSR compared to TEVAR. The estimated aneurysm-related survival at 3 years after TEVAR was 70.6%.[8] TEVAR is, therefore, the treatment of choice for anatomically suitable cases of rDTAAs.

Blunt Traumatic Thoracic Aortic Injury (BTTAI): Thoracic aortic injury carries a high mortality with over 80% of the victims dying at the scene of the accident. Most BTTAIs occur as a result of a high-speed, deceleration injury, with the aortic isthmus (just distal to the left subclavian artery) being the most common location. OSR carries a high mortality rate (18-28%) as well as a relatively high rate of paraplegia (2.3-14%). In a meta-analysis that included 7768 BTTAI patients from 139 studies, mortality was lower with TEVAR compared to OSR (9% vs. 19%). SCI was also more likely with OSR compared to TEVAR (9% vs. 3%).[9] Therefore, TEVAR is the preferred treatment for BTTAI in anatomically suitable patients (STS Class I recommendation, level of evidence B).

Thoracoabdominal Aortic Aneurysms (TAAA): Roughly 10% of all of the thoracic aortic aneurysms also involve the abdominal aorta and are classified as thoracoabdominal aortic aneurysms. Surgical management is the treatment of choice for TAAAs since there is a significant 5-year survival benefit with surgical intervention as opposed to non-surgical management (73.5% vs. 19%).[10] Although OSR has been reported to have excellent early survival (30-day survival of 95%) with acceptable morbidity, endovascular repair is the treatment of choice especially in patients with significant comorbidity (STS Class IIb recommendation, level of evidence C).[6] In a recent retrospective review of 155 patients who underwent fenestrated and branched endografts for TAAAs, technical success was accomplished in 94.2% of patients. The 30-day and 1-year survival was 93% and 82.6% respectively. The authors reported twenty-three (18.4%) primary endoleaks and an overall follow-up mortality of 16.1%.[11]

Type A Aortic Dissection: Since the mortality rate with untreated acute Type A dissection approaches 50% at 1-month, urgent OSR is the treatment of choice (ACC/AHA Class I recommendation, level of evidence B).[12] Although recently small series have reported the successful use of endovascular techniques for management of Type A dissections, OSR is still the preferred approach.

Uncomplicated Type B Aortic Dissection: Although uncomplicated type B aortic dissections are best treated initially with medical therapy (ACC/AHA Class I recommendation, level of evidence C), 20-50% of the patients who survive the acute phase require an intervention due to dilatation of the false lumen.[12] According to a recent study, the subset of uncomplicated Type B dissection patients with false-lumen diameters greater than 22 mm are at a significantly higher risk of aneurysm formation and perhaps best managed with early endovascular management.[13]

Complicated Type B Aortic Dissection: About a third of acute Type B aortic dissections are complicated at initial presentation with rupture or impending rupture, end-organ mal-perfusion, limb ischemia, unrelenting pain, or uncontrollable hypertension. These patients are best managed with either an open surgical repair or an endovascular repair (ACC/AHA Class I recommendation, level of evidence B).[12] The rationale for an endovascular repair is that

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the obliteration of the primary intimal tear with a stent graft would promote thrombosis of the false lumen. Endovascular repair of acute complicated Type B aortic dissection is associated with lower morbidity and mortality compared to OSR and has emerged as the treatment modality of choice.

Aortic Arch Aneurysms: OSR has been the treatment of choice for aortic arch aneurysms. However, recently hybrid procedures have been used to treat complex aortic arch aneurysms in high-risk patients who are otherwise not suitable candidates for OSR. In a systematic review of aortic arch hybrid procedures, that included 195 patients, the pooled perioperative mortality and morbidity rates were 9% and 21%, respectively. Technical success was achieved in 86% of the patients whereas technical failure was most commonly due to endoleaks (9%).[14]

Anesthetic Considerations for TEVAR:

Patients presenting for TEVAR are typically elderly often with significant comorbidities such as hypertension, coronary artery disease, pulmonary disease, renal disease and congestive heart failure. The risk factors for 30-day mortality with endovascular procedures are old age (>80 years), renal failure, presence of lower limb ischemia and congestive heart failure. Although, compared to open surgery, TEVAR is far less invasive, is associated with less fluid shifts, and does not require aortic cross-clamping, but it is still considered a high-risk procedure since the incidence of major adverse cardiac events is greater than 5%. Patients should undergo functional testing based on the ACC/AHA guidelines for preoperative evaluation of patients undergoing noncardiac surgery.

Monitoring: Besides standard monitoring, an arterial line is indicated for monitoring of invasive blood pressures as well as to facilitate measurement of activated clotting time (ACT) and arterial blood gases. The arterial line should be placed contralateral to the upper limb surgical access (often the left side, hence a right-sided arterial line). Since there is a potential for significant blood loss, especially if the procedure has to be converted to an open repair, large bore venous access is recommended. Central venous access may be indicated for complex procedures or in the case of poor peripheral access. Intraoperative TEE is quite a valuable monitoring tool for TEVARs. Besides the assessment of intravascular volume status and ventricular function, TEE can help confirm correct placement of guide wire as well as the endograft, assist with detection of endoleaks, verification of aneurysm exclusion by the endograft, and identification of entry and exit points of an aortic dissection.[15]

Since there is a significant risk of spinal cord injury after TEVARs, it may be prudent to monitor spinal cord function. Evoked potentials, either somatosensory evoked potentials (SSEPs) or motor-evoked potentials (MEP), are especially useful in patients who are at a high risk of SCI. There are several caveats to consider with SSEPs. SSEPs are more specific for detection of lateral and posterior sensory column ischemia and a poor monitor of the anterior motor column. Besides ischemia, SSEP signal is influenced by inhaled anesthetics as well as hypothermia. Although SSEP has a high negative predictive value (99.2%), it has a relatively lower sensitivity (62.5%) for detection of SCI, and no clinically useful predictive value for delayed-onset paraplegia.[16] Although MEPs tend to be harder to monitor due to higher sensitivity to neuromuscular blocking agents and inhaled anesthetics, they are more specific for the motor neurons in the anterior horn. In a study that compared MEPs and SSEPs in extensive DTAA and TAAA repairs in 233 patients, there was approximately 90% correlation for spinal cord infarction as well as a 98% negative predictive value for immediate-onset paraplegia.[17] Despite its theoretical advantages, MEP monitoring failed to demonstrate any significant advantage compared to SSEP monitoring with regards to detection of spinal cord injury. Based on the existing data, the current guidelines for management of thoracic aortic diseases recommend the use of either monitoring tool (SSEP or MEP) for the detection of SCI.[12]

Anesthetic goals in TEVAR: The primary goals for intraoperative management include maintenance of hemodynamic stability, preservation of perfusion to the vital organs (brain, heart, spinal cord, kidneys, and the splanchnic vessels), balancing myocardial oxygen supply and demand, maintenance of euvolemia and ensuring normothermia. Since SCI is a major concern, it is recommended that mean arterial pressures (MAP) are maintained above 90 mmHg after stent deployment in order to maintain an adequate spinal cord perfusion pressure.
Since the proximal aorta (ascending aorta, aortic arch and proximal descending aorta) is exposed to extreme hemodynamic forces, it is not uncommon to use either pharmacologic or nonpharmacologic methods to reduce heart rate and MAP in order to facilitate accurate endograft deployment.[18] Pharmacologic agents used to facilitate stent deployment are typically rapid in onset as well as short-acting, such as adenosine, esmolol, nitroglycerin,

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clevidipine, propofol, or remifentanil. Nonpharmacologic measures include rapid transvenous right ventricular pacing (RVP) and right atrial inflow occlusion. The loss of atrioventricular synchrony and a reduction in ventricular filling time with RVP causes a decrease in left ventricular filling and thereby reduced stroke volume and cardiac output. Another non-pharmacologic technique for facilitating accurate proximal endograft placement is via temporary occlusion of the inferior vena cava which then results in preload reduction and hypotension.[18]

Types of Anesthesia: Although TEVARs can be performed under regional or general anesthesia (GA), they are often performed under GA. GA allows for controlled ventilation and limits patient movement. Some of the other factors that may favor GA include TEVAR with planned fenestrated or branched endografts (which tend to be long in duration), planned TEE for physiologic monitoring, left brachial artery cannulation as well as planned hemodynamic manipulations to create a motionless field for stent deployment.

Renal Protection: Pre-existing renal impairment is an important risk factor that is highly predictive of post-operative contrast-induced nephropathy in patients undergoing TEVARs.[19] Acute kidney injury (AKI) following TEVAR can result from hypoperfusion either due to hypovolemia or as a result of graft encroachment on to the renal vessels. Other potential causes are emboli to the renal arteries as well as contrast induced kidney injury.
Strategies for minimizing renal impairment include maintenance of adequate hydration, limiting contrast load and minimizing exposure to nephrotoxic drugs (such as nonsteroidal anti‑inflammatory agents and aminoglycosides). Maintenance of normal cardiac output, MAP and normovolemia are key to reducing the risk of AKI after TEVAR. Systematic review and meta‑analysis have not shown any benefit of one type of solution over another.[20] Although N-acetylcysteine has been recommended for prevention of AKI, the supporting evidence for its use is not compelling.[21]

Spinal Cord Ischemia: SCI, a devastating complication, has a reported incidence between 0% to 10.3% after TEVAR with the average incidence between 3% to 5%.[22] The 5-year survival for patients with SCI after TEVAR has been noted to be much lower compared to the ones with no SCI (25% vs 51%, P<.001).[23] The pathophysiologic basis for SCI after TEVAR relates primarily to endovascular coverage of intercostal and segmental collateral vessels within the excluded aneurysm, thereby compromising the net collateral vascular supply to the anterior spinal artery.[24]

Neurologic deficits secondary to TEVAR may be immediate- or delayed-onset. Intraoperative or immediate-onset SCI, which presents when the patient emerges from general anesthesia, is generally associated with a poorer prognosis whereas delayed-onset SCI (when detected and treated promptly) seems to be associated with a relatively good prognosis.[25] Since injury after SCI involves hypoperfusion of the anterior spinal artery, it is manifested by a loss of motor function, pinprick sensation and preservation of sense of vibration and position. There can also be associated autonomic dysfunction, resulting in hypotension or neurogenic shock that can further compromise perfusion to the spinal cord.[15] A number of risk factors have been identified that can contribute to SCI in patients undergoing TEVAR. Longer aortic stent grafts (> 30cm) that cover a greater extent of the thoracic aorta, prior abdominal aortic aneurysm (AAA) repair, coverage of the left subclavian artery, advanced atherosclerosis, chronic renal insufficiency, advanced age, perioperative hypotension, and emergency operation have all been linked to a higher incidence of SCI.

The key strategies to reducing the risk of SCI are optimization of perfusion and oxygen delivery to the spinal cord. Oxygen delivery can be optimized by maintenance of a normal cardiac output and oxygen carrying capacity (avoiding acute anemia). The key determinants for perfusion to the spinal cord, besides patency of the anterior spinal artery, are MAP and cerebrospinal fluid (CSF) pressure (or CVP, whichever is higher). Spinal cord perfusion is, therefore, best maintained by optimization of MAP (> 90 mm Hg) and CSF pressure (< 10 mm Hg). The American College of Cardiology Foundation and American Heart Association (ACCF/AHA) guidelines on the management of thoracic aortic diseases have assigned a Class I recommendation for CSF drainage as a spinal cord protective strategy for endovascular thoracic aortic repair in high risk patients.[12] Hnath et al in a prospective observational study reported significantly lower incidence of paraplegia, compared to historical controls, in 121 patients who underwent elective or emergent TEVAR along with CSF drainage.[26] They were also able to show that the benefit was greatest in patients at a higher risk for spinal cord injury such as previous AAA repair, more extensive graft coverage and occlusion of the left subclavian, hypogastric and iliac arteries.[26]

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Summary
TEVAR, as a less invasive option, continues to have an expanded role in patients with complex thoracic aortic diseases as opposed to OSR. TEVAR is now considered the treatment of choice for traumatic thoracic aortic injury, acute complicated Type B dissection, DTAAs greater than 5.5 cm, ruptured DTAAs as well as TAAAs. The reduced morbidity and mortality with TEVAR, at least in the peri-operative period (short-term), is particularly appealing. However, despite encouraging results, the long-term durability of TEVAR is still in question. TEVAR patients need to be followed-up with serial imaging studies to rule out endoleaks and device failure. Despite some of these concerns, with continuing evolution and improvement in endovascular techniques and technology, it is expected that the use of TEVAR will continue to expand in the future.

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Respiratory Physiology for the Anesthesiologist: Gas Exchange

Luca M. Bigatello, MD **Boston, Massachusets**

Respiration provides oxygen (O_2) and removes carbon dioxide (CO_2) for the body. A remarkable arrangement of functional units (the alveoli) delimited by extra-thin walls (epithelium and endothelium) creates the interface for gas exchange between air and blood. Gas- flow in and out of the lungs (ventilation) is generated by the activity of the respiratory muscles, or of a ventilator, and opposed by resistance within the airways and elastance ("stiffness") of lungs and chest wall. Knowledge of the basic physiologic events that regulate gas exchange provides a most useful frame to interpret the information from your physiologic monitors during anesthesia, and properly set your anesthesia machine ventilator. Experience from the care of respiratory insufficiency in the intensive care unit (ICU) also supplements the anesthesiologists' armamentarium in the most complex cases such as multiple trauma, thoracic anesthesia, and laparoscopic head- down position cases.

The PaO_2.

How O_2 gets from the atmosphere to the blood (**Figure 1**). O_2 constitutes 21% of the air we breathe. At sea level, air exerts a pressure of 760 mmHg; once fully saturated by water vapor (47 mmHg), the PO_2 in the inspired air (PiO_2) is:

$$\mathbf{PIO_2} = (760 - 47)\ \text{mmHg} \times 0.21 \approx \mathbf{150\ mmHg} \qquad [1]$$

In the tissues, a bit more O_2 is consumed (O_2 consumption: $\dot{V}O_2$) for each unit (e.g., each mole) of CO_2 produced (CO_2 production- $\dot{V}CO_2$) giving a respiratory quotient ([RQ]- $\dot{V}CO_2/\dot{V}O_2$) of 0.8. Therefore, in the alveoli one volume of O_2 is exchanged for 1.2 volumes of CO_2 hence with a normal $PaCO_2$ of 40 mmHg, the alveolar PO_2 (PAO_2) at steady state will be:

$$\mathbf{PAO_2} = PIO_2 - PACO_2 \times 1.2 \approx \mathbf{102\ mmHg} \qquad [2]$$

Past the pulmonary capillaries, arterial blood normally receives a small fraction of venous blood from a minimal alveolar shunt (2 - 3%, increases with aging) and from blood that shunts the pulmonary circulation, such as some bronchial and some diaphragmatic veins, and PaO_2 decreases slightly below 102 mmHg.

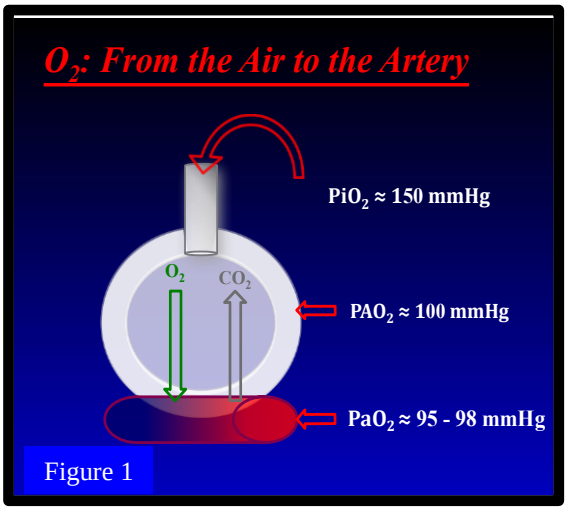

Figure 1

Causes of hypoxemia. Understanding how O_2 moves from the air to the blood (**Figure 1**) provides a convenient framework to classify the various causes of hypoxemia.

Low PIO_2. The most common cause of a low PIO_2 is breathing at high altitude. Breathing air at 5,300 feet in Denver lowers PIO_2 to 120 mmHg, and breathing air at 30,000 feet on the summit of Mount Everest lowers the PIO_2 to 40 mmHg (which is equal to the normal *venous* PO_2!). Although rare, causes of low PIO_2 at sea level are related to the accidental administration of a hypoxic mixture.

Low PAO_2: Hypoventilation. In addition to hypercapnea, hypoventilation may cause hypoxemia by increasing the alveolar PCO_2 ($PACO_2$). A $PACO_2$ of 80 mmHg will decrease PAO_2 to 150 - 80 x 1.2 = 54 mm Hg. This scenario underlies the importance to immediately administer supplemental O_2 to a patient that appears to be hypoventilating (for example, in the PACU): supplemental O_2 will rapidly increase PIO_2 and PAO_2 offsetting the effects of a high $PACO_2$.

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Impaired diffusion. Both O_2 and CO_2 equilibrate with alveolar O_2 and CO_2 well before the end of the pulmonary capillary, so that under normal circumstances PAO_2 and $PACO_2$ are nearly equal to PaO_2 and $PaCO_2$. The thinness of the path to traverse (epithelium, endothelium and interstitium) and the high diffusibility of the two gases are such that impaired diffusion is seldom the cause of hypoxemia. Ventilation / perfusion (V/Q, see below) inequality rather than impaired diffusion is much more likely to be the cause of hypoxemia. The diffusing capacity of carbon monoxide (DLCO), a sensitive test to quantify impairment of lung function, for example in COPD patients, is primarily affected by V/Q inequality rather than of gas diffusion *per se*.

Low PaO_2. The most common cause of hypoxemia is intrinsic lung disease, which alters the matching of ventilation and perfusion. **V/Q inequality** defines a continuum that ranges from no ventilation with preserved perfusion (**shunt**), to no perfusion with preserved ventilation (**dead space**) including an infinite number of combinations.

Shunt results in venous blood (PvO_2 = 40 mmHg, **Figure 2**) reaching the arterial side without addition of O_2, thus decreasing PaO_2 to a degree depending on the size of the shunt. The fraction of total pulmonary blood flow (Qt) shunted away (Qs) from unventilated alveoli can be calculated as the difference in content of O_2 between the pulmonary capillary (CcO_2) and the arterial (CaO_2) and venous (CvO_2) blood:

$$\mathbf{Qs/\ Qt} = (CcO_2 - CaO_2) / (CcO_2 - CvO_2) \qquad [3]$$

where CcO_2 is calculated using PAO_2 as a surrogate of PcO_2. Content of O_2 is:

$$\mathbf{Content\ O_2} = Hb \times 1.34 \times O_2\ Sat. + PaO_2 \times 0.003 \qquad [4]$$

Shunt occurs with intracardiac defects and in diverse pulmonary pathology such as atelectasis, pneumonia, and the acute respiratory distress syndrome (ARDS). In the presence of shunt, increasing FiO_2 will only marginally improve PaO_2 (through an increase in PvO_2); only recruitment of collapsed alveoli will effectively treat the hypoxemia.

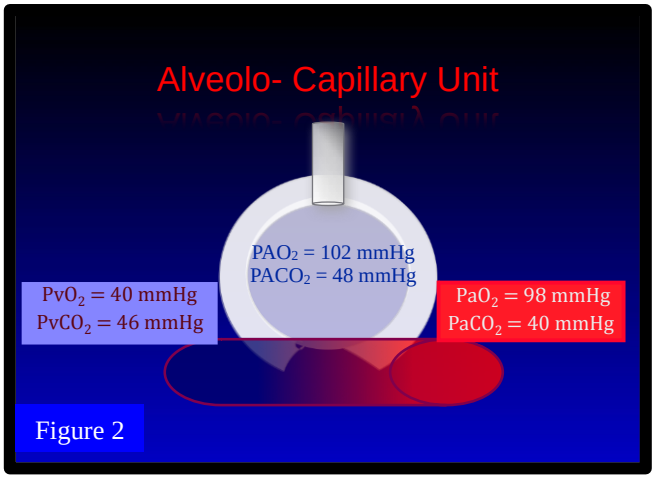

Figure 2

Low $\dot{V}/\dot{Q}$ results in arterial gas tensions approaching those of venous gas (**Figure 2**). Despite multiple possible combinations of low and high V/Q often present at the same time, **hypoxemia** is predictably the main result, because low V/Q and high V/Q do not cancel each other out. This is due to the shape of the **O_2 dissociation curve**. In a low V/Q alveolus where PaO_2 approximates PvO_2, *e.g.* 50 mmHg, O_2 Sat. will be ~ 75%, which will decrease CaO_2 by 25%; in an alveolus with a correspondently high V/Q ratio, O_2 Sat. cannot rise beyond the normal 100%, hence cannot compensate for the lost 25%; an increase in PaO_2 even well beyond 100 mmHg will compensate minimally because only 0.003 of the new PaO_2 will contribute to the CaO_2. **Figure 3** exemplifies this concept: the O_2 content leaving the alveolus with a low V/Q (16 mls / 100 mls of blood) approximates that of venous blood (14 ml) but the O_2 content leaving the alveolus with a high V/Q (20 mls) is barely higher than that of the normal alveolus (19 mls).

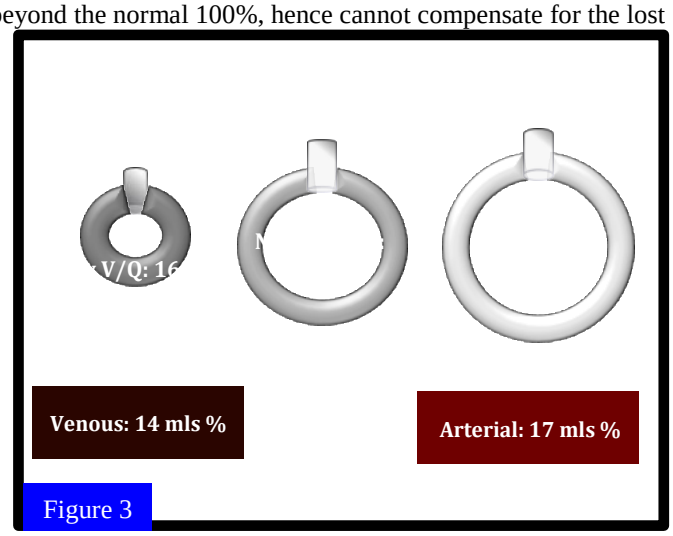

Figure 3

Low PvO_2 feeds venous blood into the arterial circulation through areas of shunt. The extent of the resulting hypoxemia depends on the magnitude of the shunt, and is limited by local hypoxic vasoconstriction (HPV) that reduces blood flow through the shunted areas. Through this mechanism, a low PvO_2 may cause significant

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hypoxemia in two clinically relevant circumstances. *First*, during shivering, due to an increase in O_2 consumption; *second*, with a low cardiac output, due to increased O_2 uptake (that's how hypotension may cause hypoxemia!).

Hypoxemia kills. Treatment of hypoxemia must be swift, and luckily it is simple during the administration of anesthesia in an uncomplicated case, i.e.: just increase the FiO_2! Not the same in the ICU during respiratory failure or in the OR in patients with severe respiratory comorbidity or during particularly procedures such as one- lung ventilation, thoracic trauma, pulmonary hemorrhage, etc. Hypoxemia kills by depriving cells of their main fuel: when PaO_2 decreases significantly, the gradient that drives O_2 from the blood into the interstitium ($PO_2 \approx 20 - 30$ mmHg) and from the interstitium into the cell ($PO_2 < 20$ mmHg) decreases as well. It is important to note that this is PO_2, not O_2 content (Equation [4]) hence therapy is strictly on PO_2, not on the other elements of O_2 content.

The $PaCO_2$.

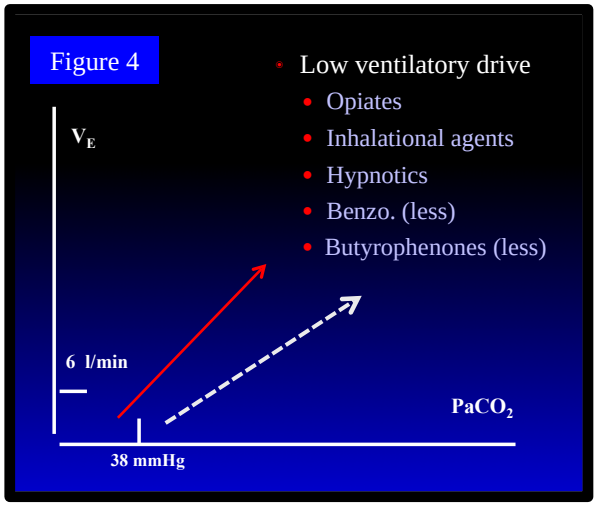
CO_2 and H_2O are end products of aerobic metabolism. CO_2 is transported in blood as carbammino Hb, bicarbonate, and carbonic acid, and is eliminated as gas from the lungs. At steady state, $PaCO_2$ results from the equilibrium of production ($\dot{V}CO_2$) by cellular metabolism and elimination by the minute ventilation (V_E):

$$\mathbf{PaCO_2} = \dot{V}CO_2 / V_E \qquad [5]$$

$PaCO_2$ is a potent stimulant of ventilation: for each increase of 1mmHg $PaCO_2$, the V_E increases nearly instantly by 1 - 2 l/min. An alteration in this relationship is a common cause of hypercarbia (**Figure 4**)

Causes of hypercarbia.

High $\dot{V}CO_2$ occurs with fever, shivering, excessive caloric / carbohydrate intake, and, to its maximum extent, in malignant hyperthermia (MH) and neuroleptic malignant syndrome (NMS). Except for MH and NMS, the increase of $\dot{V}CO_2$ is generally transient, and may be offset by an increase of V_E.



Low CO_2 elimination is the most common cause of hypercarbia and it includes two main reasons:

Hypoventilation increases $PaCO_2$ by limiting CO_2 elimination. Common causes of hypoventilation include: *a)* a decreased central drive to breathe, as it occurs with the administration of hypnotics and opiates (**Figure 4**); *b)* respiratory muscle weakness, in syndromes such as Guillain-Barre' and polyneuropathy of critical illness; and *c)* high resistive or elastic ventilatory loads (below), as it occurs in severe asthma or abdominal distention. Immediate treatment of hypoventilation includes ventilatory support and supplemental O_2 (see *hypoxemia*).

Dead space and high V/Q are a continuum of the same phenomenon, similarly to what we discussed for shunt and low V/Q. As perfusion decreases, venous blood fails to reach the alveolus, and less CO_2 is eliminated; exhaled PCO_2 decreases and, at a constant $\dot{V}CO_2$, $PaCO_2$ rises. These phenomena are at the basis of the measurement of the physiological dead space, as the fraction of unperfused ventilatory space ("dead", V_D) over the tidal volume (V_T):

$$\mathbf{V_D/V_T\ phys} = (PaCO_2 - PECO_2) / PaCO_2 \qquad [6]$$

V_D/V_T phys includes anatomical (proximal airways) and alveolar dead space (V_D/V_T alv). V_D/V_T phys is calculated using mean exhaled PCO_2 ($PECO_2$), which is measured as the PCO_2 averaged over several breaths. While the anatomical dead space is for the most part fixed (25- 30% of V_E) V_D/V_T alv is 0 in normal lungs, and it increases with the degree of lung disease in a number of conditions, such as ARDS and COPD / asthma. V_D/V_T alv can be calculated as:

$$\mathbf{V_D/V_T\ alv} = (PaCO_2 - PetCO_2) / PaCO_2 \qquad [7]$$

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$PetCO_2$ is the PCO_2 at end- expiration- 'end-tidal'. In a standard capnogram, when the expired CO_2 reaches a plateau, the $PetCO_2$ is highly representative of the $PACO_2$. A normal $PECO_2$ is approximately 30 mmHg, and a normal $PetCO_2$ is 38 - 40 mmHg, nearly the same as $PaCO_2$.

The linear correlation between $PaCO_2$ (independent variable) and V_E (dependent variable) gives us a clinical tool to follow changes on a ventilator without the need to measure $PaCO_2$ at each change in settings, similarly to how we may follow O_2- Sat. without measuring PaO_2. If we take note of the V_E before implementing a change, and we know the $PaCO_2$ at that V_E, no significant changes in V_E will reassure us that no significant change in $PaCO_2$ occurred. That is, with some caveats: *a)* assuming the $\dot{V}CO_2$ has not changed; unless we have a volumetric capnograph in use (unusual) we rely on our judgment: fever, shivering, and agitation may increase $\dot{V}CO_2$, which we need to verify; and *b)* assuming the V_D/V_T has not changed; this can be verified following the $PetCO_2$ from a time-based capnograph, used routinely in the OR and frequently in the ICU.

Hypercarbia rarely kills. Differently from hypoxemia, which must be corrected promptly, hypercarbia per se is generally well tolerated unless severe enough to cause obtundation leading to respiratory arrest, mostly at $PaCO_2$ levels above 100 mmHg. However hypercarbia may cause severe morbidity through various mechanisms in susceptible patients, such as by increasing intracranial pressure in the presence of cerebral edema, or exacerbating pulmonary hypertension in children with congenital heart disease and in adults with pre-existing right ventricular dysfunction. On the other hand, moderate hypercarbia could be a favorable condition in a number of pathologic situations, such as in shock by improving local blood flow, and in ARDS by allowing to limit tidal volume below levels known to be injurious.

Clinical applications of gas exchange physiology.

Anesthesia and Hypoxemia.

A number of factors conjure to decrease PaO_2 during general anesthesia.

Decreased lung volumes. A decrease in functional residual capacity (FRC) occurs within minutes of induction of anesthesia, with or without neuromuscular blockade, and is exacerbated by associated factors that also reduce FRC, such as morbid obesity, pregnancy, and acute respiratory failure of the low compliance type, for example ARDS. Oxygen desaturation may occur early and hastily following induction, getting the tonality of your pulse oximetry down to a baritone awfully fast if you cannot intubate swiftly. Under ideal circumstances, a calculation based on the volume of O_2 in the FRC and the average O_2 consumption shows that as much as 8 minutes are available prior to severe hypoxemia to occur. However, the clinical situations mentioned above drastically reduce this time frame; planning in advance is key in these circumstances to best utilize the short time available. A decrease in lung volumes, both FRC and tidal volume, may continue through during maintenance of anesthesia if ventilation is unsupported or only minimally supported, like for example with a low Pressure Support Ventilation (PSV) level. Getting the patient to breathe spontaneously may be helpful for other reasons, but supporting ventilation with positive end expiratory pressure (see below) a degree of inspiratory pressure to generate an adequate tidal volume is key to optimize gas exchange

Atelectasis develop during anesthesia as a consequence of decreased lung volumes and / or of a high inspiratory fraction of oxygen (FiO_2). A high FiO_2 reduce the concentration of nitrogen in the alveoli, which otherwise contributes to maintain the alveoli open at end expiration because nitrogen is not part of the exchange of gases. Thus the name of *absorption atelectasis*, and the benefit of avoiding excessively high FiO_2 unless needed to treat severe hypoxemia. It has been calculated that the presence of just 20% nitrogen may limit the degree of alveolar collapse due to high FiO_2.

Oxygen toxicity in the perioperative period. High FiO_2 can produce local and systemic damage through the generation of reactive oxygen species (ROS), which trigger chain reactions of lipid peroxidation that damage nuclear and cellular membranes and denature DNA. The clinical significance of the potential actions of ROS is still vague, and just a few data are well established: *a)* local damage resulting in a decrease in vital capacity (VC) may occur after 24 hours of breathing 100% FiO_2; further exposure may result in widespread lung injury; *b)* in one-lung ventilation, the combination of 100% FiO_2 and barotrauma may be additive in the pathogenesis of perioperative lung injury; *c)* data on the benefit of high FiO_2 ($\geq$ 80%) in preventing surgical site infection and nausea and vomiting have not been consistently produced; *d)* high FiO_2 in neonates is clearly associated with the development

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of severe ocular, cerebral, and respiratory toxicity; *e)* high FiO_2 in the elderly may also be associated with lung and systemic toxicity, but the clinical evidence is still frail.

Lung ventilation and alveolar recruitment during anesthesia.

Positive end- expiratory pressure (PEEP). The decrease in lung volumes that occurs during general anesthesia leads to a variable degree of alveolar *derecruitment* and hypoventilation. The most common way to prevent hypoxemia is to add PEEP to your ventilator settings. PEEP prevents alveolar units to fully collapse on expiration, thus improving V/Q match (see earlier in the outline) and rising PaO_2; also, by opening alveoli that were previously collapsed, lung volume increases for the same inspiratory airway pressure, which is to say that *lung compliance* improves (see below for more on compliance). Going into a bit more depth, PEEP works through an increase in *mean airway pressure*, (MAP) which is the pressure in the alveoli (measured at the airway) throughout the duration of inspiration.

MAP = inspiratory pressure – PEEP x Tinsp./Ttotal +PEEP [6]

Hence, MAP increases by rising inspiratory pressure (and tidal volume), inspiratory time (Tinsp), and PEEP. Note that in many anesthesia ventilators you will not find a knob for "inspiratory time": most commonly you adjust the time through changes in I:E ratio; also note that when on volume control a change in Tinsp leads to an opposite change in inspiratory flow and inspiratory pressure, because now the ventilator has to deliver the same tidal volume in a shorter time.

Separating peak and plateau pressures. As the flow of gas enters the lungs, it generates a pressure in the airways, then in the alveoli, and then changes lung volume (tidal volume). Thus, the pressure that we measure at the airway during inspiration is the results of a number of factors: the inspiratory flow, the tidal volume, the resistance generated by the airway, and the compliance of lung and chest wall ($\mathbf{C_{L+CW}}$).

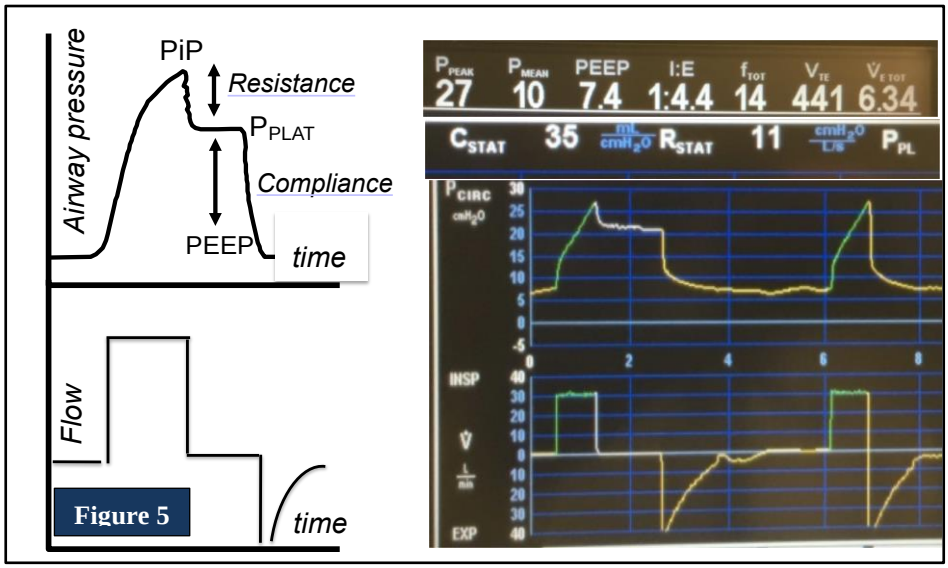

Figure 5

The pressure at end inspiration, or peak inspiratory pressure (PiP) is often quoted as the pressure that recruits or damages the lung, but this is incorrect. The portion of PiP due to airway resistance (**Raw**) dissipates along the airways before reaching the alveoli. An effective way to understand this concept occurs if you briefly kink the endotracheal tube with your fingers. The PiP will sky rocket, but the tidal volume will not increase (in fact, will decrease) and the lung will not be damaged. Hence, in the presence of an elevated Raw, PiP does not correctly reflect alveolar pressure. The latter can be estimated by performing an *inspiratory hold* maneuver (**Figure 5**), which interrupts gas flow separating the resistive and elastic components of the PiP. Once inspiration is held, the pressure (Pip) drops to a lower level (plateau pressure [Pplat]) that is determined only by the size of the tidal volume and the $\mathbf{C_{L+CW}}$. Accordingly (**Figure 5**):

$$\mathbf{C_{L+CW}} = \text{tidal volume} / (P_{PLAT} - \text{PEEP}) \quad [9]$$

$$\mathbf{Raw} = (\text{PiP} - P_{PLAT}) / \dot{V} \quad [10]$$

Under normal circumstances, the separation between PiP and Pplat is minimal, and it widens in the presence of asthma, COPD, and acute bronchospasm.

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Lung collapse during laparoscopic / robotic surgery.

Lung, chest wall, and transpulmonary pressure (Ptp). Abdominal insufflation during laparoscopic surgery further decreases FRC; addition of a steep head- down position during, for example, GYN procedures compound the loss of lung volumes, and may require very high airway inspiratory pressures to achieve adequate ventilation. This situation has rattled the mind of anesthesiologists who are concerned about lung damage from the high pressure, to the point of sometimes asking to abort the surgery. However, a more thoughtful assessment of the mechanics of ventilation in the presence of elevated intra-abdominal pressure will somewhat reassure the apprehensive anesthesiologist. The concept that needs to be considered is that of *transpulmonary pressure (Ptp)*, or pressure across the alveoli, which is the true pressure that expands or that damages the lung:

$$\mathbf{Ptp} = \text{Palv} - \text{Ppl} \qquad [11]$$

Where Ppl is the pressure in the pleural cavity. In a situation of low compliance of the lung (C_L) such as in ARDS, most of the inspiratory pressure is dissipated against the alveoli and little goes across into the pleural space, resulting in high Ptp. In the situation of low compliance of the chest wall (C_{CW}) such as with abdominal insufflation, little pressure is dissipated against the alveoli, and it moves into the pleural space where it dissipates against the stiff chest wall, and Ptp is relatively low. Hence, for the same Pplat, we may have a high (ARDS) or low (laparoscopic surgery) Ptp. The first case represents a high risk for alveolar damage, the second does not.

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Reduction of Surgical Site Infections: Is My Cloth Hat Really Killing My Patient?

Keith Candiotti, MD Miami, Florida

Surgical Site Infection (SSI) Frequency:

Surgical site infections (SSI) account for 20% of all hospital acquired infections. They are the costliest and most common of all hospital infections. SSIs are associated with an increased length of stay and a 2-11-fold increase in patient mortality. On average, an SSI adds 9.7 days to an admission and $20,000 in additional charges. The incidence of SSIs is 2-5% in all inpatients having surgery, which is approximately 160,000-300,000 patients a year in the United States. Sixty percent of SSIs are estimated to be preventable. SSIs are now a pay-for-performance metric and are often the focus of many QI/QA efforts.[1,2]

Surgical site infections are classified by the depth and tissue involved[3]. The classifications are as follows:

- Superficial SSI: includes only the skin and/or subcutaneous tissue
- Deep incisional SSI: involves fascia and/or muscular layers
- Organ space SSI: involves any part of the body opened or manipulated during a procedure, aside from those mentioned above.

Surgical Site Infection (SSI) Risk Factors:

There are two main classes of risk factors for SSIs; Intrinsic *(patient factors)*, which include modifiable and non-modifiable risks factors and Extrinsic factors.[1,4,5] Listed below are the categories and risks within each class:

Intrinsic-Modifiable Risk Factors[1,4] *(many of these can be corrected to some degree but are often dependent on patient compliance)*:

- Diabetes *(Glycemic control and DM status)*
- Dyspnea
- Obesity
- Alcoholism
- Current Smoker *(should stop 4-6 weeks before surgery)*
- Pre-operative albumin <3.5 mg/dl
- Total bilirubin > 1.0 mg/dl
- Immunosuppression

Intrinsic-Non-Modifiable Risk Factors:[1,4]

- Increased patient age
- Recent radiotherapy
- History of skin or soft tissue infections

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Extrinsic Risk Factors[1] *(Procedure-related and difficult to control):*

- Emergency Surgery
- Increasing complexity
- Higher wound classification

Extrinsic Facility-related:[1]

- Inadequate room ventilation
- Operating rooms having infrequent air exchanges
- Increased operating room traffic
- Multiple people in and out of operating rooms
- Contaminated environmental surfaces
- Ineffective cleaning of the operating rooms
- Non-sterile equipment
- Equipment remaining in rooms which is not cleaned or disinfected, *(i.e. Lights, monitors, machines etc.)*

Extrinsic Intraoperative Risk Factors:[1,4,5]

- Longer procedure duration
- Blood transfusions
- Breach in asepsis protocols
- Inappropriate antibiotic re-dosing, especially in patients who don't require it.
- Inadequate gloving
- Inappropriate surgical scrub
- Poor glycemic control
- Hypothermia

There are many steps that can be taken ahead of a patient's surgery to reduce SSI. Patients themselves play a large role in preventing SSIs along with improved processes at surgical facilities. The following interventions can be taken by patients and facilities to reduce, and greatly improve the incidences of SSIs:

SSI Pre-Hospital Interventions[6,7,8,9,10,11]*(Bathing, Smoking, Glucose control and MRSA Screening)*:

Bathing:

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- Preoperative bathing *(No actual evidence that preoperative bathing really reduces SSI)*
- Washing with chlorhexidine prior to surgery reduces skin bacterial count. [1] *(Some evidence demonstrates that chlorhexidine must dry to be effective)*
- Bathing maybe useful as part of MRSA decolonization or as part of a larger bundle of preventative measures.

Smoking Cessation:

- Smoking cessation 4-6 weeks prior to surgery reduces SSI risks. Especially, for cases involving implants or prosthetics *(Smoking increases SSI-complex process).* The priority for smoking intervention is as follows: Smokers > previous smokers > never smoked. There is no literature regarding the use of marijuana or e-cigarettes and related infection risks.

Diabetes Management:[9,12]

- Diabetes management with the use of diabetic medications and perioperative hyperglycemia control can drastically reduce risk factors for SSIs.
- Hyperglycemia in either DM or non-DM increases SSIs *(HgA1C does not appear to predict risk).*
- Maintaining acute glucose ranges within 110-150mg/dL for non-cardiac patients and <180 mg/dL for cardiac patients, appears to be beneficial. There is no documented or apparent benefit for ranges <110mg/dL *(more complications are likely*).

MRSA Screening:[13,9,14]

- Seven percent of all hospital patients screen positive for MRSA.
- MRSA prevention bundles, screening, decolonization, contact precautions, hand hygiene and vancomycin-containing antibiotics are effective at reducing MRSA and SSI in general. *(Use of vancomycin in MRSA (-) patients is associated with an increase in SSI, therefore it is not recommended for this population)*

SSI Hospital Interventions *(includes patients and caregivers):*

Patients:[15,1,16,17,18]

- Glucose control
- Perioperative glucose should be between 110-150mg/dL for *non-cardiac* patients and <180 mg/dL for *cardiac* patients
- Hair removal *(Hair removal should be avoided per the CDC. If necessary, a clipper is the preferred method for removal, not a razor. Razors can cause microscopic cuts and abrasions.[1] Razors are appropriate for use in the scrotal and scalp area only after trauma).*[2,3]

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- Skin preparation with alcohol and iodine or chlorhexidine should be used. If alcohol is not used in the preparation, then chlorhexidine should be used alone.[4,5]

Caregivers:[19,20,16,21,22,23,24]

- Surgical hand scrub with chlorhexidine or traditional water scrub are both effective. There is limited evidence to support one over the other. However, there is evidence supporting that alcohol scrubs reduce colony-forming units (CFU) in comparison to aqueous scrubs. The same is true for chlorhexidine versus povidone iodine scrubs. There is no proof that this translates into reduced overall SSIs.
- Surgical attire has been debated for many years, and many of the traditional practices are no longer supported by The Joint Commission (i.e., home laundry). There is very little evidence to support most policies that are currently in place. However, the CDC previously acknowledged that there are no well-controlled studies evaluating home versus hospital laundering of scrubs. Multiple studies have shown no increase in SSI from either home or hospital laundering.[1,2] The original recommendation from JACHO and the Association of Peri-operative Nurses is based on a single case study from one case of a nurse and her roommate who grew *Gordonia bronchialis* on their clothes. The source was believed to be her washing machine; however, it was never directly cultured for the bacteria.
- Surgical attire protocols, according to the American College of Surgeons, state that scrubs should not be worn outside the hospital perimeter. Scrubs and hats worn during dirty or contaminated cases should be changed between cases, despite not being physically dirty. Finally, scrubs should be changed daily, and scrubs worn outside the OR should be covered.
- Aside from scrubs, jewelry, caps, and masks are also considered surgical attire. All earrings and/or jewelry anywhere on the head and/or neck should be covered or removed. Masks and caps should be worn to cover the mouth, nose, and hair (skull and face) during all invasive procedures. Masks should never be worn dangling at any time, in or out of the OR. Despite the controversy, there is no evidence that skullcaps lead to an increase in SSIs as compared to bouffants.[1] Also, no direct data has linked exposed practitioner skin or hair, to an increase in SSIs. One study did demonstrate that bacterial loads in laminar flow hood theaters can be traced to the skin from the exposed ears of providers who wear skull caps.[2]

Surgical Care Improvement Project (SCIP) measures:[1,9,25,926,27,28,29,30,31,32,33,34,35,36]

In 2002 the Centers for Medicare & Medicaid Services *(CMS)* collaborated with the U.S. Centers for Disease Control and Prevention *(CDC)* on the Surgical Infection Prevention *(SIP)* project. This was in response to the inconsistent compliance with infection prevention measures. Since the initiation of these measures, individual hospitals have shown a decrease in SSI rates when adhering to SCIP compliance.

Antibiotic (ATB) Prophylaxis:

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The literature on prophylactic antibiotic administration within 1 hour of incision reducing the occurrence of SSI has been mixed. The greatest support is when the most appropriate selection of an antibiotic is used for ATB prophylaxis. ATB should only be used when indicated and not as a general practice. The choice of drug should be based on the type of procedure and the likely organisms involved. The ATB should be administered within 1 hour of the incision or within 2 hours if using Vancomycin or Fluoroquinolones are utilized; the benefits with regards to the timing of ATB is debatable. The dosage of ATB should be weight adjusted and should be re-dosed on based on the half-life of the drug or if > 1500 ml of blood loss. Vancomycin should not be used in the MRSA negative patient due to a reported increased risk of SSIs.
Antibiotics should be discontinued at the time of closure (exceptions: implant-based breast reconstruction, joint arthroplasty, cardiac procedures [exact dosing duration is unclear]). There is no evidence that ATB given after wound closure decreases SSI across a range of procedures. In addition, continuous ATB dosing increases the risk of a *C. difficle* infection from the disruption of the gastrointestinal flora, which naturally occurs in the body. Single-dose prophylaxis seems the most adequate for primary augmentation mammoplasties. Dosing past 24 hours for many surgeries remains controversial and unproven in its effectiveness.

Intraoperative Normothermia:

Maintaining normothermia reduces SSI, therefore, preoperative warming is also effective in reducing SSI even in cases of a short duration. For longer cases, over several hours, both preoperative and intraoperative warming are indicated.

Gloves:

Double gloving is highly recommended, as well as, changing gloves prior to closing incisions in colorectal cases.

Antibiotic Sutures:

Triclosan antibacterial sutures should be used for wound closure in clean and clean-contaminated abdominal cases.

Instruments:

New instruments for closure in colorectal cases, is recommended to prevent cross contamination from the GI tract to the skin.

Topical Antibiotics:

Overall, there is a lack of high-quality data to support local and topical antibiotic therapy use to decrease SSI risk. However, a recent systemic review found a possible benefit for topical antibiotics to reduce SSI for specific surgeries, i.e., spine surgery (Vancomycin), total

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joint arthroplasty, cataract surgery, possibly useful in breast augmentation and obese patients undergoing abdominal surgery. There is insufficient evidence to recommend ATB in all cases.

Supplemental oxygen:

Studies are mixed with regards to oxygen use intraoperatively and postoperatively. It is suggested that the use of 80% oxygen versus 30% was shown to support a lower SSI in a meta-analysis.[33,34] In general, 80% oxygen is recommended intraoperatively and in the immediate postoperative period after general anesthesia.

Postoperative Period:

Showering as early as 12 hours has not been shown to increase SSI as compared to waiting 48 hours. Showering may be done at the surgeon's discretion.

Conclusion:[9]

In conclusion, the human and financial repercussions from SSI are substantial. SSIs are complex and influenced by numerous factors, many of which are difficult to control. Practical measures to decrease SSI are multimodal and involve numerous different providers.
SSIs are still a significant health problem. It has been shown that with a few simple steps, it is easy to reduce the incidence of SSIs significantly. Some of the most readily achievable goals to reduce SSIs are effective glucose control, the correct use of antibiotic prophylaxis, keeping patients normothermic and the use of supplemental oxygen (which may be useful to reduce infections). It does not appear that there is any convincing evidence that surgical attire has any significant effect on the incidence of SSIs

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ANESTHESIOLOGY 2018
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Fatigue Risk Management: Making Overnight Call Safer

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Introduction

Fatigue during extended duty periods and overnight calls impairs our ability to care for our patients. A long night at work has measurable effects on vigilance, psychomotor functioning, and alertness in everyone. Anesthesiologists spend much of their time observing physiologic monitors, communicating with the surgical team, and planning for critical events that may occur throughout the perioperative period. They must therefore be able to sustain attention, rapidly detect adverse events, make diagnoses, and execute tasks that require fine motor skills. Mitigating the deleterious effects of sleep loss, circadian misalignment, and sleep inertia requires an understanding of the relationship between work schedules, fatigue, and job performance. This Refresher Course will explain the physiology of fatigue and how it can affect our ability to care for our patients. It will also discuss the scientific basis of countermeasures that are commonly used in other industries and explain how these interventions can be used by health care providers to mitigate the effects of fatigue in a hospital setting.

Sleep Physiology

Humans have a physiologic need to sleep. Although the specific function of sleep remains controversial, sleep deprivation can significantly impact performance and long-term health. Neuronal activity during waking appears may also be partly responsible for sleep homeostasis. Areas of brain that are most active while awake generate more slow-wave activity during the subsequent sleep period. Many studies have shown that cognitive impairment and cardiometabolic stress are exacerbated by shift work and sleep loss. Sleep deprivation has been shown to reduce brain cell proliferation in rats. In humans, morbidity of chronic sleep deprivation includes cognitive dysfunction, obesity and diabetes mellitus, and cardiovascular disease, among others.[1-3] Sleep fragmentation has recently been associated with cerebral arteriosclerosis and subcortical infarcts in older adults.[4] Individuals exhibit varying susceptibility to fatigue, and are affected by factors such as circadian rhythm, time since awakening, duration of wakefulness, and cumulative sleep debt. Pre-existing sleep disorders, sleep deprivation, and sleep fragmentation exacerbate impairment caused by fatigue.

Fatigue and Performance Impairment

Fatigue causes cognitive slowing, short-term memory lapses, decreased vigilance, and microsleep episodes.[5] In one study, residents who worked a 30-hour call shift every third day experienced twice as many lapses in attention during the night and 1.5 times as many during the day than did residents who worked a maximum of 16 hours during the day or night.[6] Resident performance on the Psychomotor Vigilance Task (PVT) was substantially worse with time awake and time while working for 30 hours every third night.[7] In yet another study, residents made 36% more serious medical errors and 57% more non-intercepted serious errors, including 21% more serious

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medication errors while working on extended-duty shifts.[7] The effects of fatigue are not limited to the hospital: Drowsy driving is a well-established cause of motor vehicle crashes after working a night shift, and is associated with microsleep episodes and decreased ability to stay in the correct lane.[8] The odds ratio of a motor vehicle crash is significantly increased after working a traditional 28-hour call period.[9]

Long work shifts on consecutive days can lead to reduced sleep duration and insufficient time for recovery from extended duty work shifts. As a result, a chronic sleep debt begins to accumulate, decreasing cognitive performance. In one study of chronic sleep restriction and acute sleep deprivation, healthy adults were randomized to sleep for 4, 6, or 8 hours per night for 14 consecutive days or 3 nights without sleep. Effects were measured with electroencephalogram, subjective sleepiness score, and a psychomotor vigilance test. As expected, subjects initially reported increased sleepiness after chronic sleep restriction. As the duration of sleep restriction increased, however, subjective sleepiness increased only slightly. After 14 days of sleep restriction, when performance on objective tests of psychomotor ability was at its worst (and comparable to several nights of sleep deprivation), subjects reported feeling only slightly sleepy. [10] This suggests that most individuals are not aware of the extent to which sleep loss affects their performance. Moreover, recovery after a period of chronic sleep loss is only temporarily restored to baseline after a single night of adequate sleep, suggesting that several days of recovery sleep are required.[11]

In response to the known detrimental effects of fatigue, the Accreditation Council for Graduate Medical Education (ACGME) has implemented guidelines that include a maximum work schedule of 80 hours per week, averaged over 4 weeks, and shifts that are less than 24 hours in duration. The guidelines further recommend that program directors avoid creating maximum-duration scheduling. The new guidelines are designed to be somewhat more flexible, in that residents may choose to remain after their shift or return to the healthcare institution before their rest period is over for educational activities or to facilitate the care of critically ill patients. The guidelines also require that residents and faculty receive training in fatigue, including recognizing signs of fatigue and education about fatigue mitigation.

Fatigue Countermeasures

Although it is impossible to completely eliminate the effects of fatigue, interventions such as caffeine, strategic naps, microbreaks, and bright light can help to alleviate its effects when anesthesiologists must work overnight or for extended periods of time.

Caffeine is a commonly used stimulant and can temporarily improve performance and alertness in people who are sleep-deprived. It is commonly available in a variety of foods and beverages (*e.g.*, coffee, tea, mints, and gum), and is effective and easy to use. In healthy individuals, the half-life of caffeine is 5-6 hours. Low dose caffeine (0.3 mg/kg, equivalent to1 small, weak cup of coffee) every hour has been shown to maintain performance during periods of sleep loss and circadian misalignment.[12] Doses of 200 mg, administered six hours apart, have also been shown to improve performance at night, and may be more convenient when working in an operating room and frequent access to caffeine is not feasible.[13] A large dose of caffeine in the morning (200 mg, equivalent to a large,

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strong cup of coffee) can reduce sleepiness and improve driving performance after a night of sleep loss, but may also inhibit recovery sleep.[14]

Strategically-planned naps can temporarily mitigate the effects of fatigue caused by sleep loss during extended duty work shifts. Taking a 20-minute nap during a night shift can improve alertness, psychomotor vigilance, and performance even when only a short duration of sleep is achieved during the rest break.[15] Another study found that taking a nap prior to the onset of sleepiness can improve subsequent alertness and performance for up to 30 hours.[16] Factors that limit the restorative effects of on-call naps include the expectation of being called and poor sleeping arrangements (*e.g.*, a noisy environment or overhead pages).[17] In general, longer naps are associated with better performance, but only after the effects of sleep inertia have dissipated.

Sleep inertia is a period of impaired performance that occurs immediately after awakening and lasts 15-60 minutes. The duration of impairment is variable and is more pronounced after awakening from deeper sleep and at the circadian nadir. Sleep deprivation can also worsen impairment caused by sleep inertia. Whenever possible, therefore, an adequate amount of time should be allowed after awakening from a nap for sleep inertia to dissipate. This will minimize the negative effects of sleep inertia on cognitive performance and decision-making. Caffeine may be used to mitigate the effects of sleep inertia but is most effective when taken before a short nap.[18] A dose of 200 mg of caffeine before a nap minimizes the performance decrements caused by sleep inertia. Exposure to bright light immediately after awakening is also effective, as is washing the face with cold water.[19]

Exposure to blue-enriched light improves alertness and neurocognitive performance in a dose-dependent manner. Light exposure suppresses melatonin release, improves subjective alertness, and produces EEG changes consistent with increased alertness.[20] Exposure to blue-enriched light has been shown to improve alertness and decrease subjective sleepiness in people who work at night, suggesting that light is a promising, nonpharmacologic way to improve performance in overnight shift workers.[21] Exposure to 200 lux of blue light (wavelength 469 nm) range also improves working memory,[22] decreases reaction time, and reduces attentional lapses.[23] Light exposure should be limited to short periods of time to improve alertness without causing a significant circadian shift.[24,25]

Bright light may be impractical in the operating room because some procedures (*e.g.*, laparoscopic or endoscopic procedures) require a darkened room. It may also be impractical to modify pre-existing architectural lighting to include blue light. Commercially-available light sources can provide blue or white light at the anesthesia workstation without affecting the room lighting. These devices provide light in the 469-nanometer wavelength at an intensity of 200 lux and can be used by anesthesia providers who must work at night.

Conclusions

Anesthesia providers who work overnight experience acute and chronic sleep loss, sleep inertia, and circadian misalignment, all of which can impair performance. Strategic naps, caffeine, and controlled exposure to light are practical countermeasures that can increase alertness and improve performance during periods of extended wakefulness and when working overnight. Each of these strategies are successfully used as part of fatigue risk

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management strategies in other occupations (*e.g.*, airline pilots, military personnel) and increase alertness and improve performance. Caffeine, napping, and bright light also appear to have synergistic effects, so a combination of these countermeasures, especially when combined with adequate sleep during regular duty periods, can effectively mitigate the effects of fatigue and improve patient safety.

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Hot Topics and Controversies in Acute Pain Management

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Acute pain management continues to be challenging. Studies have demonstrated continued unmet needs with the majority of patients experiencing significant pain at some point following surgery.[1] Analgesic gaps (periods of breakthrough pain) continue to be a problem for most patients. The last year has brought an unprecedented focus on the opioid crisis and possible opioid chronic use with even the short term use of opioids for acute pain. There is now evidence that the short term use of opioids following surgery in previously opioid naïve patients is associated with an increased risk of chronic opioid use.[2] There is keener attention to minimizing intraoperative opioids, opioids in the immediate postoperative setting, as well as at discharge.

Recent findings now support that between 6-10% of opioid naïve surgical patients will develop persistent opioid use.[3] Perhaps most alarming in this study was the finding that severity of surgery was not a factor in developing chronic opioid use, suggesting that it is opioids themselves and not the degree of pain that is the driver for long-term use. Information from the CDC demonstrates an increased risk of long-term opioid use by prior opioid-naïve patients starting at prescriptions of five days and increasing with duration of opioid use.[4]

There is increasing awareness to opioid related side effects and the need to minimize opioids generally through the use of multimodal analgesic techniques. Opioid related respiratory depression and sleep apnea are now major considerations in the postoperative period. The recent Joint Commission Sentinel Event Alert of August 2012 highlights the need for greater caution when prescribing opioids including patient risk satisfaction, heightened monitoring and less reliance on opioids. At the other end of the opioid spectrum, we have the challenge of managing postoperative pain in the presence of opioid tolerance and chronic opioid use. There is also an emerging theme of chronic pain following surgery. The recently published (2016) combined societies Guidelines on Postoperative Pain continues to resonate the theme of multimodal nonopioid and nonpharmacological approaches to acute pain management.[5]

The Perioperative Surgical Home (PSH) is a recent and important development in our specialty. Anesthesiologists may be taking the lead in perioperative medicine but there remains controversy and competition among various specialties as to whom will take the lead. Acute pain management and the resulting outcome benefits are an integral part of the PSH.[6-8] Acute pain management services have historically done a portion of this effort as well as the creation of Enhanced Recovery After Surgical (ERAS) pathways.[9] The management of acute pain with an eye to demonstrating outcome improvement will be an important part of the PSH and ERAS and a critical role for the future of anesthesiology taking us well beyond the walls of the operating room. While much of the focus of ERAS and PSH has been on cost savings, the ultimate goal is improved patient outcome and disability free recovery following surgery. Relatively simple techniques have demonstrated longer term benefits.[10] As this area has developed, there seems to be a bewildering number of ERAS pathways, many with multiple components. There may also be a "tug of war" with ownership (surgery or anesthesiology or perhaps even hospitalists). It is important that we do not make these complications barriers to implementation. Mariano recently cautioned that this may be a misunderstanding of the PSH.[11] The PSH and ERAS is not a single massive undertaking and must be customized to the specific institution. Any evidence based systematic pathway is a valid approach even with a more simplified approach.

This Refresher Course Lecture will present current and emerging concepts in acute pain management, many of which remain controversial. This lecture will emphasize the impact of the operating room anesthesiologist on longer term outcome.

CDC and FDA Guidance on Opioids

Opioid associated risks are now major concerns even with acute pain and chronic non-cancer pain. CDC issued specific guidance on the use of opioids for non-cancer pain.[12] Previously in 2013, the FDA changed the labels for extended release opioids clarifying that these potent agents are only for stable chronic pain when all other agents fail. In March of 2016, the FDA issued guidances (which will lead to label changes) for immediate release opioids

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which are commonly used for acute pain. Summarizing these changes, opioids are not first-line analgesics and are only for moderate to severe pain when other agents have failed. Further, the lowest effective dose should always be used. Finally, opioids are only for short term use. The prevailing theme is that the role of opioids needs to be reevaluated. Certainly much acute pain can be managed without opioids or with opioids as adjunctive agents for short periods.

Multimodal Analgesia

Historically, opioids have been heavily relied upon as single agents for postoperative pain. Opioids have been accepted as potent and effective analgesics but at the price of opioid related side effects. Patients typically balance side effects with pain relief – often requesting less pain relief rather than suffer opioid related nausea and vomiting.[13] These gastrointestinal side effects are distressing to patients and the most common reasons for refusing treatment. Further, opioids have limited efficacy for some types of pain, particularly visceral and neuropathic pain. Acute postoperative pain is often a mixed pain syndrome with multiple components and hence may not be relieved well with opioids alone. With aggressive multimodal analgesia incorporating regional/local anesthesia techniques, opioids may be minimized and in some cases eliminated.

The concept of multimodal analgesia entered the acute pain literature in the early 1990's when Kehlet described the benefits of "balanced" analgesia.[14] Today, multimodal analgesia, the application of two or more analgesics acting at different pain pathways and by different mechanisms, is considered standard practice to enhance analgesia and minimize reliance on opioids. The ASA Guidelines on Acute Pain Management supports the use of nonopioids as around the clock agents with opioids as supplemental agent. The most commonly employed agents are local anesthetics, acetaminophen, NSAIDs, COX-2 selective inhibitors, gabapentin and pregabalin, and ketamine. While these agents may be viewed as less potent than opioids, emerging information suggests they may be able to play a more significant role than previously thought.[15] Opioid reduction or "sparing" is at the heart of many of the challenges and controversies in acute pain management. Opioid reduction alone is not sufficient! True opioid sparing requires not only a reduction in total opioid but also some concomitant benefit usually observed as a reduction in opioid related side effects. Future acute pain management strategies will likely rely much less on opioids.

Opioid Related Respiratory Depression and Sleep Apnea

The effects of opioids on respiration are well known. Opioids are known to inhibit the ventilator response to both hypoxia and hypercapnea. In recent years there has been increasing awareness to critical respiratory events.[16-17] The emphasis place on "pain the 5th vital sign" by the Joint Commission several years back may have increased the use of opioids in the hospital setting in an attempt to improve pain assessments. The increasing incident of sleep apnea, often blamed on increasing obesity in our society, is also considered a risk factor for opioid use.

Obstructive sleep apnea (OSA) is usually associated with obesity, snoring or other signs of airway obstruction. Yet, the majority of patients with OSA are undiagnosed and many are not obese.[18] Further, OSA may coexist with central sleep apnea (CSA).[19] Further, it has been demonstrated that patients with OSA may develop respiratory depression from opioids but that it is in fact on a central basis and not obstructive.[20] Up to 50% of long term opioid dependent patients may exhibit CSA.[21] The severity of central sleep apnea is proportional to the daily chronic opioid dose with morphine doses greater than 200 mg/day being a significant.[22-24] Chronic opioid use reduces the proportion of time spent in REM sleep. CSA worsens during non-REM sleep further increasing the risk of a respiratory event in the chronic opioid.[25,26] Postoperative sleep-disordered breathing is now recognized as a risk factor for postoperative respiratory events. Chung and colleagues identified that at least 18.3% of non-sleep apnea patients develop moderate to severe sleep disordered breathing postoperatively.[27]

While respiratory depression (RD) is a serious problem, definitions of RD vary widely. Reported incidences range from 1% to approximately 40%.[28] However, these definitions include transient oxygen desaturation or transient respiratory rates below 10 breaths per minute. While these events should not be taken lightly, it is difficult to predict which or how many of these events will progress to *critical* situations requiring intervention. In one series of over 2000 patients with standard patient controlled analgesia settings, the incident of critical respiratory depression

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was 0.1-0.3%.[29] The controversy here is determining if and what type of monitoring is appropriate for patients receiving opioids and how to minimize opioid use.

An ASA task force provided guidance on managing patients with OSA.[30] There are no specific analgesic recommendations but rather favor minimal opioid use and multimodal analgesia. Local/regional anesthetic techniques are encouraged as is epidural analgesia without opioid.

There are various monitoring techniques recommended for the OSA patient but no definitive approach. Pulse oximetry is generally recommended although capnometry may be a more sensitive indicator. Observational monitoring in the PACU with an OSA prescreening tool may have a role in risk stratifying patients who would benefit from the most aggressive monitoring.[31] The STOP-Bang scoring system has also shown merit in identifying at-risk patients.[32]

Using the STOP-Bang questionnaire, one team of investigators found 41.5% of a standard preoperative elective population had OSA. These investigators also identified a ten-fold increase in pulmonary and cardiac complications in patients with OSA.[33] Clearly, patients with OSA may benefit from advance planning. Early identification is key. This allows planning an anesthetic to minimize reliance on opioids both intra- and post-operatively as well as designing an appropriate multimodal approach with appropriate monitoring.

The role of postoperative CPAP has remained somewhat controversial. Liao and colleagues found that auto-titrated CPAP in surgical patients with OSA reduced the apnea-hypopnea index (AHI) but that only 26-48% of patients used their CPAP device more than 4 hours each night.[34] In a systematic review by Nagappa, there was no significant difference between postoperative adverse events with or without CPAP although the AHI was reduced.[35]

The recent closed claims analysis identified that the vast majority of incidents occur in the first 24 hours and were deemed largely preventable.[36] Opioids were a common theme along with other nonopioid sedative agents. Continuous delivery of an opioid by infusion (intravenous or neuraxial) was a significant factor. This follows the emerging signal with extended release / long acting oral opioid formulations leading to respiratory deaths. While enhanced monitoring may reduce critical opioid events, clearly opioids are a major factor and it behooves us to minimize their use when possible.

Emerging Views on Opioids

Mu-opioid receptors are ubiquitous within the CNS and at peripheral sites. The analgesic action of opioids within the CNS is well known. Opioid adverse events are related to both central and peripheral receptors. Peripheral opioid receptors have a role in ileus, constipation, hormonal regulation, tumor growth, angiogenesis and immunological function. While long term opioid use has clear risks, there is emerging evidence that the short term use of opioids may have significant consequences. Use of opioids for as little as one month may produce lasting changes in the brain.[37] Elderly patients given opioids for postoperative pain are at risk for long term opioid use.[38]

Opioids may reduce survival after cancer surgery.[39] In retrospective studies, perioperative plans that reduce opioids have been shown to increased cancer survival following surgery for breast cancer, prostate cancer and possibly bowel cancer. These typically involve regional anesthetic techniques (paravertebral blocks, epidurals). Opioids are known to enhance angiogenesis leading to tumor growth and to inhibit the immunological response which may alter survival. Recent work in rodents with peripheral opioid antagonism demonstrated an inhibition of tumor growth.[40]

Opioid Tolerance and Hyperalgesia

Long term use of opioids is known to produce tolerance or decreased efficacy requiring dose escalation. Some patients on chronic opioids also exhibit hyperalgesia or altered pain sensitivity.[41] As a group, patients on chronic opioid therapy for pain or methadone maintenance are well known to present significant postoperative pain challenges.

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There is now much clearer evidence that intraoperative opioids can contribute to tolerance and hyperalgesia .[42] Intraoperative opioids are associated with an increase in postoperative opioid requirement. Collard *et al* identified significant increase in PACU fentanyl opioid rescue use in patients receiving remifentanil or fentanyl vs. esmolol.[43] Here again, the evidence supports incorporation of nonopioid multimodal approaches and opioid reduction even during the anesthetic. In a recent review paper, Hayhurst and Durieux found evidence that opioid tolerance and hyperalgesia occurs very rapidly and can account for this postoperative experience of increased opioid use in a dose-dependent fashion[44]. Further, the opioid tolerant patients have greater respiratory depression at the same level of analgesia as opioid naïve patients. Higher doses of intraoperative opioids are now implicated in higher levels of postoperative pain and opioid use.

For these patients in the postoperative period, increased opioid requirements are expected but often pain is unrelieved with opioids alone.[45] Opioid tolerant patients benefit from aggressive multimodal analgesia with regional anesthetic techniques. Recently, ketamine has shown efficacy in this setting. In opioid tolerant spine surgery patients, Loftus and colleagues demonstrated that pre- and intra-operative ketamine reduced pain and opioid requirements in the immediate postoperative period and up to six weeks following surgery.[46-48] Low dose ketamine is now commonly employed in opioid tolerant patients. There is some controversy as to when and where ketamine should be administered. Loftus and colleagues demonstrated benefit from pre- and intra-operative administration. Postoperative ketamine infusion is a useful adjunct in multimodal analgesia for these patients but further studies are warranted to evaluate dosing and duration of treatment.

Chronic Pain Following Surgery

Chronic pain may be a consequence of surgery. Until recently, normal resolution of acute pain was expected to be a routine occurrence. There is a significant burden of long-term pain following surgery. The incidence following thoracotomy and radical mastectomy may exceed 50%. The incidence following inguinal hernia repair is 19-40%. There is now an understanding that healing with neuronal plasticity may occur resulting in chronic postsurgical pain (CPSP). CPSP has been linked to severity of acute pain.[49] Following thoracotomy, patients who experience pain of greater intensity and for a longer duration had a higher risk of persistent pain. Kehlet has identified not only intense acute pain but also, nerve injury and intense inflammatory response as associated factors.[50]

Surgery often results in an intense peripheral inflammatory response (peripheral sensitization) as a consequence of the release of local inflammatory mediators. This “inflammatory soup” causes peripheral sensitization leading to central sensitization (the release of central inflammatory mediators) which in turn results in further pain sensitization.[51] Even in the presence of total neuronal blockade (spinal anesthesia), there is still a central humoral response to peripheral inflammation. Hence, local anesthetic techniques alone cannot inhibit this process of central sensitization.

Total knee arthroplasty has a reported incidence of CPSP approaching 9%. A recent study utilizing a complex multimodal regimen with pregabalin for total knee arthroplasty showed a marked reduction in chronic neuropathic pain.[52] While this is one study, it provides a basis for the potential use of multimodal analgesia as an approach to reducing the prevalence of CPSP. Still, another study with chronic pain following total joint arthroplasty supports that patients may have underlying vulnerabilities such as major depression or chronic pain elsewhere.[53] There is some evidence correlating CPSP to individual pain response with experimental pain models.[54]

In a number of surgical models, perioperative pregabalin either alone or within a complex multimodal regimen has been shown to reduce pain in the immediate postoperative period and in some studies in the months following surgery.[55-60] Recently, intraoperative lidocaine infusion was shown to reduce chronic pain following breast surgery.[61]

Ultimately, chronic post-surgical pain is likely to be multifactorial in origin. Current best evidence suggests that a multimodal analgesic approach may offer the best current approach for reducing long-term pain after surgery. If specific at-risk individuals can be identified in the future, targeted approaches might be possible. In a recent brief report, Eisenach and Brennan are less optimistic that current evidence supports any path to reducing chronic postsurgical pain.[62]

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It is increasingly clear that we must differentiate normal acute pain, prolonged acute pain and chronic postsurgical pain. The drivers for each are likely to be different but with some overlap. Enhanced recovery pathways with multimodal analgesia may reduce pain, opioid use and facilitate earlier discharge in the majority of patients but may not impact chronic pain development or prolonged pain in outliers. (Elsewhere in this RCL, drivers for severe postoperative pain are discussed.)

Anesthesia and Longer Term Outcome

In addition to the implications for cancer survival and chronic pain, our intraoperative anesthetic management may also influence important aspects of quality of life. A recent study demonstrated that pre-incision dosing of ketamine during on-pump cardiac surgery attenuated postoperative cognitive dysfunction. A concomitant reduction C-reactive protein was also noted.[63] Surprisingly, high-dose dexamethasone did not reduce cognitive dysfunction so this ketamine effect is not from anti-inflammatory properties.[64] Intraoperative lidocaine was shown to improve quality of life and reduce pain at three months following complex spine surgery along with a slight reduction in 30 day complications. Lidocaine, in addition to its local anesthetic properties, is known to have potent anti-inflammatory properties.[65]

A substantial body of literature supports the use of perioperative lidocaine infusions.[66] In addition to its anti-inflammatory properties, lidocaine decreases ileus, reduces opioid requirements and pain. Lidocaine is particularly effective in soft tissue injury models. In addition to improved quality of life indicators, lidocaine improves quality of recovery in laparoscopic bariatric surgery.[67]

Lidocaine exhibited potent antitumor activity in hepatocellular carcinoma by inducing apoptosis and inhibiting tumor cell migration.[68] Across multiple outcome measures, there is increasing support for the use of perioperative lidocaine.

Expanding Role for Ketamine

There is increasing use of ketamine both intraoperatively and postoperatively. While the utility of ketamine is gaining acceptance, concerns for potential side effects have limited use. Recent publications have reviewed large databases where ketamine is routinely used on standard wards, demonstrating remarkable safety compared to opioid-related side effects.[69] Other authors applaud the use of postoperative ketamine as a means to reduce the known complications of opioids in the postoperative period.[70] Ketamine has particular utility in managing patients with opioid tolerance as demonstrated in a number of studies. Of note recent studies support longer term outcome improvement. In opioid dependent spinal fusion patients, Nielson et al found ketamine improved pain control and reduced opioid use with a trend toward less persistent pain at 6 months.[72] Further, patients who received ketamine had no greater incidence of nausea, vomiting, hallucinations or nightmares.

Combined Society Guidelines

The recently published consensus guidelines on postoperative pain from the American Pain Society, The American Society of Regional Anesthesia and the American Society of Anesthesiologists are an excellent source of comprehensive postoperative pain management.[5] The document is highly recommended reading for anyone managing surgical patients. These evidence-based guidelines support the use of multimodal analgesia and in particular the use of intraoperative ketamine and lidocaine, non-pharmacological approaches, setting expectations and safety guidance.

Conclusions

Acute pain management continues to be challenging. While significant strides have been made in many areas, specific patient populations and surgical pain models remain underserved. Opioid related adverse events, particularly respiratory depression are now identified for their significant impact on poor outcome. Patient satisfaction, largely driven by experience with pain and treatment side effects, is now an important component for reimbursement within the Affordable Healthcare Act. Multimodal analgesia is now recognized as standard care and

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is familiar to our surgical colleagues. The most current literature supports opioid reduction techniques and multimodal analgesia from the preoperative period and through the recovery period. Integration of multimodal analgesia into our anesthetic plan will promote early utilization both pre- and intra-operative to maximize the benefits. Enhanced recovery pathways (ERAS) and perioperative medicine become increasingly important for the care of our patients and the future of our specialty. The emerging information on opioids suggests that these agents will likely play a lesser role in our future approaches both in our anesthetic management and for acute pain management. The role of the anesthesiologist has potentially far reaching implications on the long-term welfare of the surgical patient but only if we as a specialty embrace our role as perioperative physicians.

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Traumatic Brain Injury across the Spectrum of Severity from Concussion to Severe Injury

Severe Traumatic Brain Injury: How Can We Improve Outcomes?

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Traumatic brain injury (TBI) is one of the most serious, life-threatening conditions in trauma victims. Prompt and appropriate therapy is necessary to obtain a favorable outcome. Perioperative management of head-injured patients focuses on aggressive stabilization of the patient and avoidance of systemic and intracranial insults that cause secondary neuronal injury. Secondary brain injury complicates the course of the majority of head-injured patients, adversely influencing outcome. These secondary insults are potentially preventable and treatable.

I. Epidemiology

There were approximately 2.8 million TBI-related emergency department (ED) visits, hospitalizations and deaths reported in the United States in 2013.[1] Of these, there were approximately 282,000 TBI-related hospitalizations and approximately 56,000 TBI-related deaths. For individuals hospitalized after TBI, almost half (43%) develop a TBI-related disability one year after injury.[2] TBI occurs most frequently in adolescents, young adults, and people older than 75 years of age. In all age groups, males are affected two times more often than females and are more likely to sustain severe head injury. The leading causes of TBIs are falls (47%), being struck by or against an object (15%), and motor vehicle crashes (14%).[1] From 2007 to 2013, the rates of TBI-related emergency department visits increased by 47%, hospitalization rates decreased by 2.5% and death rates decreased by 5%.[1]

II. Head Injury Guidelines

In 1995, the Brain Trauma Foundation (BTF) approved guidelines for the initial resuscitation of the severe head injury patient and treatment of intracranial hypertension recognizing the need to standardize care to improve outcome in head-injured patients.[2] A task force was formed in 1998 to review and update the scientific evidence for the guidelines. Evidence-based guidelines for the management of severe TBI were published in 2000[4a] and updated in 2007.[4b] The most recent guidelines (4th edition) were published in 2017.[5] The authors state that there will be no 5th edition. The BTF is moving to a "Living Guidelines Model" of continuous monitoring of the literature with rapid updates to the evidence review, and revisions to the recommendations as the evidence warrants. These guidelines represent a comprehensive review of the literature and provide the best treatment recommendations for the acute care management of the hospitalized severe TBI patient. Evidence-based guidelines for prehospital management of TBI[6], pediatric brain injury[7], and surgical management[8] have also been published.

Current guidelines recommend that all regions establish organized trauma systems and protocols for resuscitation. Resuscitation protocols from prehospital to critical care management have been developed and instituted based on available information. This lecture will discuss the various guidelines and new research initiatives to address how we can improve outcomes. The guidelines and controversies in management will be discussed as we take a patient through the resuscitation protocol as described in Table 1.

III. Prehospital Management

The "prehospital guidelines" are accepted as the standard by prehospital and emergency department clinicians.[6] even though; there was insufficient data to support any Level I recommendations for prehospital assessment, treatment, transport, and destination. Therefore, after the guidelines and recommendations were published and implemented, several studies were performed to determine whether or not outcome was improved by following these guidelines.[9, 10, 11, 12, 13] The studies support the direct transfer of patients with severe TBI to a Level I or II trauma center, but controversy remains regarding whether patient outcome is improved by paramedic intubations in the field and mode of transport.[13, 14, 15, 16, 17, 18, 19, 20, 21]

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Table 1: Severe head Injury (GCS 8 or less) Resuscitation Protocol

Prehospital Management and ER ATLS Evaluation
- Emergency diagnostic or therapeutic procedures as indicated
- Prioritize CABs (circulation, airway, and breathing), assessment and treatment

Endotracheal Intubation: Ventilation ($PaCO_2$ 35 - 40 mmHg); Oxygenation ($SaO_2 > 90\%$)

Fluid Resuscitation/Hemodynamics: Maintenance of SBP ≥ 100 to 110 mm Hg or above depending on age

Herniation? Deterioration? Rx: ± hyperventilation; Mannitol (0.25-1 g/kg IV)

CT scan: Surgical lesion → O.R.

Neuro ICU:
- ICP and/or other multimodality monitors
- ICP/CPP management
- Individualized assessment/multi-targeted approach

IV. Preanesthetic Assessment and Stabilization

Preanesthetic assessment of the head-injured patient includes: airway (cervical spine), breathing (ventilation and oxygenation), circulatory status, associated injuries, neurological status (Glasgow Coma Scale), preexisting chronic illness, and circumstances of the injury (time of injury, duration of unconsciousness, associated alcohol or drug use).

Secondary insults complicate the course of more than 50% of head-injured patients. An outcome study using data from the Traumatic Coma Data Bank revealed that hypotension after head injury is associated with greater than 70% of patients experiencing significant morbidity and mortality.[3, 22, 23] The combination of hypoxia and hypotension is significantly more detrimental (> 90% of patients with severe outcome or death). We know that hyperglycemia and hypoglycemia can be detrimental to neurosurgical patients. However, currently there is insufficient evidence to support the routine use of tight glycemic control (target BG 80–110 mg/dL) in the operating room or the ICU. [24, 25] The optimal blood glucose level for patients with damaged or injured brain is unknown.

Emergency Therapy. The first step is to secure an open airway and ensure adequate ventilation to prevent secondary injury from hypoxia and hypercarbia.[26, 27] When a cervical spine fracture has not been excluded by radiographic evaluation, cervical alignment with manual in-line stabilization (MILS) is recommended during emergent intubations.[28, 29] (Please note that a cadaver study suggests that MILS does not limit movement across a complete C_{4-5} fracture dislocation with ligamentous injury). If facial fractures and soft tissue edema prevent direct visualization of the larynx, a fiberoptic intubation or intubation with other airway imaging devices may be attempted. In the presence of severe facial and/or laryngeal injuries, a cricothyrotomy may be required. Nasal intubations are avoided in the presence of a suspected basal skull fracture, severe facial fractures, and bleeding diathesis.

Following control of the airway in the head-injured patient, attention should focus on resuscitation of the cardiovascular system. A major concern during fluid resuscitation is the development of cerebral edema. Based on animal research, it appears that the best way to avoid cerebral edema after fluid resuscitation in the injured brain is to maintain normal serum osmolality and colloid oncotic pressure. Therefore, circulating blood volume should be restored to normovolemia with glucose-free isotonic crystalloids and colloid solutions. Glucose-containing solutions are avoided to enhance perioperative glycemic control. Hypertonic saline (HTS) has been proposed as an alternative to normal saline (NS) for fluid resuscitation in patients with hemorrhagic shock and TBI. Controversy continues regarding the selection of the best resuscitation fluids for patients with severe TBI.[30, 31, 32, 33, 34]

A full ATLS trauma evaluation is on-going as therapeutic interventions to control intracranial hypertension are instituted. The head is elevated to 15^0 and maintained in a neutral position. Mannitol (0.25 to 1 g/kg) is administered to acutely lower ICP.[35, 36] Although mannitol is considered the mainstay of hyperosmolar therapy, HTS has gained acceptance as an alternative agent for controlling intracranial hypertension. Neither mannitol or HTS solutions have been associated with improved outcomes.[37, 38, 39, 40, 41, 42] After tracheal intubation, the patient is given a muscle relaxant and mechanically ventilated to a $PaCO_2$ of 35-40 mmHg. Hyperventilation to a $PaCO_2$ of less than 35 mm Hg is avoided unless transtentorial herniation is suspected.[43, 44, 45, 46]

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V. Intraoperative Management

Anesthetic Management. In some patients, severe intracranial hypertension precipitates reflex arterial hypertension and bradycardia (Cushing's triad). A reduction in systemic blood pressure in these patients can further aggravate cerebral ischemia by reducing cerebral perfusion pressure (CPP = MAP - ICP). CPP should be maintained between 60 and 70 mmHg.[47, 48, 49, 50, 51] CPP less than 50 mm Hg should be avoided. The choice of anesthetic agents depends on the condition of the patient. In general, drugs and techniques that reduce intracranial pressure are selected and the overall management goal is to maintain cerebral perfusion and homeostasis.[52, 53, 54, 55, 56] Intraoperative hypotension secondary to blood loss or precipitated by anesthetic drugs must be avoided by appropriate volume expansion.[51] Maintenance of ventilation ($PaC0_2 \geq$ 35- 40 mm Hg) and oxygenation ($Pa0_2$ > 60 mm Hg) is extremely important.

VI. Postoperative Care/Critical Care.

In the critical care unit (CCU), the main objectives are to enhance recovery from primary brain injury and prevent secondary injury.[57, 58] This requires provision of optimal systemic support for cerebral energy metabolism and adequate CPP, and normalizing of ICP for the injured brain. Prompt recognition and treatment of systemic complications that contribute to secondary injury are essential to head injury management. To achieve this, multimodality systemic and cerebral monitoring should be instituted.[59, 60, 61] Monitoring of ICP, CPP and CBF should be standard practice. In addition, monitors of cerebral oxygenation e.g. jugular bulb oximetry, partial pressure of brain tissue oxygen ($Pbt0_2$), and brain metabolism, have been shown to provide more specific information for managing cerebral hypoxia and ischemia. However, technology has lagged behind in the development of safe, reliable, and continuous cerebral monitors for detecting ischemia.

There is controversy concerning the best management protocol for optimal recovery in TBI patients.[5, 61, 62, 63, 64, 65] A management protocol that uses individualized assessment and a multi-targeted approach to institute therapy and reduce the risk of iatrogenic injuries has gained acceptance.

VII. Summary

The major goal of perioperative management of TBI patients is to prevent secondary damage. Therapeutic measures based on established guidelines and recommendations must be instituted promptly throughout the perioperative course.[66, 67, 68, 69, 70] Recent investigations have shown that not all of the recommended guidelines improve outcome, and more randomized, controlled trials are necessary to clearly address unresolved clinical guidelines.[71, 72] Another challenge for improving metropolitan and regional care of these vulnerable patients is the development of systems and protocols that provide consistent application of the guidelines. There is no doubt that an aggressive approach to managing head-injured patients can reduce mortality, but we must also improve functional status among survivors.[73, 74, 75] Intensive rehabilitation efforts used in combination with new therapeutic agents show promise for reducing morbidity in this high risk population. Therefore, future studies must focus on all aspects of perioperative care including rehabilitation to reduce disability in survivors.

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Controversies in the ICU Management of TBI Patients

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INTRODUCTION

Clinical outcomes after traumatic brain injury (TBI) are determined not only by the severity of the initial injury but also by secondary injurious processes including biochemical, excitotoxic and inflammatory responses that lead to further (secondary) brain injury.[1] Secondary injury may be further exacerbated by systemic physiological insults. The critical care management of TBI is based on the central concept that prevention of secondary brain injury is associated with improved outcomes.[2]

All patients with severe TBI should be managed in an intensive care unit (ICU) offering immediate access to multidisciplinary clinical neuroscience teams and other relevant specialties, supported by appropriate imaging and investigational facilities. Those with mild or moderate TBI may also require ICU admission for systemic organ support and following neurosurgical interventions or multi-system trauma. While mild and moderate TBI were previously believed to have innocuous effects on cerebral physiology, there is accumulating evidence that, like after severe TBI, they may adversely affect the cerebral microvasculature. This can manifest as autonomic dysregulation and impairment of cerebrovascular autoregulation that persist for up to 2 weeks post-injury,[3] changes in regional cerebral blood flow,[4] and variable effects on intracranial pressure (ICP).[5] The consequences of these pathophysiological changes and their impact on therapeutic interventions are currently unknown, but should be borne in mind during the ICU management of extracranial injuries in patients with mild and moderate TBI.

NEUROMONITORING

Neuromonitoring plays a key role in the critical care management of TBI. It allows an individualized approach to patient management in which therapeutic interventions intended to prevent or minimize secondary brain injury are guided by monitored changes in physiologic variables rather than generic thresholds.[6;7]

Intracranial and cerebral perfusion (CPP) pressures are the most frequently monitored variables, but provide limited assessment of the adequacy of cerebral perfusion.[8] Cerebral oxygenation monitoring provides information about the adequacy of cerebral perfusion, and increasingly complements ICP monitoring [9]. A Phase II randomized clinical trial demonstrated that management of severe TBI guided by brain tissue oxygenation monitoring in addition to ICP reduced the incidence of brain tissue hypoxia, with a trend toward lower mortality and more favorable outcome compared to ICP monitoring-guided treatment alone.[10] Bedside assessment of autoregulatory state by monitoring indices such as the pressure reactivity index (PRx) is also being adopted into clinical practice to identify individualized CPP targets.[11]

Any impact of monitor-guided therapy on outcomes is dependent on the thresholds chosen to initiate intervention and subsequent management in response to changes in monitored variables, and these remain undefined in many circumstances.[7] However, interventions that result in transition from an abnormal to normal brain state are more likely to be efficacious than those focusing on response to individual thresholds.[12] It is unclear whether all TBI patients can benefit from neuromonitoring, although it seems plausible that those with certain injuries or physiologic phenotypes might have most to gain from neuromonitor-guided interventions. Incorporating patient demographics and brain imaging with multimodality neuromonitoring strategies might better optimize individualized treatment decisions.[7]

GENERAL PRINCIPLES OF MANAGEMENT

In the absence of effective pharmacological neuroprotective strategies, the ICU management of TBI focuses on prevention and treatment of intracranial complications, optimization of systemic physiology, and management of non-neurological complications.[13] This requires a coordinated approach providing meticulous general intensive care support as well as interventions targeted to the injured brain.[14] Although the general principles of the critical care management of TBI are well-defined, several specific interventions or therapeutic targets remain undefined or controversial.

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Cardiorespiratory support
One area in which there is no doubt is that secondary systemic physiological insults, particularly hypotension and hypoxemia, have adverse effects on TBI outcomes. A single episode of hypoxemia (PaO_2 <60 mmHg, Pa or SpO_2 <90%) or hypotension (systolic BP <90 mmHg) is strongly associated with worse outcomes after severe TBI, and the combination of the two is more deleterious than either insult alone.[15] The Brain Trauma Foundation recommends that systolic blood pressure should be maintained ≥ 100 mmHg in patients aged 50 to 69 years and ≥ 110 mm Hg in those aged 15 to 49 years or older than 70 years.[16] Maintenance of euvolemia with intravenous isotonic crystalloids is the primary cardiovascular goal.[17] Albumin is associated with increased mortality after TBI and must be avoided, as should hypotonic fluids because of the risk of worsening cerebral edema. Continuous infusion of hypertonic saline has been associated with survival benefits in TBI-related intracranial hypertension,[18] but its routine use during the critical care management of TBI remains controversial.[17] A vasopressor is indicated if adequate intravascular filling is insufficient to maintain arterial blood pressure and CPP targets. There is no evidence to support the use of one agent over another, but norepinephrine has a predictable and consistent effect on blood pressure and cerebral hemodynamics, and is widely used.

Endotracheal intubation and mechanical ventilation are indicated in patients with severe TBI because of the high risk of pulmonary aspiration, pneumonia and compromised respiratory drive. High tidal volume ventilation is a major risk factor for the development of acute lung injury after TBI, and a protective ventilation strategy (tidal volume < 6ml/kg) should be used if brain-directed therapy permits.[19] Moderate levels of PEEP (≤15 cmH_2O) do not have clinically significant effects on ICP or CPP and are indicated to optimize PaO_2 as part of a protective ventilation strategy.[20] Ventilation should be adjusted to maintain normocapnea ($PaCO_2$ 35-40 mmHg). A short period of hyperventilation might be justified to manage an acute rise in ICP, but there is a risk of hypocapnea-induced cerebral ischemia, particularly in the early post-injury phase.[14]

Glycemic control
It has been recognized for decades that hyperglycemia (blood glucose >180mg/dL) exacerbates secondary neuronal injury after TBI and is associated with worse outcomes, but the optimal method and target for glycemic control remains undefined. A recent systematic review and meta-analysis of 10 randomized controlled trials (1,066 patients) found that intensive glycemic control with intravenous insulin was not associated with reduced mortality after TBI.[21] Interestingly in this analysis there was a (non-significant) trend towards lower rates of poor neurological outcomes despite a greatly increased incidence of hypoglycemia in the intensive insulin therapy group; this apparent contradiction requires further investigation. In the absence of clear evidence, moderate level glucose control is recommended, maintaining serum glucose concentration <180mg/dL while avoiding hypoglycemia (serum glucose < 60 mg/dL) and large swings in glucose concentration.[22]

Temperature management
More than half of critically ill TBI patients develop pyrexia secondary to infection or hypothalamic dysfunction. High temperature is independently associated with worse outcomes, and there is some evidence that fever management to normothermia might be beneficial after TBI.[23]

Therapeutic hypothermia (TH) has established neuroprotective actions in preclinical studies through stabilization of the blood-brain barrier, ICP reduction and inhibition of inflammation and intracellular calcium overload. Although TH has also been shown to be beneficial after TBI in several single-center clinical studies, outcome benefits have not been confirmed in large-scale randomized trials.[24] Moderate TH (34 – 35ºC) is an effective means of reducing raised ICP and is often incorporated into ICP management protocols (see below).

Hemoglobin
Anemia is common in critically ill TBI patients but whether it represents a marker of disease severity and longer ICU length of stay or has a direct influence on neurological outcomes is unclear. Although it is generally believed that a restrictive transfusion strategy common in general critical care is incompatible with TBI management because of the increased susceptibility of the injured brain to ischemia, there is insufficient high-quality evidence to recommend a minimum hemoglobin threshold to trigger red cell transfusion.[25] A randomized controlled trial demonstrated no statistically significant difference in outcomes between hemoglobin concentrations of 70 vs. 100

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g/L, but the higher transfusion threshold was associated with a higher rate of thromboembolic events [26]. In the absence of definitive evidence, it is generally recommended that hemoglobin concentration should be maintained between 70 and 100 g/L after TBI, although an individualized approach to red cell transfusion guided by multimodality neuomonitoring is gaining traction.[27]

Seizures

Early post-traumatic seizures occur in more than 20% of TBI patients. Although clinical guidelines recommend seven days of antiepileptic drug therapy,[16] seizure prophylaxis remains controversial because early seizures are not clearly associated with worse outcomes and prophylaxis does not prevent late onset seizures. If prophylaxis is preferred, levetiracetam may be superior to phenytoin because of its more favourable safety profile.[28]

BRAIN DIRECTED THERAPIES

The sole goal of identifying and treating TBI-related intracranial hypertension has been superseded by a focus on the prevention of secondary brain injury using a multi-faceted neuroprotective strategy incorporating a stepwise approach to maintenance of cerebral perfusion and oxygen/substrate delivery.[29]

Management of intracranial pressure

Intracranial hypertension is a major cause of mortality and poor neurologic outcome after TBI,[30;31] but there is limited evidence that its monitoring and management improves clinical outcomes.[32] The only randomized controlled trial investigating the impact of ICP monitoring after TBI (BEST-TRIP) challenges the established practice of maintaining ICP below a universal and arbitrary threshold because it found no difference in outcomes when treatment was guided by ICP monitoring compared to treatment guided by imaging and clinical examination in the absence of ICP monitoring.[33] It is increasingly recognized that individualized interpretation of ICP values in association with other monitored variables, such as autoregulatory reserve, CPP and cerebral oxygenation, allows identification of circumstances in which modestly elevated ICP might be cautiously accepted.[7] One area of particular uncertainty is what, if any, action should be taken in response to increases in ICP in the context of normal brain tissue oxygenation.

All clinical guidelines advocate the early treatment of intracranial hypertension after TBI; the Brain Trauma Foundation guidelines recommends ICP $\geq$ 22 mmHg as an appropriate treatment threshold.[16] The optimal management of intracranial hypertension incorporates tiered strategies administered in a stepwise manner, starting with safer interventions (e.g. head-up position, sedation/analgesia, osmotic agents) and reserving higher risk options (barbiturates, decompressive craniectomy) for patients with intractable intracranial hypertension or multimodal neuromonitoring evidence of resistant brain hypoxia/ischemia.[34] The relative risk of death is increased by 60% if escalation from lower to higher tier ICP-lowering interventions is necessary.[35]

While first and second line treatments of raised ICP are routinely applied, there remains little evidence to guide their use or that they improve outcomes.[36] The Eurotherm3235 study investigated TH as part of a tiered approach to ICP management and was suspended early because of worse functional outcomes and higher mortality in the hypothermia group.[37] While this study provides evidence against the early (second tier) use of hypothermia to control ICP, it does not address its role in the management of refractory intracranial hypertension for which it is most commonly used in clinical practice in an attempt to limit the use of high-risk interventions.

Decompressive craniectomy is increasingly undertaken as a final-tier, life-saving intervention in patients with refractory intracranial hypertension. In the RESCUEicp trial, secondary decompressive craniectomy was associated with lower mortality but higher rates of vegetative state and severe disability in survivors compared to maximal medical therapy in patients with ICP >25mmHg refractory to other interventions for more than 1 hour.[38] While decompressive craniectomy effectively controls ICP and reduces mortality it raises important ethical issues because of the high risk of survival with severe disability.[36]

Cerebral perfusion pressure

Cerebral perfusion pressure is the difference between mean arterial pressure and ICP. For its accurate calculation, the arterial pressure transducer must be referenced at the same level as ICP (tragus of the ear) because measuring blood pressure at the level of the heart results in a calculated CPP that is erroneously high when the head of the bed is

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elevated.[7] While consensus guidelines recommend that CPP should be maintained between 60 and 70 mmHg after TBI,[16] with evidence of harm from lower or higher values,[31] there is also accumulating evidence that the optimal CPP to minimize the risk of cerebral hypoperfusion and ischemia exists on an individual basis. Targeting an individualized CPP range identified by continuous monitoring of cerebral autoregulatory state avoids the risks of low CPP on the one hand and excessive CPP on the other, and is associated with improved outcomes after TBI.[11]

PROGNOSTICATION

Accurate early prognostication after severe TBI is notoriously difficult. There is limited evidence from controlled studies to guide decision-making, and risk prediction models are insufficiently precise for use in individual patients.[39] A period of physiological stabilization and observation is strongly recommended to improve the quality of decision making and avoid a 'self-fulfilling prophecy' whereby early withdrawal of life sustaining therapies leads to death.[40] In one study, up to 15% of patients with severe TBI who ultimately had a favorable outcome did not begin to follow commands until more than 2 weeks after injury.[41] Despite early and aggressive support some patients will not achieve a degree of neurological recovery which is acceptable to them. As soon as this is recognized there should be a timely switch to compassionate and individualized end-of-life care.[42]

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Traumatic Brain Injury across the Spectrum of Severity from Concussion to Severe Injury

Mild to Moderate Traumatic Brain Injury: Management Update and the Anesthesiologist's Role

Monica S. Vavilala, MD **Seattle/WA**

Outline

1. Definition of mild and moderate TBI
2. Epidemiology of mild and moderate TBI
3. Biomarkers of mild and moderate TBI
4. Outcomes after mild and moderate TBI
5. Guidelines for care of patients with mild and moderate TBI
6. Controversies in acute care management of patients with mild and moderate TBI
7. Anesthesiologists role in care of patients with mild and moderate TBI
    1. Preoperative evaluation and screening
    2. Optimization of care
    3. Recovery
    4. Results of SPA survey
8. Future Directions

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Nerve Injury after Peripheral Nerve Block: Evaluation, Management, Best Practices, and Medicolegal Concerns

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Introduction

Nerve injury after peripheral nerve blockade (PNB) for surgical procedures and post-operative pain relief continues to be a source of attention and concern for patients, anesthesiologists, and surgeons, despite significant advances in training and equipment technology for nerve localization. When a significant nerve injury is recognized for the first time after surgery, a cascade of events can be set into motion leading to strained professional relationships between anesthesiologists and surgeons, not to mention the potential for medicolegal action by patients.

Incidence of nerve injury after peripheral nerve block and risk factors

The absence of a standard definition of nerve injury after surgery has hampered understanding of the incidence and severity of the problem. The use of the term, post-operative neurologic symptoms (PONS), or peripheral nerve injury (PNI), is an attempt to adopt a standard definition of incidence, without describing severity or causation. Temporary sensory and motor injuries are common; permanent motor injuries are rare. In contrast to neuraxial blocks, up to 19% of patients receiving PNBs may report sensory or motor abnormalities on the first post-operative day after surgery, decreasing to 2% three months later, with less than 0.2% persisting beyond 1 year.[1-3] Among elective procedures, orthopedic arthroscopic and open shoulder procedures report some of the highest overall injury rates, with diffuse brachial plexus injuries, as well as single nerve injuries to the axillary, musculocutaneous, suprascapular and radial nerves.[3] Fortunately, long term severe injuries (motor loss or significant neuropathic pain) lasting longer than 6-12 months are exceeding rare, with level III evidence consistently demonstrating an incidence of 2-4 severe nerve injuries per 10,000 PNBs, in both the pre (nerve stimulation) and post-ultrasound introduction era.[4-9]

In clinical practice, it is not unusual for surgeons to assume that a regional anesthesia technique is the cause of a newly discovered post-operative neurologic injury. This attitude reflects a lack of understanding of the current literature. The differential diagnosis should always consider patient related, surgery related, and anesthesia related causes. Although causation may be difficult to determine at times, there are many high-quality studies that can shed light on this controversy. Three large single-institution clinical registries reporting the incidence of nerve injury after elective orthopedic joint replacements for hip, knee and shoulder surgery, have demonstrated that PNB does not increase the risk of PONS; on the contrary, in patients having shoulder replacement the odds of a PNI was reduced by about 50%.[10] Further evidence that PNB is not associated with increased risk of PONS comes from a large case series of over 7,000 PNBs associated with a variety of surgical procedures, with a neurologist determining causation of long term severe injuries, based on the results of electrodiagnostic studies. The authors of this study concluded that non-anesthesia related causes of injury were 9 times more likely than anesthesia related causes.[7] Additionally, a large single institution case series of over 380,000 surgical procedures during a 10-year time interval, was not able to identify PNB as an independent risk factor for the development of PONS. On the other hand, patient related risk factors such as diabetes mellitus, hypertension, and tobacco use, as well as surgery procedure types (neurosurgery, cardiac surgery, orthopedic surgery, and general surgery), were all demonstrated to be independent risk factors for the development of PONS.[6]

What can we conclude from this information? A postoperative neurologic injury is most likely multifactorial in nature, and although an anesthesia related cause should be part of the differential diagnosis, it should never comprise the entire differential diagnosis, as other causes are more common, including surgery specific procedures. Patients with underlying microvascular disease (tobacco use, hypertension, diabetes) and those with chemotherapy-induced neuropathy (CIPN) (cisplatin, oxaliplatin, carboplatin, vincristine, paclitaxel), especially those with sub-clinical injury, are at risk for post-operative double crush injuries, which may manifest as new clinical nerve deficits post-operatively.[6,11]

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A recent publication from the 2nd ASRA Practice Advisory on Prevention of Neurologic Complications after regional anesthesia cites class II recommendations to conclude that PNB may increase the risk of new or progressive deficits in patient with diabetic peripheral neuropathy (DPN), and also recommends decreasing the concentration of local anesthetic, total volume, and eliminating or reducing the concentration of adjuvant vasoconstrictors (epinephrine).[1,11] Patients with central nervous system disorders such as multiple sclerosis, amyotrophic lateral sclerosis, and post-polio syndrome may have subclinical injury, along with a natural waxing and waning of the disease, which may be exacerbated after surgery. Although there is insufficient evidence to suggest that PNBs may increase the risk of PONS in these patients, if it occurs, it may be incorrectly attributed to the PNB. The decision to offer a PNB in these patients should be individualized after a risk-benefit discussion.[11] Consideration may also be given to performing blocks after surgery, in patients at higher risk for developing complications, after a postoperative neurologic assessment has been completed.

Mechanisms of nerve injury and classification system

Each individual axon is surrounded by a connective tissue layer known as the endoneurium. Individual axons are packed together to form fascicles (100-1000 µm diameter), surrounded by a circumferential impermeable connective tissue layer (perineurium), containing non-fenestrated capillaries. Collections of fascicles are then further surrounded by an outermost connective tissue layer, (epineurium), which is a thick, but permeable layer. Deep to the epineurium, but between fascicles (interfascicular) lies a loose areolar connective tissue layer, composed of adipose cells, fibroblasts, mast cells, arteries, arterioles, veins, capillaries, and lymphatics. This layer is also known as the sub-epineurium.

Although nerves are delicate structures, their connective tissue architecture affords several layers of protection to prevent direct axonal injury. A variety of mechanisms can injure the axonal and connective tissue components of the nerve, resulting in demyelination and or axonal loss, with disruption of electrical conduction. These injuries can include stretch and compressive forces; ischemia; blunt and penetrating trauma; thermal injury; tissue edema; hematoma formation; toxic or metabolic injuries; and inflammatory or infectious etiologies.[12] Mechanisms of injury can be surgery related (positioning, tourniquets, retractors, scalpel, hematoma, edema, thermal, inflammatory), patient related (ischemic, inflammatory), or anesthesia block related (needle trauma, inflammation, hematoma, local anesthetic toxicity).[12,13] Although nerves tend to pinwheel away from a compressive force exerted by an advancing block needle in clinical settings, if a block needle penetrates the epineurium, inflammatory changes will occur.[14] However, the major danger appears to be associated with intrafascicular penetration, and subsequent generation of high intrafascicular pressures causing ischemia, either with or without fascicular disruption. These changes can occur experimentally even with injections of saline, although local anesthetic injections are much more neurotoxic.[12, 13] Advancing short bevel block needles of sizes and diameters commonly used clinically, directly into fascicles, is difficult to achieve experimentally, due to the resistance encountered trying to penetrate the tough perineurium, as well as due to the large diameter of needles relative to fascicle size. Nerve fascicles range in size from 100-1000 µm, while a 22-gauge block needle is 700 µm in diameter.[13] Unfortunately, block needles can also injure the nerve fascicles by disrupting small vascular structures in the interfascicular space (sub-epineurium), creating intraneural hematomas, which can subsequently compress nerve fascicles. Additionally, block needles approaching in close proximity to the nerve may disrupt the external vasa nervorum, leading to hematoma formation outside the epineurium, which may cause nerve compression and ischemia.

Nerve injury can be graded based on anatomic levels of injury, which also provide a clinical prognosis.[12,15,16] The Seddon classification divides injury into three grades; neurapraxia (myelin injury only), axonotmesis (axon injury only), neurotmesis (axon injury and connective tissue disruption involving the endoneurium, perineurium, and epineurium). Neurapraxic injuries will resolve spontaneously with full recovery, axonotmetic injuries have a mixed prognosis for spontaneous recovery and may require surgical intervention, while neurotmetic injuries require surgical nerve reconstruction with mixed outcomes. Motor nerve injury on clinical exam is graded on the following 6-point British Medical Research Council (MRC) scale: 0=no visible twitch; 1=visible twitch; 2=movement insufficient to overcome gravity; 3= movement sufficient to overcome gravity; 4= movement against gravity plus additional resistance; 5=normal strength.[16]

The Sunderland classification system further refines the Seddon system, to clarify the level of connective tissue disruption. Sunderland grade 1 and grade 2 correspond to neurapraxia and axonotmesis, grade 3 is considered

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neurotmesis with disruption of endoneurium continuity, grade 4 is neurotmesis with disruption of endoneurium and perineurium continuity, while grade 5 is complete nerve transection, including disruption of the epineurium. In general, nerve reconstruction surgery tends to have a poorer prognosis with Sunderland grade 4 or higher injury level.[16] The overwhelming majority of patients diagnosed with PONS see complete resolution of their symptoms within 3 months; hence, most injuries are neurapraxic, or Sunderland grade 1 injuries.

The clinical challenge is to diagnose Sunderland grade 3 or higher injuries as soon as possible, to provide counseling and surgical referral on a timely basis. In general, nerve reconstructive functional outcomes are improved with earlier surgery, usually between 6 and 9 months, although recovery has been reported with repairs initiated up to 18 months after injury.[16] On the other hand, when spontaneous recovery occurs, outcomes are usually better than with reconstructive surgery, with the full extent of possible recovery not being apparent for up to two years.[16] This may create tension between the anesthesiologist advocating watchful waiting, hoping for complete neurologic recovery, and the surgeon pressing to go ahead in order to obtain the best reconstructive result with nerve grafting or nerve transfers.

Evaluation of neurologic symptoms after surgery: Imaging (US, MRI, MRN) and electrodiagnostic testing (NCS, EMG)

Early recognition and documentation of PONS is important for several reasons, including diagnostic and therapeutic interventions for reversible lesions, such as hematoma evacuation, as well as for medicolegal protection. Barriers exist to early recognition of PONS secondary to patients' residual sedation and misunderstanding of the significance of extended duration of motor or sensory nerve loss after surgery. The presence of casts, splints, stabilization devices and dressings may impair a patient's perception of motor or sensory abnormalities and contribute to a delay in diagnosis. An urgent neurology consult is warranted in any patient with significant motor or sensory loss that persists beyond the expected duration of the block. A recent review article presents an algorithm for the evaluation and management of a new postoperative neurologic deficit following regional anesthesia.[15]

The goal of imaging or electrodiagnostic testing (EDX) is to help determine the location, severity, and prognosis for recovery of the neurologic abnormality; unfortunately, EDX cannot always establish causation (surgery, anesthesia, patient).[17] EDX is also useful in demonstrating the presence of a pre-existing neurologic lesion that may not have been clinically apparent prior to surgery. High resolution (12-20 MHz) ultrasound (US) is being increasing utilized as part of the initial evaluation of PONS, to help localize and define the severity of the lesion.[18] US images of affected peripheral nerves can be traced along the course of the nerve and spot potential disruption in nerve continuity, consistent with neurotmetic injury, which can be verified with magnetic resonance imaging (MRI) or magnetic resonance neurography (MRN). However, the lateral and axial resolution of US is superior to that of MRI/MRN. Non-specific pathology visualized with US imaging includes increases in cross-sectional nerve area (CSA), along with loss of fascicular detail, as compared to the asymptomatic side.[18] MRN is a term used to signify alterations in processing of the conventional MRI signal to enhance peripheral nerve imaging. A two-dimensional T1 fat suppressed and T2 enhanced water weighted signal will display the outline of nerve roots, plexus and peripheral nerves, and display a bright or hyperintense image in areas with increased water content associated with edema. Unfortunately, this signal is not able to distinguish between neural edema associated with less severe injuries, such as neurapraxia, versus more serious axonotmetic or neurotmetic injuries. [16] MRI imaging is also able to demonstrate early denervation injuries (axonal) in muscle, before they become apparent on EMG examination.[16]

The utility of EDX studies lies in their ability to localize the site of injury in the peripheral nervous system (nerve roots, plexus, proximal peripheral nerve, distal peripheral nerve) and to distinguish between demyelination and axonal injury, and hence prognosis for recovery.[19] EDX studies consist of nerve conduction studies (sensory and motor), along with needle electromyography. Compound motor nerve potentials (CMAPs) are measured bilaterally by stimulating peripheral nerves suppling normal and abnormal muscles. Nerves are stimulated proximally and distally, with muscle depolarization associated with individual fibers summated together and measured with surface electrodes on target muscles. A characteristic signal is obtained with measurement of latency, amplitude and duration. Latency measures onset of depolarization of the fastest myelinated fibers, while amplitude reflects the summation of individual muscle fiber depolarization potentials based on the number of axons recruited with supramaximal stimulation current.[19] Duration reflects synchrony and efficient muscle contraction. Signals are biphasic or triphasic in nature, with deflections above baseline described as negative by convention, and those

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deflections below baseline being described as positive.[19] Sensory nerve action potentials (SNAPs), as well as CMAPs are commonly measured. SNAPs are low amplitude (µA), short duration (1-2mS) signals, as compared to CMAP higher amplitude (mA), longer duration (5-6mS) signals. Temporal dispersion and phase cancellation have a greater effect on SNAPs versus CMAPs, and in cases of severe neuropathic injury, SNAPs may be difficult or impossible to detect.[19]

In general, demyelination injuries are characterized by slower conduction and increased latency (conduction velocity <75% of lower limit of normal, latency > 130% of normal).[19] As conduction velocity slows, temporal dispersion and wave phase cancellation will occur, with increasing time separation of depolarization signals from faster and slower fibers, leading to an increase in duration, and a decrease in measured peak amplitude of CMAP and SNAP signals. When demyelination is focal and severe enough to prevent depolarization, the term "conduction block" is used to describe this phenomenon. The site of injury can be determined by progressively stimulating the peripheral nerve of interest from distal to proximal, until a jump in latency is detected, or in the case of conduction block, no CMAP is detected.

Axonal injuries are characterized primarily by a decrease in peak amplitude, with limited effect on conduction time and latency. Conduction velocity is within 75% of the lower limit of normal conduction velocity, while latency is within 130% of the upper limit of normal.[19] Unlike demyelinating injury, once axonal injury occurs, within 3-5 days, Wallerian degeneration prevents depolarization distal to the site of injury, and CMAPs and SNAPs can no longer be detected at distal muscle or sensory sites innervated by the affected nerve. However, within the first several days after injury, the nerve is still electrophysiologically active distal to the site of injury, and can still be stimulated, generating distal CMAP and SNAP potentials. This phenomenon is known as a pseudo-conduction block since it mimics a demyelination conduction block.[17, 19]

EMG studies confirm the results obtained by nerve conduction studies and provide additional localization information for proximal injury sites than cannot easily be measured with NCS. Denervation potentials measured with needle EMG (fibrillation waves, positive sharp waves) are never associated with demyelination injuries; when present they indicate more serious axonotmetic or neurotmetic injuries.[17,19] The presence of denervation potentials imply injury to the nerve at or proximal to the branch point of the most proximal muscles with denervation potentials. [19] EMG studies also assess the number and type of motor unit action potentials (MUAP), and measure recruitment and activation of motor units. MUAPs can sometimes be detected, when asking a patient to try and contract a muscle, even when no visible motor activity is apparent on clinical exam. This is a positive sign, and indicates that partial innervation is still present, without neurotmetic injury. However, this pattern cannot distinguish between severe demyelinating injury versus axonal injury, as in either case, recruitment of additional motor units will be impaired.[19] After several weeks, the underlying etiology will become apparent, as a demyelinating injury will rapidly recover, and motor unit recruitment will increase or return to normal. Abnormal recruitment of motor units appears as a "picket-fence" tracing pattern on EMG exam; normal recruitment appears as a "complete interference" pattern on EMG exam, with no space between adjacent MUAP spikes.[19]

The change in morphology of MUAPs is used to follow the presence of reinnervation after axonal injury. With moderate injury, normal motor units adjacent to injured motor units will send out collateral branch point sprouts to innervate adjacent muscle fibers innervated by damaged nerves. This will increase the size of the motor unit (number of fibers innervated by a given axon) and increase the duration and number of phases of the MUAP. These collateral sprouts are initially unmyelinated and appear as delayed low amplitude satellite potentials.[19] With increasing severity of injury, no normal adjacent motor units exist, and collateral branching cannot occur. Axons can only extend unmyelinated growth sprouts from the proximal uninjured axon stump. These low amplitude potentials connote more severe injury and are termed nascent potentials.[19]

EDX studies are typically obtained initially 3-4 weeks after injury, when the most information is obtainable from a single study.[15] The exam can be uncomfortable, since small caliber 25-gauge unipolar recording needles are inserted multiple times in a variety of different muscles, in a non-sedated patient. Pathologic denervation potentials associated with axonal injury are first detected in muscle 3-4 weeks after injury, when CMAP and SNAP amplitude loss due to Wallerian degeneration will be complete in NCS.[15,17,19] Demyelinating injuries can be reliably distinguished from axonal injuries at this time, and patients can be either reassured about the prospects of full

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recovery or counseled about the possibility of partial recovery and the potential need for future reconstructive surgery. With evidence of moderate to severe axonal injury, EDX studies can be repeated at 3 months and 6 months to assess the presence and magnitude of reinnervation, with referral to a reconstructive peripheral nerve surgeon for injuries not demonstrating further improvement.

An alternative approach is to obtain EDX studies several days after the initial injury is manifested, which several authors advocate.[16,17] The advantage of an early exam is the ability to demonstrate a pre-existing injury with reinnervation, characterized by polyphasic, long duration MUAPs with satellite or nascent potentials, along with the presence of positive sharp waves and fibrillation potentials. These EMG changes are consistent with chronic injury and would not be detectable until at least 3-4 weeks after injury. Delaying initial EDX studies until one month after injury would limit the ability to establish that an injury was present prior to the surgical and anesthetic procedure, and not caused by it. Early EDX studies in the setting of axonal injury, prior to complete Wallerian degeneration, also allow the ability to localize the site of the neuropathic lesion. Normal distal muscle CMAPs will still be manifested, as the nerve stimulating site moves distal to proximal, until the stimulating needle is at the level of injury. After Wallerian degeneration, abnormal distal CMAPs will be measured at any point along the nerve, including proximal needle stimulating sites where the nerve is undamaged.

During the recovery process, a regular program of physical therapy should be prescribed in order to maintain joint range of motion and prevent flexion contractures, utilizing splints if needed.[15] Neuropathic pain can be managed with a tiered approach, utilizing first line agents such as tricyclic antidepressant secondary amines (nortriptyline, desipramine) or SSNRI's (duloxetine), gabapentinoids (gabapentin, pregabalin), and topical 5% lidocaine patches.[15] Opioids may be considered as second-line agents.

Reconstructive surgical options and pain management for severe injuries

Peripheral nerve reconstruction surgery should be considered for any persistent serious motor nerve injury on clinical exam (MRC grade 0-3) that affects shoulder, elbow or hand function, with minimal evidence of reinnervation on EDX studies at 6 months.[16] Axon regeneration occurs at a rate of about 1 mm per day, or 1 inch per month, but until distal reinnervation occurs, deterioration continues in the muscle fiber, neuromuscular junction, and endoneurial tunnel basement membrane.[16] Irreversible functional changes in target tissues will occur between 1-2 years after denervation, leaving reinnervation moot, with muscle and tendon transfers from normally innervated tissue the only option to partially restore function. When neuropathic injury is distal, there may be sufficient time for spontaneous reinnervation; however, with proximal injury, surgical reconstruction is more likely to be required. Neurotmetic injuries with complete nerve transection (Sunderland 5), should be surgically repaired as soon as possible, to prevent painful neuroma formation.[16] A sharp, clean transection (unlikely with a block needle) should be repaired immediately before stump retraction occurs. There are multiple options to repair nerves and restore function. In general, best results are obtained when the proximal and distal nerve stumps can be trimmed and directly opposed with microsurgical techniques involving fascicular reattachment and restoring epineural continuity. However, if the resulting neurorrhaphy has any residual tension, the repair is likely to scar with neuroma formation, leading to a poor functional outcome. In this setting, an autologous nerve interposition graft, harvesting a non-critical nerve such as an intercostal, sural, superficial radial, or lateral antebrachial cutaneous nerve, is used to bridge the gap. For best results harvested sensory nerves are used to repair sensory nerve injuries, while mixed or motor nerves are used to repair motor nerve injuries.[16]

Since the late 1990's, treatment has shifted from interposition grafts to nerve transfer techniques, where improved results have been obtained (MRC 3-4), especially in the setting of proximal injuries, by mobilizing the distal portion of a viable nerve branch, and connecting it to the distal portion of the denervated nerve, close to the target muscle.[16] For example, in the setting of an injury to the suprascapular nerve and axillary nerve, shoulder abduction can be restored by mobilizing the distal portion of the spinal accessory nerve, thereby denervating the lateral aspect of the trapezius, and connecting the mobilized segment of the spinal accessory nerve to the distal portion of the suprascapular nerve (end to end or end to side), restoring function to the supraspinatus and infraspinatus muscles. To further improve function and restore abduction, a terminal branch from the radial nerve supplying either the long or medial heads of the triceps can be mobilized, without adversely affecting triceps strength, and connected to the distal anterior branch of the axillary nerve to restore function to the deltoid and teres minor muscles. Using the same concept, in the setting of a musculocutaneous nerve injury, elbow function can be

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restored by mobilizing a proximal branch of the ulnar nerve, containing fascicles innervating the flexor carpi ulnaris muscles (without compromising wrist flexion), and connecting them to a branch of the musculocutaneous nerve near the biceps muscle. Clearly, this is demanding, extensive and meticulous surgery, requiring intraoperative nerve stimulation and microsurgical suturing technique, along with an extended recovery period. Even the best outcomes will not completely restore pre-injury strength and function.

Best practices to prevent nerve injury

The 2nd ASRA Practice Advisory on Neurologic Complications Associated with Regional Anesthesia updates the previous 2008 version and offers guidance on potential best practices to potentially reduce the risk of block related nerve injury.[1] This is not a standard of care, nor is it a guideline, due to the limited evidence basis underlying the recommendations. Adherence to the advisory is intended to provide optimal care but cannot guarantee the avoidance of adverse outcomes. As in the previous advisory, the current advisory recommends against a routine practice of deep sedation or general anesthesia when performing regional anesthetic procedures in adults, although the practice in children does not appear to increase baseline risk. However, a recent publication challenges the Practice Advisory recommendation not to perform nerve blocks in adults under regional anesthesia, and suggests that subsets of patients may benefit from fascial plane blocks performed under general anesthesia, such as pectoralis blocks (PecI&II) and transversalis plane blocks, without incurring additional risk.[20] The Practice Advisory also affirms that there are no data to demonstrate superiority of one nerve localization technique over another (ultrasound, nerve stimulation, paresthesia technique) with respect to reducing the incidence of PNI. Other important points include the following: 1) the presence of an evoked motor response at a current of <0.5 mA indicates needle-nerve contact, or intraneural needle placement [21]; 2) there are no human data that confirm or refute the effectiveness of injection pressure monitoring for limiting PNI; 3) the practice of subjectively assessing injection pressure by hand feel is inaccurate [22] ; 4) ultrasound can detect intraneural injection [23]; 5) intraneural needle insertion does not invariably lead to functional nerve injury [24,25]; 6) intrafascicular needle insertion and injection should be avoided since it can cause histological and/or functional nerve injury; 7) ultrasound does not have the resolution to distinguish between interfascicular and intrafascicular injection; 8) adequate images of needle-nerve interface are not consistently obtained by all operators in all patients. A simple and inexpensive technique to measure and limit opening injection pressure during PNB has been described, utilizing a compressed air injection technique, by inserting an air bubble in the injection syringe, and limiting compression to < 50% of the initial bubble volume.[26]

Although not addressed in the recent advisory, all local anesthetics are neurotoxic, myotoxic, and cytotoxic in animal experimental in vitro models. However, there is no clinical evidence to choose one local anesthetic in favor of another to reduce the likelihood of PNI. Adjuncts such as clonidine, buprenorphine, dexamethasone, and dexmedetomidine appear to be safe in commonly used perineural concentrations and show less neurotoxicity than ropivacaine in animal models. [27,28] Lastly, there is accumulating evidence to suggest that depositing local anesthetic at a distance farther away from the target nerves, in muscle or fascial planes, may be equally effective in producing a successful block compared to deposition of local anesthetic adjacent or circumferential to the nerve.[29] Although yet to be proven, this practice could potentially decrease the likelihood of needle-induced nerve injury.

Medicolegal concerns and risk reduction

A review of the ASA closed claims data from 1990-2007 demonstrates that only 2% of all malpractice claims were related to PNBs.[30] Many of these claims were for temporary injuries of all types, and a majority of all claims involved nerve injury. Two-thirds of the nerve injury claims were felt to be block-related by the reviewers. Unfortunately, malpractice risk occurs with PNBs, even when injuries are only temporary in nature. Given that the benefits of PNBs are short term (enhanced quality of recovery), and that catastrophic debilitating outcomes are possible, it is imperative to discuss and document the possible serious complications that can occur, including permanent nerve injury.[31] The results of a survey of academic anesthesiologists performing regional anesthesia indicates that there is room for improvement with respect to disclosure of serious complications related to regional anesthesia.[32] The option to choose regional anesthesia should always be part of a shared decision making process between the patient and the anesthesiologist, after a discussion of the material and patient specific risks, without coercion from anesthesiologists or third parties, including surgeons, and documented on an anesthesia consent form separate from the surgical consent form. Consideration may be given to offering PNB after a surgical procedure, after neurologic status has been documented, for patients deemed to be at higher risk for developing PONS.

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Should a patient suffer a serious nerve injury after a PNB and decide to hire a plaintiff's attorney to pursue litigation, to prove malpractice, the attorney will need to introduce evidence to convince a jury that the physician breached the standard of care, and that by breaching the standard of care, an otherwise preventable injury occurred. Given the multifactorial nature of PNI after surgery, this is a high hurdle to overcome. Frequently, these cases may hinge on a physician's ability to demonstrate that deliberate intraneural injection did not occur, either via documented nerve localization techniques or by lack of compromise of patient awareness and communication abilities during the block procedure. Fortunately, the electronic medical record can be a powerful tool to capture detailed information related to the block process, and defend your practice against negligence, should a serious PNI occur. Approximately 80% of cases that go to trial result in a verdict favorable to the defendant.

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Anesthesiologist's Guide to Perioperative Glycemic Management

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Introduction:
Management of patients with diabetes mellitus (DM) and those who are hyperglycemic and do not carry the DM diagnosis (albeit many of them are undiagnosed diabetics) is among the many challenges anesthesiologists face in the perioperative period. To address these challenges, many protocols have been developed. Ideal protocols should be detailed enough to decrease variability in the overall care, however flexible enough to allow for physician judgement that is the hallmark characteristic of personalized care since one size will never fit all.[1]
This review will outline a practical and comprehensive plan for perioperative glycemic management based on the available evidence, and when evidence is lacking, expert opinions, and consensus statements will be utilized. Topics discussed include: the prevalence of pre-operative hyperglycemia and the decision making process for proceeding with or delaying surgery, intraoperative hyperglycemic surgical stress response and the added effect of perioperative steroid, risks associated with hyper and hypoglycemia, a recommended target for perioperative glucose concentration, principles and strategies for safe intraoperative insulin dosing, postoperative glycemic management and a proposed algorithm for managing diabetic patients on continuous subcutaneous insulin pump therapy perioperatively.

The Prevalence of Preoperative Hyperglycemia and Undiagnosed Diabetes:
Diabetes affects 8.3% of the US population.[2] Fifty percent of diabetics will require surgery during their lifetime. A third to half of patients with type 2 DM do not know they are diabetic at the time of surgery.[3] Abdelmalak et al, reviewed the records of 35,000 noncardiac surgery patients and found that 21% of the patients without a diagnosis of DM are hyperglycemic and more than half of those have undiagnosed diabetes.[4] Similar findings have been reported by Hatzakorzian and colleagues who prospectively studied 500 noncardiac surgery patients.[5] Among the nondiabetics, patients who are older, male,[4,5] with higher body mass index (BMI), and higher ASA Physical Status ,[4] are more likely to have hyperglycemia.

In 2012, The Endocrine Society published their Clinical Practice Guidelines recommending blood glucose (BG) testing in all patients on admission to the hospital (including admissions for surgery) regardless whether they have DM or not and further monitoring of admitted nondiabetics with BG > 140 mg/dL for 24-48 hours with appropriate therapeutic intervention. They also recommend HbA1c testing for inpatient nondiabetics whose BG concentration is >140 mg/dL, and all diabetics if it has not been done in 2-3 months prior to admission.[6] These recommendations are on the basis of high prevalence of inpatient hyperglycemia, its associated poor outcomes and the opportunity to diagnose diabetes.[6] Anesthesiologists have been known for their leadership and focus on patients' safety. Perhaps this can be one area where we can add to patient care by identifying hyperglycemic patients who are not diagnosed with DM and those with uncontrolled DM. Identifying the undiagnosed diabetics and directing them to the appropriate care has the potential to impact these patients' overall life-long well-being, beyond the perioperative period. The burden and complications of type 2 DM can be reduced if it is diagnosed and treated early.[7,8]

Pre-operative HbA1c and Surgical Outcomes:
HbA1c is accepted as a marker for chronic glycemia in the few months preceding the time of measurement. Pre-operative HbA1c <7 in diabetic patients undergoing noncardiac surgery was found to be associated with a lower rate of infectious complications. [9,10] Bishop and co-workers have linked HbA1c >11.5 to surgical site infections,[11] but Wilson and co-workers have refuted that notion.[12]

Pre-op Hyperglycemia and Surgical Outcomes:
Retrospective data support the notion that pre-operative hyperglycemia is harmful in the perioperative setting. In noncardiac, nonvascular surgery, pre-operative BG levels > 200 mg/dL were associated with a 2-fold increased risk in overall mortality and a 4-fold increased cardiovascular mortality risk.[13] Another study in patients undergoing total joint replacement showed a 4-fold increased risk of pulmonary embolism (PE)with pre-operative levels > 200 mg/dL.[14] In cardiac surgery patients, pre-operative BG > 110 mg/dL has been associated with a longer hospital stay and increased mortality.[15] Abdelmalak, et al, reviewed the records of 62,000 relatively high risk patients who

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underwent elective noncardiac surgery. One-year mortality – but not composite outcome of in-hospital morbidity including cardiopulmonary and infectious complications, was independently associated with pre-operative BG concentration.[16] Additionally, hyperglycemia is associated with increased production and/or impaired scavenging of reactive oxygen species,[17] polymorphonuclear neutrophil dysfunction,[18] and decreased intracellular killing.[19,20] It is thus unsurprising that poor wound healing and increased infection risk are blamed on hyperglycemia.[21]

Delaying Surgery for Pre-operative Hyperglycemia:

While the association of hyperglycemia with poor outcomes has been established, interventions aimed at hyperglycemia management to improve outcomes have not been clearly demonstrated yet. There is no reliable data to support that if a specific "optimal target" glucose concentration and/or HbA1c are achieved and maintained for a given "optimal duration" of time pre-operatively, that it would in fact result in improvement in surgical outcomes.

Thus, unfortunately current data offer no concrete guidance on whether an elective procedure should be delayed in light of a given level of hyperglycemia or HbA1c.[22] Moreover, when joint arthroplasty was delayed for HbA1c >7%, only 40 percent of the delayed patients were able to achieve such a target within a time range of 7-1043 days![23]

Patients scheduled for surgery (plus family and loved ones) have already re-planned their lives, and took time away from work to be available for the scheduled surgery and psychologically prepared for it. Cancelling their surgery would constitute a major inconvenience with potential financial implications to the patient/family and the hospital to say the least. Therefore, the decision should be an individualized one, depending on the surgery, patient characteristics including chronic glycemic state, clinician's experience with glucose management, etc. Thus, many clinicians do not end up delaying elective surgery for mild to moderate hyperglycemia but rather treat it, and the associated osmotic diuresis induced hypovolemia. On the other hand, many believe that it might be prudent to delay elective surgery when faced with glucose concentrations >350 mg/dL and /or any concentration associated with diabetic ketoacidosis (DKA) and/or hyperosmolar state;[24,25] DKA can easily be diagnosed based on the clinical presentation and when certain simple laboratory criteria are met; the triad of Hyperglycemia > 250 mg/dL, acidosis (arterial pH <7.3, serum bicarb < 18 mEq/l, and anion gap of >10) and ketonemia, urine and serum ketones are positive.[26] To avoid hyper and hypoglycemia pre-operatively in patients diagnosed with diabetes and treated with oral hypoglycemics and/or insulin, several plans have been recommended for scheduling their meds and doses pre-operatively. Table 1, presents one of these popular algorithms that is currently being used at the author's institution.

Diabetes Preoperative Medication Guidelines:

Diabetic Medication:	Day Prior To Surgery	Day of Surgery
Oral Hypoglycemic	Continue same dose	Hold all on the Day of Surgery
Noninsulin injectables, Glucagon like peptide 1 (GLP1)	Pt should take normal prescribed dose the night prior to surgery.	Hold all on the Day of Surgery
Dipeptidyl peptidase (DPP-4)	Continue	Continue
Sodium Glucose Co-transporters-2 inhibitors (SGL2is)	Continue	Hold
Insulin pump	Follow Insulin Pump Protocol	Follow Insulin Pump Protocol
Long Acting Basal Insulin (Levemir, Lantus, NPH)	Pt. should take 75% of prescribed dose the night prior to surgery.	Pt. should take half of the prescribed dose the morning of surgery.
Mixed Insulin (combination of long and short acting i.e.: 70/30 or 75/25)	Pt. should take 75% of prescribed dose the night prior to surgery.	Pt. is to check FBG, if >200mg/dL, pt. is to take half the normal prescribed dose. If <200mg/dL no insulin is to be taken.

*Above regimens & doses can be adjusted on clinical judgment & individual patient basis
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Diabetics Vs. nondiabetics, who should we monitor, and who should we treat?:

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Abdelmalak and colleagues have shown that patients without a diagnosis of diabetes and with pre-operative hyperglycemia had higher one-year mortality than patients with diabetes with the same level of pre-operative hyperglycemia. Patients with diagnosed diabetes and pre-operative glucose concentrations in the lower euglycemic range had higher one-year mortality than patients without diabetes with the same levels of pre-operative euglycemia.[16] In the GLUCO-CABG trial controlling postoperative glucose to 100-140 vs. 141-180 mg/dL resulted in reduction in postoperative complication among patients without diabetes and not in those with diabetes.[27] Such findings highlight the complex relationship between glucose metabolism and outcomes and corroborates with the evidence from the ICU as well. Hyperglycaemia upon admission to the ICU has been shown to be an independent risk factor for in-hospital mortality only in patients without diabetes.[28] By the same token, Krinsley and colleagues showed that diabetics had better outcomes at higher targets than nondiabetics in the ICU.[29]

Collectively, both diabetics and nondiabetics, should be monitored and treated, and emerging evidence suggests that treating hyperglycemia may be more beneficial for nondiabetics compared to diabetics.

Hyperglycemic surgical stress response:
Major surgical procedure ⇨ release of catecholamines, glucagon, cortisol, and growth hormone ⇨ insulin resistance, glycogenolysis, gluconeogenesis ⇨ hyperglycemia.[30] Abdelmalak et al described the magnitude of intraoperative hyperglycemic response to surgical stress during major noncardiac surgery that is inversely proportional to the pre-operative glucose concentration, and described the intraoperative pattern of that response in patients with and without diabetes diagnosis .[31] All patients had a sizable intraoperative hyperglycemic response, albeit those who did not have the diagnosis of diabetes had a steeper rise compared to those diagnosed with diabetes. Most of that rise was from incision to the mid surgery time points, followed by a plateau phase till the end of surgery.

Steroid Induced Intraoperative Hyperglycemia:
Abdelmalak, et al,[31] have also described the hyperglycemic effects of a small dose of steroids (8 mg of dexamethasone IV) on glucose concentrations in patients with and without diabetes. Surprisingly, patients with diabetes who received steroids, compared to those who received placebo, did not have significantly different glucose concentrations. However, those without diabetes who received dexamethasone showed a small increase

PERIOPERATIVE GLUCOSE CONTROL PROTOCOL

The target range for blood glucose is 140-180 mg/dl.

Discontinue all previous orders for insulin and oral glucose lowering agents
Must use infusion pump and run with maintenance fluid
Insulin concentration will be 1 unit of regular insulin/ml of normal saline
- Please prime the tubing with 25-50 ml of the insulin solution

Blood glucose monitoring
- Check BG in 30 minutes after starting the insulin infusion or after a bolus or change of infusion rate. BG may be checked at longer intervals (e.g., 60 min) if there was no intervention in the term of an insulin bolus or a change of infusion rate and if the concentration has been stable for two readings.
- BG may be checked via ABG or bedside monitor. However, sampling site and lab analysis should remain consistent.
  - Verify BG results using an alternate method (e.g. fingerstick) for:
    - Variations in BG lab results ≥ 100mg/dl on consecutive blood draws
    - Suspicion of false lab results or contaminated specimen
    - BG results reading "Hi" or "Low" on the accu-check meter

Calculation of Insulin infusion change
- If DECREASING RATE by 50%: New rate= Current rate 0.5
- If DECREASING RATE by 25%: New rate= Current rate 0.75
- If INCREASING RATE by 50%: New rate= Current rate 1.5
- If INCREASING RATE by 25%: New rate= Current rate 1.25

Initiation of Insulin Infusion†

Blood Glucose (mg/dL)	*Bolus – (IV)*	*Start Infusion at:*
181-200	2 units	2 units/hour, recheck in ½ hour
201-250	3 units	3 units/hour, recheck in ½ hour
251-300	4 units	4 units/hour, recheck in ½ hour
300-350	6 units	6 units/hour, recheck in ½ hour
>350	7 units	8 units/hour, recheck in ½ hour

How To Adjust Insulin Infusions

Please use the re-check glucose concentration (½ hour after the initial bolus and infusion as above) to identify the corresponding row in the table below. Choose the recommended next step from the column that corresponds with the amount of change in glucose concentrations from the prior value.

Blood Glucose (mg/dL)	Decreasing Blood Glucose (↓ by more than 30 mg/dL)	Stable Blood Glucose (No more than 30 mg/dL ↓ or ↑)	Increasing Blood Glucose (↑ by more than 30 mg/dL)	Re-check in
<70	Hold infusion, give 12.5-25 ml dextrose 50%. Notify staff anesthesiologist	Hold infusion, give 12.5-25 ml dextrose 50%. Notify staff anesthesiologist	Hold infusion, give 12.5-25 ml dextrose 50%. Notify staff anesthesiologist	Immediately
71-140	Stop infusion	Stop infusion	Decrease the infusion by 50%	½ hour
141 – 180	Stop infusion	Continue same rate	Increase rate by 25%* ***Max. increase = 10 units/hr**	½ hour
181-200	Decrease rate by 25%	Bolus 2 units I.V. and increase rate by 25%* ***Max. increase = 10 units/hr**	Bolus 2 units I.V. and increase rate by 25%* ***Max. increase = 10 units/hr**	½ hour
201-250	Continue same rate	Bolus 3 units I.V. and increase rate by 50%* ***Max increase = 10 units/hr**	Bolus 3 units I. V. and increase rate by 50%* ***Max. increase = 10 units/hr**	½ hour
251-300	Bolus 3 units I.V. and continuous same rate	Bolus 3 units I. V. and increase rate by 50% ***Max. increase = 10 units/hr**	Bolus 4 units I.V. and increase rate by 50% ***Max. increase = 10 units/hr**	½ hour
301-350	Bolus 4 units I.V. and continue same rate	Bolus 4 units I.V. and increase rate by 50% ***Max. increase = 10 units/hr**	Bolus 5 units I. V. and increase rate by 50% ***Max. increase = 10 units/hr**	½ hour
351-400	Bolus 5 units I. V. and continuous same rate	Bolus 5 units I. V. and increase rate by 50% ***Max. increase = 10 units/hr**	Bolus 7 units I. V. and increase rate by 50% ***Max. increase = 10 units/hr**	½ hour
>400	Bolus 7units I.V. and continuous same rate Notify staff anesthesiologist	Bolus 7 units I. V. and increase rate by 50% ***Max. increase = 10 units/hr** Notify staff anesthesiologist	Bolus 10 units I. V. and increase rate by 50% ***Max. increase = 10 units/hr** Notify staff anesthesiologist	½ hour

1. The above are guidelines only. Insulin infusions may need modification for certain individuals based on clinical judgment and different clinical situations.
2. Round infusion rates to nearest 0.5 mL/hour.

Figure 1: An example of and intraoperative insulin infusion titration algorithm targeting moderate glucose control 140-180 mg/dL. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2018. All rights reserved.

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(approximately 30 mg/dL) compared to those who received placebo.

On the other hand, Murphy et al, found no significant increase in glucose concentrations in the first 24 hours after surgery in nondiabetics who received either 4 or 8 mg of dexamethasone perioperatively. [32]. Thus, one may not need to worry much about the long claimed hyperglycemic effect of PONV prophylaxis doses of dexamethasone neither in diabetics nor in nondiabetics. Other factors may contribute to intraoperative hyperglycemia, such as infusing dextrose containing IV fluids, hypothermia, and dextrose containing cardioplegia solutions in cardiac surgery. Thus, whatever methodology or algorithm one would use intraoperatively to manage hyperglycemia, ought to be a dynamic one, i.e. adjusts to the above mentioned factors that may impact the intraoperative glucose concentration such as the one the author utilized in a prior study,[33] and currently uses a modified version of the same.[34] (Figure 1)

Intraoperative Glycemic Management:

Intraoperative management is aimed at treating hyperglycemia, and avoiding hypoglycemia. Prevention and treatment of hyperglycemia has been shown to improve outcomes, on the other hand, tight glucose control did not. In the ICU, in a landmark paper, Van den Berghe and colleagues showed in a prospective randomized trial that intensive insulin therapy to maintain blood glucose at or below 110 mg/dL substantially improved ICU outcomes.[35] However, a more recent trial aimed at treating hyperglycemia targeting tight glycemic control (80-110 mg/dL) did not improve outcomes.[36] Furthermore, some investigations of tight glucose control in the ICU reported a higher risk of hypoglycemia without a mortality benefit.[36-39]

In the perioperative period, a prospective study of 2,467 cardiac surgical patients revealed that continuous IV insulin infusion reduced the incidence of deep sternal wound infection in diabetic patients. Subsequently, the same authors found that continuous insulin infusion reduced mortality in patients with diabetes undergoing coronary artery bypass grafting.[40,41] However, a single center randomized trial by Gandhi et al where they randomly assigned 400 cardiac surgery patients to tight glycemic control (80-100 mg/dL) intraoperatively or usual care (no insulin during surgery unless BG levels were > 200 mg/ dL) did not show any difference in outcomes between the two groups.[42] Carvalho and colleagues studied the effects of a glucose, insulin, potassium (GIK) regimen while maintaining normoglycemia (the so-called GIN therapy) during cardiac surgery and showed that such a strategy provided more cardioprotection than GIK without maintaining normoglycemia.[43] The intraoperative hyperinsulinemic clamp technique maintaining normoglycemia compared to conventional low dose insulin infusion during cardiac surgery reduced morbidity and mortality in cardiac surgery,[44] however, a validation study is probably needed, besides , it is a labor intensive technique and the feasibility of its application in everyday practice is yet to be demonstrated.

Duncan and colleagues, in their retrospective study, reported that in cardiac surgery, intraoperative glucose concentrations > 200, and < 140 mg/dL were associated with increased morbidity and mortality, and 141-170 mg/dL was a safer range.[45] In a randomized trial, Abdelmalak et al reported that intraoperative tight glucose control did not improve surgical outcomes in patients undergoing major noncardiac surgery.[46] Finfer and colleagues in their randomized trial in ICU patients, showed that a glucose target of <180 mg/dL was associated with improved outcomes compared to a tight target of 81-108.[36] ***Thus, current recommendations from different national societies (citing only a sample here) favor rather moderate targets in the range of 140-180 mg/d,.[6,36,47] vs. tight or more liberal targets.***

The advances in technology may help clinicians in paying more attention to glycemic management. The use of a novel intraoperative audiovisual alert system has resulted in an increase in initiation of insulin treatment and in re-checking glucose value afterwards.[48]

Route of insulin administration perioperatively:

While the subcutaneous route is being viewed as a safe route by many clinicians and may have a role in managing moderate hyperglycemia in ambulatory surgery patients,[49], it has the disadvantages of a very slow onset compared to IV as well as longer duration of action, that makes titratability a challenging task to say the least, and would not allow for timely management of dangerously severe hyperglycemia and thus the risk of "stacking" doses that may eventually result in hypoglycemia.[49] [22] In addition, the change in the subcutaneous circulation due to fluid shifts and change of temperature from exposure to cold operating rooms, to forced air skin warming devices application make absorption of SQ insulin variable and not very reliable.[30]

Thus, the intravenous (IV) insulin route is recommended whenever feasible especially in long surgeries. When deciding between IV boluses vs infusion, glycemic variability considerations comes to play as it is an independent

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risk factor for mortality in the ICU.[50,51] and in septic patients.[52] This may explain why the use of IV insulin infusion with boluses, presumably with better glucose management and low variability, results in less all-cause mortality and fewer poor cardiac outcomes than intermittent IV bolusing of short-acting insulin despite the same glycemic control target.[53]

The intravenous algorithm used will need to be a dynamic one adjusting for variability in individual patient's response (insulin sensitivity), the stage of surgery and other factors affecting intraoperative glucose concentrations (see above discussion on hyperglycemic surgical stress response), such algorithm should also dictate when glucose measurements should be performed, and an intervention plan for detected hypoglycemia. An example of such protocol is presented in Figure 1.[34]

In all cases, no one algorithm will replace physician's judgement based on an ongoing assessment of the changing clinical status of the patient which is essential in making decisions in dosing and titrating insulin perioperatively.

Intraoperative Insulin Sensitivity:

Some insulin dosing algorithms adjust for patient-related factors such as weight,[6] and diabetic status,[54,55] while others do not.[36-38] There is no consensus about which baseline factors should be included, although insulin sensitivity has been related to various factors in non-operative settings. In noncardiac surgery, it appears as if the diabetic status, and body weight contribute little if any (contrary to the common belief) to the response to a given insulin bolus.[56] Regardless of the insulin sensitivity, the use of a dynamic insulin algorithm like the one presented (Figure 1) in which insulin dosing does not depend only on the measured glucose concentration but also on the delta change from the prior measurement, should account for differences in insulin sensitivity resulting from identified or unidentified factors as well as other external factors influencing glucose concentrations like the administration of glucose containing solutions, and glucose containing cardioplegic solutions in cardiac surgery.

Safety of Glycemic Control:

While hyperglycemia is detrimental, hypoglycemia is not without risk and even more dangerous than hyperglycemia. Hypoglycemia per se can increase mortality and morbidity and results in increased neurological damage. Severe hypoglycemia was shown to result in somnolence, unconsciousness, seizures,[57] and — when sustained sufficiently — irreversible neurologic sequelae and/or death.[58] Not only severe but also moderate hypoglycemia was found to be associated with mortality in ICU patients.[59] Clinicians understandably are concerned about tightly controlling glucose perioperatively due to the high incidence of hypoglycemia in association with intensive glucose control;[36-38,60] whose symptoms are masked by general anesthesia and sedation,[61] and no proven benefit.[36-38] Even when we were able to tightly control glucose without inducing severe hypoglycemia in noncardiac surgery patients,[33] no benefit was shown.[62] Thus the proposed moderate control target was met with acceptance as it is associated with much lower risk of hypoglycemia and have been proven beneficial at least in the ICU population.[36]

Management of Hyperglycemia as an Outcome Measure:

In 2017, The Centers for Medicare & Medicaid Services (CMS) has approved the "Treatment of Hyperglycemia with Insulin" as an outcome measure among those to be reported to the Anesthesia Quality Institute's National Anesthesia Clinical Outcomes Registry (AQI -NACOR), Qualified Clinical Data Registry (QCDR) to meet the Merit-based Incentive Payment System (MIPS) requirements. It is defined as "The percentage of patients, aged 18 years and older, who undergo elective inpatient surgery and who have a blood glucose level of > 200mg/dL and who receive insulin prior to anesthesia end time" . However it was rejected in 2018 due to high performance rate and lack of variability for improvement. [63]

Management of diabetic patients with insulin pumps:

Although evidence is lacking when it comes to managing patients using insulin pumps perioperatively, several individual or institutional care paths have been developed.[64,65]

Figure 2 outlines a proposed plan for perioperative management of insulin pump patients that is being utilized currently at the author's institution. The reader is referred to reference number 34 for a comprehensive discussion of this topic, and rationale for every proposed step in this algorithm.[34]

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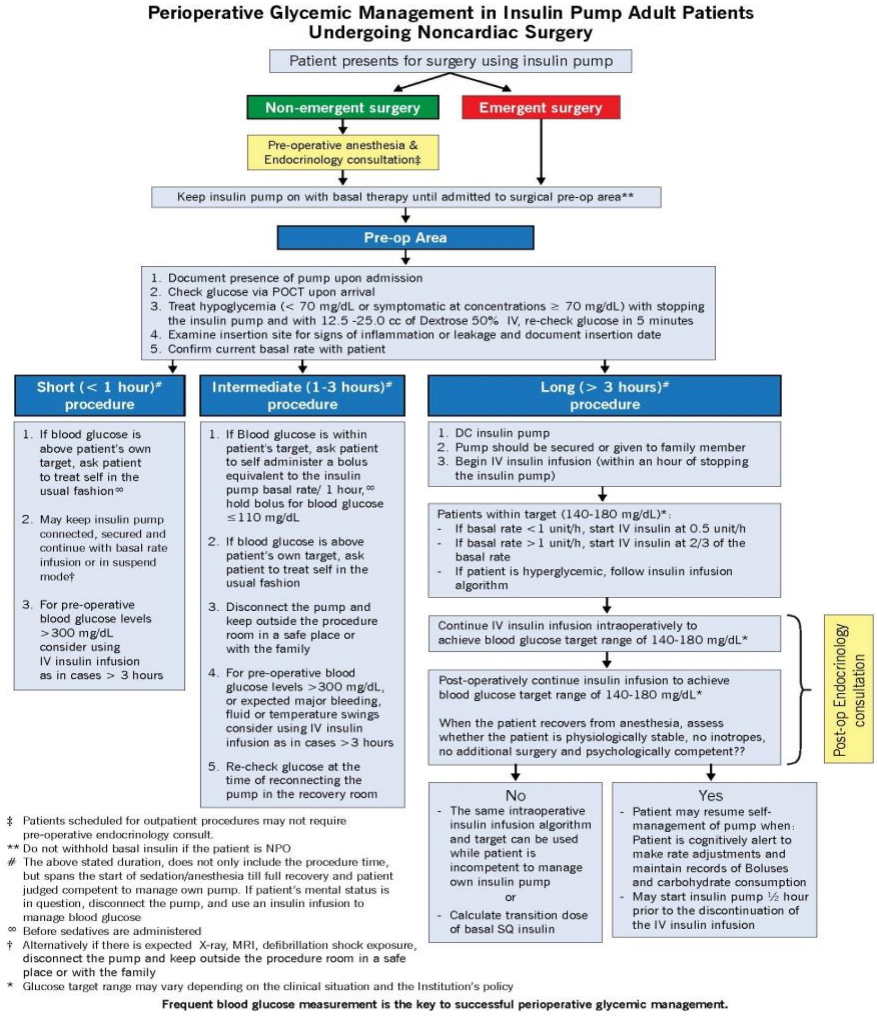

Figure 2: Perioperative Glycemic Management in Insulin Pump Patients Undergoing Noncardiac Surgery. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2018. All rights reserved.

Postoperative Glycemic Management:

In noncardiac surgery patients, Ramos et al,[66] in their retrospective study of 995 patients, concluded that postoperative hyperglycemia increased the risk of postoperative infections irrespective of diabetic status. Frisch and colleagues in their retrospective study of over 3000 noncardiac surgery patients showed that patients with hyperglycemia had worse outcomes (i.e. postoperative infections, acute renal failure, acute myocardial infarction, and 30-day mortality), as well as longer ICU and hospital stays. In both cardiac and noncardiac surgery, postoperative hyperglycemia increased the infectious complication risk.[67] Thus, avoiding hyperglycemia is recommended postoperatively and moderate targets are preferred.[6] In doing so, the use of SQ insulin is appropriate. Insulin regimen in the form of a long acting basal, plus boluses [preprandial (if feeding is started), referred to as basal bolus regimen has been found to be superior to the Sliding Scale of SQ Insulin(SSI) alone.[68] And more recently, both basal bolus and basal plus (Long acting insulin for basal needs in addition to SSI to treat accidental hyperglycemia) regimens have both been more effective compared to SSI alone.[69] SSI is based on repeated responses to hyperglycemia resulting in glucose variability. It is thought that compared to SSI, the other two techniques provide less glycemic variability which has been linked to poor outcomes as discussed above.

Glucose Measurement:

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The central laboratory's measurement of blood glucose remains the gold standard; however, it is costly and takes time. Point of care testing (POCT) devices while they tend to overestimate the actual glucose concentration value,[70] they are cheap, readily available, and fast; providing a good resource for implementing effective glucose management strategy.[6] The advantage of the continuous interstitial fluid glucometer is that it is convenient and it provides frequent readings; however, the drawback is that it has a lag period between blood and tissue glucose concentrations. When one methodology is used (such as POCT), the sampling site and the methodology should remain consistent throughout the procedure.

Emerging Technology and Advances:
An inhalational insulin has been approved by FDA. There are more than one noninvasive glucometer, for example the "App" based glucometer (GlucoWise™, Medwise, London, UK). FDA has recently approved a system referred to as "Artificial Pancreas" developed by Cleveland Clinic investigators where a closed loop communication connects a continuous SQ glucometer with a SQ continuous insulin pump. These devices and new technologies' role in the perioperative period is yet to be investigated.

Summary: An alarming proportion of our surgical patients are hyperglycemic and many are undiagnosed diabetics. Hyperglycemic surgical stress response is real and is not linear throughout surgery. Perioperative steroids induce a small hyperglycemic response if any. Close monitoring of blood glucose levels intraoperatively is of prime importance especially if treatment has been initiated. Signs and symptoms of hypo and hyperglycemia are for the most part masked by general anesthesia. Consequences of untreated hypoglycemia are grave. Current evidence supports IV insulin infusion with boluses for BG management intraoperatively. Insulin pump patients should be managed very carefully according to a standard protocol.

A perioperative glucose management strategy should be implemented to some degree for hyperglycemic patients. Intra-operative tight glucose control is not beneficial in cardiac or in noncardiac surgery. It is pre-mature to mandate certain glucose values in light of insufficient evidence. Current recommendations call for moderate control.

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ANESTHESIOLOGY 2018
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Situational Awareness and Crisis Management: Strategies to Improve Patient Safety in Anesthesia Practice

Amanda Burden, MD **Camden, NJ**

Title: Situational Awareness and Crisis Management: Strategies to Improve Patient Safety in Anesthesia Practice

Anesthesiology is a complex and dynamic field

The operating room is a dynamic and complex environment; critical events can happen without warning. When these events occur, the anesthesiologist must both lead an interprofessional team whose members have varying levels of training and at the same time care for a critically ill patient. At any time, one or more factors, including patient comorbidity, procedural or equipment challenges may combine and lead to a crisis that threatens the patient's well-being or life.[1-5] Anesthesiologists must be able to identify, understand and manage the rapidly changing patient and situation information while leading the team.

Crisis resource management (CRM), a paradigm first designed to improve aviation safety[6] and later adapted by Gaba et. al, to anesthesiology and healthcare provides tools that help the anesthesiologist and the team manage the critical situation.[1-2] CRM is designed to focus the attention of individuals and the entire team on factors aimed at improving patient safety by reducing the causes of adverse events and improving responses to evolving events. While medical knowledge and technical skills are essential components to patient care in a crisis, nontechnical skills such as leadership, communication and situational awareness are equally critical for the safe care of the patient.[1-2,7] To manage the crisis effectively, the anesthesiologist must manage the full situation. Gaba describes a set of principles and actions that comprise effective CRM (Table 1).[2] Situational awareness is an essential element of CRM.

Table 1. CRM Key Points – borrowed with permission from Gaba et. al.

Dynamic Decision Making	Team Management
Know the environment	Call for help early
Anticipate and plan	Designate leadership
Use all available information	Establish role clarity
Allocate attention wisely	Distribute the workload
Mobilize resources	Communicate effectively
Use cognitive aids	Establish situational awareness and a shared mental model

Adverse Events in anesthesiology are associated with "human factors"

Human Factors (HF) is a discipline that addresses human behavior, abilities, limitations, and their relationship to the work environment. HF applies these considerations to the design and evaluation of safer and more effective tools,

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machines, systems, tasks, jobs, and environments.[8] These issues may be physical, organizational or even cultural. HF aims to optimize the human and environmental factors to enhance safety.

Situational awareness is a key component of human factors; all decision making and action flows from this awareness. SA involves the anesthesiologist's perception and understanding of the dynamic information that is

present in his or her environment. It is also the process of integrating relevant information from the environment into a concise picture. SA involves perception as well as understanding and integration of information from the dynamic environment into clear decisions and actions. Situational awareness includes having team awareness and being aware of what other members of the team are doing.[9] It is a process the anesthesiologist must work through while she or he quickly detects, integrates and interprets data gathered from the environment and the resulting knowledge or awareness of the situation.[10-12]

Potential patient safety impact of gaps in Situational Awareness

What are the benefits of being able to assess a situation well and having "good situational awareness?" How would you build and maintain adequate situational awareness? What are the risks associated with having an incomplete or even a wrong situational assessment and awareness? What can be done in order to assure adequate situational awareness? Is it possible to avoid the pitfalls associated with having inadequate situational awareness? Situational awareness is an everyday occurrence, we use it for routine events like driving; it is also part of more complicated and risky situations (e.g., a physician assessing a potentially septic patient or a pilot assessing the potential of landing gear problems during final approach). Situational awareness involves several cognitive functions such as perceiving, understanding, reasoning, and thinking, all of which influence decisions and actions.

Importance of Situational Awareness in Healthcare

Situational awareness was first discussed and studied in aviation and aerospace, in the mid=1990s, Gaba et. al., wrote that situational awareness is an equally important factor in the complex, dynamic, and risky field of anesthesiology.[13] Situational awareness is now thought to be one of the most essential nontechnical skills for the achievement of safe anesthesia practice.[14] As such, there is a need for a better understanding of situational awareness and the development of new ways to learn about and acquire situational awareness in healthcare settings. The World Health Organization recently cited situational awareness as critical in all areas of healthcare.[15] Since its origin in aviation psychology literature, situational awareness is now considered central to safe and effective decision-making and performance in high hazard areas and domains. Situational and environmental conditions can combine with tasks that are unstable, time-pressured, have high stakes, and involve multiple team members. This dynamism and complexity can alter judgments and can impact both individual and team decision-making.[16] Reason stressed the importance of contextual based decision-making where the situation and environment are recognized as playing an influential role in the decision-making process.[17] As such, any degradation or loss of situational awareness is cited very often as being associated with environmental or situational conditions in addition to the more obvious human (individual and team) and performance issues.

The theory of situational awareness is frequently used to explain how decision makers are able to incorporate information from the environment in a way that allows them to "know what is going on around them" and make critical decisions.[18] Jones and Endsley suggest that well-informed decisions require that all relevant elements in the environment are understood.[19] It is also important for decision makers to understand how these elements interact and impact the situation over time. Endsley suggests that situational awareness can be decomposed into three levels: perception, comprehension and projection.[20] The integration of these three levels is best defined as the "perception of the elements in the environment within a volume of time and space, the comprehension of their meaning, and the projection of their status in the near future.[20]"

It is essential to both understand what situational awareness is and to also understand how to achieve situational awareness in practice. Guidance on how to attain this knowledge and assess the situation is critical.[21] This

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assessment requires understanding of the environment and the task, the capabilities and limitations of the team members and how those factors may affect behavior and performance. There are many factors all of which may ultimately influence the performance of the individual team members and the team as a whole.[1-5] When analyzing a situation with many factors that influence performance, start with the basic elements of the situation – the physical and human environments. The physical environment includes aspects of the physical space where the situation occurs, the devices and other conditions such as lighting, noise, temperature, etc. The human environment includes any other healthcare workers. The human environment also includes organizational aspects such as shift work and handovers. These can include: staffing, management and authority gradients, policies and protocols as well as training and supervision of residents. In addition to the environment, the capabilities and limitations of the individuals or teams must also be considered. All of these issues act together in an interdependent fashion and may produce distractions, interruptions, fatigue, workload, and stress.[22-24]

Strategies to prevent gaps in Situational Awareness and Improve Patient Safety

CRM principles are designed to help the anesthesiologist prevent gaps in Situational Awareness. Ideally addressing the situation will begin early, before the situation unfolds. In this preliminary and preparatory phase, activities such as briefing and planning should be performed. The preparation phase should be considered as the first critical step in building adequate situational awareness. During this time, as many situational elements as possible can be identified: Who is the patient? What do we know about the patient? Where are we going to treat the patient? What is available there in terms of devices and tools? Who is going to work with me? What is the procedure we are supposed to perform? When do we start? How long has the patient been in this state? Identifying these points and briefing the team about the patient and the plan in advance can help the team prepare to manage the patient.

As the situation unfolds, the key is to build and maintain situational awareness in an effort to assure patient safety. Building situational awareness requires continuously scanning the procedural room and the patient to identify what is occurring, understanding any changes, and thinking ahead. This allows the anesthesiologist to anticipate and plan for events as they unfold. This process is cyclical and allows the anesthesiologist to continuously acquire the most up to date knowledge to eventually implement and, if needed, revise decisions and actions. This process also includes continuing to survey the situation to look for any obstacles to building and maintaining situational awareness. Once the situation is terminated, participants may reflect and debrief on what happened. The process of using CRM principles to continuously maintain an awareness of the patient is a crucial tenant of the practice of anesthesiology and allows for safe care of the patient.

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Opioid Free Anesthesia and Analgesia: A Paradigm Shift - From Bariatric Anesthesia to Your Daily Anesthetic Practice

Dr Adrian Sultana MD FANZCA **Sydney, New South Wales, Australia**

Introduction

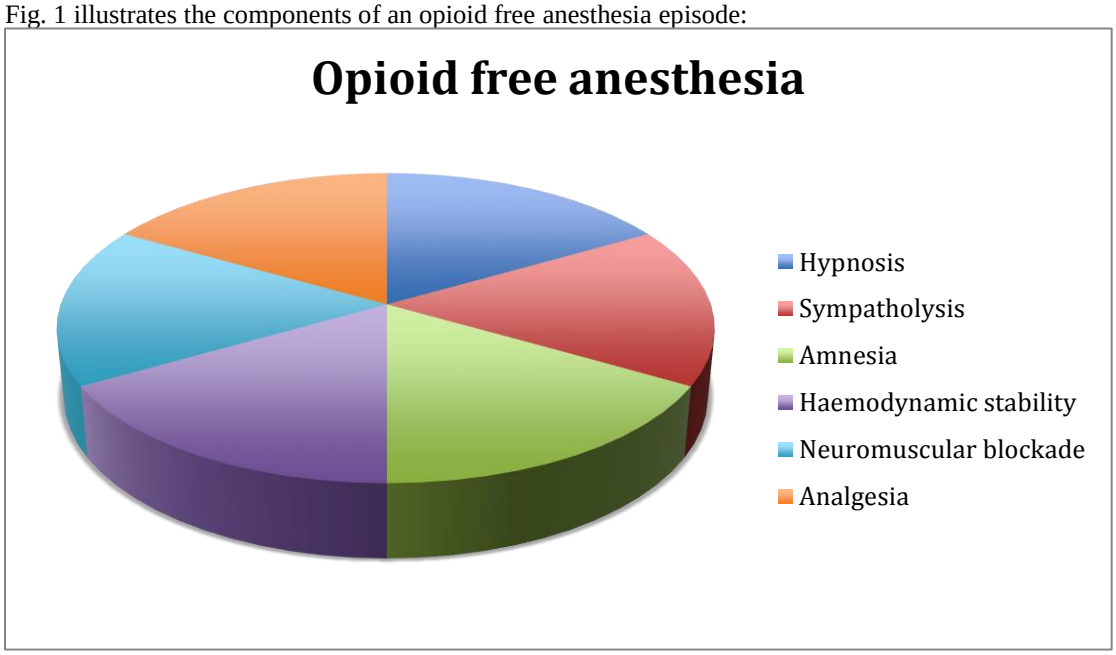
Opioid Free Anesthesia (OFA) is a technique where no intra-operative systemic, neuraxial, or intra-cavitary opioid is administered during the anesthetic. Opioid Free Analgesia similarly avoids opioids in the perioperative period. Bariatric anesthesia is encountering a paradigm shift[1] or scientific revolution in the way anesthesia is administered while excluding or severely limiting opioids.

Bariatric anesthesiologists worldwide[234] have accumulated data using an opioid free regime[5] that could be useful in many clinical scenarios.

The goals of avoiding opioids in the obese surgical population include the reduction or prevention of:

- Respiratory depression
- Central muscle rigidity
- Pharyngeal muscle weakness
- Obstructed breathing
- Negative inotropy
- Nausea, vomiting, ileus and constipation
- Urinary retention
- Tolerance and addiction
- Dizziness
- Excessive somnolence
- Opioid Induced Hyperalgesia[6] (OIH)
- Worse outcomes in Oncology

Fig. 1 illustrates the components of an opioid free anesthesia episode:



Our unit has adopted a multimodal approach that completely avoids intraoperative opioids. We hereby present this "method" while reminding our audience that not all the techniques may be applicable to specific practice regions or environments.

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Hypnosis is provided with 0.7 -1.0 MAC desflurane in oxygen/air or a Total Intravenous Anesthesia Technique with propofol titrated to a processed EEG Monitor.

Sedation, analgesia and sympatholysis are achieved with a dexmedetomidine, infusion[7]
Dexmedetomidine is a selective Alpha -2 agonist with profound properties as a co-anesthetic (table 1)

Analgesia and N-Methyl D-Aspartate (NMDA) antagonism are administered via a very low dose of ketamine[8] (25 mg over 2-4 hours of surgery).

Ketamine reduces the incidence of chronic postsurgical pain, opioid consumption and time to first analgesic request. Also, ketamine is especially useful when combined with magnesium.[9]

Co-anesthesia and sympatholysis are further enhanced with an intravenous lidocaine infusion.[10]

While the use of systemic lidocaine and other adjuncts for acute pain management are off-label, it would be shortsighted to deny critical groups of patients their benefits.[11]

Co-analgesia is achieved with:

Intravenous Dexamethasone in large doses (> 100 ug/kg of lean body mass)[12]

Magnesium infusion[13]

Parenteral Acetaminophen and Non-steroidal Anti-Inflammatories[14][15]

Gabapentinoids[16]

Laparoscopic Working Space: is provided for the surgeon by employing profound neuromuscular blockade during the intra-abdominal part of the procedure. Block is quantitatively monitored and appropriately reversed at the end of surgery.[17]

Hemodynamic Stability Can Be Achieved Without Opioids: even when challenged by the opposing influences of pneumoperitoneum (hypertension and tachycardia) and steep head-up tilt (hypotension).

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Fig. 2: An actual patient screenshot showing "sympatholysed" hemodynamics at the peak of pneumoperitoneum utilizing a low Minimum Alveolar Concentration (MAC) of Desflurane and the parenteral multimodal mixture which we shall describe in this refresher course.

Table 2 Clonidine vs Dexmedetomidine

CLONIDINE	DEXMEDETOMIDINE
Alpha 2 > Alpha 1	Alpha 2 > Alpha 1
220:1	1620:1
Partial agonist	Full agonist
Mildly lipophilic	Highly lipophilic
Reduces MAC by 50%	Reduces MAC by 90%
Plasma T1/2: 9-12 hours	Plasma T1/2: 2-2.5 hours
PB 50%	PB 94%
Elimination half life – 8 hours	Elimination half life -2 hours
Distribution half life > 10 minutes	Distribution half life -5 minutes
Inactivation at the locus coeruleus "similar to normal sleep"	

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A Method Of Opioid Free Anesthesia For Bariatric Surgery

Mulier's group have recently updated their method for OFA and we outline their technique:
Dexmedetomidine loading dose of 0.25 mcg/kg (maximum 20 mg) is given prior to induction.
The maintenance infusion is then given as follows:
Dexmedetomidine 50 mcg (1 mcg/ml)
Ketamine 50 mg (mg/ml)
Lidocaine 500 mg (10 mg/ml)
Mixed in the same syringe with NaCl 0.9% up to 50 ml

- This is the syringe that is given for *maintenance* at the following rates:
- 0.1 ug/kg/h of Dexmedetomidine
- 1 mg/kg/h of Lidocaine
- 0.1 mg/kg/h of ketamine
- Quite simply: 1ml/hr. of the mixture for every 10kg of patient actual body weight
- Anesthesia is induced with propofol and neuromuscular blockade with rocuronium together with airway management along conventional lines.
- Maintenance is with either desflurane (Sydney) or sevoflurane (Bruges) or indeed propofol TCi –TIVA and we are able to report a marked reduction in anesthetic requirement which we attribute to the adjunctive effect of Dexmedetomidine/Ketamine/Lidocaine
- Postoperatively the same mixture is used as an analgesic on the Post Anesthesia Care Unit and the High Dependency Unit at half the rate. Although Dexmedetomidine causes drowsiness there is a remarkable sparing of upper airway integrity supported by the recent work of Capasso[18]
- Intravenous magnesium is administered as follows: Loading dose of 40-50 mg/kg Lean Body Mass (LBM) followed by a maintenance infusion of 10 mg/kg/hr.
- Obstetric anesthesiologists will have no difficulty remembering that magnesium potentiates neuromuscular blocking agents and is a potent vasodilator!

Pitfalls of Opioid Free Anesthesia

- Excessive sympatholysis may need to be treated with ephedrine
- Inadequate sympatholysis responds to Clonidine in conventional small boluses of 0.5 to 1.0 mcg/kg of LBM
- Theoretical risk of inadequate anesthesia would require rescue with opioid and /or hypnotics if failure were suggested by elevation of processed EEG parameters or hemodynamic responses.
- Post-operative excessive sedation is a hallmark of Dexmedetomidine pharmacokinetics and responds to dose tapering.

Contraindications To Opioid Free Anesthesia Include:

- Allergy to one of the drugs.
- Heart block
- Shock
- Pre-existing Bradycardia
- Unstable Ischemic Heart Disease
- Autonomic Neuropathy Syndromes With Orthostatic Hypotension.

Dose tapering of Dexmedetomidine may also be required in borderline cases particularly the elderly;
Conversely, dose escalation may be required in opioid tolerant or antipsychotic medicated patients.

Alternative Demographic and Surgical Opportunities for Opioid Free Techniques[19]

- Patients with respiratory compromise
- Obstructive Sleep Apnea (OSA) without obesity
- Patients with opioid dependence and certain chronic pain syndromes, and
- Oncology patients with clear benefits for ERAS protocols after colorectal and breast cancer surgery[20].

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Summary

Opioid Free Anesthesia is an alternative to standard opioid-based techniques in the management of morbidly obese patients for bariatric surgery.

Evidence based methods including core analgesics and adjuvant drugs such as magnesium, ketamine, alpha 2 agonists and systemic lidocaine are effective in avoiding large doses of opioids and in particular avoiding the use of remifentanil.

Hypnosis, analgesia, amnesia, sympatholysis and hemodynamic stability are achieved during pneumoperitoneum for upper gastrointestinal surgery while immobile surgical conditions are maintained with accurate neuromuscular blockade.

Similar analgesic adjuvant agents can be used postoperatively to maintain opioid free or opioid sparing analgesia.

While clinicians have embraced these concepts and techniques enthusiastically, large prospective studies from independent units worldwide are awaited.

Such studies would cement the evidence base for opioid free anesthesia and analgesia

Dr Adrian Sultana MD FANZCA

Conflict of interest: none

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Disaster Management: How to Prepare for the Next Disaster or Mass Casualty Event

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Introduction

Recent natural disasters (hurricanes, earthquakes, tornadoes) and man-made disasters (bombings and mass shootings) have increased awareness of the need to be prepared should one of these events occur that would affect the hospital or health care facility at which you work. An earthquake or tornado that destroys infrastructure or a storm that shuts off electrical power to your facility are examples of disasters for which one should be prepared, as well as a mass casualty incident or event in which your hospital is overwhelmed with casualties. Independent of the reason for the disaster, there are certain principles with which one should be familiar so-as to be prepared for a mass casualty situation.

Nomenclature

*Mass casualty incidents vs mass casualty event***:** Health care facilities provide emergency care on a daily basis and have emergency departments (EDs) that are staffed and equipped to provide this care be it a patient or patients that have experienced blunt trauma in a motor vehicle accident, had thermal injury in an industrial accident, or penetrating injury from a gunshot or knife. A mass casualty incident is one in which the number of patients overwhelms the staff and resources of the ED, in which case the hospital activates its mass casualty protocol, and additional staff are called into the facility, a triage system is implemented to expedite care to the most seriously injured, and patients with less serious injuries, or patients who are "expectant" ie not expected to survive their injuries, may be managed in other parts of the hospital. A mass casualty event is one in which the hospital itself it overwhelmed and unable to provide the necessary care to the injured. A small hospital may not have the resources to manage a large number of patients, and a large hospital may have had structural damage from an earthquake or tornado making it impossible to care for even small numbers of patients. For the purpose of this discussion our focus will be on mass casualty incidents.

Emergency Preparedness

There are four components of an emergency preparedness plan: prevention/mitigation, preparedness, response and recovery:

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Prevention/mitigation:
The health care facility at which you work should have an emergency response plan, which should be tested every year, and the anesthesia department should likewise have a plan for how its personnel will be assigned in a mass casualty incident eg the ICU, OR, ED or triage outside of the hospital. As part of the plan, a hazard analysis should have been conducted – what disasters are most likely to occur in the area? It wouldn't make sense for a hospital in AZ to plan for a hurricane but it would make a lot of sense for a hospital in CA to have plans for an earthquake, eg the Northridge CA Earthquake in 1994 that disabled 4 of 8 hospitals in the region. Similarly, a hospital near a refinery should have a plan that might differ from a hospital close to a nuclear power plant. Other factors also must be taken into account during emergency response planning – during large sporting events, concerts or Presidential visits, the facility and EMS must be at higher level of anticipation of an incident occurring.

In addition to a hazard analysis the facility should also have engaged its employees so that personnel critical to a "calling tree" have accurate information, that all employees know where the "Command and Control Center" is, and what areas of the hospital might be used for "surge capacity."

Finally, as part of the Prevention/Mitigation strategy, the hospital, in cooperation with the Departments of Surgery. Anesthesiology and Emergency Medicine should consider sponsoring a "Stop the Bleed" Program so that the community at large is better able to respond to a mass casualty incident or event. "Stop the Bleed" is a program developed by several national organizations to train civilians in the use of tourniquets and pressure dressings. The top cause of preventable death in trauma is bleeding. 20% of people who have died from traumatic injuries may have survived if bleeding had been stopped more promptly. The belief and hope are that if enough civilians are trained in how to stop or attenuate hemorrhage that outcomes from terrorist attacks with IEDs and from mass shooting events might be improved.

Preparedness:
Equally important as the hospital's emergency response plan is the anesthesiologist's preparedness plan for his or her family, and for herself or himself if they are called into the hospital for a mass casualty incident or event. The most basic family plan should provide back up of all important legal documents and should have provisions on what to do if there is a home fire (location and use of fire extinguishers, escape routes, and what to do in case of a fire). Plans should be made for care of children, pets and any disabled or elderly adults within one's home should one or both parents respond to a disaster. There should be an established meeting point for family members and care takers outside the house and one outside the neighborhood if the house has to be evacuated, or if unable to return to the home because of a flood or damage from a storm or earthquake.

As part of one's personal preparedness an individual should have cash on hand, and fuel in his or her vehicle – depending on the nature of the disaster electricity may be out and if so, ATMs and fuel pumps at gas stations won't work. Some individuals have a "go bag" – somewhat similar to what one might take if she or he were on call overnight at the hospital -- complete with toiletries, change of clothes and some snacks. More prepared individuals even have a "trauma" bag in their vehicle, complete with tourniquets, airways etc. Always remember to bring your hospital ID with you. If the hospital is locked down as part of the emergency response plan, you will need an ID card to access the facility. Once within the facility report to Command and Control.

Response
Facilities' response plans are very dependent on anesthesiologists – we have the requisite knowledge and skills to evaluate and resuscitate patients in the ED (manage airways, gain IV access – either peripherally or centrally, ventilate patients), anesthetize patients transported to the O.R., and provide critical care and pain management services post-operatively.

However, anesthesiologists have much more to offer a health care organization than their clinical skills. We excel at prioritizing tasks, looking for points of weakness in systems, and preventing or at least mitigating the effects of a failure. We use checklists to ensure that anesthesia work stations are fully functional prior to anesthetizing a patient,

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and algorithms, such as the ASA Difficult Airway Algorithm, are used to guide our practice in uncommon but potentially lethal situations.

Mass casualty incidents are resource-intensive, highly stressful, sudden-impact events; trauma anesthesia checklists are very helpful in preparing for and in managing a patient who has sustained traumatic injury when everyone's nerves are on edge. The O.R. Mass Casualty Checklist was developed by the ASA's Committee on Trauma and Emergency Preparedness (COTEP) to aid during mass casualty incidents.

OPERATING ROOM PROCEDURES FOR MASS CASUALTY

Objective

To be able to manage the flow of patient care in the OR's during a mass casualty situation.

Steps (Indicate date and time for each item)

- ☐ **Refer to facility's Operation's Manual**

Open up appropriate annex

- ☐ **Activate call-in tree**

Assign an individual to activate. Use clerical personnel or automatic paging system, if available

- ☐ **Assess status of operating rooms**

Determine staffing of OR's 0-2, 2-12 and 12-24 hours. Hold elective cases.

- ☐ **Alert current OR's**

Finish current surgical procedures as soon as possible and prepare to receive trauma

- ☐ **Assign staff**

Set up for trauma/emergency cases

- ☐ **Anesthesia Coordinator should become OR Medical Director**

Work with OR Nursing Manager to facilitate communication and coordination of staff and facilities

- ☐ **Report OR status to Hospital Command Center (HCC)**

Enter telephone, email address of HCC

- ☐ **Ensure adequate supplies**

Coordinate with anesthesia techs/supply personnel to ensure adequate supplies of fluids, medications, disposables, other

- ☐ **Contact PACU**

Accelerate transfer of patients to floors/ICU's in preparation for high volume of cases

- ☐ **Anesthesiologist should act as liaison in Emergency Department (ED)**

Send an experienced practitioner to the ED to act as a liaison

- ☐ **Consider assembly of Stat Teams**

Combination of anesthesia, surgical, nursing, respiratory personnel to triage, as needed

- ☐ **HAZMET/WMD event**

Review special personal protective procedures, such as DECON & isolation techniques. Consider if part of the OR or hallways should be considered "hot" or should have ventilation altered. Good resources include CHEMM/REMM websites

- ☐ **Coordinate with blood bank**

Verify blood availability

- ☐ **Coordinate with other patient care areas**

ICU's, OB, Peds, etc to ensure continuity of care for new and existing patients

Developed by the ASA Committee on Trauma and Emergency Preparedness

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The checklist can be customized to one's institution and used by the OR medical director, hopefully an anesthesiologist, to manage resources and personnel. The first step in the process for the OR medical director is to implement the hospital's emergency response plan. If additional personnel are needed Short Text Service (STS) messaging to contact staff as it is the service most likely to work during a disaster. If individuals are called to come in, branched tree lists are more efficient than linear lists when notifying essential personnel. All ORs should be notified of the situation, and surgeons should be directed to complete surgical procedures in an expedited but safe fashion. Elective cases should be delayed or canceled. An assessment of staffed OR availability (0-2, 2-12 and 12-24 hours) should be transmitted to the hospital Command and Control Center. Anesthesia and nursing staff should set up and fully stock available rooms and prepare for emergency procedures. A senior anesthesiologist should proceed to the ED to serve as a liaison to the OR suites; this technique, used in Israel, facilitates communication between the ED and the OR, optimizing resources and response times. Well-staffed anesthesiology departments may be able to provide teams to the ED for help with triage and resuscitation. The Command and Control Center should coordinate with the PACU, ICUs, blood bank, obstetrics, pediatrics, radiology and other departments to increase surge capacity, as well as to maintain routine levels of care. As part of the hospital plan steps should be taken to address the needs of patients that require "routine" procedures eg C-sections, appendectomies or emergency cardiac procedures. Endoscopy suites can be utilized as overflow areas to manage patients who are less critically ill. If patients have been exposed to hazardous materials such as chemicals, toxins or radioactive materials, several anesthesiologists within the department must be prepared to don personal protective equipment and assist in decontaminating and treating patients exposed to toxic compounds, providing this treatment outside the ED in the triage area prior to patients entering the ED.

For those anesthesiologists providing care within the operating room, as soon as aware of a mass casualty, following the checklist mentioned above, the operating rooms that will be used during the emergency response should be warmed to 27°C, warming blankets placed on OR beds, fluid warmers set-up, emergency airway equipment made available, and emergency drugs including vasoactive drugs and drugs for rapid sequence intubation (eg ketamine, succinylcholine etc.).

For managing situations such as this, damage control surgery and damage control resuscitation are of paramount importance.

Damage Control Surgery for Abdominal Injuries
Avoid hypotension, hypothermia, acidosis
Repair or ligate vascular injuries
Splenectomy if injured
Repair or resect intestines
Pack liver hemorrhage
Pack and leave open abdomen if necessary
Continue resuscitation and warming in ICU
Come back another day

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Of critical importance, especially in a mass casualty incident, surgery is performed to control bleeding and to repair vital organs. Wounds are packed open, the patient stabilized, and postoperatively resuscitation is continued and the patient brought back to the OR for definitive repair another day. The goal is to minimize surgical time and to repair only that which is absolutely necessary.

Damage Control Resuscitation refers to what we as anesthesiologists do. Damage control resuscitation is defined as rapid hemorrhage control through early administration of blood products in a balanced ratio (1:1:1 for units of plasma to platelets to red blood cells [RBCs]; a ratio that is the closest approximation to reconstituted whole blood), prevention and immediate correction of coagulopathy, & minimization of crystalloid fluids.

Damage Control Resuscitation
Correct intravascular volume deficits
Treat acute coagulopathy of trauma
Preserve oxygen-carrying capacity
Repair the endothelium
Prevent dilutional coagulopathy.

Recovery: The fourth facet of disaster management is *recovery* (returning the facility to its pre-disaster status. This process should include a briefing to identify what went well, and how the response and outcomes might be improved in the future. Behavioral health services may need to be provided to personnel who developed psychological sequelae from the incident.

Summary

While we all hope never to have a disaster occur that affects our local community, as anesthesiologists, experience shows that preparedness improves outcome. Preparedness includes a plan to protect family and self during a disaster, and to be prepared to report to the hospital. Flexibility is of vital importance, as one may be assigned to an area other than the hospital ORs. Checklists are very helpful to guide anesthesiologists in preparing to treat casualties. However, the concepts fundamental to our specialty are always the same - airway control, ventilation, and support of the circulation by restoring intravascular volume through the administration of blood products and fluids, and if necessary the use of vasoactive drugs to increase systemic vascular resistance and cardiac contractility.

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Controversies in Pediatric Anesthesia: Should the FDA Warning Affect Pediatric Anesthesia Practice?

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The potential for anesthetic neurotoxicity in infants and young children is a crucially important question for the millions of young children undergoing anesthetics every year in the U.S. and around the world. Although the experimental animal data is very clear that gamma aminobutyric acid (GABA) agonist, and N-methyl-D-aspartate antagonist anesthetics and sedatives have neurodegenerative and long term neurobehavioral effects, including in non-human primates, the human data is not definitive. This presentation will focus on human studies published over the past 2 years, which represent the highest quality data available to date. Ongoing studies will also be presented to demonstrate current clinical research approaches, even though outcome data is not yet available.

Published Studies

GAS Study

The General Anesthesia vs. Spinal Anesthesia (GAS) Study compared inguinal hernia repair with sevoflurane general anesthesia vs. spinal anesthesia in infants less than 6 months of age. This multicenter, multinational study enrolled 722 infants, and the primary outcome is full scale IQ on the Weschler Preschool and Primary Scale of Intelligence at age 5 years. Although the primary outcome has not yet been reported, the secondary outcome was the Bayley Scales of Infant and Toddler Development-III, done at age 2 years. There was no difference between the groups in any test at age 2 years, whether analyzed by intention-to-treat, or per-protocol basis. The median duration of the anesthetic was 54 minutes. This remains the only fully prospective, randomized, controlled trial of anesthetic technique and neurodevelopmental outcomes in children.

PANDA Study

The Pediatric Anesthesia and Neurodevelopment Assessment (PANDA) Study assessed 108 sibling pairs at age 8-15 years, with a battery of neuropsychological tests. In each pair, one of the siblings had general anesthesia for inguinal hernia repair at less than 3 years of age, the other was unexposed. There were no differences in neurodevelopmental outcomes, specifically full scale, verbal, or performance IQ. Median anesthetic time was 80 minutes.

Swedish Cohort Study

In a large retrospective study from Sweden, 33,514 children with 1 anesthetic exposure before age 4 years were compared to 159,619 matched control children with no anesthetic exposure. The primary outcomes were school grades at age 16, and IQ at age 18. One anesthetic exposure was associated with 0.41% lower test scores, and 0.97% lower IQ scores, than in unexposed children. Multiple exposures had the same associations, i.e. were not greater than with a single exposure. The magnitude of these associations was small; the effect of gender, maternal educational level, and even month of birth during the same year were larger than the anesthetic exposure effect.

Mayo Clinic Retrospective Study

A recently published study from Mayo Clinic assessed the incidence of learning disability diagnosis (retrospectively from school and medical records) in children who had anesthesia at less than 3 years of age, compared to a propensity-matched control group without anesthesia exposure. In 457 children with a single anesthetic exposure there was no difference in the incidence of learning disability, up to age 19 years, compared to the unexposed group. However, in the 116 children with 2 or more anesthetic exposures, this incidence of learning disability was doubled to 29.9%; and the 95% confidence intervals did not overlap, indicating a statistically significant association. In

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addition, anesthetic duration of greater than 90 minutes also had a statistically significant association with learning disability diagnosis, with a hazard ratio of 1.82.

MASK Study

The Mayo Anesthetic Safety in Kids (MASK) Study has completed enrollment and may be published by the date of this lecture. More than 500 children receiving general anesthesia at less than 3 years of age were brought back for formal neuropsychological testing over multiple domains. 250 children were 7-11 years old, and 250 were 15-19; and 100 in each group had multiple anesthetic exposures. A propensity matched control group with the same numbers of children, except not exposed to anesthesia, was also included. The recently published MASK Study demonstrated decreased fine motor skills and processing speed in reading tasks for children and adolescents who had multiple anesthetic exposures at younger than 3 years of age, averaging 187 minutes of exposure.

Ongoing Research

Recognition Memory Study
A unique recognition memory test, along with other neuropsychological testing, is being utilized in children 6-11 years of age, in 4 groups: those anesthetized at 0-2 years of age for >2 hours, 0-2 years of age for <30 minutes; 4-7 year olds anesthetized for >2 hours, and a control group of 6-11 year olds not exposed to anesthesia. This study will address the issue of age and duration of exposure, and is expected to complete enrollment in the next 1-2 years.

TREX Study

Dexmedetomidine is an alpha-2 presynaptic agonist drug that produces sedation, and has been used as a sedative and as an adjunct to general anesthetic technique. In animal model studies, including rodents and non-human primates, dexmedetomidine does not cause neuroapoptosis or other forms of neurodegeneration at usual clinical doses, in contrast to all the anesthetic gases, and other sedatives binding GABA or NMDA receptors. Opioids such as remifentanil also have not demonstrated neurodegenerative effects with short term exposure in animal models. The Toxicity of Remifentanil and Dexmedetomidine, or TREX Study, is assessing whether this combination of drugs may be associated with improved neurodevelopmental outcomes after anesthesia. The pilot TREX study assessed 60 1-12 month olds undergoing lower abdominal surgery, with a regimen of dexmedetomidine-remifentanil, and a caudal anesthetic. The manuscript is in preparation for submission, but this approach was safe and feasible. A multicenter, multinational randomized controlled trial of dexmedetomidine plus low dose sevoflurane, vs. standard dose sevoflurane, in children <2 years of age undergoing >3 hours of anesthesia, has been organized and has enrolled its initial subjects. Primary outcome will be full scale IQ at age 3 years. About 500 subjects will need to be enrolled and results will not be available for several years.

Dexmedetomidine Cardiac Study

A phase I pilot study of dexmedetomidine safety and pharmacokinetics (PK) in infants under 6 months of age undergoing corrective cardiac surgery has completed enrollment. A dose escalation approach was used to acquire data to construct a PK model, which was then validated in phase 2 of the study. A robust PK model was constructed; safety was excellent, and a manuscript will soon be in preparation. The pilot study was the basis for the design of a multicenter randomized controlled trial of dexmedetomidine neuroprotection in corrective infant cardiac surgery, which is in the grant submission phase.

MRI Diagnostic Yield/Anesthesia Study

Many thousands of young children undergo sedation or anesthesia for brain MRI procedures annually for diagnoses such as developmental delay, seizures, and autism. The diagnostic yield of MRI in patients without neurological exam abnormalities is very low, leading to the question of whether they should be performed at all in this setting. Texas Children's Hospital is in the data collection phase of a retrospective study of brain MRI for these indications in children less than 3 years of age, focusing on the diagnostic yield, and anesthetic and sedative exposure. We

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hypothesize that 10% of these MRIs in this patient group will have a positive diagnostic yield, and are collecting all anesthetic and sedative exposure data in detail. We expect to have abstracts at major anesthesia meetings in the next year.

FDA Warning

On December 14, 2016 the U.S. Food and Drug Administration (FDA) issued a Drug Safety Communication (DSC) about general anesthetic and sedation drugs for children less than 3 years of age undergoing prolonged anesthetics greater than 3 hours, or repeated anesthetics, "warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years…..may affect the development of children's brains." This DSC reviewed the available animal and clinical data, and concluded that, "….several of the studies have increased concerns that longer or repeated exposures may contribute to various cognitive and behavioral problems, including neurodevelopmental delay-related diagnoses, learning disabilities, and attention deficit hyperactivity disorder." This DSC resulted in a labeling change for 11 common general anesthetics and sedative agents that bind to gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors, including all anesthetic gases such as sevoflurane and isoflurane, and the intravenous agents ketamine, propofol, midazolam, lorazepam, pentobarbital, and etomidate. The DSC also stated that, "Parents…..should discuss with their child's health care professional the potential adverse effects of anesthesia on brain development, as well as the appropriate timing of procedures that cannot be delayed without jeopardizing their child's health." All of the common sedative drugs, with the exception of opioids, N_2O, and dexmedetomidine are included on the list of drugs covered by the FDA warning.

The FDA warning has generated substantial controversy and conversation among pediatric anesthesiologists and sedation physicians. The timing was unexpected, because two recent well-designed studies, the GAS and PANDA studies, indicated that relatively brief, single exposures to anesthesia for inguinal herniorrhaphy in early childhood were not associated with lower neurodevelopmental scores. Some institutions, including Texas Children's Hospital, have initiated a proactive education program for parents and providers for children who are included in the FDA warning, i.e. patients less than 3 years of age undergoing prolonged or repeated anesthetics or sedations. The patient education materials and discussion points present the problem, emphasize the uncertainty to date of these findings, and encourage discussion of the medical necessity of the surgery or diagnostic procedure, i.e. could it be postponed until a later date without risk to the child? The vast majority of procedures are medically indicated and should proceed, because the low, unproven theoretical risk of longer term neurodevelopmental problems from the anesthetic or sedative drugs, is almost always less than the health risk to the patient of postponing the procedure. However, there is considerable discussion whether some procedures, i.e. MRI for developmental delay in a patient with no neurological or syndromic findings, have significant diagnostic yield; this question needs to be carefully studied to determine if some of these procedures are not necessary. At Texas Children's Hospital, this institutional approach has been very well received by parents, who overwhelmingly have appreciated the information and the discussion; few if any procedures have been postponed because of the FDA warning. The education program has been extended to all sedation areas and critical care units.

Many authorities and prominent institutions have questioned the validity of the FDA warning, and have advocated not changing their current approach to parent and provider education concerning anesthetic neurotoxicity. Only if a parent asks about anesthetic neurotoxicity will they have a discussion about the problem. They feel strongly that the evidence behind the FDA warning is lacking for the human data, and that the animal data, as compelling as it might be, is not sufficient for them to change their practice.

The State of Texas has a Medical Disclosure Panel that regulates informed consent language for all medical and surgical procedures, and anesthesia and sedation, that is mandated for the patient or parent to read, understand, and sign before any procedure. Standard risks for all procedures are included, and the panel's standard for inclusion is a risk that a reasonable patient or parent would want to know before consenting to the procedure. In the case of potential anesthetic and sedative neurotoxicity with prolonged or repeated exposure in young children, the panel has decided that this is a risk that a reasonable parent would want to know, and it is being included in the standard consent language.

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Research into so called "non-toxic" anesthetics and sedatives is ongoing, and to date in the dozen or so animal studies of dexmedetomidine, including non-human primates, this drug does not cause neuroapoptosis/neurodegeneration or longer term neurobehavioral adverse effects, except at very high doses much higher than in clinical use. In addition, Dexmedetomidine will ameliorate the neurodegenerative effects, and the longer term neurobehavioral effects caused in the animal models by agents such as isoflurane, ketamine, or propofol. Human pilot studies are being completed with dexmedetomidine as a major component of the anesthetic in young children, and this regimen appears to be feasible and safe. Randomized controlled trials are beginning to get underway to determine if dexmedetomidine would be associated with improved neurobehavioral outcomes. Results of this research will not be available for a number of years.

Conclusions:

Much important human data has been published in the past 2 years, with significant upcoming data expected within the next 2-5 years. The GAS and PANDA studies are reassuring that a single brief anesthetic exposure is not associated lower neurodevelopmental testing scores. However, multiple exposures, or prolonged exposures are associated with higher incidence of learning disability in the recent Mayo Clinic retrospective study. The MASK study has yielded important new information about subtle effects in multiple domains after repeated anesthetis, ; and the TREX study will also add important new data in the coming years. Dexmedetomdine does not cause neurodegeneration in animal studies and has emerged as a leading agent to assess in clinical studies for association with neurodevelopmental outcomes.

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Continuous Peripheral Nerve Blocks, Liposome Bupivacaine, Cryoanalgesia, and (or?) Percutaneous Peripheral Nerve Stimulation in 2018

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Continuous Peripheral Nerve Blocks

Introduction. Continuous peripheral nerve blocks (CPNB) consist of a catheter that is percutaneously inserted adjacent to a peripheral nerve, followed by local anesthetic administration *via* the catheter. Therefore, the terms "perineural local anesthetic infusion" and CPNB are often used synonymously. The maximum duration of a single-injection peripheral nerve block is currently 8-24 hours. Therefore, when a prolonged neural blockade is desired, CPNB provides an option.

Indications. CPNB is used to prolong intraoperative surgical anesthesia; treat intractable hiccups; induce sympathectomy and vasodilation to increase blood flow following a vascular accident, digit transfer/replantation or limb salvage; alleviate the vasospasm of Raynaud's disease; and treat peripheral embolism. CPNB can provide analgesia during transportation following trauma, or waiting for surgical treatment. Reports describe CPNB to treat chronic pain, such as intractable phantom limb pain, pain from terminal cancer and trigeminal neuralgia, and complex regional pain syndrome. However, the most common indication is providing postoperative analgesia (the only indication validated with randomized, controlled clinical trials [RCT]).

Most providers use CPNB exclusively for surgical procedures that are expected to result in pain not easily controlled with less-invasive analgesic techniques because there are intrinsic risks with the techniques,[1] or in patients with an intolerance to alternative analgesics (e.g., opioid-induced nausea). Although recommendations for the use of various catheter locations for specific surgical procedures exist, there is little published data specifically illuminating this issue. In general, axillary, cervical paravertebral (CPVB), infraclavicular, or supraclavicular infusions are used for surgical procedures involving the hand, wrist, forearm, and elbow (infraclavicular the most effective); interscalene catheters are used for surgical procedures involving the shoulder or proximal humerus (interscalene optimal risk-benefit ratio); thoracic paravertebral catheters are used for breast or thorax procedures; psoas compartment catheters are used for hip surgery; fascia iliaca, femoral, and psoas compartment catheters are used for knee or procedures thigh (occasionally hip surgery, although this is somewhat controversial); and popliteal or subgluteal catheters are used for surgical procedures of the leg, ankle, and foot (popliteal optimal risk-benefit ratio). CPNB has been described in hundreds of pediatric patients, although it is not as thoroughly validated as in adults.

Patient Selection. Little published data is available regarding the balancing of potential perineural infusion risks and benefits for patients with significant comorbidities. Investigators often exclude patients with known hepatic or renal insufficiency, in an effort to avoid local anesthetic toxicity. For infusions that may affect the phrenic nerve and ipsilateral diaphragm function (e.g. interscalene or cervical paravertebral catheters), patients with heart or lung disease are often excluded since *continuous* interscalene perineural infusions have been shown to cause frequent ipsilateral diaphragm paralysis. Although the effect on overall pulmonary function may be minimal for relatively healthy patients,[2] practitioners must be aware of the possible related risks and be prepared to manage complications.

Catheter Insertion (Nerve Stimulation). Various catheter insertion techniques have been used, inducing paresthesias, eliciting a facial "click", and fluoroscopic guidance. However, most reports involve electrical stimulation. One common technique involves giving a bolus of local anesthetic *via* an insulated needle to provide a surgical block, followed by the introduction of a "nonstimulating" catheter. Many studies report a high success rate using this procedure,[3-6] but the catheter tip may be unknowingly misplaced during insertion.[7,8] To help counter this risk, the perineural catheter may be first inserted, followed by a local anesthetic bolus *via* the catheter itself.[9-12] Unfortunately, this technique requires waiting at least 15 minutes for block onset/failure, followed by removal of the catheter/dressing, re-preparation, and catheter reinsertion for failed a failed insertion.[13] In addition, a partial block is possible suggesting the catheter tip is not optimally located, but often precluding replacement using electrical current.

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Alternatively, catheters which deliver current to their tips have been developed in an attempt to improve initial placement success rates.[14] These catheters provide feedback on the positional relationship of the catheter tip to the target nerve prior to local anesthetic dosing. There is data to suggest that in the area of the popliteal fossa, using stimulation during catheter advancement results in the catheter tip being placed closer to sciatic nerve.[15-18] The clinical relevance is questionable femoral and interscalene catheters. [19-27] Regrettably, stimulating catheters guarantee neither a complete surgical block nor an effective postoperative infusion.[21,28-30] Furthermore, an acceptable muscle contraction may not always be obtained during catheter insertion;[21,31-34] and, stimulating catheters often require an increased insertion time and cost more than their non-stimulating counterparts,[18] resulting in many questioning their cost-benefit ratio. Finally, the minimal acceptable current resulting in a muscle contraction remains unknown.

Also remaining unknown is the optimal distance to insert the catheter past the needle tip. However, increasing the insertion distance is correlated with an increased the risk of catheter coiling, and perhaps the ultimate distance between the catheter and target nerve.[35] With catheter insertion over 5 cm, numerous catheter knots have been reported;[36] and, a maximum insertion of 5 cm appears warranted. Likewise, remaining unknown is the optimal minimum insertion distance; but, studies suggests that 0-1 cm results in a minimal risk of secondary block failure,[6] but possibly an increased risk of subsequent dislodgement.

Catheter Insertion (Ultrasound). The limited length of this article precludes an in-depth discussion of ultrasound-guided perineural catheter insertion; but, the information is available elsewhere.[37] While ultrasound guidance would intuitively seem to increase the accuracy of catheter tip location, identifying the catheter tip is often challenging. Multiple practitioners observe the location of injected fluid,[38] an agitated fluid/air mixture,[39] or simply air.[40,41] For most anatomic locations, ultrasound-guided insertion decreases insertion time and associated discomfort compared with an electrical technique (and provide at least similar analgesia). [31,32,34,42-45] The majority of reports of combining ultrasound and nerve stimulation suggest little benefit,[39,46-50] Currently, insufficient data are available to determine either the optimal techniques/equipment for these insertion modalities, as well as their associated risks & benefits.[37]

Infusates. The majority of perineural infusion publications have involved bupivacaine or ropivacaine, although levobupivacaine and shorter acting agents have been reported. While the available data suggests bupivacaine and levobupivacaine are more potent than ropivacaine,[51] all three provide similar analgesia within human trials, although the ropivacaine concentration is often increased up to 50% to compensate for decreased potency.[51,52] When a bupivacaine perineural infusion is paused, the motor and sensory effects greatly outlast those of ropivacaine.[52] This is often important when titrating dose to limit undesired CPNB effects. Also unknown is whether the primary determinant of CPNB effects is only local anesthetic dose/mass, or if volume (rate) and/or concentration have an influence.[53-55] Currently, additional research is warranted, and no optimal concentration/rate combination may be recommended for all anatomic locations.[56] For bupivacaine/levobupivacaine and ropivacaine, the most-commonly-cited concentrations are between 0.1-0.125% and 0.1-0.2%, respectively. Unfortunately, no adjuvants—such as clonidine, epinephrine, and opioids—have been found to improve analgesia and/or decrease undesirable CPNB-related side effects; and infusing solely long-acting local anesthetic appears warranted.

Local Anesthetic Delivery Regimens. Currently available data suggest that following procedures producing moderate-to-severe pain, providing patients with the ability to self-administer local anesthetic doses increases perioperative benefits and/or decreases local anesthetic consumption. Unfortunately, insufficient information is available to base recommendations on the optimal basal rate, bolus volume, or lockout period accounting for the many variables that my effect these values (e.g. catheter type, location, surgical procedure). Until recommendations based on prospectively-collected data are published, practitioners should be aware that investigators have reported successful analgesia using the following with ropivacaine (0.2%) or bupivacaine (0.125%): a basal rate of 5 (lower extremity) or 8 (upper extremity) mL/h; a bolus volume of 2 – 5 mL; and a lockout duration of 20 – 60 min. Additionally, the maximum safe dose remains unknown. However, multiple investigations involving patients free of renal or hepatic disease have reported blood concentrations within acceptable limits—and an absence of toxicity symptoms/signs—following multiple weeks of perineural infusion with similar dosing schedules.[57,58]

Infusion Pumps. There is no single optimal infusion pump for every clinical scenario; and, therefore, pump preference is usually dictated by desired device characteristics.[59] Although elastomeric infusion pumps cannot match

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their electronic counterparts in delivering a basal infusion rate within ±5% expected for the entire infusion duration, whether the increased variability is clinical significant—or in which clinical situations it is relevant—remains unknown.[59] Providing an adjustable basal infusion rate permits titration of local anesthetic dose for inadequate analgesia, an insensate extremity, undesired side effects (e.g., muscle weakness),[60] or maximizing infusion duration (e.g., ambulatory patients with a set reservoir volume). Furthermore, multiple clinical benefits are provided with a patient-controlled bolus option, such as increasing analgesia and decreasing opioid consumption. Electronic pumps provide an adjustable basal rate, patient-controlled bolus doses, and a variable bolus lock-out period.[59] And, while most elastomeric devices include a fixed basal infusion rate, a few provide similar flexibility to electronic pumps.

Elastomeric pumps are often preferred for their smaller size and lighter weight; lack of audible alarms; disposability; and silent operation (electronic pumps may disturb patient sleep). In addition, elastomeric devices with no bolus dose capability and a manufacturer-fixed basal rate are usually less costly. However, inexpensive disposable "cassettes" provide sterile infusion for individual patients utilizing reusable electronic pumps. A few disposable electronic pumps are available. At least within the United States, the infusion pump/reservoir must now be filled under a laminar flow workbench.[61] Of note, at least within the United States, there are no national guidelines regarding the maximum safe CPNB duration.[61]

Ambulatory Perineural Infusion. While length limitations of this article preclude an extensive discussion of ambulatory CPNB, this information is available elsewhere.[59] Ambulatory perineural infusion may be provided to outpatients using a portable pump. Perineural infusion is often provided for ambulatory surgery without an overnight hospital stay;[59] but may also shorten hospitalization duration,[62,63] and/or bestow benefits following discharge to either a rehabilitation facility or home.[6,58] Ultrasound guidance—with its demonstrated decreased insertion time—is often beneficial in high-turnover ambulatory centers where time constraints are often severe.[31,34,45,64] Patient selection criteria are often more stringent for ambulatory CPNB since outpatients are rarely directly monitored; and not all patients desire or are capable of accepting the additional responsibility of caring for the catheter and pump system. Patients with hepatic or renal insufficiency are often excluded from ambulatory CPNB to decrease the risk of local anesthetic toxicity. Caution is warranted during interscalene and cervical paravertebral infusion (frequently induce diaphragm weakness) for obese individuals and those with heart/lung disease who may not be able to compensate for mild hypoxia and/or hypercarbia.

Ambulatory perineural infusion may reduced time until discharge *readiness*;[6,29,62,65] and, in select cases, *actual* discharge.[62,63] Early discharge after total knee arthroplasty may decrease hospitalization-related costs.[66] However, caution is warranted prior to allowing discharge with a continuous posterior lumbar plexus and femoral nerve block given that these catheters are associated with an increased risk of falling.[67] Nonetheless, relatively small published series document the feasibility of total joint arthroplasty with only a single-night hospital stay—or even on an outpatient basis—when patients are provided CPNB at home.[68-72]

Benefits. The most-common indication for CPNB is to provide postoperative pain control, and it appears that most CPNB benefits are dependent upon successfully improving analgesia.[56] RCT-documented benefits include decreased postoperative pain, supplemental analgesic requirements, opioid-related side effects, sleep disturbances, dissatisfaction, discharge readiness, actual discharge, and inflammatory markers. In addition, an accelerated resumption of passive joint range-of-motion is documented following total knee arthroplasty procedures with 48-72 hours of continuous femoral perineural infusion. Analgesia is most impressive when the perineural infusion effects the entire innervation of the surgical site; as is often the case for shoulder and foot procedures (interscalene and sciatic perineural catheters, respectively).[4,7,62] Unfortunately, even though brachial plexus infusions (theoretically) cover the entire surgical site for procedures at or distal to the elbow, they provide less impressive analgesia.[73]. Severely lacking are RCT-documented benefits of continuous axillary,[74] supraclavicular,[75] and transversus abdominus plane blocks.[56] And, while the benefits of infraclavicular infusion are validated,[73] analgesia is often less-than-optimal unless a high enough dose of local anesthetic is administered, frequently rendering the extremity insensate. Similarly, for surgical sites innervated by multiple nerves (such as the knee, hip and ankle), a single perineural usually provide less-than-optimal analgesia without the concurrent use of additional analgesics.[6,29,55] While a lumbar epidural provides roughly equivalent analgesia to femoral perineural infusion for hip and knee arthroplasty, CPNB results in a more-favorable side-effect profile without the risk of epidural hematoma during concomitant anticoagulant administration.[76-78]

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While the evidence for CPNB benefits *during* the infusion is vast,[56] there are few studies documenting benefits *following* catheter removal. Exceptions include increased health-related quality-of-life in one study[79] (but not five others);[80-84] improved analgesia after a few days[5,85,86] or six months;[87] faster tolerance of passive knee flexion resulting in earlier discharge from rehabilitation centers;[77,78,85] and more-rapid resumption of lavatory use and unassisted standing.[85] Noticeably absent is evidence of medium- or long-term improvements in measures of health-related quality-of-life.[80-84,88] See below for additional information.

Complications. Relatively minor CPNB-related complications occur at a frequency similar to single-injection peripheral nerve blocks.[89] In contrast, severe and permanent infusion-related injuries are uncommon. Unfortunately, generalizations are difficult given the multiple anatomic locations for perineural infusion as well as diverse equipment and techniques. For example, the incidence of secondary block (infusion) failure reported by three different trials includes 1%,[90] 20%,[7] and 50%.[9] Catheter insertion-related complications include inaccurate catheter tip placement; and—in extremely rare cases—intraneural, intrathecal, epidural, intravascular, and even interpleural catheter insertion. Complications during the perineural infusion include catheter obstruction or dislodgement; catheter site fluid leakage; infusion pump disconnection, malfunction, or undesired pause; allergic reaction or simply skin irritation to the catheter dressing and/or liquid adhesive; and, catheter-induced brachial plexus irritation. One of the most common complications is an insensate extremity that may be unnerving to patients, hinders rehabilitation, and often believed to be a risk factor for injury.[54,55] In such cases, pause the infusion until sensory perception returns, and then restarted the infusion at a lower basal rate. Conversely, breakthrough pain or persistent inadequate analgesia may be treated with patient-controlled bolus doses and increasing the basal infusion, respectively.

More serious—and remarkably uncommon—complications include systemic local anesthetic toxicity; myonecrosis with repeated large boluses of bupivacaine; retroperitoneal and peri-catheter hematoma formation; catheter knotting, retention, shearing, or breakage; a prolonged Horner's syndrome; and lower lobe collapse during infusions affecting the phrenic nerve. In patients with preexisting neuropathy and/or diabetes, limited evidence suggests that prolonged local anesthetic exposure may increase the risk of nerve injury. Infusions affecting the femoral nerve is associated with an increased risk of falling following knee and hip arthroplasty.[67] Catheter site infection and abscess are rare (infection incidence 0-3%;[91,92] but most reports <1%),[11,89,93] although inflammation (3-4%)[1,90,94] and bacterial colonization (6%-57%) are more common. Risk factors include the absence of perioperative antibiotic prophylaxis, male sex, axillary/femoral catheter insertion, and presence in an intensive care unit.[1] The infection risk is also correlated with infusion duration;[1] but, nevertheless, a minimal incidence of infection has been reported for CPNB during inter-continental transportation for up to 34 days[95] and provided at home for up to 83 days.[58]

Because all surgical procedures are associated with a variable incidence of nerve injury—regardless of the application of a regional anesthetic/analgesic—it is often problematic to determine what percentage (if any) of a new-onset neurologic deficit is attributable to CPNB. Keeping this limitation in mind, the incidence of *transient* adverse neurologic symptoms *associated* with CPNB is 0-1.4% for interscalene,[1,11,89,90] 0.4-0.5% for femoral,[1,96] and 0-1.0% for sciatic catheters.[1,90,96,97] Another study reported a 0.2% incidence of neurologic deficits lasting longer than 6 weeks in nearly 3,500 catheters from multiple anatomic locations.[90] In this latter study, it remains unknown if the deficits resolved after the 6-week study period; but multiple prospective investigations report that the overwhelming majority of neurologic symptoms present at 4-6 weeks resolve spontaneously within three months of surgery.[1,11,89] *Long-term* and/or *permanent* nerve injury has occurred.[98] Five large,[1,11,89,96,97] prospective series that followed patients for at least three months reported 3 cases of unresolved adverse neurologic events.[89,96,97] These investigations combined (4,148 total subjects) suggests the risk of neurologic injury lasting longer than nine months *associated* with CPNB is 0.07% (all of the risk may not be conclusively attributed to the perineural infusion).[1,11,89,96,97] While ultrasound-guidance may decrease the incidence of many/most of these reported complications,[99] to date there are few data supporting this proposition;[100,101] and case reports suggest that completely abolishing such events is unlikely.[102-104]

There has been a significant amount of data published in the last few years involving neurologic risk in the presence of a CPNB.[105] In most cases of postoperative neurologic symptoms, it is problematic assigning causality to the surgical procedure, CPNB, or simply general anesthetic (e.g., positioning injuries on an unrelated part of the body). Interpreting the available data is further complicated due to a lack of controls and/or randomization, which lead to

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multiple types of bias. An excellent example is a prospective, uncontrolled cohort study of patients with continuous popliteal-sciatic nerve blocks (n=151) following foot and ankle surgery reporting an alarming 41% incidence of postoperative neurologic symptoms (PONS) within 2 weeks, 24% at 34 weeks, and 4% following 48 weeks.[106] A similar retrospective study (n=157) found a 1.9% incidence of unresolved PONS at 11 months.[107] These risks are an order of magnitude higher than previous estimates for popliteal infusions (0-0.4%),[108,109] and are most-likely due to numerous biases, beginning with selection bias.

Another relatively new retrospective investigation of 1,182 continuous interscalene and femoral nerve blocks identified 4 (0.3%) patients with PONS at any time point, with one of these cases resolving by 6 months.[110] Of note, these investigators reported an increased incidence of PONS lasting more than 6 months among patients with continuous versus single-injection peripheral nerve blocks (0.24% vs. 0.07%, P=0.08).[110] It is important to be aware of the very high risk of selection bias from this retrospective, nonrandomized cohort (e.g., larger surgical procedures—with inherently higher neurologic risk—more represented in the catheter group). The most reliable, recently-published data is derived from two *prospective* investigations of over 2500 interscalene and femoral catheters, reporting a PONS incidence of 4.9-5.3% resolving by 6 months, with all but 0.3-0.7% of these resolving by 11 months.[111,112] To emphasize, it is critical that practitioners are cognizant of the fact that these values approximate association and not necessarily causation: an unknown percentage of subjects with PONS would have experienced them without any regional analgesic due to the surgery or other factors. Unfortunately, the available data does not suggests that ultrasound guidance has a "meaningful impact on the incidence of PONS," so switching from a different insertion technique is not expected to decrease the rate of PONS.[113]

The risk of falling following knee and hip arthroplasty have become better appreciated within the previous decade.[114,115] Single-injection femoral nerve blocks do not appear to increase this risk;[116] but data from randomized, controlled trials suggest that a continuous femoral or psoas compartment block is associated with a 4-5 time increased risk of falling,[117-119] although some investigators have questioned this correlation.[120,121] Regardless of the relationship between CPNB and falls, this complication continues to occur even with the implementation of specific, intensive fall-prevention programs.[122-125] While replacing continuous femoral nerve blocks with adductor canal infusions have been proposed as a method to decrease the risk of falling due to decreases induced quadriceps weakness,[126,127] such an association has yet to be demonstrated.[127,128]

Benefits. Novel indications for CPNB have been published within the past few years, suggesting benefits for an even wider array of morbidities.[129-150] New RCTs have provided evidence that adding a perineural infusion following a single-injection peripheral nerve block improves postoperative analgesia (and in most cases decreases supplemental analgesic requirements) using interscalene,[151-153] paravertebral,[154] adductor canal,[143-148] femoral,[155-158] and sciatic catheters (Table 3).[159-162] Compared with epidural infusions,[163] CPNB provides similar analgesia[164] but improves hemodynamic stability (presumably by inducing less sympathectomy),[165-167] and following knee arthroplasty shortens the time to achieve flexion goals, improves analgesia, and lowers supplemental analgesic requirements.[157] Compared with intrathecal morphine, continuous posterior lumbar plexus blocks provide similar analgesia with lower supplemental opioid requirements and incidence of pruritis.[168] And, data continues to accumulate demonstrating that CPNB provides superior analgesia compared with continuous wound infusions.[169,170]

Due to the association between continuous femoral nerve blocks and falling after knee arthroplasty,[117,118,125] the last 10 years have seen a plethora of research validating adductor canal catheter effectiveness following major knee surgery,[143-148] based on the theory that any risk of falling will be decreased due to less induced quadriceps weakness compared with femoral infusion (Table 3).[126,127] Of the 6 RCTs directly comparing continuous adductor canal and femoral nerve blocks,[126,127,171-174] 3 demonstrated dramatic improvements for subjects with adductor catheters in the ability to stand, sit, ambulate, and climb stairs.[126,171-173] One study did not investigate ambulation;[174] but, the 2 remaining RCTs failed to detect mobilization improvements using an adductor infusion—although they did document and quantify improved quadriceps femoris strength (52% vs. 18% of baseline in one).[126,127] It is noteworthy that these two latter studies provided solely a fixed basal infusion (8 mL/h) without either patient-controlled or repeated provider-administered bolus doses,[126,127] which may have decreased adductor infusion effectiveness. In addition, two of the RCTs detected improved analgesia for subjects with femoral infusions at either rest (unicompartment arthroplasty)[173] or with movement (tricompartment arthroplasty),[172] while the others failed to detect differences between the two catheter locations. Lastly, one of the investigations reported a decreased time

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until discharge favoring the adductor catheters (3.1 vs. 3.9 days),[171] although there were issues raised regarding its protocol/findings[175-177] and a similar RCT detected no decrease in time until discharge readiness or actual discharge,[172] albeit with slightly different criteria. What does appear likely is that continuous adductor canal blocks are associated with greater mobilization ability while providing at least similar analgesia compared with their femoral counterparts.[178] What remains unclear is the ideal catheter insertion location/protocol,[179,180] optimal method of local anesthetic delivery (e.g., basal infusion vs. repeated bolus doses, basal rate, bolus volume, etc.) and if an optimized delivery regimen can shorten hospitalization duration.[181-183]

In an effort to further improve analgesia following total knee arthroplasty,[184,185] three recent RCTs have investigated the effects of adding a continuous sciatic nerve block to a continuous femoral or posterior lumbar plexus (psoas compartment) block.[160-162] All demonstrated lower pain scores and decreased supplemental analgesic consumption,[160-162] and one detected a lower incidence of nausea and vomiting as well as improved knee flexion and ambulation.[161] As has been previously opined, there are potential drawbacks to providing a continuous sciatic nerve block such as the extra time required to place a second catheter, an inability to fully evaluate sciatic nerve function postoperatively,[186] and interference with physical therapy goals (e.g., foot drop, leg weakness).[187]

While there are relatively few demonstrated benefits of CPNB following catheter removal,[188] there are significant additions to our knowledge base within recently-published data. Two RCTs found that a 2-3 day postoperative continuous interscalene or femoral nerve block resulted in less pain,[152,189] opioid requirements,[152,189] and sleep disturbances[152] on postoperative day 7 compared with a control group following shoulder and knee procedures, respectively. Similarly, two RCTs add to the previous evidence that a continuous femoral nerve block following total knee arthroplasty improves joint flexion for up to 6 months.[157,189]

However, it is the possibility of decreasing persistent post-surgical pain that has perhaps garnered the most attention and optimism.[190,191] Four new RCTs add data to the single previous positive study that involved the addition of a femoral catheter to a popliteal infusion for major ankle surgery.[192] One study reported that providing a continuous femoral nerve block following total knee arthroplasty reduced chronic pain at 3 and 6 months;[189] and, another involving the same surgical procedure found that providing a continuous sciatic nerve block in addition to a femoral infusion resulted in a reduction of dynamic pain at 3 months (no difference at 12 months for either trial).[193] Finally, two RCTs investigating continuous paravertebral blocks following mastectomy detected improvements in analgesia up to a full year following surgery,[194,195] including superior physical and mental health-related quality-of-life[194] and decreased pain-related physical and emotional dysfunction.[195]

Liposome Bupivacaine

Liposomes consist of two hydrophobic tails and a hydrophilic head,[196] and can form vesicles to act as a medication "depot" (Figure 1).[197,198] Following administration, the liposomes gradually break down, resulting in an extended release of medication.[199,200] Combining liposomes and a local anesthetic (lidocaine) was first proposed in 1979,[201] initially used in humans in 1988,[202] and first reported for postoperative analgesia in 1994.[201,203] Although multiple subsequent reports were published,[204-212] a liposome local anesthetic was not approved by the United States FDA until 2011 (Exparel liposome bupivacaine, Pacira Pharmaceuticals, Parsippany, New Jersey) for administration at the surgical site to provide postoperative analgesia in adults.[198]

Two multicenter RCTs demonstrated superior postoperative analgesia of this approved medication compared with placebo wound infiltration following hemorrhoidectomy[213] and bunionectomy.[214] In contrast, when compared with bupivacaine HCl ("standard" bupivacaine), 10 of 12 published RCTs were negative for their primary (and most secondary) analgesic end points.[215-221] Of the two positive RCTs versus bupivacaine HCl, one involved hemorrhoidectomy,[222] although another similar trial had negative results.[215] The second positive RCT involved submuscular augmentation mammoplasty in which mean pain scores were reduced by less than 1 on the 0-10 numeric rating scale and the investigators concluded, "…it is our assertion that the additional cost of liposomal bupivacaine is unjustified for this particular use."[223] Some of these 14 RCTs were dose-response studies, not powered to be a conclusive test of efficacy; and, when combined with the placebo-controlled trials, there were some detected positive associations for secondary end points such as pain scores at individual time points,[224] opioid use (although differences were minimal),[224] and duration until first use of opioid analgesics.[215,224] However, considering

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the new medication costs an estimated 100 times that of bupivacaine HCl, it is incumbent upon those proposing the conversion to produce data conclusively demonstrating superiority.[221]

There are no RCTs directly comparing CPNB with liposome bupivacaine wound infiltration.[225] The only direct comparison to a single-injection femoral nerve block following total knee arthroplasty suggests that liposome bupivacaine infiltration provides inferior analgesia during the duration of the peripheral nerve block without subsequent differences between the two treatments.[226] Considering there are now four negative published RCTs comparing liposome bupivacaine with bupivacaine HCl following total knee arthroplasty,[215,217-219] and the literature is replete with positive studies involving CPNB,[188] the evidence certainly does not suggest even equivalence between these two modalities.

In contrast to wound infiltration, recently-published data from one RCT strongly suggests that liposome bupivacaine within a single-injection subcostal TAP block provides statistically and clinically superior analgesia to bupivacaine HCl up to 3 days following robotic assisted hysterectomy.[227] In a separate RCT, few differences were detected between a continuous subcostal TAP block and epidural infusion following open renal or hepatobiliary surgery,[142] although this investigation was designed as a superiority study and the negative findings should be viewed as inconclusive and not equivalence. Therefore, a randomized comparison of a TAP with liposome bupivacaine bolus compared with either a epidural infusion or perineural local anesthetic TAP infusion appears warranted.[228,229] Of note, the United States FDA recently revised the label for the single approved liposome bupivacaine formulation explicitly including, "infiltration into the transversus abdominis plane (TAP) which is a field block technique [is] covered by the approved indication for EXPAREL."

Although no liposome local anesthetic is currently approved for use within the epidural space[230] or peripheral nerve blocks, a great deal of related research has been completed (if not all published).[198] Both preclinical toxicology and clinical data indicate that liposome bupivacaine has at least as favorable safety profile as bupivacaine HCl.[231-241] Though phase 1-3 clinical trials involving the use of liposome bupivacaine have been reported for intercostal and ankle blocks,[197,198,231] the most published data may be found for femoral nerve blocks.[242,243] Liposome bupivacaine in a femoral nerve block produced over 72 hours of analgesia with an incomplete motor block in healthy volunteers,[242] and demonstrated analgesic activity for up to 72 hours versus placebo in subjects following total knee arthroplasty (albeit extraordinarily minimal analgesic differences following 24 hours).[243] It is emphasized that at the time of this writing, there are no liposome bupivacaine local anesthetics approved for use in the epidural space[230] or peripheral nerve blocks (other than TAP and interscalene blocks).

Cryoneurolysis (Cryoanalgesia)

Cryoneurolysis is the application of exceptionally low temperatures to reversibly ablate peripheral nerves, resulting in temporary analgesia termed "cryoanalgesia".[244] The first cryosurgical apparatus was described in 1961,[245] and modern cryo probes transmit a gas (usually nitrous oxide or carbon dioxide) at high pressure down their length, through a minute opening, and into the sealed distal tip at a lower pressure (Figure 2a).[246] Due to the Joule-Thompson effect, a large drop in temperature occurs when the gas moves from a high to low pressure inducing brisk expansion and absorption of heat.[247] The gas is returned out of the body through a larger-diameter (low pressure) cylinder in the middle of the shaft. This closed circuit ensures that all gas exits the body. The intense cold temperature at the probe tip produces Wallerian degeneration—a reversible breakdown of the nerve axon—subsequently inhibiting transmission of afferent and efferent signals. However, because the temperature resulting in irreversible degeneration—about -100°C—is colder than the boiling point of the gas (carbon dioxide: -79°C; nitrous oxide: -88°C), the remaining endoneurium, perineurium, and epineurium remain intact and the axon regenerates at a rate of approximately 1-2 mm/day.[246]

Cryoneurolysis has been used *via* the surgical incision to treat acute pain following thoracotomy,[248-264] tonsillectomy,[265] and herniorrhaphy.[266,267] Alternatively, ultrasound may be used to guide[268,269] a percutaneously-inserted probe to a peripheral nerve to provide analgesia, and has been described for various chronic pain conditions.[270-275] The combination of ultrasound and newly-designed, FDA-approved hand-held cryoneurolysis devices[276,277] may now make percutaneous cryoanalgesia a valuable postoperative analgesic alternative to CPNB (Figure 2b).[244] The largest limiting factors when applying this technique to acute pain states are (1) the inhibition of efferent signals effectively paralyzing innervated muscles; and, (2) the relatively unpredictable duration of action

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measured in multiple weeks, and often months. Therefore, the modality has historically been used to target sensory-only nerves,[278] although mixed motor-sensory nerves have been cryoablated to treat spasticity[279] and preclinical studies found no lasting changes to the structure or function of motor nerves following remyelination.[276,277]

Surgical procedures possibly amenable to cryoneurolysis include iliac crest bone harvesting (superficial superior cluneal nerves), total knee arthroplasty (anterior femoral cutaneous and infrapatellar saphenous nerves), various thumb surgeries (superficial branch of the radial nerve), rotator cuff repair (suprascapular nerve), and digit/limb amputations, among others.[244,246] Although there are available cryoneurolysis devices currently approved by the United States FDA for relief of pain, the use of cryoanalgesia to treat acute pain requires a great deal of further investigation with both RCTs and large series. It remains undetermined whether the duration of denervation can be shortened (e.g. decreasing the freezing interval or number of cycles); and, the incidence of adverse events such as neuralgias following thoracotomy.[262-264] Direct comparisons with CPNB are unavailable, but some theoretical benefits of cryoneurolysis include an ultra-long duration of action, no catheter management/removal, the lack of an infusion pump and anesthetic reservoir to carry, a lower risk of infection, and no risk of local anesthetic toxicity, catheter dislodgement or leakage.

Percutaneous Peripheral Nerve Stimulation

Electric current applied in both the central and peripheral nervous systems induces analgesia. There are numerous theories regarding the mechanism of action,[280] but most are usually based on Melzack and Wall's "gate control theory":[281] current activates large-diameter myelinated afferent peripheral nerves which then—within the spinal cord— impede pain signal transmission from small-diameter pain fibers to the central nervous system.[282,283] Implanted spinal cord and peripheral nerve stimulators have since been used to treat multiple chronic pain states.[284-288] In contrast, the use of peripheral nerve stimulation to treat acute/postoperative pain is extraordinarily rare,[289-291] in no small part due to cutaneous pain fiber activation with transcutaneous electrical nerve stimulation[282] and the invasive requirement of surgically implanting/removing peripheral nerve electrodes/leads.[292,293]

Electrical leads are now available with a diameter small enough to allow passage through a needle, allowing percutaneous insertion (Figure 3a).[294-296] Perineural placement is possible using ultrasound guidance,[297,298] and has been reported to treat chronic pain.[299-302] More recently, postoperative pain was treated using ultrasound-guided percutaneous peripheral nerve stimulation.[303] Femoral—and in 2 cases sciatic—leads were inserted in subjects (n=5) 8-58 days following total knee arthroplasty.[303] Percutaneous peripheral nerve stimulation decreased pain an average of 93% at rest (reduced from a mean of 5.0 to 0.2 on a 0-10 numeric rating scale), with 4 of 5 subjects experiencing complete resolution of pain. During passive and active knee motion pain decreased an average of 27% and 30%, respectively. Neither maximum passive nor active knee range-of-motion was consistently affected in this small cohort of subjects.

There are no direct comparisons with CPNB, but theoretical benefits of percutaneous peripheral nerve stimulation are numerous.[303] Leads function optimally when inserted 0.5-3.0 cm from a target peripheral nerve, negating the importance of location within a particular facial plane. Electrical generators are now so minute that their footprint is smaller than a business card and may be literally adhered to a patient's limb—so, there is no large portable infusion pump or local anesthetic reservoir to carry (Figure 3b). Helically coiled leads are designed to minimize the risks of migration and fracture, and decrease the infection risk to approximately 0.05 per 1000 indwelling days.[303] These characteristics permit a dramatically-long duration of lead retention—well-over a year in some cases[304-306]—raising the possibility of preoperative insertion and continued postoperative stimulation for the entire interval of surgically-related pain.[304-308] There are theoretically no induced sensory, proprioception, or motor deficits, enabling full engagement in physical therapy and likely lacking any association with an increased falling risk. Obviously, there is no risk of local anesthetic toxicity or leakage. Conversely, practical implementation of percutaneous peripheral nerve stimulation to treat acute pain states is dependent upon multiple factors that are currently undetermined: the time required for lead insertion, the cost of leads and electrical generators, the maximum provided analgesia, and the future availability of a United States FDA-approved lead and generator.[309]

References: ***https://drive.google.com/file/d/15z9Nny3Ncmxk51k2A3Uv7BW-MOID-3VH/view?ts=5ae7fe70***

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The Aging Anesthesiologist

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Life is a sexually transmitted, dangerously unstable, invariably fatal condition. N. Gayman

The learning objectives of this lecture are to:
1) Recognize some of the important physiologic changes commonly associated with normal aging.
2) Discuss how the aging process might impact the practice of late- career anesthesiologists.
3) Understand the pros and cons of mandatory cognitive and competency screening for late- career anesthesiologists.
4) Discuss considerations that are important in decisions regarding retirement from clinical practice.
5) Examine the impact of the aging population of anesthesiologists on the overall anesthesiology workforce.

INTRODUCTION: We are all getting older. In 1990, some 31 million Americans, fewer than 13% of the population, were older than 65 years of age. [a] By the year 2020 it is projected that there will be 50 million Americans older than age 65 years – more than 16% of the total population.[b] And by 2035, more Americans will be older than 65 years than will be younger than 18 years. The fastest growing segment of the American population is among those age 65 years or older.[c]

The population of American physicians is aging in a parallel fashion. In 2010, the average age of physicians in the U.S was 50.7 years. [1] By 2016, the average age was 51.3 years. Those 60 years of age or older grew to 29% of the actively licensed physician population in 2016, up from 25% in 2010.

And not to be left behind, the age of practicing anesthesiologists also continues to increase. In 1990, the largest age group of active members of the American Society of Anesthesiologists (ASA) was the 35 to 44-years of age group. [d] This age group accounted for close to 33% of the overall membership As of 2017, the 55 to 64 age group had become most numerous. The average age of ASA members is currently 50 years of age, up from 47 years in 2008. [d] 37 % of current ASA members are age 55 years or older. Anesthesiologists older than 65 years now account for 8% of those active.

Aging has implications for the nature of each individual anesthesiologist's practice and the overall anesthesiology workforce. In the following discussion, we will consider some of the common physiological changes associated with aging and how they might affect the practicing anesthesiologist, his or her colleagues, and their patients.

THEORIES OF AGING: All living creatures, including anesthesiologists, age. On a cellular level, aging involves a wide variety of sequential changes that result in degradation of the efficient functioning of many vital biologic processes. Increased vulnerability to injury and illness ensues. The end stage of these changes is death.

Human aging involves parallel changes that occur in the physical, psychological, spiritual, and social domains. Some of these changes provide an advantage to the aging individual, such as enhanced wisdom and broadened experience, while others impose a handicap, such as decreased intellectual processing speed and impairment in various aspects of cognition.

There are several different models for aging. Most commonly referenced is "chronological aging", which refers to the elapsed time since an individual's birth. However, "biological aging"—an individual's physical and psychological state as he/ she ages—is more relevant to our discussion of the professional life of an anesthesiologist.

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[a] The World Bank: Population Ages 65 and Above. Available at: http://data.worldbank.org/indicator/SP.POP.65UP.TO.ZS?locations=US&name_desc=false. Accessed 5/14/2018
[b] United States Department of Commerce. U.S. Census Bureau. Available at : https://www.census.gov/library/visualizations/2018/comm/historic-first.html. Accessed 5/14/2018
[c] United States Department of Commerce. U.S. Census Bureau. Available at: https://www.census.gov/newsroom/releases/archives/2010_census/cb11-cn192.html. Accessed 5/14/2018
[d] American Society of Anesthesiologists - personal communication

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There are a variety of theories as to the exact causes and mechanisms of aging. As a generalization, the theories all fall into two overlapping categories. The *programmed theories* hold that aging follows a biological timetable that is the continuation of the processes that regulate childhood growth and development. The timetable is driven by the automatic sequential switching on and off of certain genes. One currently popular model suggests that telomeres, the DNA caps on the ends of chromosomes, play a pivotal role by regulating and ultimately impeding cell division. The *damage* or *error theories* emphasize environmental assaults that cause wear and tear with resultant cellular damage.

Whatever the underlying process, aging progresses through all stages of life. It is characterized by degenerative changes in the structure and functional reserve of cells and tissues. The accumulation of these changes over time results in the characteristic phenotype of aging. The final stage of the process is death of the organism.

PHYSICAL CHANGES ASSOCIATED WITH AGING: The accumulation over time of the cellular changes described above results in the characteristic aging phenotype.

Aging is not a homogenous process. There are large differences within and between species in how aging progresses. Even within any one individual, different organ systems age at different rates and in dissimilar manners. One common finding among all aging systems is a decrease in physiologic reserve. Aging organ systems must work at maximum capacity in order to maintain homeostasis. They are limited in the capacity to recruit additional resources when confronted with a stressful challenge, such as infection. This state, called "homeostenosis", leads to increased vulnerability to disease. Aging is among the greatest risk factors for developing life ending disease.

Several age related physiologic changes which ultimately appear in all individuals at varying times and in various degrees of intensity carry the potential of directly impacting an anesthesiologist's practice:

1) There is a generalized decrease in muscle mass with accompanying loss of strength, fine motor skills and stamina. Older workers are particularly vulnerable to fatigue and have a decreased tolerance to shift work cycles and a greater tendency to late night errors. [2] It is not surprising that extended work hours and night call are among the most stressful aspects of anesthetic practice for older anesthesiologists and the most important reasons for retirement. [3]

2) Presbycusis, (hearing loss in the high frequency range) begins in early adulthood and progressively causes deterioration of hearing. Anesthesiologists have been shown to be particularly vulnerable to age related hearing loss, especially in the higher ranges where many of the alerts and alarms of anesthetic equipment occur. [4] Many of the common anesthesia alarms are below the threshold of detectability in 39% of anesthesiologists age 65 years and older. [4] The problem is exacerbated by the high ambient noise commonly experienced in operating rooms that can exceed that found in the hospital's cafeteria or boiler room. [5]

3) Visual impairments resulting from cataracts and other age related ailments can contribute to a reduction of visual acuity. This can be especially problematic when an older physician is attempting to complete visually complex clinical tasks.

4) There is an accelerated death of neurons, as well as a decrease in the size of neurons and the number of connections between them. This results in a measurable decrease in brain weight and volume as individuals age. The loss of gray matter is typically greatest in the frontal and temporal lobes. There are also significant changes in the volume and structure of white matter. Also observed are reductions in the total length of the brain's myelinated axons. These organic losses may be countered by other changes such as the development of redundant neural pathways and synaptic plasticity. Neurotransmitters and receptors also change with age- with some decreasing and others increasing.

COGNITIVE CHANGES ASSOCIATED WITH AGING: Cognitive changes frequently associated with aging carry the potential of impacting the practicing anesthesiologist. These can manifest as disturbances involving both crystalized (skills that accumulate over a lifetime of experience, such as language and general knowledge) and fluid intelligence (the ability of an individual to reason and problem solve when encountering a unique situation). Typically, crystalized intelligence tends to be preserved even in the later years of life while fluid intelligence begins to decline after the third decade of life. For many aging individuals, loss of explicit memory (recollection of specific facts and events) is the most obvious and troubling of the losses in fluid intelligence.

Processing speed, which is the speed at which cognitive activities are translated into motor responses, also begins to decline during the third decade of life and progresses throughout the remaining lifetime. The slowing of processing speed can adversely affect performance of other neuropsychological tasks. Attention deficits, involving

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selective or divided attention tasks, tend to increase as individuals age. This can be particularly troubling in a noisy, dynamic, emotionally charged environment such as an operating room.

Other commonly observed cognitive changes that are particularly significant to anesthetic practice include: difficulties with learning; deterioration in creative thinking and problem solving abilities; slowing of on the spot reasoning, intellectual quickness and reaction time; decreased ability to form quick and effective decisions; and reduced performance on stressful and complex tasks.

In addition to normal cognitive changes, older individuals are more vulnerable to the many diseases that are associated with a heightened risk for dementia, such as diabetes, stroke, and cardiovascular disease. As many as 20% of those over age 75, and 50% of those older than 85, have some degree of dementia. [6] In many cases, memory and language dysfunction are among the most prominent features.

It is important to note that many important characteristics of an individual's psychology and intellect are frequently spared during normal aging. For example, optimism, resilience, compassion, judgment, and wisdom all are frequently preserved and even enhanced with age. These preserved attributes serve to augment retained clinical experience and skills and permit many anesthesiologists to continue to conduct a safe and successful practice.

HOW NORMAL AGING MIGHT IMPACT THE PRACTICE OF ANESTHESIOLOGY: Each of the age-associated changes described above has the potential to impact the practice of anesthesiology [7] For example, decreased visual acuity can make it more difficult to read drug labels or monitor displays in the varying light conditions found in operating rooms. Musculoskeletal disease can hinder an older anesthesiologist's ability to attend to an off- site emergency. Hearing loss can interfere with the aging anesthesiologist's ability to hear vital conversations and alarms amid the cacophony commonly occurring in a modern operating room.

Cognitive impairment poses the most threatening challenge to safe anesthetic practice and has received the most attention. The correlation between normal cognitive aging and an enhanced risk of motor vehicle accidents provides some insight into the manner in which cognitive impairment might adversely affect safe anesthetic practice. [8] Several studies have demonstrated an age-dependent decline in the knowledge base and performance on certification examinations among older physicians. [9] However, there is considerable variability, such that although older physicians tend to perform less well **on average,** many individuals score at the same or at a higher level than their younger colleagues. As observed by Eva, "one of the more robust findings in ageing research is that the variability across the scores individuals receive tends to increase with age." [9]

The literature on the relationship between physicians' age and clinical outcomes is inconsistent and inconclusive. Several reports have identified increased complication rates in certain high risk procedures performed by older surgeons. For example, a study of carotid endarterectomy found that mortality increased as a function of surgeons' age. [10] A different study that examined outcomes of inguinal hernia surgery found that the risk of recurrence after laparoscopic repair was 1.72 times higher for older surgeons older than for their younger colleagues. [11] The authors of this study suggested that the cognitive changes associated with aging rendered the older surgeons less able to learn and perform complex new procedures -in this case laparoscopic surgery. And in a meta-analysis of physicians' performance on a variety of quality measurements, 73% of the studies demonstrated a negative association between age and length of time in practice and evidence of good performance. [12] Most of the studies reviewed in this report demonstrated a global decline in all of the measures studied. Participation in traditional continuing medical education activities and recertification did not affect the findings in this meta- analysis.

However, not all studies have identified physicians' age as an independent risk factor for unfavorable procedural outcomes. Experience can play a salutary role in overcoming some of the deficiencies that might occur due to a decreased fund of current scientific knowledge. A study of operative mortality in a select group of high risk procedures reported that surgeons' age was not an important predictor of adverse outcomes in 5 of the 8 procedures studied. [13] Even in those procedures where older surgeons did have a higher mortality rate, the effect of age was largely restricted to surgeons with low procedure volumes.

Comparable data are sparse for anesthesiologists. In one study that employed a simulator to test the ability of an operator to insert an emergency percutaneous cricothyroidotomy, age and years from residency were predictors of poor performance as measured by procedural time, checklist scores, and global rating scores. [14] Another simulator based study that examined how successfully a medical emergency was managed found that younger board-certified anesthesiologists (<age 40 years) outperformed their older colleagues. [15] A retrospective analysis of malpractice cases among Canadian anesthesiologists demonstrated a 50% greater risk of being found

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responsible for litigation among anesthesiologists older than 65 years as compared with anesthesiologists younger than age 51. [16] In addition, the severity of injury was 2 fold greater among older anesthesiologists. On the other hand, an abstract presented at the ASA Annual meeting in 2015 failed to show any differences in clinical outcomes when comparing cases conducted by older (>age 54) vs younger anesthesiologists. [e] The authors did observe a significant difference in practice patterns such that older anesthesiologists were less likely to be involved in complex surgical procedures.

ORGANIZED MEDICINE'S APPROACH TOWARDS "FITNESS FOR DUTY" ASSESSMENTS AMONG AGING CLINICIANS: Optimally, physicians would recognize their own limitations and restrict their practice before any patient harm occurs. Unfortunately, impaired physicians are often the last to know. Physicians tend to be poor self- analysts and routinely fail to identify or report their own failing competence. [17] In fact, physicians who are the least competent are frequently the least able to accurately judge their own skills and often give the appearance of being the most self- confident. [18]

Physicians are also rarely able or willing to report failing competence among their colleagues. Although most physicians acknowledge the duty to report incompetent or impaired colleagues, only 2/3 have taken appropriate action when faced with the situation. [17] In the absence of adequate self- policing as a safeguard for public safety, many health care organizations, medical boards, certifying bodies and medical societies, including the American Medical Association, the American College of Surgeons, and the Australian and New Zealand College of Anaesthetists, are developing their own policies and procedures. [19] [20] These span the spectrum from benign neglect to imposition of a mandatory retirement age. Most are somewhere in the middle and rely upon voluntary action by the involved physician. The recommended evaluation process typically requires a physical examination and focused case reviews on a regular basis once the clinician has achieved a predetermined age (most commonly 65 or 70 years). Many also include a neuro-psychological assessment and completion of a cognitive test, such as the MicroCog, St Louis Mental Status Examination, or the Montreal Cognitive Assessment.

The ASA has historically been relatively silent on the subject stating only that, "The practice of quality anesthesia care requires that anesthesiologists maintain their physical and mental health and special sensory capabilities." [f] The ASA Committee on Occupational Health currently plans to introduce a statement on the aging anesthesiologist for consideration by the 2018 ASA House of Delegates.

There are strong differences of opinion regarding the advisability of mandatory screening of all physicians based solely upon age. Advocates point to the fiduciary responsibility of organized medicine to police itself. Opponents cite the lack of validation of the frequently employed screening tools when applied to the varying demands imposed by practitioners in different specialties. To be equitable, any comprehensive evaluation must be specific to the clinician's specialty and desired privileges. Done properly, these policies will avoid discrimination or imposition of unnecessary restrictions on older physicians. Optimally, these policies will serve the dual function of identifying impaired physicians and encouraging those with no impairment to continue in their practice.

LEGAL CONSIDERATIONS: Many industries in which public safety is at risk impose age –related work restrictions. For example, commercial airline pilots must undergo regular health screenings starting at age 40 and must retire at age 65 (increased from age 60 in 2007). The mandatory retirement age for air traffic controllers is age 55 years and for FBI agents age 57. There are age- related requirements for automobile driving in many states. In contrast, there are no laws or regulations in the United States that mandate health screening or retirement age for health care providers (or Presidents of the United States).

The practice of medicine is a privilege and is accompanied by many responsibilities, including the obligation to remain physically, mentally and emotionally competent in one's profession. Historically, neither licensure nor hospital privileges have been specifically limited by the chronologic age of the practitioner. However,

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[e] Practice Patterns Change While Outcomes Remain Steady Among Older Anesthesiologists. Anesthesiology News 12/17/2015. Available at: https://www.anesthesiologynews.com/Policy-Management/Article/12-15/Practice-Patterns-Change-While-Outcomes-Remain-Steady-Among-Older-Anesthesiologists/34414/ses=ogst. Accessed 5/17/2018

[f] American Society of Anesthesiologists. Guidelines for the ethical practice of anesthesiology. Available at https://www.asahq.org. Accessed 6/2/2018

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most state laws and hospital bylaws do require that a physician and/ or their colleagues report when there is substantial suspicion that professional skills may be compromised by any potential source of impairment, including age. Several federal laws, including the Age Discrimination in Employment Act of 1967 [g] and the Americans with Disabilities Act of 1990 [h] protect many workers from discrimination in employment due to age alone and outlaw compulsory retirement based solely upon age. Title II of the Americans with Disabilities Act pertains specifically to medical licensure and prohibits state and local governments from excluding qualified individuals from any government program, such as medical licensure or renewal.

However, there are important exceptions to protections afforded by these laws. An important limitation to their applicability is whether the worker is an "employee" with a written agreement with their employer. An anesthesiologist who is a contracting agent with a health care institution might not be eligible for protection according to that requirement. Also important is the condition that any individual who poses a direct threat to the health and safety of others is not considered a "qualified person" under the Americans with Disabilities Act. A case decided by the U.S. Court of Appeals for the Fifth Circuit (EEOC v. Exxon Mobil Corp), affirmed Exxon's right to consider age as a "bona fide occupational qualification," and has wide ranging implications for those considering such actions for other workers in safety sensitive areas such as anesthesiology.[i]

EMPLOYMENT ARRANGEMENTS FOR LATE CAREER ANESTHESIOLOGISTS: A predicted shortage of anesthesiologists has created an imperative to develop arrangements that enable competent senior clinicians to continue working. Several factors play a role in plans to continue to employ senior associates. The size and business structure of a group and the collective philosophy of its members are major considerations. Polices for distributing call and vacation, dividing income, providing benefits and governing the group all are important factors. Because administrative costs and malpractice premiums are associated with each employee whether they are full or part time, the assignment of overhead expenses can be particularly problematic.

"Winding down" employment arrangements fall into 3 general categories:1) a shared position where 2 or 3 anesthesiologists agree to carry all of the clinical, administrative, and financial responsibilities of one partner; 2) a part time position in which 1 individual continues to perform all of the functions of a full time clinician but at a reduced rate- for example 2/3 call, 2/3 clinical time, etc.; 3) a part time position that completely eliminates some aspects of practice (for example night call) and limits exposure to the most complex procedures and other stressful elements of practice. Additional details on how these arrangements might work can be found in a review by Baxter.[21]

The most challenging aspect of any of these arrangements is the manner to value these tradeoffs, which is specific to each situation and can only be made on a practice by practice basis. One size does not fit all regarding flexible work schedules. Each group of anesthesiologists must develop a program specific to its unique situation. Those that work best usually address the following considerations: (1) assurance that any agreement conforms to applicable law; (2) a prerequisite that the senior partner has achieved a minimum combination of chronological age and years of service; (3) a clear agreement on the parameters of the part-time position, including responsibilities and limitations; (4) a detailed description of the total compensation package, including benefits; (5) a minimum work commitment to receive benefits; (6) an understanding of residual (if any) shareholder status and voting rights; (7) a declaration of plans to fully retire within a defined period; (8) a clear reinstatement policy; and (9) fairness for all—the plan must be available to other partners at a future time.

RETIREMENT: As previously discussed, there are no mandated retirement ages for physicians in the U.S.A. The decision to retire usually remains solely at the discretion of the individual anesthesiologist. Age is inevitably one of the leading factors in decisions concerning retirement. The median age of retirement for anesthesiologists as of 2012 was approximately 64 years.[3] Commonly cited reasons for retirement among older anesthesiologists include on-call responsibilities, financial considerations, lack of professional satisfaction, health concerns, and changes in governmental policies and the health care business climate. On the other hand, those older anesthesiologists who decide to postpone retirement cite career satisfaction, financial obligations, and the need to maintain health insurance for family members as the primary reason to remain in the workforce.

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[g] 29 U.S.C. § 621 through 29 U.S.C. § 634

[h] 42 U.S.C. §§ 12101 et seq.

[i] EEOC v. Exxon Mobil Corp. Available at: http://www.ca5.uscourts.gov/opinions%5Cunpub%5C13/13-10164.0.pdf Accessed 5/25/2018

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MORTALITY: As observed by the great Hank Williams Sr. "I'll Never Get Out of This World Alive"[j]. Death is the expected final outcome of normal aging. There is a wide range of lifespans both within and between species and populations. The life expectancy of Americans has increased substantially in the last century. A male who was age 65 in 2016 could expect to live until age 84.3. [k] A woman who was age 65 could expect to live until age 86.6. About 25% of 65-year olds today will live past age 90. The longest recorded human life was a French woman who passed away in 1997 at age 122 years.

Anesthesiologists are also living longer. Early reports expressed concern that the stressful nature of the job and the consequence of excessive exposure to potentially toxic substances such as anesthetic gases and radiation resulted in premature deaths among anesthesiologists. A more recent study has challenged that assumption and concluded that the age adjusted mortality rate among anesthesiologists is not different than among other physicians. [22] The commonest causes of death among anesthesiologists has also changed over the past 50 years. Early reports cited a concern about an excess risk of cancer related mortality. More recent reports cite a disproportionate number of drug related deaths and suicide. [23]

CONCLUSION: Aging is a universal process that affects every clinician. Aspects of aging impart both advantages and disadvantages to the late- career anesthesiologist. A working arrangement can frequently be forged that benefits the anesthesiologist, the group, and their patients.

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Postpartum Hemorrhage: How to Prepare for It, How to Prevent It, and What to Do When Blood is Pooling on the Floor

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The learner will: 1) List options available to control and mitigate the consequences of obstetric hemorrhage; 3) Discuss how contemporary transfusion practices apply in the obstetric setting; and 3) Draw from published guidelines and protocols to inform both individual clinical practice and systems solutions to prepare for these emergencies.

Definitions

Postpartum hemorrhage is defined by ACOG as cumulative blood loss ≥1000 mL, regardless of mode of delivery.[1] Blood loss ≥500 mL following vaginal delivery should prompt action to monitor and control blood loss. The risk for adverse health outcomes accumulates with **persistent postpartum hemorrhage,** when bleeding exceeds 1000 mL and persists despite the use of first-line uterotonics and uterine massage, particularly if bleeding is accompanied by signs or symptoms of hypovolemia. The National Partnership for Maternal Safety recently defined indicators of **severe maternal morbidity** as ICU admission or transfusion with 4 or more units of blood products, and recommended that women with these indicators receive multidisciplinary review for the purpose of identifying opportunities for systems improvement.[2]

Etiology

Primary postpartum hemorrhage develops within 24 hours of delivery and is due to uterine atony, retained placenta, genital tract trauma, placenta accreta, increta or percreta, uterine inversion, or coagulopathy. Coagulopathy may be inherited or result from conditions such as amniotic fluid embolism, HELLP syndrome, abruption or intrauterine fetal demise.[3] *Secondary postpartum hemorrhage* is relatively infrequent, develops over 24 hours after delivery, and is ascribed to subinvolution of the placental site, retained products of conception, infection, or inherited coagulation defects.

Epidemiology

Postpartum hemorrhage complicates at least 3% of all deliveries, and appears to be increasing in frequency.[4] Approximately 3% of women receive any blood products; many are transfused to treat normal blood loss in the setting of antepartum anemia. Hemorrhage accounts for close to half of obstetric intensive care unit admissions,[5] and 38% of cardiac arrests during the hospitalization for delivery.[6]

Uterine atony underlies 80% of all cases of postpartum hemorrhage.[4] Population-level factors driving the increasing frequency of uterine atony include: 1) increasing population prevalence of obesity, multiple gestation, and advanced maternal age; 2) increasing inductions of labor; and 3) increasing cesarean deliveries, from 21% of all births in 1997 to 31.9% in 2016. Unrelenting uterine atony leads one-third of all peripartum hysterectomies.[7] Uteroplacental inflammation (e.g., chorioamnionitis, vasculitis, funisitis, endometritis, and cervicitis) appears to be a major contributor to uterine atony that is sufficiently severe to require peripartum hysterectomy.[8]

Placenta accreta with or without placenta previa is the leading cause of massive blood transfusion.[9] Accreta leads to approximately half of all peripartum hysterectomies, and rates have increased in conjunction with the burgeoning population of pregnant women with prior cesarean deliveries.[9]

Historically, hemorrhage was the leading cause of maternal death in the United States, but currently accounts for 11% of the total, or 1.8 maternal deaths per 100,000 live births.[10] The majority of hemorrhage-related deaths are preventable.

Anticipated Postpartum Hemorrhage

Even with the physiologic anemia of pregnancy, a hematocrit less than 32% should be treated to reduce the risk of peripartum blood transfusion (e.g., oral or intravenous iron). In addition, three groups need special antenatal preparation: 1) women with abnormal placentation; 2) those with inherited coagulation disorders; and 3) those who refuse blood products.

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Abnormal Placentation

With placenta accreta, the decidua basalis (i.e., the decidual basal plate) is absent, and the basal plate of the placenta adheres to a floor of uterine myometrium. With placenta increta, chorionic villi invade into the myometrium, and with percreta, the placenta penetrates the uterine serosa, and may even grow into other pelvic structures, most commonly the bladder. Placental location mediates the relationship between prior cesarean and risk of accreta. When placenta previa is present, the incidence of a morbidly adherent placenta increases from 3% among primary cesarean deliveries, to 11%, 40% and >60% after one, two, and three or more prior cesarean deliveries, respectively.[11] When the placenta does not involve the cervix or lower uterine segment, accreta is relatively rare (1%), even with multiple prior cesarean deliveries.[11]

Intrapartum blood loss is difficult to predict.[12] Antenatal recognition and controlled surgical delivery improve outcomes.[13] Accreta is often evident on the anterior surface of the uterus, and in such cases, as long as the mother and fetus are stable, it may be possible to close the abdomen and transfer the patient to a center of excellence for planned cesarean hysterectomy.[13,14] Ultrasonography to locate the placenta and evaluate for markers of placenta accreta is recommended for every woman who has undergone prior uterine surgery, or found to have a low-lying placenta on the routine first or second trimester ultrasound.[15] Magnetic resonance imaging (MRI) may help to confirm the diagnosis when ultrasound is inconclusive, and define the extent of invasion into surrounding organs in the case of placenta percreta. Women with a diagnosis of abnormal placentation based on ultrasonography are more likely to require blood transfusion and peripartum hysterectomy, and require more units of blood products transfused, when compared with women without definitive ultrasound findings.[12,16]

Surgical management is directed towards delivering the neonate, then closing the uterus with the placenta left *in situ*, followed by planned peripartum hysterectomy.[15] Optimal management by the anesthesiologist ensures sufficient intravenous access and blood products to respond to massive hemorrhage, hemodynamic and hemostatic monitoring capability (e.g., central venous and peripheral arterial access), sequential compression stockings to prevent venous thromboembolism, padding and positioning to prevent nerve compression injury, warming devices to ensure normothermia, standard preoperative antibiotic prophylaxis in the hour prior to surgical incision and repeated if surgery is prolonged (i.e., ≥3 hours) or if heavy bleeding occurs.[17] Given inaccuracy of models to predict total blood loss in these cases, the total number of recommended blood products to prepare depends on institutional capacity to maintain ongoing supply in the face of massive hemorrhage.[12] Aggressive uterotonic administration, cell-saver auto-transfusion, massive transfusion management, and electrolyte and hemostatic measurement and management are discussed below.

Combined spinal epidural (or standard epidural) anesthesia is frequently feasible[18] allows the mother to be awake for the delivery, may be extended for prolonged surgery, and is associated with improved neonatal Apgar scores at birth.[19] General anesthesia is preferred for cases with massive transfusion in the event of airway edema, fluid overload with pulmonary edema, or transfusion associated lung injury (TRALI). The decision about the primary anesthetic technique will weigh the magnitude of anticipated blood loss, the extent of the operative plan, the availability of additional anesthesia staff to assist with an unplanned conversion to general anesthesia, and the anticipated risk of a difficult airway.

Prophylactic embolization catheters may be inserted preoperatively into the anterior internal iliac or uterine arteries to facilitate balloon inflation or embolization immediately following delivery of the infant.[17] Efficacy was not verified by a recent randomized controlled trial.[20] Routine use is not recommended by the Society for Maternal-Fetal-Medicine due to lack of demonstrated efficacy as well as potential complications including arterial injury, abscess, tissue infection and necrosis.[17] The Retrograde Endovascular Balloon Occlusion of the Aorta (REBOA) was developed to treat penetrating trauma of the thorax and abdomen; recent reports describe its use for obstetric hemorrhage.[21] With either balloon catheters, pidural anesthesia should be initiated prior to femoral sheath insertion, to facilitate optimal positioning for both procedures and patient comfort.

Inherited Coagulation Disorders

Von Willebrand disease, hemophilia A and B, and factor XI deficiency account for approximately 90% of inherited bleeding disorders.[22-24] Inherited platelet disorders (e.g., Bernard Soulier Syndrome, Glanzmann thrombasthenia) are rare. Given the clinical heterogeneity within each diagnosis, consultation with a hematologist and blood bank personnel will help to clarify optimal management for each patient. Sixteen percent of women who have von Willebrand disease will experience PPH within 24 hours of delivery, and 29% will experience delayed postpartum bleeding.[25]

Jehovah's Witnesses and other women who refuse blood products

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Antepartum consultation should review a comprehensive list of blood products, alternatives, and blood conservation strategies to determine acceptability of each intervention for the patient.[26] Antepartum iron and erythropoietin are often acceptable ways to optimize hematocrit prior to delivery, aiming for a hematocrit ≥35%, and may be continued postpartum in the event of significant blood loss.[27,28] Neuraxial anesthesia with a catheter-based technique may reduce intraoperative blood loss; furthermore, an awake patient may change her mind in the face of impending death. Prophylactic administration of tranexamic acid may have a modest effect on cumulative blood loss (reducing blood loss by <150 mL) if administered early in the event of hemorrhage.[29]

Volume replacement with crystalloid or colloid can decrease viscosity of the blood and thereby improve peripheral perfusion and minimize cardiac work. However, excessive crystalloid resuscitation can contribute to dilutional coagulopathy and decreased oncotic pressure. Cell-saver autotransfusion is discussed below, and a continuous circuit technique is often acceptable for patients who would otherwise refuse blood products.[28,30] In the event of massive blood loss and profound anemia (hgb ≤4 g/dL) prolonged postoperative sedation, intubation, thermoregulation, and paralysis may be required to limit oxygen consumption while erythropoietin and iron are used to restore the patient's red cell mass. Erythropoietin requires 48-72 hours for a significant reticulocyte response in peripheral blood, and 10-14 days to increase hemoglobin levels. Laboratory testing should be minimized using pediatric tubes and finger-stick testing where possible.[27]

Risk stratified blood product preparation

Blood transfusion is rare following elective cesarean delivery (<1%), but risk is increased among women with antenatal anemia, placenta previa, or multiple gestation pregnancy, particularly when multiple risk factors present in combination.[31] Systems to collect a blood specimen 1-3 days prior to planned Cesarean delivery may reduce unnecessary surgical delays.[32,33] Federal law requires the use of a sample less than 3 days old for all pretransfusion blood compatibility testing in pregnant or recently delivered women (http://goo.gl/3EUGPw).

Risk factors for blood transfusion may be evident before delivery (e.g., previa), on admission to the labor and delivery unit (e.g., severe anemia), at the end of the first stage of labor or upon transfer to the operating room for unplanned cesarean (e.g., chorioamnionitis), or on transfer to postpartum care. The Association of Women's Health Obstetric and Neonatal Nurses (AWHONN) published a structured risk assessment tool for nurses to apply at each time point, paired with anticipatory actions (www.pphproject.org). The AWHONN list is sensitive, but not very specific to predict hemorrhage and/or blood transfusion. The following list focuses on the most significant risk factors for blood transfusion and prolonged blood product preparation.[31,34,35]

Table 1. Blood product preparation based on the level of risk for peripartum blood transfusion

Recommendations AND Indication	Conditions

Prepare ≥2 units PRBC
Indication: Transfusion risk > 10%
 	
Indication: Prolonged T&S
Prolonged T&C
	• Severe anemia (antepartum Hct <25%)
	  ○ Mild anemia (Hct 25.1-29.9%) + other risk factors
	  ○ Thrombocytopenia (platelets <100k) + other risk factors
	• Multiple gestation + other risk factors
	• Active bleeding
	• History of previous severe postpartum hemorrhage
	• Coagulation disorder including HELLP
	• CD for placenta previa, IUFD, or chorioamnionitis
	• Positive antibodies on T&S (Anti-D is usually Rhogam[†])
	• History of difficult crossmatch
	• Sickle cell disease requiring extended crossmatch

Prepare for Massive Transfusion[‡] • 4-20 units PRBC • 4-20 units FFP • 1-4 platelets (5-pk)	• Maternal history of prior Cesarean deliveries **AND** a placenta overlying the uterine scar or placenta previa • Imaging indicates placenta accreta, increta, or percreta • Planned cesarean hysterectomy

CD = cesarean delivery; FFP = fresh frozen plasma; Hct = hematocrit; HELLP = hemolysis, elevated liver enzyme, low platelet syndrome; PRBC = packed red blood cells

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† Extra time is needed to discriminate between anti-D antibiodies due to RhoGAM® and any additional antibodies that could interfere with a type and crossmatch.[36]
‡The exact number of units determined by a patient-specific assessment of risk for massive blood loss, and institutional resources to rapidly procure additional blood products.[12,37]

Unanticipated Postpartum Hemorrhage

System Factors
Clear multidisciplinary guidelines and regular skills training (multidisciplinary drills) reduce the incidence of massive PPH and hemorrhage-related morbidity,[38-40] and are recommended for all units by the National Partnership for Maternal Safety.[41] Simulation-based training for obstetric hemorrhage encounters can reveal specific management deficits, and thereby facilitate targeted quality improvement and staff education.

Accumulating evidence suggests treatment delays increase risk for severe obstetric hemorrhage and hemorrhage-related maternal death.[42-44] Bundling personnel, equipment, and drug resources ensures rapid and reliable delivery to the bedside.[41] Group paging systems can simultaneously request an entire Obstetric Medical Emergency Team.[45,46] Likewise, an obstetric hemorrhage cart can be used to store essential equipment.[38] An obstetric hemorrhage drug pack containing uterotonics allows for efficient retrieval in the event of an emergency. Hemorrhage drills may be used to measure the time interval from the request for uterotonic medication to administration.[41]

Obstetric hemorrhage is noted to be a particularly traumatic birth complication, regardless of the clinical outcome.[41] Patient, family, and staff support both during and after a hemorrhagic event are increasingly recognized as critical for restoring well-being, and mitigating complications such as post-traumatic stress disorder.[41]

The Staged Approach
A Unit-Wide stage-based obstetric hemorrhage emergency management plan with checklists is recommended by the National Parternship for Maternal Safety,[41] and is based on 4 stages of obstetric hemorrhage (0 through 4).

Stage 0
Stage 0 begins with delivery, and focuses on ongoing risk assessment and active management of the third stage of labor. Prophylactic oxytocin decreases postpartum blood loss, and the need for additional uterotonics;[47] controlled cord traction and uterine massage provide limited benefit above oxytocin alone.[48-50] The dose required to initiate acceptable uterine tone following cesarean delivery is lower than previously assumed, 350 milliunits for elective cesarean and 3 IU for cesarean in labor.[51,52] An initial infusion of 18 IU/hour (e.g., 30 IU in 500 mL, infused at 300 mL/hour) is effective to achieve acceptable uterine tone within 5 minutes in 90% of women undergoing elective cesarean delivery.[53-55] Alternatively, some authors recommend a 3 IU loading bolus over 15 seconds, while supporting blood pressure with phenylephrine.[56,57] In women undergoing cesarean delivery after oxytocin labor augmentation, the combination of oxytocin and ergometrine reduces the need for additional uterotonic agents when compared with oxytocin alone,[58] and may reduce the need for blood transfusion in high risk women.[59]

Universal serial assessments of cumulative blood loss, vital signs, fundal height, and uterine tone should be completed for all deliveries (http://www.pphproject.org). Accurate blood loss estimation is improved by the use of calibrated drapes, formal staff training in blood loss estimation,[60] and gravimetric measurements.[61] Blood contained in absorbing materials (e.g., pads, sponges) can be quantified by weight, subtracting the dry weight of each item, assuming 1 gm weight = 1 mL blood.[26,61]

Because hemorrhage is often concealed or underestimated, monitoring protocols with clear triggers to escalate care are essential.[26,42] The Modified Early Obstetric Warning System is an aggregate weighted scoring system that centers in the UK use to identify women developing critical illness.[62] The Maternal Early Warning System suggests close evaluation if the heart rate exceeds 120 beats per minute; late signs of hemorrhage include hypotension, narrow pulse pressure, pallor or mottled appearance, cold and clammy extremities, oliguria (<0.5mL/kg/hr), anxiety, restlessness, confusion, palpitations, dizziness, diaphoresis, and dyspnea or air hunger. An obstetric shock index (HR/SBP) >1 has been associated with postpartum hemorrhage,[63,64] and a value ≥1.4 indicates the need for urgent attention.[65,66]

Stage 1: Postpartum Hemorrahge
EBL>1000, brisk gush or boggy uterus, or multiple clots AND vital signs stable. At this point, both the anesthesiologist and the obstetrician should be notified. Monitoring intensity of both vital signs and EBL should

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increase. Targeted therapy includes appropriate venous access, initial fluid resuscitation, uterotonics, and analgesia to facilitate initial obstetric interventions to investigate and control the source of bleeding. The diagnostic evaluation should address the five Ts: (1) **Tone**—uterine atony; (2) **Trauma**—lacerations or genital tract trauma; (3) **Tissue**—retained placenta; (4) **Thrombin**—abnormalities of coagulation; and (5) **Turned inside out—**uterine inversion.

Rapid intravenous infusion of oxytocin may cause peripheral vasodilation, hypotension, flushing, nausea, chest pain, myocardial ischemia, and in the face of substantial hemorrhage, cardiovascular collapse.[52] Limiting the infusion rate to ≤30 IU/hour appears to minimize serious hypotensive and ishemic effects.[67] When bleeding persists despite this maximal oxytocin infusion, second-line agents are indicated, including: 1) methergine 200 mcg IM if the patient is not hypertensive, repeated once after 15 minutes; or 2) prostaglandin $F_{2\alpha}$ 250 mcg IM every 15-20 minutes up to 8 total doses (avoided in women with asthma). Methergine appears to be the most frequently chosen second line uterotonic, and may have superior efficacy when compared with prostaglandin $F_{2\alpha}$, based on observational data.[68,69] In contrast, misoprostol does not appear to offer benefit when added to oxytocin.[70]

Stage 2: **Continued bleeding despite stage 1 interventions AND <1500 mL cumulative blood loss.**

With **persistant postpartum hemorrhage**, it becomes very important to mobilize a full team. The patient should be moved to an operating room, large bore venous access secured, and a full panel of laboratory values sent, hematocrit, platelets, PT, and fibrinogen. Cross-match of at least 2 units of erythrocytes is usually indicated, and protocols for emergency release of blood products are recommended.[32,41] Fibrinogen <2 g/L is an early predictor of the severity of subsequent PPH.[71,72] Ongoing uterotonics, thermoregulation, antibiotic coverage, and venous thromboembolism prophylaxis should be addressed. Tranexamic acid and fibrinogen concentrate are being investigated for the early treatment of postpartum hemorrhage, and are discussed below.[73,74] Decisions about transfusion, requesting additional blood products, activating a massive transfusion protocol, converting to general anesthesia, initiating cell salvage, and establishing invasive hemodynamic monitoring depend on the ongoing state of the patient, the rate of blood loss, and the degree to which obstetricians are effective in diagnosing and controlling the source of bleeding.

Stage 3: EBL>1500, >2 u PRBC given, vital sign instability, evidence of coagulopathy, or ongoing bleeding. Stage 3 qualifies as **major obstetric hemorrhage**. Following manual exploration and repair of lacerations, stepwise escalation of surgical therapy includes D&C, intrauterine balloon (e.g., Bakri balloon), and uterine compression suture (e.g., B-Lynch, O'Leary, multiple squares), selective embolization, peripartum hysterectomy, and abdominal packing. In some cases, intraoperative manual aortic compression or cross clamping may facilitate surgical control.[75] Vacuum-induced uterine tamponade is an investigational technique to treat atony.[76] Uterine inversion requires anesthesia and uterine relaxation to facilitate manual replacement.

While a hemoglobin transfusion threshold of 7 g/dL is generally appropriate, laboratory results are inaccurate in the face of ongoing hemorrhage, and transfusion should proceed empirically without waiting for laboratory results. Failure to maintain adequate hematocrit during acute obstetric hemorrhage has been associated with end organ dysfunction.[77] Observational data suggests that hemostatic resuscitation with low transfusion ratios (FFP: PRBC and Platelet: PRBC ratios of 1:1 to 1:2) may increase survival in massively transfused trauma victims,[78] and may decrease the need for advanced interventional procedures in postpartum hemorrhage.[79] However, this evidence base suffers from survival bias. A prospective RCT in trauma patients did not demonstrate improvements in overall survival when early resuscitation with plasma, platelets, and erythrocytes administered in a 1:1:1 ratio was compared with a 1:1:2 ratio.[80] Caution is advised. Plasma and platelets are pro-inflammatory, and may increase risk of pulmonary injury (e.g., TRALI) among individuals who ultimately receive ≤4-6 units of erythrocytes. [81-83] In the absence of consumptive coagulopathy or antenatal thrombocytopenia, platelets are rarely necessary before the cumulative blood loss exceeds 5 litres.[84] Goal-directed therapy guided by TEG or ROTEM may reduce the quantity of plasma and platelets transfused and the risk of major complications, such as transfusion related acute circulatory overload (TACO).[85,86]

Although massive transfusion protocols specifically for obstetric hemorrhage have been described,[87,88] standard institutional protocols are generally appropriate, as long as the higher transfusion threshold for fibrinogen is noted (≥ 2 g/L). Effective protocols are activated by phone, allow for initial supply of uncross-matched products if necessary, and supply batches of blood products that approximate the recommended 1:1:1 ratio, with the option to request cryoprecipitate early.[89,90] Subsequent matched blood products are continuously prepared to maintain blood product availability, and the protocol is automatically discontinued once additional blood products have not been requested for at least one hour.

For massive blood transfusion, laboratory specimens (i.e., hematocrit, platelets, ionized Ca, K, PT, fibrinogen, lactate) should be sent every 30-60 minutes to establish trends. Serial coagulation tests are more helpful than single

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time point measurements in assessing for development of coagulopathy.[5] Additional FFP may be needed to maintain the PT ≤1.5 times normal, platelets to maintain the platelet count over 50 x 10^9/L, and cryoprecipitate or fibrinogen concentrate 4 g to maintain the fibrinogen over 2 g/L.[71,72,91] Central laboratory turn-around time within 20 minutes is possible,[92] but centralized viscoelastic monitoring with point-of-care real time display is emerging as a preferred strategy to facilitate goal directed therapy.[85,86,93] With ROTEM, amplitude at 5 minutes (A5) on the FIBTEM assay shows strong correlation with the Claus Fibrinogen measurement.[86]

In the event of unanticipated massive hemorrhage, an interosseous needle may be rapidly inserted in the tibial plateau or proximal humerus and used to initiate fluid resuscitation while additional intravenous access is established.[94] Temporizing maneuvers include leg elevation, manual compression of the aorta at the umbilicus, and non-pneumatic anti-shock garments.[95] Permissive hypotension (MAP 50 mmHg) may help to limit bleeding, but is not well studied in the postpartum patient.[27]

Adjunctive agents:

Tranexamic acid (1 g over 10 minutes, repeated once after 30 minutes if necessary) was recently studied in the World Maternal Antifibrinolytic (WOMAN) Trial.[96] This trial enrolled 20,060 women in predominantly low and middle income countries, and found that tranexamic acid administered within 3 hours of a diagnosis of severe postpartum hemorrhage decreased hemorrhage-related mortality from 1.9% to 1.5%, with no identified increase in seizures, thromboembolic events, or end-organ injury. In high-resource settings, benefit is most likely in the setting of fibrinolysis (e.g., AFE, abruption, ROTEM lysis index at 30 min >3%). Be aware that fatal drug errors have been reported in which tranexamic acid was administered in place of local anesthetic in spinal anesthesia.[97]

Lyophylized fibrinogen concentrate 2-4 g has been reported to be helpful in coagulopathic obstetric patients.[98,99] Although derived from human serum, fibrinogen concentrate is pasteurized, available in a standard concentration, and may be reconstituted and administered rapidly in a low volume.[100] Rigorous investigation suggests that it is most likely to be beneficial with administered using goal-directed treatment algorithms for women with evidence of hypofibrinogenemia.[74,85,86] Replacement is only beneficial when fibrinogen concentrations fall below 200 mg/dL.

Registries of **recombinant factor VIIa** report a high success rate to control hemorrhage when other interventions have failed, with reported doses ≤90 mcg/kg.[24,101] Temperature, acidosis, calcium, platelets and fibrinogen should be first optimized for maximal hemostatic effect. Caution is advised. Recombinant factor VIIa has been associated with a high rate of devastating thrombotic complications.[102]

Cell salvage—Large numbers of women have received cell salvaged blood during cesarean and vaginal delivery.[103-105] Newer machines in combination with leukocyte reduction filters have demonstrated effective clearance of fetal squamous cells, phospholipid lamellar bodies, plasma heparin, cytokines, and other coagulopathic mediators, alleviating concern about the risk for amniotic fluid embolism. The use of a leukocyte depletion filter has been associated with acute hypotension at the time of transfusion of cell salvaged erythrocytes.[106] Cell-salvaged blood does contain up to 2% fetal red blood cells; Rhesus-negative women require dose-adjusted RhoGAM® administration. Emergency cell salvage may be most appropriate in institutions where cell saver devices are routinely used, and dedicated technicians are available to set up the equipment.[107]

Reporting and Systems Learning: Post-event debriefs are short clinical team meetings conducted immediately after a patient safety event, designed to build teamwork and identify opportunities for improvement. In addition, formal in-depth multidisciplinary reviews of serious hemorrhages (≥4 units of erythrocytes transfused or ICU admission) are recommended by the Joint Commission and the National Partnership for Maternal Safety (www.safehealthcareforeverywoman.org).[41]

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Rules for safe sedation in GI endoscopy suite

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Introduction

The remarkable growth in both numbers and complexity of gastro intestinal (GI) endoscopic procedures is beyond dispute. For example, the number of endoscopic procedures performed at the Hospital of the University of Pennsylvania is displayed in Figure 1. As it can be appreciated, in the year 2016-17 the number of endoscopic procedures exceeded those performed in the operating rooms. Moreover, the growth in the number of GI endoscopic procedures during the last ten years is more than tenfold. While diagnostic upper endoscopy and screening colonoscopy form the bulk of these procedures in any hospital, advanced procedures such as Endoscopic Retrograde Cholangiopancreatography (ERCP), endoscopic ultrasound, and therapeutic endoscopy contribute to a significant minority, especially in academic centers.

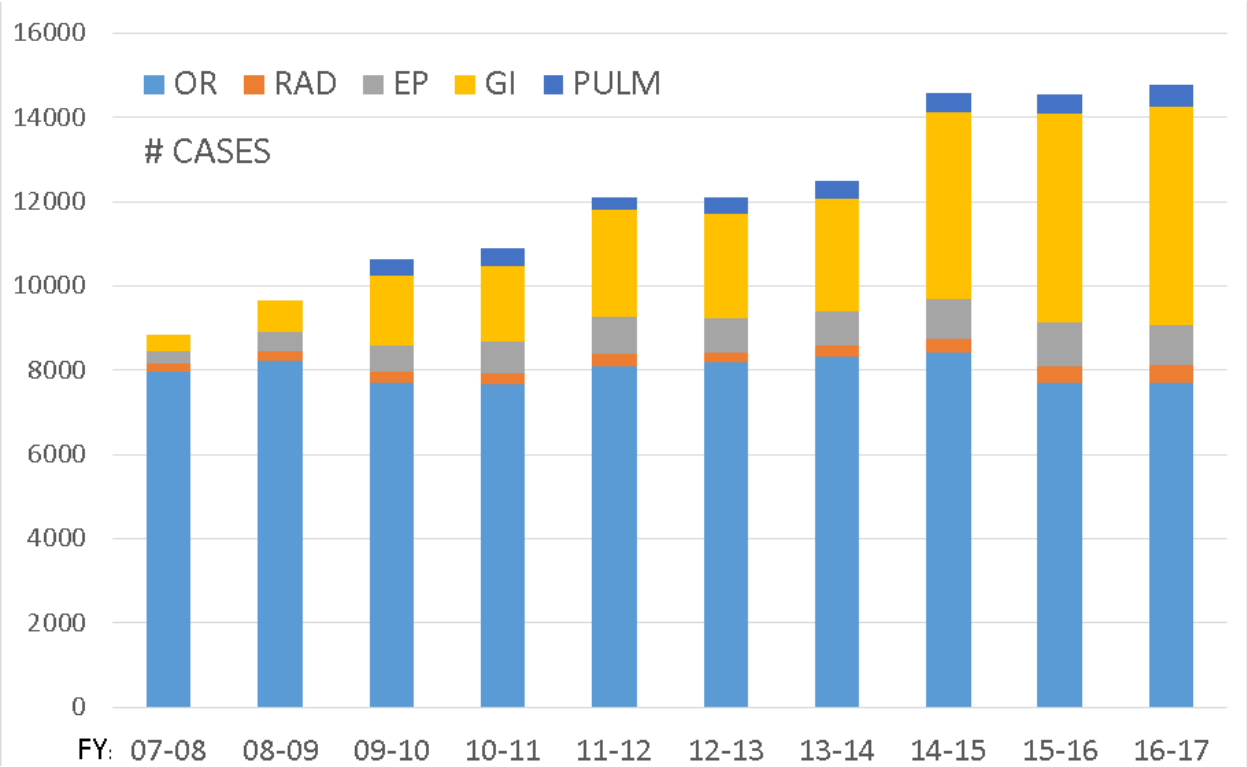

Figure 1: Comparison of the total number of gastrointestinal endoscopic procedures to the OR and other procedures at the hospital of the university of Pennsylvania, Philadelphia, PA, USA. (OR- Operating room, RAD-Radiology al procedures, EP- Electrophysiology, GI- Gastrointestinal, PULM- Pulmonary, FY- Fiancial year)

In addition, Natural Orifice Transluminal Endoscopic Surgery (NOTES) has expanded the range of options available to the interventional gastroenterologist.(1) Endoscopic procedures such as Peroral Endoscopic

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Myotomy (POEM), direct endoscopic pancreatic necrosectomy, and bariatric endoscopy are some of the benefits of this technology. Some of the procedures included in the fast growing area of endobariatrics are intragastric balloons, intragastric suturing and plications, small bowel therapies, and aspiration therapy. As a result, the field of anesthesia for GI endoscopy is both exciting and challenging.

While some of the challenges are attributable to the nature of the procedures, others are the result of changing demography of population undergoing such procedures. A significant number of patients presenting for endoscopy are elderly. Advancements in other fields, such as interventional cardiology, has increased the population with various cardiac diseases. Frequently, patients present for evaluation before heart or lung transplant and almost always before weight loss surgery.

Common adverse events

The range of adverse events related to sedation in patients undergoing GI endoscopic procedures is wide(2,3). These include both fatal and non-fatal. Some of those reported in the published literature (our own and others) are the direct result of the procedure itself and include bleeding and perforation. Nevertheless, every effort should be made to anticipate and prepare for such adverse events. Even these complications occur with higher frequency with propofol sedation(4). Some of the sedation related adverse events are hypoxemia, aspiration, hypotension and cardiac arrhythmias. In addition, an anesthesia provider should anticipate post procedure events such as acute pancreatitis and pain. Some intraprocedural adverse events such as aspiration might have ramifications that continue in the post procedural period.

Fortunately, sedation related adverse events are mostly preventable by adapting a rigorous preprocedural evaluation and safe sedation techniques.

General guidelines to minimize the frequency of adverse events

A thorough preprocedural evaluation should focus on determining risk factors for any of the adverse events and specifically the twin dangers of hypoxemia and aspiration. Obstructive sleep apnea, morbid obesity, history of difficult airway, achalasia, symptoms suggestive of gastric outlet obstruction, dysphagia are specifically sought and explored. Uncontrolled arrhythmias, poorly controlled diabetes may not be grounds for rescheduling, however need further discussion and possible post procedural observation.

Although a detailed and focused evaluation helps to tailor the anesthesia appropriately, creating and implementing some general protocols is helpful.

Propofol is the most widely used anesthetic in GI endoscopy. It has a long track record of safety. Variability of response to various sedative agents used in endoscopy sedation is well known. An interindividual variability of 300% to 400% is reported (5,6). The addition of fentanyl adds to this variability. For a successful completion of the procedure, gastroenterologists expect their patients to be comfortable, many times to the point of being unresponsive. Apnea is likely especially in those groups like elderly whose brain is highly sensitive.(7) In this age group, the dose requirements could be less than one third of standard adult doses. Similarly, those who are using prescription/nonprescription opioids/ sedatives are likely to be resistant to propofol, thereby increasing its requirements for

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achieving the desired level of sedation. The overriding concern during endoscopic procedures is to maintain spontaneous ventilation, while providing appropriate depth of sedation. By administering propofol with an infusion pump-either continuous or target controlled, one can reduce variability. Irrespective of the mode of administration of sedative agents, titration to an appropriate depth should be the dominant principle.

Hypoventilation and consequent hypoxemia is almost inevitable in patients undergoing endoscopic procedures. Hypoventilation is certain to increase the alveolar carbon dioxide, thereby reducing the alveolar oxygen concentration (alveolar gas equation). As a result, administration of supplemental oxygen is mandatory in patients undergoing both upper endoscopy and colonoscopy. There is one major difference in terms of ability to intervene between these two groups of patients. While it is easy to support ventilation by positive pressure in the event of hypoxemia that does not respond to measures like chin lift and jaw thrust during colonoscopy, such an intervention requires withdrawal of endoscope in patients undergoing upper endoscopy.

Nearly all of the endoscopic procedures are performed as non-emergencies. As a result, one should have low threshold to intervene. Monitoring typically includes pulse oximetry, end tidal carbon dioxide, electrocardiography and non-invasive blood pressure monitor. Given the slope of the oxygen hemoglobin dissociation curve, corrective measures including withdrawal of an upper GI endoscope to facilitate bag-mask ventilation should be part of anesthesia provider's armamentarium. If a patient undergoing upper GI endoscopy desaturates to somewhere between 85-90, and fails to respond to simple corrective maneuvers such as chin lift, jaw thrust, increased supplemental oxygen and insertion of a nasal airway (if one is already not in place), then it is appropriate to extubate and consider positive pressure ventilation by a bag-mask. Among the maneuvers, chin lift is simple and effective and often ignored. It causes widening of the entire pharyngeal space, most pronounced between tip of the epiglottis and posterior pharyngeal space. Occasionally, chin lift and jaw thrust can reduce the posterior pharyngeal space, potentially worsening upper airway obstruction. (8,9)

Often, major catastrophes occur as a result of lack preparedness.(2) Equipment to support airway and secure airway should be always available. Emergency drugs should be at hand all the time.

The anesthesia provider should watch carefully for any signs of aspiration and treat appropriately. Although the absolute risk of complications is low, the use of anesthesia services for colonoscopy is associated with a somewhat higher frequency of complications, specifically, aspiration pneumonia.(10) In spite of taking all precautions and performing a focused preprocedural evaluation, gastric contents might be observed in the oral cavity during a colonoscopy. Typically, they find their way into the left lung. Desaturation is invariably observed. One approach is to stop the procedure and further evaluate the patient for signs and symptoms of aspiration related lung injury. Occasionally emergency intubation followed by suctioning (sometimes with the assistance of a bronchoscope) is necessary.

Another approach to improve the safety is to create a small core group of anesthesia providers. It is shown that both safety and efficiency can be improved with such an approach (11). It is reported that experience in providing deep sedation improved patient safety and decreased the operating room turnaround time, thereby lowering operating room costs associated with these procedures. In addition, complications rates during ERCP were found to be primarily dependent upon the skill of anesthesia provider rather than ASA status in elderly.(12)

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In conclusion, by employing a focused preprocedural evaluation, careful preparation of the procedure rooms, appropriate titration of sedatives, and preemptive approach in management of adverse events, one can reduce the GI endoscopy sedation related adverse events significantly. In addition, by maintaning a core group of anesthesia providers, both safety and efficiency can be enhanced.

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ANESTHESIOLOGY 2018
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Perioperative ACLS

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Managing cardiac arrest in the operating room: pre-cardiac arrest considerations, high-stake perioperative cardiac arrest circumstances and therapeutic approaches

Cardiac arrest in the operating room (OR) and in the immediate postoperative period is a potentially catastrophic event, is almost always witnessed and is often anticipated. Since patients are monitored closely, the event is generally rapidly recognized and treated. Existing guidelines and standard resuscitation methods, including the American Heart Association Cardiac Life Support algorithms, were not specifically developed with the perioperative patient in mind, but rather for those individuals who suffer out-of-hospital cardiac arrest. The anesthesiologist plays a critical role in optimally managing both intraoperative and immediate postoperative cardiac arrests. Formulation of an appropriate diagnosis and rapid application of applicable interventions aimed at treating the underlying cause of cardiac arrest are essential for optimal patient outcome. Failure to rescue does occur; however, data indicate that it is less frequent than generally thought. All practicing anesthesiologists must have standard procedures that allow for the immediate assessment and management of cardiac arrest in the perioperative environment. This summary will primarily focus on pre-cardiac arrest considerations, triggers of high-stakes perioperative cardiac arrest events, and therapeutic approaches that are based on the underlying cause.

(i) Perioperative cardiac arrest incidence, outcomes and causes:

Perioperative cardiac arrest is a complication associated with disastrous consequences. Knowledge of the patient's co-morbidities, underlying pathophysiology, predisposing factors, early detection, aggressive resuscitation and post resuscitation care are the key elements leading to a successful outcome. Analysis of data obtained between 2010 and 2013 by the National Anesthesia Clinical Outcomes Registry, an emerging resource for examination of perioperative and anesthesia-related outcomes, demonstrates that the risk of cardiac arrest is 5.6 per 10,000 cases, with an associated mortality of 58.4%.

Patients undergoing emergency surgery, those with high American Society of Anesthesiology (ASA) physical status scores, and those who are at the extremes of age (neonatal, geriatric) have the highest incidence of perioperative cardiac arrest.

Frequent causes of perioperative cardiac arrest that are not explicitly covered in conventional ACLS include: (i) vagal responses to surgical manipulation, vagotonic anesthetics, sympatholysis from anesthetic agents, beta-blockers, and the suppression of cardiac-accelerator fibers arising from T1 through T4 in patients undergoing neuraxial anesthesia; (ii) hypoxia associated with difficult airway management; (iii) pulseless electrical activity (PEA) from hypovolemia; and (iv) circulatory collapse due to auto-positive end-expiratory pressure (auto-PEEP) and inhalational anesthetic overdose. There are also 8 triggers of high-stakes perioperative events, namely severe anaphylaxis, tension pneumothorax, systemic local anesthetic toxicity, malignant hyperthermia, severe hyperkalemia, hypertensive crisis, trauma-related cardiac arrest, and pulmonary embolism that may lead to cardiac arrest on the operating table. These perioperative crises, which will be described in the continuation of this summary, are complex, heterogeneous and require rapid implementation of etiology-based resuscitation procedures to prevent mortality from cardiac arrest.

(ii) Pre-cardiac arrest considerations in unstable patients:

To prevent patients from developing cardiac arrest, anesthesia providers must maintain a high index of suspicion that a crisis is either about to occur or is already occurring. There are many pitfalls within the perioperative space that impede the early recognition of trouble. These include: The inability to identify mental status alteration whilst patients are sedated or under general anesthesia; mechanical ventilation masking tachypnea, hypopnea, or apnea; lack of urine production due to surgically elevated anti-diuretic hormone; surgical draping, positioning, and dimly lit operating rooms all of which frustrate patient assessment.

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Considerations for a patient in crisis:

(a) Escalation of care: The anesthesia provider must acknowledge when augmentation of patient monitoring is required. Factors include: Patient history, underlying pathology and pathophysiology, current clinical status, anesthetic technique, and the surgical procedure being performed. Unstable patients should be monitored with an arterial line and care determined by arterial blood gas evaluations, including assessments of oxygenation, ventilation, base deficit, and lactate levels. Insertion of invasive monitors should not delay supportive care and evaluation of the underlying cause. Monitoring via central venous access is reasonable and appropriate when knowledge of central pressures and central venous oxygen saturations might help guide resuscitation, or when providers anticipate the need for catecholamine or inotropic therapies. If available, the application of continuous non-invasive measures of arterial blood pressure and/or cardiac performance may be considered as a monitoring bridge whilst invasive monitors are placed. Over the past decade, clinicians have increasingly performed point of care ultrasound to make quick diagnoses and crisis management decisions.

(b) Progression to crisis: Administration of titrated boluses of vasoactive drugs (i.e. phenylephrine, ephedrine, vasopressin, norepinephrine, and epinephrine) is appropriate and recommended. Small boluses of vasopressin (arginine vasopressin (AVP) 0.5 – 2 u IV) generally will improve hemodynamics when escalating bolus doses of catecholamines have failed. Additionally, vasopressin administration should be considered for the management of hypotensive vasoplegia in the setting of ARB and ACEIn exposure. Methylene blue administration has been used successful in the management of cardiopulmonary bypass associated hypotensive vasoplegia. The role that Angiotensin 2 might play in the intra- and peri-operative management of unstable patients is yet to be defined.

(c) Left ventricular failure: Echocardiography and invasive monitors such as the pulmonary artery catheter guide the management of left ventricular (LV) failure. Hypotensive euvolemic patients with left ventricular shock are managed with inotropic agents in the vast majority of cases. In patients with known, significant diastolic dysfunction, therapy with lusitropic agents such as milrinone will enhance ventricular relaxation and improve cardiac output. Mechanical support with intra-aortic balloon pumps, ventricular assist devices, and extra-corporeal life support (ECLS) (also referred to as extra-corporeal membrane oxygenation (ECMO)) are being increasingly utilized in hospitalized patients with severe LV shock.

(d) Right ventricular failure: Similar to left ventricular shock, right ventricular (RV) shock is best guided using a combination of invasive monitors such as the pulmonary artery catheter and/or echocardiography. In most instances, an acute rise in pulmonary vascular resistance (often in the setting of a chronic cause of pulmonary hypertension) causes and sustains RV shock. A combination of inotropes, systemic arterial vasoconstrictors, and pulmonary artery vasodilators such as nitric oxide are used to manage these patients. Salvageable patients with right ventricular shock refractory to medical management are increasingly being rescued with mechanical support including ECMO/ECLS and ventricular assist devices when available.

(e) Hypovolemic hypotension and Dynamic Indices: Hypovolemia, a decrease in blood volume, is the most common cause of perioperative hypotension, circulatory crisis, and shock. Under the correct conditions, dynamic indices including pulse pressure variation (PPV), systolic pressure variation (SPV), stroke volume variation (SVV), and plethysmographic variability Index (PVI) are the best indicators of volume responsiveness in hypotensive patients. These indices are most reliable in intubated, mechanically ventilated patients who are synchronous with the ventilator (TV $\geq$ 8 cc/kg) and who have a regular r-r interval. Though controversial, recent literature suggests that dynamic indices may be used to assess volume responsiveness in cooperative, spontaneously breathing patients. Obstructive and RV shock cause factitious elevation in SPV and PPV. All conditions met, hypotension in association with a dynamic index of less than 10% suggest that hypotension and shock will not improve with fluid resuscitation. It is critical to recognize that one cannot rule out hypovolemic hypotension in the setting of "gray zone" range dynamic indices. In this setting, other methods of assessing volume responsiveness,

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such as a volume challenge whist monitoring for cardiac stroke volume changes, must be considered. Although ultrasound assessment of inferior vena cava diameter variation with respiration may predict volume responsiveness, it cannot be easily performed during abdominal, cardiac, and thoracic operations, or in patients in the lateral, prone, or sitting positions.

(f) Ventilation during severe shock or cardiac arrest: Basic Life Support (BLS) guidelines continue to emphasize avoiding hyperventilation during CPR. Patients who are intubated should be ventilated at a rate of 10 breaths·min^{-1} or less, with an inspiratory time of one second. Tidal volume should be limited to a "chest rise" (approximately 500 mL in a 70-kg adult) when the patient is being ventilated with an Ambu bag or similar device. Studies of ventilation during shock repeatedly demonstrate that the duration of increased intrathoracic pressure is proportional to the ventilation rate, tidal volume, and inspiratory time. Because positive pressure ventilation decreases venous return, and hypoventilation seems to cause no harm, patients in shock should be ventilated with the lowest settings compatible with a saturation of 90%.

(g) Auto-PEEP: This phenomenon, which is also known as gas trapping or intrinsic PEEP, occurs in patients with obstructive lung disease. In these patients, mechanical ventilation that does not allow sufficient time for complete exhalation produces a gradual accumulation of air (volume) and an associated increase in pressure (end-expiratory pressure) within the alveoli. This pressure is transmitted to the pulmonary capillaries and decreases both venous return and cardiac output. The presence of auto-PEEP can be inferred whenever the expiratory flow waveform does not return to the zero baseline in between breaths. Patients at risk for auto-PEEP are best ventilated with the least tolerable tidal volume and rate. Generally, small tidal volumes (< 6 mL/kg), a low respiratory rate (< 10 /min), and a short inspiratory time [1.2-2 seconds] (which will produce a paradoxical and acceptable increase in the peak inspiratory pressures) will produce the lowest risk of auto-PEEP associated circulatory depression.

(iii) Triggers of High-stakes Perioperative Cardiac Arrest:

(a) Severe anaphylaxis: When symptoms of severe anaphylaxis are present, moderate doses of intravenous (IV) epinephrine (100 to 300 mcg) should be immediately administered to halt mast cell degranulation. Repeated treatment with increasing doses as clinically indicated may be required. If the patient has a pulse, the dose of Epinephrine should not exceed 1 mg. Doses of epinephrine greater than 1 mg IV may be given to pulseless patients. While the role of epinephrine in cardiac arrest in general is under increasing debate, epinephrine should still be used in any patient who is suspected of having an anaphylactic reaction. Because laryngeal edema can develop very quickly in these patients, immediate endotracheal intubation is appropriate. Ongoing management of anaphylaxis should include continuous IV infusions of epinephrine (0.05-0.3 mcg/kg/min).

(b) Tension pneumothorax: Pathologic increases in intrapleural and intrathoracic pressure as a consequence of air that leaks in via a "one-way" valve, if unrecognized or improperly managed, can be deadly. This complication is especially concerning in patients receiving positive pressure ventilation in which increased intrapleural pressure throughout the respiratory cycle produces a marked decrease in venous return, leading to reduced cardiac output, hypotension, tachycardia, hypoxemia, and if uncorrected, cardiac arrest (PEA). Subcutaneous emphysema is often present on physical exam. Immediate management includes treatment with 100% oxygen and the insertion of a tube thoracostomy by trained personnel or large bore peripheral IV catheter in the mid-clavicular line at the second intercostal space.

(c) Local Anesthetic Systemic Toxicity (LAST): is a life-threatening adverse reaction resulting from local anesthetic reaching toxic systemic circulating levels.

Patients with LAST may present with neurologic symptoms including a metallic taste and/or tinnitus at low levels of toxicity, and at higher levels; agitation, obtundation, and seizures. Cardiovascular complications may include arrhythmia, hypertension, tachycardia and/or progressive hypotension and bradycardia.

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The initial treatment of LAST includes ensuring adequate oxygenation and ventilation and using a benzodiazepine to prevent seizures. Early treatment of LAST with infusion of lipid emulsion 100ml of 20% (ILE) is believed to prevent or mollify cardiovascular complications. If LAST progresses to cardiovascular collapse, high quality CPR will distribute the intralipid throughout the body and may allow ROSC with little or no permanent end-organ damage. Extracorporeal life support should be instituted in cases without ROSC after appropriate therapy and adequate CPR.

(d) Malignant hyperthermia (MH): MH is a rare life-threatening condition that is triggered by exposure to either a volatile anesthetic agent (halothane, enflurane, isoflurane, desflurane or sevoflurane) or succinylcholine. In susceptible individuals, these drugs induce a drastic and uncontrolled increase in oxidative metabolism in skeletal muscle (hypermetabolic state) resulting in a dramatic increase in oxygen consumption, CO2 production, and body temperature. In turn, circulatory collapse and death is likely to occur if not immediately identified and treated.

MH is treated with datrolene sodium (2.5 mg/kg intravenously), which has reduced mortality from MH from 80% to 1.4%. Early signs of MH are hypercapnia and sinus tachycardia; additional signs of MH are general muscle rigidity, rising body temperature and tachypnea. Blood gas analyses often reveals the presence of both respiratory and metabolic acidosis. The time to datrolene administration is directly linked to morbidity and mortality from MH, and thus early diagnosis is crucial. If MH is suspected, all volatile anesthesia agents should be immediately discontinued.

(e) Severe hyperkalemia: Hyperkalemia is one of the few potentially lethal electrolyte disturbances. Prompt recognition and expeditious treatment of severe hyperkalemia saves lives. Severe acute hyperkalemia is rare in the perioperative setting. The most common causes of elevated plasma potassium are renal pathology and drug therapy.

Patients may experience bradycardia, hypotension, electrocardiographic changes with peaked T-waves, QRS widening, diminished P waves and a range of arrhythmias including atrio-ventricular blocks, ventricular tachycardia, and ventricular fibrillation. Neurological manifestations of hyperkalemia include muscular weakness and respiratory failure due to flaccid muscle paralysis.

Treatment with beta-2 agonists (albuterol) and glucose with insulin can be initiated to promote potassium shift towards the intracellular compartment. If electrocardiographic changes are already present, administration of calcium as a membrane stabilizer is recommended. Treatment with loop diuretics is appropriate in patients that make urine. Renal replacement therapy is often the treatment of choice in patients who make little or no urine. If medication resistant hyperkalemia is considered reversible, therapy with extracorporeal life support is appropriate.

(f) Hypertensive crisis: Severe increases in arterial blood pressure may lead to cardiovascular and neurological complications. Intraoperative hypertension is common and easily treated; however, prolonged hypertension may lead to organ dysfunction and poor outcomes. Morbidities associated with hypertensive crisis include: myocardial ischemia, mitral regurgitation, systolic heart failure, intracranial hypertension, pulmonary edema, acute kidney injury, aortic dissection, and bleeding at vascular anastomotic sites. Causes of hypertensive crisis include excessive surgical stimulation, aortic cross clamping, light anesthesia, airway compromise, hypertension due to withdrawal of antihypertensive medications, endobronchial intubation and hypercarbia.

If hypertension is difficult to manage, the differential diagnosis should be expanded to include: pheochromocytoma, hyperthyroidism, malignant hyperthermia, elevated intracranial pressure, carcinoid syndrome, autonomic dysreflexia from spinal cord injury, and increased circulatory volume. Management steps are outlined in Table 1.

(g) Traumatic cardiac arrest (TCA): Cardiac arrest in the setting of trauma is a potentially catastrophic event that is associated with high mortality. TCA may occur due to hemorrhage, vasodilatory hypotension, cardiac trauma (acute pericardiac tamponade, ischemia, penetrating trauma), hypoxia, acidosis, electrolyte disturbance, nerve reflex, drug usage, anesthetic technique and/or the procedure being performed. Treatment of TCA is a team sport, with all measures carried out concurrently rather than

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sequentially. Success comes from rapid diagnosis and targeting treatment of all potentially reversible pathologies or complications.

If TCA is caused by hypovolemia, the main treatment objective is to achieve immediate hemostasis and reestablishment of intravascular volume. It is vastly easier to stop bleeding with pressure than it is to replace the blood that is being lost. Compressible external hemorrhage should be managed with direct or indirect pressure, pressure dressings, tourniquets and topical hemostatic agents. Non-compressible hemorrhage is more difficult; external splints/pressure, blood products, intravenous fluids and tranexamic acid are all used during patient transport and until surgical control has been obtained. At present, the preferred fluid for the resuscitation of a patient with TCA is blood and blood products. A more detailed discussion of the management of traumatic cardiac arrest is beyond the scope of the is summary and is not covered in this lecture.

Subsequent management of TCA will include damage control resuscitation (DCR), which combines permissive hypotension and hemostatic resuscitation with damage control surgery. Permissive hypotension allows intravenous fluid administration to a volume sufficient to maintain a radial pulse and aiming for a systolic blood pressure of 80-90 mmHg. Hemostatic resuscitation is an early use of blood products to prevent exsanguination, dilution of hemostatic blood components and trauma-induced coagulopathy. Tranexamic acid (TXA) increases survival from traumatic hemorrhage and is incorporated into the protocols for care at most institutions that routinely manage TCA.

(f) Pulmonary embolism (PE): Signs of PE under general anesthesia include: (i) unexplained hypotension with concurrent decrease in E_tCO_2; (ii) desaturation that is only moderately responsive to increased F_IO_2; (iii) transitory bronchospasm with increased airway resistance; (iv) rapid changes of heart rhythm (often dysrhythmias or bradycardia after a transitory tachycardia): (v) unexplained increased of central venous pressure (CVP) or all pulmonary pressures (PAC); and (vi) rapid progression to cardiac arrest (usually PEA).

Thromboembolism, venous gas embolism (VGE), and fat embolism are recognized complications that may occur during anesthesia and surgery and are considered the most common cause of perioperative pulmonary embolism.

Thromboembolism causes circulatory crisis via a combination of mechanical obstruction and the release of inflammatory mediators, which increase right ventricular (RV) afterload. In severe cases, the associated increase in pulmonary vascular resistance is so great that the right ventricle is unable to maintain its output. As the RV fails, it typically dilates, and the interventricular septum flattens and shifts toward the left ventricle further impeding left filling, thus decreasing left ventricular output.

Acute thromboembolism causes cardiac arrest in approximately 5% of cases. Echocardiography of the patient with right ventricular shock will typically reveal right ventricular dilatation and dysfunction, with an under filled left ventricle. The management of intraoperative or perioperative thromboembolism is highly dependent upon the procedure and patient. Therapeutic options range from supportive measures to anticoagulation, thrombolysis, and in rare circumstances operative thrombectomy.

Like thromboembolism, gas embolism is an important cause of circulatory arrest. Patients experiencing gas embolism are breathlessness, develop continuous cough and arrhythmias, myocardial ischemia, acute hypotension with loss of end-tidal carbon dioxide, and cardiac arrest. The risk of venous air entrainment and embolization increases when the surgical field is above the right atrium. Of course, a high index of suspicion for venous gas embolization, other than air, must be maintained when other gases are used during surgery (carbon dioxide or argon). Clinical management includes immediate inhibition of further gas entrainment, removal of right ventricular "air-lock" if present and hemodynamic support focused on improving RV function.

Procedures associated with increased risk of gas embolism include laparoscopy, endobronchial laser procedures, central venous catheterization or catheter removal, hysteroscopy, pressurized wound irrigation, prone spinal surgery, posterior fossa surgery in the sitting position, and endoscopic retrograde cholangiopancreatography.

Surgical procedures at risk of VGE should be specifically monitored. Right parasternal precordial Doppler (PPD) ultrasound has very high sensitivity (88%) for air embolism. Trans-esophageal echocardiography allows for recognition of air embolism size and assessment of ventricular function.

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Patients who survive an embolic event are likely to require continued evaluation and management in an intensive care unit. Management steps are outlined in Table 1.

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Updates in Infant Neuraxial Anesthesia- Caudal Catheters, Spinal Without General Anesthesia, and Other Clinical Pearls

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Objectives:
Examine new literature regarding spinal in infants without general anesthesia.

Recognize common dosing errors in infant spinal anesthesia and how to avoid them.

Review optimal methods for threading caudal catheters to the thoracic epidural space.

Compare ultrasound, nerve stimulation, flouroscopic, and landmark techniques for safe epidural placement in children.

Discuss controversial areas in pediatric epidural placement.

Description:
There have been several advances in pediatric neuraxial anesthesia. The use of infant spinal with sedation has emerged as a helpful technique. Dosing for spinal in the infant age group is not well-known and discussion will occur about what drugs to administer. Several methods exist for placing thoracic epidurals from the caudal and lumbar space. The risks and benefits of each method will be examined.

Spinal Anesthetic Innovations

Franklin Chiao, M.D..
Karen R. Boretsky, M.D

Spinal anesthesia in children can serve as a primary anesthetic in infants for many surgeries (Table 1). The increasing concern about potential anesthesia neurotoxicity in the adolescent brain, and the higher incidence of hemodynamic and respiratory instability in patients having general anesthesia versus regional anesthesia (GAS study) has lead to a resurgence of interest in this technique[1].

Anesthesia attendings have a much higher success rate in performing spinal in children. In a Vermont Infant Spinal Registry study with over 1500 patients, failure was almost 15 times lower(1.1% versus 17%)[2]. While overall success rate for non-attendings was still greater than 80%, there is likely a considerable learning curve and many variables in the performance of the spinal such as positioning and needle angle. This difference in success rate is something to consider particularly when there may be a challenging regional anesthetic. There is no clear literature comparing CRNA versus residents success rates or impact of CSF flow and block failure. Use of ultrasound to assist placement of the spinal may be beneficial and it is suggested in difficult cases[3].

Frequent concern about dosing bupivacaine at 1mg/kg is heard from anesthesiologists who primarily take care of adult patients. This is unfounded as studies show higher csf turnover and safe plasma levels of local anesthetic in infants after spinal [4]. Safe levels were even observed in patients who had repeat doses of spinal local anesthetic.

One major challenge is optimizing operating conditions. Traditionally, sucrose and a pacifier helped to sedate the child in the periprocedure period. Meanwhile, spinal deafferentiation caused additional sedation after successful placement. These are largely ineffective in the older infants such as those around 1 year of age. Some of these children no longer use pacifiers, and their ability to move is stronger. A recent publication demonstrated potential utility to using an alpha 2-agonist such as dexmedetomidine for periprocedural sedation [5]. This report showed intranasal, and/or intravenous delivery minimized both crying, and movement without any clinically relevant

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hemodynamic alterations. This supplementation may serve as a helpful adjunct and perhaps even decrease conversion from spinal to general anesthesia. General anesthesia causes more hypotension in infants than spinal anesthesia. Research has shown negative effects of hypotension in infants[6].

Alterations in cerebral oxygenation after spinal anesthesia is minimal. In a recent paper, 103 infants were examined and no significant change in oxygenation was noted[7]. Similar results were found in a second paper[8]. Cerebral autoregulation appears to be intact after spinal anesthesia.

Table 1. Types and Number of Surgical Procedures Performed Under Spinal Anesthesia

Surgical procedure	Number of procedures
Anoplasty	19
Circumcision	65
Colostomy	41
Cystoscopy	24
Exploratory laparotomy	55
Gastroschisis	31
Inguinal hernia repair	855
Meningomyelocele repair	25
Omphalocele	5
Orthopedic lower extremity procedures	22
Patent ductus arteriosus ligation	20
Pyloromyotomy	136

Epidural Anesthetic Updates

Franklin Chiao, M.D..
Karen R. Boretsky, M.D.

Several techniques assist in performing neuraxial anesthesia. Ultrasound of the epidural space has provided an increased degree of success in locating the epidural space. This is particularly useful in younger children in whom the spine is not as ossified. Electrostimulation needles have greatly improved the accuracy in placing catheters in the neuraxial space. The Tsui catheter is particularly useful for this purpose.

Local anesthetics research has some notable findings. In our experience, the volume of amide local anesthetic in an adequate concentration required to provide similar analgesia to chloroprocaine would exceed safe dosing limits. Similar high 2-chloroprocaine doses via epidural infusions in former preterm infants showed low or negligible plasma 2-chloroprocaine concentrations. (Henderson) . The elimination half-life of 2-chloroprocaine is 20-40 seconds compared to 7.7 hours for bupivacaine and 3.9 hours for ropivacaine . In a retrospective comparison study of ropivacaine and 2-chloroprocaine for thoracic epidural analgesia for postthoracotomy pain in infants, Muhly compared epidural infusions of 2-chloroprocaine to ropivicaine and showed epidural infusion rates of 0.45 ml/kg/hr and 0.27 mg/kg/hr respectively and slightly less opioid consumption in the 2-chloroprocaine group . The mean infusion rate of 1.5% 2-chloroprocaine was 0.7 ml/kg/hr which is comparable to a study by Bardain of 11 infants with paravertebral catheter infusions of 1.5% 2-chloroprocaine at rates of 0.5-0.8 ml/kg/hr and comparable to existing studies of epidural catheter infusions of 2-chloroprocaine ranging from 0.25-1.5 ml/kg/hr. The epidural 2-chloroprocaine infusions reported no tachyphylaxis or adverse effects. There have been isolated reports of toxicity

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associated with 2-chloroprocaine (a seizure and a cardiac arrhythmia) , and each event was self-limited, lasting 30-40 seconds, with no permanent sequelae.

Studies of amide local anesthetics in epidural catheter infusions show a potential for accumulation in neonates and infants, leading to recommendations to stop infusions at 48 hours, thus limiting the utility of amide local anesthetics. We describe a population of high acuity patients (average ASA status 3.13) undergoing high pain and high-risk surgery where a longer duration of regional anesthesia was desirable. We were able to continue relatively high volumes of 2-chloroprocaine for an average of 5.2 days without demonstrated major complications. Although other studies report small numbers of patients with 2-chloroprocaine infusions for up to 8 days in small numbers of patients, the maximum duration of infusion of 2-chloroprocaine of 13 days in our study exceeds that from other reports. In addition to facilitating relatively larger hourly volumes for infusions, the use of 2-chloroprocaine facilitates longer catheter dwelling times.

Controversies
Giorgio Ivani, M.D..

Several controversies exist in pediatric regional anesthesia. The choice between performing a regional technique such as an epidural awake or asleep has generated a lot of debate. Deciding whether to use air or saline for loss of resistance during epidural placement will be discussed. Traditionally, clinicians have steered away from loss of resistance to air in pediatrics because pneumocephalus can occur. Benefits and safety improvements from test dose will be questioned and examined[9].

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Table 1: Management of high-stake perioperative events that may lead to cardiac arrest in OR

	Severe Anaphylaxis	Pneumothorax	LAST	Malignant Hyperthermia	Severe Hyperkalemia	Hypertensive Crisis	Pulmonary Embolism
Initial Management	**Pre-arrest:** Stop/remove the inciting agent or drug; stop procedure if possible; arterial blood pressure monitoring; oxygen at FIO2 of 1.0; intubate ASAP for respiratory distress; epinephrine 100-300 mcg in escalating doses ± vasopressin 2U IV; H1 blocker (diphenhydramine 50 mg IV); H2 blocker (famotidine 20 mg IV) ± corticosteroid (50-150 mg hydrocortisone IV or methylprednisolone 1-2 mg/kg IV).	**Unstable patient:** Needle thoracostomy.	**Pre-arrest:** Cease administration of local anesthetic; immediate tracheal intubation with 100 oxygen; transcutaneous or intravenous pacemakers for all symptomatic bradycardic rhythms with pulse; 20% lipid emulsion 1.5 mL/kg IV load, then 0.25 mL/kg/min (~20 mL/min); seizures treated with benzodiazepines.	Discontinue volatile anesthetics and switch from the anesthesia ventilator to manual Ambu bag ventilation from a separate source of oxygen; continue $ETCO_2$ monitoring; stop procedure if feasible; consider switching to IV anesthetic; sodium dantrolene: give 2.5 mg kg-1 or 1 mg lb-1 initial dose and repeat bolus of sodium dantrolene; start active cooling with ice packs and stop it at 38°C;	**Cardiac protection:** calcium chloride or calcium gluconate 1 to 2 gr IV and repeat as required for EKG signs of hyperkalemia. **Drive potassium into intracellular space:** 1 ampule of D50 and 10 units of insulin IV; 50 meq of sodium bicarbonate; albuterol 4-10 puffs.	Deepen anesthetic and administer antihypertensive medications if necessary; place patient in reverse Trendelenberg position; stop surgery if appropriate.	**Pre-arrest:** stop the infusion of the gas or ask the surgeon to flood the surgical field; administer 100% oxygen and intubate for significant respiratory distress or refractory hypoxemia; place patient in Trendelenburg position and rotate toward the left lateral decubitus position; maintain BP with fluid resuscitation and vasopressors/beta-adrenergic agents if necessary.
	Cardiac arrest: CPR if no carotid pulse detected for 10 sec; epinephrine 100-1000 mcg IV, can repeat every 3-5 min or replace with one dose vasopressin 40U IV; if auto-PEEP suspected, disconnect the ventilator briefly and administer adjunctive therapies listed in pre-arrest (H1 and H2 blockers± corticosteroids); extra-corporeal life support in patients getting good CPR.	**Stable patient:** Tube thoracostomy.	**Cardiac arrest:** CPR for prolonged period (at least 60 minutes); if local anesthetic toxicity suspected, epinephrine 10-100 mcg IV is preferable; sodium bicarbonate to maintain a pH >7.25 in patients; therapy with H1 and H2 blockers; aminodarone for ventricular arrhythmias; extra-corporeal life support appropriate if the diagnosis is certain.	remain observant for hyperkalemia, metabolic acidosis, respiratory acidosis, myoglobinuria with oliguria and dysrhythmias; invasive pressure monitoring when feasible; supportive measures for disseminated intravascular coagulation.	**Eliminate potassium or increase corporeal capacity:** 20-40 mg furosemide IV, increase to 1 to 1.5 mg/kg if oliguric response; 30 or 60 g kayexelate OG/NG/PR; induce renal replacement therapy by transfusing washed pRBC (hypokalemic and will absorb serum potassium); in patients with hyperkalemic cardiac arrest, extra-corporeal life support.		**Cardiac arrest:** Circulatory collapse addressed with CPR, and consideration of CPB/emergent thrombectomy if available
Subsequent Management	Determine blood tryptase levels; monitor in ICU for at least 24 hours to avoid recurrence.	Definitive management with tube thoracostomy; If pneumothorax due to lung injury, thoracic surgery.	Monitor for recurrence or delayed progression.	Monitor for 72 hours and treat/cool as required; consider caffeine-halothane muscle biopsy post-crisis.	Monitor serum potassium serially, continue to treat cause(s) of hyperkalemia.	Monitor for recurrence; circulatory collapse should be addressed with CPR.	Consider the right ventricular shock algorithm.

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Vasoplegia Following Cardiac Surgery - More Than Magic Bullets and Hail Marys

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INTRODUCTION

Vasodilatory shock is a common complication of major cardiovascular surgery, affecting 5-45% of procedures.[1,2,3,4] In the majority of these cases shock is limited in severity and duration. However, a subset of patients exhibit profound vasoplegia which carries with it significant morbidity and mortality.[1] Its pathophysiology is often assumed to be similar to sepsis-induced vasodilatory shock, though the inciting factor and some mediators may differ. Management of vasoplegic shock is largely via pharmacological therapy in the form of vasopressor medications. Several recent trials have investigated the role of these drugs as well as use of non-vasopressor adjuncts. These adjuncts occasionally lead to relatively rapid hemodynamic improvement where more traditional agents have failed. Particular attention has recently been directed towards methylene blue and hydroxocobalamin, among others. The findings from recent trials and the emergence of potentially new therapies are the impetus for this review, and will be discussed in conjunction with an overview of the basic mechanism and approach to management of vasoplegia following cardiovascular surgery.

VASOPLEGIA DEFINITION AND RISK FACTORS

Definition

Vasoplegic syndrome, also sometimes termed vasodilatory or distributive shock, is characterized by end-organ hypoperfusion due to profoundly low systemic vascular resistance (SVR) despite normal or supranormal cardiac output.[1] Although post-cardiotomy vasoplegia is a well-documented entity, the lack of a strict definition has hampered more robust investigation and accounts for its wide purported range of incidence. Generally, the syndrome is recognized by a persistent need for high dose vasopressor drugs to maintain appropriate blood pressure.

The low SVR state described in vasoplegic syndrome is found in a number of disease entities, including sepsis, glucocorticoid deficiency, hepatic failure, or long lasting severe shock of any cause.[5] Sepsis is the most common cause of vasoplegia and therefore has been the focus of many clinical trials.[5] However, while the hemodynamic consequences are similar, the differences between sepsis and cardiac surgery related vasoplegia remain relatively unexplored. Therefore, it is prudent to acknowledge that treatments for sepsis, and the evidence supporting those choices, may not be entirely generalizable to a postoperative population.

Incidence, Risk Factors and Outcomes

Vasoplegic syndrome is common after major cardiovascular surgery and is associated with poor outcomes, largely due to end-organ failure. Patients exhibiting postoperative vasoplegia suffer high rates of renal failure, prolonged hospital stays, and death.[6]Although the rate of post-cardiac surgery vasoplegia hovers somewhere in the range of 5-25% in groups without preoperative features of risk, in those with known predisposing factors this rate is anywhere from 30-50%.[6,7]Many preoperative factors have been associated with a higher incidence of post-operative vasoplegia, namely, preoperative use of angiotensin-converting enzyme (ACE) inhibitors, preoperative use of beta-blockers, and higher co-morbid disease burden prior to surgery.[7] Patients with low preoperative systolic ejection fraction have consistently shown a high affinity for development of vasoplegia.[2] Intraoperative aspects such as the need for vasopressors prior to or during CPB, warmer core temperatures while on bypass, and longer duration of CPB also confer a higher risk of developing vasoplegia. [2]

PATHOPHYSIOLOGY OF VASOPLEGIA

Cellular Physiology

From a cellular perspective, vasodilatory shock is complex, but is fundamentally a deficit in vascular smooth muscle contraction. In general, vascular smooth muscle contracts when intracellular calcium levels rise, through surface receptor binding and opening of voltage-gated calcium channels (where angiotensin and catecholamines bind). This rise in cytoplasmic calcium concentration generates a stepwise reaction in which calcium phosphorylates myosin, which in turn catalyzes cross-linking of myosin-actin filaments and generates contraction of the muscle and vasoconstriction.[5]

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This process is balanced by regulatory vasodilatory molecules, such as nitric oxide (NO) or atrial natriuretic peptide. These molecules trigger vasodilation via several mechanisms, all leading to a rise in intracellular cGMP concentrations. Inverse to the contractile process, this results in activation of myosin phosphatase, dephosphorylation of myosin, and vasodilation.[5]

Thus, the downstream effect of vasoconstriction is dependent on influx of calcium into the cytoplasm via voltage-gated channels. If these channels are deactivated, such as may occur with intracellular acidosis or depletion of ATP through membrane hyperpolarization, vasoconstriction will not be possible even if the cell is exposed to high levels of catecholamines. High levels of other compounds, including nitric oxide, atrial natriuretic peptide, adenosine, and others, can also lead to activation and prolonged opening of these channels. Presumably, this is an important physiologic mechanism to counteract periods of temporary local tissue ischemia. However, this can become counterproductive if prolonged periods of vasodilation lead to a persistently low pressure system and compromise of flow to other vessel beds.[7]

Nitric oxide, implicated as an activator of K_{ATP} channel opening, is a particularly important intercellular mediator of vasodilatory shock. Nitric oxide is synthesized by the NOS family of enzymes, which are differentiated by their typical organ location and baseline activity. Constitutive, calcium-dependent isoforms of NOS are responsible for constant, low-level nitric oxide production, which is important for inter-neuronal signaling, regional blood flow autoregulation, and immunologic modulation. Inducible, calcium-independent NOS isoforms (iNOS) synthesize nitric oxide on demand, and take several hours to respond to physiologic stress. This inducible NOS is often implicated as the mediator of distributive shock, and may precipitate mitochondrial dysfunction, apoptosis, and multi-organ failure. However, it plays important physiologic roles and perhaps should be thought of as a "necessary poison", having both direct and indirect injurious and protective effects.[8] For example, induction of NOS is important to increase myocardial NO levels, which encourages left ventricular relaxation and appropriate filling during diastole.[9,10] Ultimately, nitric oxide increases intracellular cGMP (thereby decreasing myosin phosphorylation), inactivates calmodulin, and also encourages opening of calcium-sensitive potassium efflux channels (K_{CA} channels) to blunt the effects of vasoconstriction. Thus, presence of nitric oxide leads to a state in which vascular smooth muscle contraction is antagonized.[6]

In addition to membrane hyperpolarization and high concentrations of nitric oxide, vasopressin is an important modulator of vasodilation. Prolonged shock is associated with a relative vasopressin deficiency, which may be inadequate for the severity of physiologic stress.[11] Initially, vasopressin serum concentrations are quite high in acute hypotension, but gradually taper to lower than normal levels. This drop-off is thought to be caused by depletion of neurohypophyseal stores after prolonged arterial baroreflex stimulation.[11,12] This is mechanistically important, as vasopressin directly inactivates K_{ATP} channels,[13] blunts the nitric oxide-induced increase in cGMP (by binding to AVPR1 receptors), and reduces nitric oxide synthesis.[14] Vasopressin thus mitigates the effects of membrane hyperpolarization, myosin dephosphorylation, and nitric oxide accumulation, and is an important modulator of vasomotor tone.[5]

Precipitants of Vasoplegia during Cardiovascular Surgery

Triggering factors for vasoplegia following cardiovascular surgery are poorly understood. Considerable investigation into the underlying mechanism has been performed, largely focusing on the physiologic response to extracorporeal circulation. CPB causes a broad-based immunologic response secondary to ischemia-reperfusion injury of the heart and lung, endotoxin release from mucosal surfaces, and complement cascade activation following exposure of blood to CPB circuitry.[15] These processes result in increased production of oxygen free radicals, endothelins, nitric oxide, platelet activating factors, thromboxane A_2, prostaglandins, a wide variety of cytokines, and other vasoactive molecules. Of particular interest, CPB leads to increased production of inducible nitric oxide, the concentration of which directly correlates with the length of CPB.[16] High serum concentrations of these molecules have also been found to correlate with development of the systemic inflammatory response syndrome, supporting the hypothesis that postoperative vasoplegia is, at least in part, an inflammatory response.[17] The downstream effects of these inflammatory and vasoactive agents are variable (e.g. potential vasoconstriction or vasodilation differs by concentration and physiologic action of each molecule), but lead to derangement of baseline vascular reactivity and tone.[16] Possibly, patients with chronically high levels of inflammatory mediators, such as those with pre-existing heart failure, may be particularly prone to a predominantly vasodilatory effect.[18] This may explain why patients with reduced ejection fraction are more likely to develop vasoplegia following CPB.[2]

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Nevertheless, a generalized inflammatory response with increased nitric oxide production is not the sole cause of post-CPB vasoplegia. Indeed, poor neurohumoral control of vascular tone in the form of a vasopressin deficiency plays a significant role. Serum vasopressin levels are known to increase during CPB, and in patients who do not develop vasoplegia, remain elevated or normal postoperatively. However, serum vasopressin concentrations in patients who develop postoperative vasodilation have been found to be inappropriately low, suggesting a chronic depletion of neurohypophyseal vasopressin stores. This relative vasopressin deficiency is similar but more severe than that seen in septic shock, suggesting that CPB is a particularly stressful trigger, and can lead to severe vasoplegia in susceptible patients.[5,6,19,20]

Thus, the development of postoperative vasoplegic shock is likely secondary to the coupling of a profound inflammatory response and a potential for relative vasopressin deficiency. These are themselves caused by the immunologic reaction that occurs to CPB and other non-specific perioperative triggers in the background of chronic cardiovascular neurohumoral stress. When these risk factors are combined with patient-specific risk factors, such as an extensive non-cardiac disease burden or need for complex surgical repair, there is a high likelihood of developing postoperative vasoplegic shock.

MANAGEMENT OF VASOPLEGIA

Early management of the postoperative vasoplegic syndrome focuses on recognition of the problem. Namely, the clinician should confirm the presence of hypotension, low SVR, and normal/supranormal cardiac output. Alternative etiologies of vasodilatory shock should be considered; early administration of antibiotics is important if infection is suspected.[21,22] It may be necessary in some patients, such as those who have had long aortic cross-clamp times or have undergone complex procedures, to transduce central (e.g. femoral) pressure, as it may be significantly higher than radial artery pressure. This is a common issue following CPB and may mitigate the need for aggressive anti-vasoplegic therapy.[23] Ultimately, adequate understanding of the existence and severity of vasoplegia is important in order to guide therapy.

Prevention

In an ideal setting, the clinician caring for the patient at risk of postoperative vasoplegia would be able to intervene prior to the onset of shock. However, many of the risk factors listed above are not modifiable in the immediate preoperative period or are inherent components of the surgical procedure to be performed. Furthermore, the pathophysiology of the vasoplegic syndrome is nuanced and associated with basic physiologic mechanisms of homeostasis. Manipulation of these mechanisms has generally not been associated with clinical benefit, such as unsuccessful trials of nitric oxide antagonism.[10] One group of investigators did find a reduction in the incidence of postoperative shock after empiric, early administration of vasopressin to patients at high risk of postoperative vasoplegia.[25] However, it is difficult to determine if this approach was reflective of a particular preventative benefit from vasopressin as opposed to treatment of unrecognized shock with any vasopressor. Others have advocated that ACE inhibitors should be withheld preoperatively from patients at high risk of perioperative vasoplegia.[26] However, the appropriate timeline to hold administration of these agents and the potential outcomes associated with this approach have not been investigated. Thus, the clinician with concern for potential vasoplegia should be aware of the treatment options below.

Fluid and Blood Product Resuscitation

Identifying fluid responsiveness is an important component of early treatment of postoperative vasoplegia. Due to perioperative hemorrhage, hypovolemia may be concomitant with vasoplegic shock; judicious transfusion of blood products should be used to correct severe anemia. Generally, restrictive transfusion strategies are preferred over more liberal strategies.[26] However, overly aggressive fluid resuscitation (beyond 20 – 30 mL/kg) leads to excessive vascular shear stress, unnecessary increases in cardiac filling pressures, and harmful accumulations of extravascular lung water.[27] Ultimately, inordinate fluid administration is associated with increased mortality in pure vasodilatory shock, and should be avoided.[28]

Vasoactive Drugs

The cornerstone of vasoplegic shock management is the use of vasoactive agents to restore vascular tone. These agents act on various receptors to increase SVR and raise mean arterial pressure, and are thus broadly termed “vasopressors.” Catecholamines are the mainstay of treatment, but may be required in high doses and may yield insufficient

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hemodynamic stability. Other, non-catecholamine, vasopressors have not historically been used for vasodilatory shock, but may be particularly beneficial and have been more intensely scrutinized in recent years; they are described here. Table 1 summarizes the agents discussed below.

Table 1: **Vasoactive Drugs for the Management of Vasoplegia** to be inserted here

An important caveat to the decision to choose any one particular vasoactive agent over another is the observation that many of these recommendations are based on results from randomized trials of vasopressors for septic shock. Thus, while likely generalizable to patients with post-CPB vasoplegia, they may not be directly comparable. This is particularly important when considering the potential for concomitant cardiogenic shock. Ventricular dysfunction is common following cardiovascular surgery as well as in sepsis.[29] Thus, while increasing SVR remains the goal of treating vasoplegic states, the use of vasopressors must be balanced with the need to ensure appropriate left ventricular afterload to allow for effective end-organ perfusion. While outside the scope of this review, assessment of cardiac performance (such as that which is easily performed with echocardiography) is therefore a critical component of managing vasoplegia.[30]

Catecholamines

Catecholamines exert their physiologic effects by modulation of adrenergic receptors. They have traditionally been the agents of choice to treat vasodilatory shock. Norepinephrine, phenylephrine, epinephrine, and dopamine have all been used successfully to increase mean arterial pressure (MAP) without limiting end-organ perfusion. Norepinephrine has been extensively studied in sepsis-induced vasodilatory shock. It may provide a mortality benefit when compared to other catecholamines, and is the recommended first-line agent specifically in septic shock.[22,31,32] However, trials comparing norepinephrine to combinations of other catecholamines, such as epinephrine or dobutamine, have failed to show a definitive benefit.[33] On the other hand, dopamine carries an increased risk of arrhythmia as well as mortality when compared to norepinephrine in randomized, controlled trials and should probably not be used as a first-line agent.[34]

A frequent concern when using high dose vasopressors is the potential for severe peripheral vasoconstriction and end-organ injury. However, there is insufficient evidence to support this theory. Nevertheless, the need for high dose catecholamines should prompt the clinician to consider switching to, or adding, a non-catecholaminergic agent.[35]

Vasopressin

Use of non-catecholaminergic agents for treatment of vasodilatory shock bypasses some of the difficulties when dealing with severe vasoplegia, including membrane hyperpolarization and associated catecholamine resistance.[5] Non-catecholamines may also simply exert a synergistic effect, and allow for reduced doses of any one particular agent, creating a more balanced approach to vasopressor therapy.[35] This is perhaps especially notable with vasopressin, the use of which is biochemically supported by the presence of a vasopressin deficiency following CPB.[6,19]

Vasopressin binds to AVPR1a, AVPR1b, and AVPR2, oxytocin, and purinergic receptors. The AVPR1a receptor is especially important, as it promotes vasoconstriction by inhibiting K_{ATP} channel opening and reduces nitric oxide production, providing an entirely catecholamine-independent mechanism of mediating vasodilation. Several recent randomized, controlled trials have focused explicitly on outcomes following use of vasopressin for septic shock. In the VASST trial, patients with septic shock who were already receiving norepinephrine were randomized to either norepinephrine or vasopressin. The investigators did not identify a difference in their primary outcome of mortality between groups at 28 days, but did observe a significant reduction in catecholamine dose necessary to achieve target mean arterial pressure in the vasopressin group and did not identify harm associated with vasopressin.[36] Of note, post hoc analysis of VASST found improved renal outcomes in patients in the vasopressin group who had mild kidney injury at enrollment.[37] The 2016 VANISH trial explored this finding further. Powered primarily to detect a difference in renal failure between vasopressin and norepinephrine for septic shock, the authors randomized patients to vasopressin and hydrocortisone, vasopressin and placebo, norepinephrine and hydrocortisone, or norepinephrine and placebo. There was no significant difference in renal failure between vasopressin and norepinephrine groups, but dialysis was used less frequently in the groups that received vasopressin, which suggests it may reduce the severity of renal failure as compared to norepinephrine.[38] Ultimately, VASST and VANISH were large, well-performed trials which failed to identify a definite benefit of vasopressin over catecholamines for septic-type vasodilatory shock, though the observation that vasopressin may limit the severity of renal failure is intriguing.

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Of importance, the vasopressin deficiency seen after CPB is even more severe than that seen during septic shock. Patients with post-CPB vasoplegia may therefore theoretically obtain greater benefit from vasopressin administration than the septic shock population.[19] Several small early trials had demonstrated vasopressin safe and potentially effective after cardiopulmonary bypass, but were generally been underpowered to address clinical outcomes and did not have head-to-head comparison with norepinephrine.[19,39] To address these issues, Hajjar *et al.* conducted the recent VANCS trial, in which patients with post-CPB vasoplegic were randomized to vasopressin or norepinephrine as a primary agent. Patients who had been randomized to vasopressin had a significant reduction in a composite endpoint of 30-day mortality or severe postoperative complications, driven almost exclusively by a decrease in the occurrence of acute renal failure.[40]

Taken as a group, VASST, VANISH, and VANCS represent a large population of patients with either septic or CPB-induced vasoplegic shock who generally benefit from vasopressin as a single or additive vasopressor. However, this is largely limited to a reduction in need for catecholamines or a decrease in the severity or incidence of renal failure, rather than an improvement in mortality. Nevertheless, a reduction in renal failure (and the potential need for dialysis) is an important finding, which should promote the perioperative use of vasopressin. The results of the VANCS trial are especially encouraging in patients with vasoplegia following cardiac surgery. and lend support to the practice of early, and possibly preferential use, of vasopressin over catecholamines.

Methylene Blue

Several endogenous compounds, including nitric oxide, carbon monoxide, and oxygen free radicals produce local vascular vasodilation, which may be an important counterbalance of systemic vasoconstriction in early shock states but can become pathologic if widespread vasodilation results in global hypoperfusion. Most of these substances, of which nitric oxide has been the most extensively investigated, mediate vasodilation via cGMP second messenger pathways, and are thus broadly antagonized by agents which disrupt this signaling cascade.[41] Methylene blue is one of these agents and, more than any other drug, is often considered a rescue agent capable of treating post-CPB vasoplegia. It directly competes with nitric oxide for activation of guanylyl cyclase, the enzyme responsible for synthesizing cGMP from GTP. Furthermore, it inhibits inducible NO synthase, potentially reducing the upswing in nitric oxide concentration that occurs with CPB and other physiologic stress. Methylene blue therefore prevents NO-mediated dephosphorylation of myosin and associated vasodilation.[5] However, the potential downstream effects of its broad-sweeping action upon basic physiologic mechanisms of vascular reactivity are unknown.

Adverse reactions with methylene blue are uncommon, but can be serious. They are largely explained by the global antagonism of nitric oxide-mediated vasodilation, and include coronary vasoconstriction, decreases in splanchnic blood flow, and increases in pulmonary vascular resistance. Furthermore, methylene blue is reduced in red blood cells to leukomethylene blue, which requires NADPH. This can precipitate hemolytic anemia, especially in patients with G6PD deficiency. Methylene blue and leukomethylene blue are excreted in the urine, reliably coloring urine green. Methylene blue also interferes with pulse oximetry readings, though this is transient, and has been associated with a non-specific elevation in liver function tests.[42] Additionally, methylene blue is a potent inhibitor of monoamine oxidase, and may precipitate serontonin syndrome, particularly in patients taking selective serotonin reuptake inhibitors. While, these side effects are uncommon, they are relatively wide ranging and associated with severe disruption of normal cardiovascular physiology.[43]

Early case reports identified successful use of methylene blue to rapidly reverse severe vasoplegia after CPB with only single 1.5 - 2 mg/kg boluses.[44,45] These reports prompted small scale prospective interventional studies, which confirmed methylene blue's ability to rapidly and dramatically improve mean arterial pressures of post-CPB vasoplegic patients and suggested a possible mortality benefit of the drug.[46,47,48,49] Retrospectively, methylene blue may be most efficacious if administered early in the course of vasoplegic shock (e.g. while still in the operating room as opposed to postoperatively), where it may reduce the risk of mortality or end-organ failure.[50] However, not all studies have been supportive of use of methylene blue. In one retrospective analysis methylene blue was associated with an increased likelihood of developing renal failure and mortality. However, the vasoplegic patients in this study who had received methylene blue were sicker than their counterparts who were not given the drug, and the authors were not able to solidify their findings with propensity matching.[51]

Without question, readily available non-catecholamine vasopressors (e.g. vasopressin and methylene blue) have a role in treating post-CPB vasoplegia. However, until more rigorous trials are performed, they are limited to additive and/or rescue roles. A recent systematic review and meta-analysis, which did not include the VANISH or VANCS trials but

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did include more than 1,600 patients over 20 trials, concluded that vasopressin, terlipressin (discussed below), and/or methylene blue did improve survival when compared to catecholamines. However, this analysis incorporated patients with diverse etiologies of vasoplegic shock and included some potentially biased studies. Additionally, neither vasopressin, terlipressin, nor methylene blue were superior to catecholamines when analyzed independently.[52] Thus, evidence supports the use, but not superiority, of non-catecholamine vasopressors to improve outcomes in vasodilatory shock.

Corticosteroids

The use of corticosteroids to treat vasodilatory shock has been controversial for several decades, and is based on the assumption that hypothalamic-pituitary-adrenal axis may be suppressed in periods of critical illness. Putatively, corticosteroids ameliorate the underlying inflammatory process that causes loss of vascular tone, and may also increase the efficacy of vasopressors by increasing the expression of vascular adrenergic receptors. However, clinical investigations of corticosteroids for vasoplegia have not shown a mortality benefit, but have found an increased risk of infection. This was most recently demonstrated in the CORTICUS trial, published in 2008, which evaluated the use of a five day course of 50 mg of hydrocortisone every six hours in patients with septic shock. The authors found no significant mortality benefit with hydrocortisone compared to placebo, both in patients who were unresponsive to corticotropin stimulation and in those who were responsive (presumably adrenally suppressed and not suppressed, respectively). However, patients who received hydrocortisone had more rapid reversal of shock.[53] This finding was also seen in an earlier trial, published in 2002, which also found a mortality benefit with corticosteroids in corticotropin non-responders who were hypotensive despite fluid resuscitation and administration of vasopressors. Additionally, formative work precluding the VANISH trial demonstrated evidence for interaction of corticosteroids and vasopressin, with a halving of vasopressin dose in those receiving steroids, interestingly without a change in overall vasopressin levels. Cumulatively, these studies support the notion that corticosteroids may hasten the resolution of vasodilatory shock, though do not provide an overall mortality benefit, possibly unless the patient is hypotensive despite vasopressors.[54]

The use of corticosteroids for treatment of non-septic vasoplegic shock has not been explicitly evaluated. However, their role in the cardiac surgery population must be considered in light of the potential for increased perioperative complications (including delayed wound healing, poor glucose control, and gastrointestinal bleeding) as well as recent findings from the 2015 SIRS trial.[55] In this trial, methylprednisolone did not confer a benefit with respect to mortality or end-organ function when given before and during CPB to high-risk patients undergoing cardiac surgery.[55] Similarly, the earlier DECS trial did not find significant benefit from intraoperative use of dexamethasone given to patients undergoing cardiac surgery with use of CPB.[56] However, both the DECS and SIRS trials were designed to detect a reduction of adverse outcomes (e.g. death, stroke, myocardial infarction), rather than the effect on vasoplegia. In summary, neither of these studies focused explicitly on postoperative vasoplegic shock. Thus, it is plausible that corticosteroids may hasten reversal of post-CPB shock, as they do in sepsis, but fail to reduce mortality rates.

FUTURE DIRECTIONS

Several potential therapies have not yet permeated into conventional practice, but are supported by case series or early investigations. They may become viable treatment options in the near future, and are discussed here.

Vitamin C

Vitamin C (ascorbic acid) has known anti-inflammatory effects and may also improve autoregulation of micro-circulatory blood flow. These qualities, putatively similar to those of corticosteroids, may reduce the dose of vasopressors required to achieve hemodynamic goals.[57]A recent preliminary, retrospective study of patients with severe septic shock identified a dramatic reduction in mortality in patients who were treated with a daily intravenous combination of 6 g vitamin C, 50 mg of hydrocortisone every 6 hours, and 200 mg of thiamine every 12 hours. Of importance to our review, the authors of this trial found a significant and rapid reduction in vasopressor requirements in patients who received the study regimen. [57] The effects of the individual agents (e.g. vitamin C without use of hydrocortisone) on hemodynamics is unknown. Ultimately, the generalizability of these results to a post-cardiotomy population is uncertain. Future research may encourage the use of vitamin C as another non-catecholamine vasopressor.

Hydroxocobalamin

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There are isolated case reports of hydroxocobalamin's successful use in the setting of vasoplegic syndrome.[58,59]Although traditionally used in the treatment of cyanide poisoning, the mechanisms of hydroxocobalamin-induced hypertension are yet to be fully elucidated, but may lie in its ability to bind the vasodilatory compound hydrogen sulfide. Unlike methylene blue, it does not carry a risk of serotonin syndrome, though is more expensive and may cause chromaturia.[60] In terms of dosing, successive aliquots of 250mg of intravenous hydroxocobalamin have been administered alongside infusions of 500 mg/hr in liver transplantation. The same group has reported the use of 5g administered intravenously over 15 minutes in the cardiac surgical setting.[61] Although premature to advocate for its widespread use, it may be another possible rescue therapy in the setting of profound refractory vasoplegia.

Terlipressin

Terlipressin is an established vasopressin analogue used primarily outside of North America with similar pharmacodynamic properties to vasopressin. However, it has a much longer half-life than vasopressin (4 - 6 hours as opposed to 6 minutes), and thus can be intermittently bolused without the need for continuous infusion. Additionally, it has preferential selection for AVPR1-type receptors, and thus may allow for more selective vasoconstriction, without NO liberation that may occur with agonization of AVPR2 receptors. Small studies comparing terlipressin and norepinephrine have shown them to be equally effective at raising MAP.[62] However, the isolated increase in SVR that occurs with terlipressin, without perhaps being offset by beta-adrenergic effects of norepinephrine or AVPR2 effects of vasopressin, could possibly be harmful. Because of its long half-life, long-lasting reduction in cardiac index and oxygen delivery caused by high SVR could be detrimental, and may require the addition of an inotropic agent.[63] When compared head-to-head with vasopressin, terlipressin performed similarly, but was associated with a reduction in platelet counts. [62,64] Ultimately, larger, controlled trials need to be performed before terlipressin can be considered an appropriate anti-vasoplegia agent.

Angiotensin II

Angiotensin II is an endogenous hormone that makes up a component of the renin-angiotensin-aldosterone axis and is a direct, potent vasoconstrictor. It has a serum half-life of approximately 30 seconds, though has up to 30 minutes of effect while in parenchymal tissue. It has wide-ranging homeostatic effects, including stimulation of aldosterone release and antidiuretic hormone secretion. Much of its downstream effects are designed to increase sodium and water retention while ensuring appropriate vascular tone, and it has therefore been recently scrutinized as a possible non-catecholamine rescue vasopressor. Chawla *et al.* performed a small study of angiotensin II, starting at 20 ng/kg/min, versus placebo to evaluate the concomitant need for norepinephrine and found a significant, dramatic reduction in norepinephrine requirement in the group receiving angiotensin II.[65] A follow-up trial randomized patients with septic shock to either angiotensin II or placebo with a primary endpoint of an increase in MAP at 3 hours post infusion. Although somewhat limited, with an inclusion criterion of a relatively normotensive MAP range of 55-70mmHg, the results were encouragingly in favor of angiotensin II.[66] Further research is needed to determine the effects of angiotensin II on patient outcomes before it can be added to the anti-vasoplegia armamentarium. The role of exogenous vasopressin, if combined with angiotensin II, also needs to be elucidated, as angiotensin II naturally encourages the release of vasopressin from the neurohypophysis.

CONCLUSION

Vasoplegic shock is common after cardiovascular surgery. While it is often a component of the inflammatory response that occurs with CPB, alternative diagnoses with similar presentations, such as sepsis, should be considered. After appropriate fluid resuscitation has been performed, vasopressors become the primary form of treatment. Catecholamines, norepinephrine in particular, are the best studied and are the suggested first-line treatment agents. Recent investigations have supported the use of non-catecholamine drugs, especially when used in conjunction with norepinephrine. Vasopressin and methylene blue are relatively well-studied and are attractive additive and/or rescue agents. Both of these drugs, as well as other agents capable of increasing SVR may see expanded roles in the near future when treating severe vasoplegia.

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Available upon request

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ANESTHESIOLOGY 2018
SAN FRANCISCO OCTOBER 13-17

Burnout in Anesthesiology Practices: Realities and Remedies

Amy E. Vinson, MD **Boston/MA**

Introduction:

In a recent editorial in the Journal of the American Medical Association (JAMA), Dr. Thomas Schenk aptly stated that "Physicians in 2018 are the proverbial 'canary in the coal mine.' While the canary may be sick, it is the mine that is toxic. Caring for the sick canary is compassionate, but likely futile until there is more fresh air in the mine."[1]

Burnout and wellness in physicians is garnering increased attention in the lay and academic literature. Despite this increased press, understanding of these concepts is often lacking or misguided, which can lead to a delay in action to mitigate the negative effects. This is especially true following adverse clinical events. This lecture will explore the impact of burnout, the intersection with adverse events and peer support, and offer a framework from which a practice or department can bolster their defenses against such a disruptive force. One such structure is peer support that can offer not only "point-of-care" comfort, but a referral network providing more longitudinal care. We will also delve into the role of the Physician Anesthesiologist and the characteristics in a leader that foster wellness and create a culture of wellness in a practice or department.

The Merriam Webster Dictionary defines burnout as the **"exhaustion of physical or emotional strength or motivation usually as a result of prolonged stress or frustration."**[2] What is important here is the multifaceted nature of burnout – it is physical, emotional and motivational. It is also not equal to stress, but the consequence of stress. Certain levels of stress can be good, fun and sustaining, but unmitigated and repetitive stress without corresponding moments of respite are unsustainable and will almost certainly lead to some degree of burnout.

Moment for Mindfulness

Before diving deeper into burnout, it's causes and possible solutions, we must reorient to a reality that we probably take for granted. Every day, in the course of our jobs, we intersect with other human beings during some of the most profound moments of their lives. We bear witness to some of the most unfair situations imaginable. We risk injury or death to the patients we care for as we vigilantly strive to do no harm. We worry we will make a mistake, that we will get sued, that we will harm a patient. We worry that we are becoming hardened to what we see – sometimes we worry that we no longer worry! This worry is a normal response for a compassionate human being caring for other human beings, but we may often feel we cannot speak up and admit that the weight is having an effect on us, since we are all in the same boat - but it ***is*** *affecting us, as well as our patients and our careers, so we must discuss it.*

Historical Perspectives:

The modern term "burnout" was first coined by Dr. Herbert Freudenberger in a 1974 article outlining the pathway ("burnout cascade") to what he described as the "burnout syndrome".[3] He described the steps (e.g. a compulsion to prove oneself, denying basic needs, denying emerging problems) leading towards full blown burnout and what is striking is how many of these steps are taught, rewarded, reinforced and revered in medical training. While certainly not the intended consequence, the medical training pathway is exceptional at training doctors to be burned out – it should not be surprising that it is now such a serious problem.

In the late 1970s and early 1980s Dr. Maslach and colleagues developed what is now the most widely used metric of burnout: The Maslach Burnout Inventory (MBI).[4] Since that time it has been broadly utilized in nearly every service related industry or situation, from home health care providers, to teachers, to first responders and

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medical care providers. It describes burnout across 3 major areas: Emotional Exhaustion, Personal Accomplishment, and Depersonalization.

Emergence of new data and renewed concern:

Following years of studies into the prevalence of burnout in various service-related industries, Shanafelt et al conducted the first large study of the prevalence of burnout and satisfaction with work-life balance in physicians. The results were striking and attracted significant attention in both the lay and academic press. He found that nearly half (45.8%) of physicians demonstrated at least 1 major symptom of burnout, with anesthesiologists faring a little worse than average.[5]

Understandably, this revelation was followed by an emergence of national discussion on the topics of wellness, burnout, mindfulness and other aspects of well-being. Unfortunately, knowing may be half the battle, but a follow-up study in 2015 demonstrated a worsening of burnout with more than half (54.4%) of US physicians now demonstrating at least 1 major symptom of burnout (anesthesiologists again demonstrating slightly worse than average levels of burnout).[6]

The Impact of Burnout on the Physician:

If burnout were an isolated problem, it would be difficult to justify intervention. However, concomitant impacts to provider health, career longevity, suicidality and professionalism have been well documented to be associated with burnout. A population based national survey in Finland, the Finnish Health 2000 Study, found a positive association between burnout and physical illness in the general public (64% with burnout vs. 54% without burnout). Specifically they found particular association between burnout and cardiovascular disease in men and musculoskeletal disorders in women.[7] Further results of this large study revealed a significant risk of disability pension and sick absences associated with increased burnout scores.[8,9] A Canadian economic model estimated $213 million in future service reductions due to burnout-induced early retirement.[10] In an age of physician shortages, we cannot afford to prematurely lose physicians to burnout.

Additionally, the concern for burnout raises awareness for other aspects of un-wellness and dysfunctional coping mechanisms, such as substance use disorder. While long appreciated as a significant concern in anesthesiology, the burden of substance use disorder had previously not been well defined. In 2015, Warner et al published the results of an exhaustive review of available databases to determine the ultimate outcome for residents found to be suffering from substance use disorder during residency from 1975 to 2009.[11] They reported a dramatically increased risk of death following training (hazard ratio of 7.9), notably producing a Kaplan-Meier plot of anesthesiology residents suffering with SUD.

Suicidality is increased in medical students and physicians. A meta-analysis of studies of physician suicide in 2004, demonstrated a suicide rate ratio (compared to the general public) of 1.41 (95% CI 1.21-1.65) for male physicians and 2.27 (95% CI 1.90-2.74) for female physicians.[12] Dr. Pamela Wible has been following, writing about, and studying the phenomenon of physician suicide for years and recently published an article in the Washington Post that attracted considerable attention and concern. She outlined her experience studying 757 physician suicides, and notably stated that “Male anesthesiologists are at highest risk”.[13] The ASA has recently formed an ad hoc Committee on Anesthesiologist Suicide Rate to study and intervene on this serious matter.

The Impact of Burnout on the Patient Experience and Safety:

Burnout impacts not just our own health, but also the quality of care for our patients. Burnout in medical students has been shown to be associated with diminished levels of professional conduct, empathy and clinical care.[14,15] One study of general internal medicine doctors suggested that patients of more satisfied physicians were themselves more satisfied with their care.[16] Similarly, a study of the impact of baseline clinician mindfulness on patient satisfaction in a family medicine HIV clinic demonstrated that more mindful clinicians were rated higher in terms of communication, patient satisfaction and positive emotional tone. They were also as, if not more, efficient than average.[17]

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Medical errors and burnout are linked, and likely represent a feedback loop. Burnout and medical errors are associated in surgeons, as demonstrated by Shanafelt et al.[18] In anesthesiologists, perioperative catastrophes can often have a tremendous impact as well. In a national survey, Gazoni et al demonstrated that 84% of respondents had experienced a perioperative catastrophe, 88% required time to recover, 19% never fully recovered from the event, 12% contemplated changing careers, but only 7% were afforded any time whatsoever to recover. Strikingly, 67% self-reported that the care they provided in the 4 hours following a perioperative catastrophe was likely compromised.[19]

The Quadruple Aim

"In no relationship is the physician more often derelict than in his duty to himself."
"Begin at once the cultivation of some interest other than the purely professional."

These 2 statements, by Sir William Osler (often considered the father of modern medical education) were made to a group of physicians in training at the turn of the 20th century.[20] Clearly, compromised self-care and struggles with work-life balance are nothing new in the medical community. The ACGME has sought to address the well-being of trainees, first by changing the training measurements to a milestones-based system, including aspects of wellness and then, more recently, introducing an entirely new section addressing well-being in the revised ACGME Common Program Requirements, published in July of 2017. These new requirements apply not only to trainees, but in some instances to all staff in a department hosting any trainees and include aspects such as the availability of formal counseling, modes to discuss wellness concerns, and accommodation for routine medical, dental and psychiatric care.[21]

In 2008, in an effort to solidify goals of healthcare improvement, Berwick et al published their rubric of the "Triple Aim": "improving the experience of care, improving the health of populations, and reducing per capital costs of healthcare."[22] Put more simply: *Increased Patient Satisfaction, Reduced Costs, Improved Outcomes*. In 2015, in response to the growing body of literature demonstrating a connection between physician wellness and patient care, Sikka et al suggested adding a fourth to form a "Quadruple aim": "improving the experience of providing care" or, put more simply, *Increased Provider Satisfaction*.[23]

The Role of Organizational Structure and Leadership in Burnout Prevention:

Operating from the Quadruple Aim framework, Dike Drummond (a physician burnout coach and family physician) outlines what he believes, based on available data and his expertise developed from coaching burned out physicians, are the 5 major sources of burnout.[24] They are:

- The practice of clinical medicine (the healthcare landscape, including electronic health records)
- Your specific job (stressors particular to each specialty)
- Having a life (e.g. work-home conflict)
- The conditioning of our medical education (the reinforcement of behaviors and attitudes known to be steps in the burnout cascade as described above)
- The leadership skills of your immediate supervisors (an area of increasing interest as leaders of departments and practices seek to mitigate the negative effects of burnout)

A recent survey by Shanafelt et al seeks to understand the leadership qualities most tightly linked to burnout. Asked about 12 leadership characteristics (e.g. "Inspires me to do my best", "Empowers me to do my job", Recognizes me for a job well done") they found that every single one was associated with levels of burnout to a similar degree.[25] While initially daunting, what this can mean is that a leader may start with a few of these characteristics and focus on their development and move on to the others over time.

Further reassurance came from a national survey of academic anesthesiology chairs by Vinson et al, wherein chairs were asked their priorities for wellness related topics in their department. Out of 22 topics, ones relating to individual pursuance of wellness were rated lowest (e.g. spirituality support, access to cultural events,

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nutrition counseling, meditation training), while those relating to modifiable department level support were rated highest (e.g. conflict management, dealing with adverse events, stress management, burnout counseling, addiction counseling).[26] The author believes that this indicates chairs' awareness of the onus for mitigating burnout not resting on the shoulders of the individual alone, but largely on the department to create a culture of wellness and support.

Regarding support, clinical practice can often provide us with opportunities when support is required. Wu defined the provider involved in an adverse medical event as the "second victim",[27] a term which, though somewhat controversial,[28] is most widely used to describe the phenomenon of emotional distress in medical providers involved in an adverse event. In a 2009 study of the national history of recovery following medical catastrophes, Scott et al demonstrated a wide range of *normal* responses following a major adverse event.[29] These include both physical and psychosocial symptoms and highlight the vast range of "normal" responses to such an event. Another study by Schwappach et al also sought to define what was *normal* following a major adverse event and, following a review of available literature, could only conclude that the norm following a major adverse event is "an intense emotional response".[30]

Inquiring as to what support structures are available for residents following adverse events, Vinson et al surveyed anesthesiology program directors and residents regarding what they found helpful and what was utilized in the aftermath of an adverse clinical event.[31] They found that individual meetings with department leadership and peer support programs were most highly utilized and efficacious, whereas more sterile environments such as M&M and Legal QI/QA interventions were less efficacious (though frequently encountered following an adverse event). The author proposed that programs:

- Foster individual meetings with department leadership
- Develop point of care peer support (preferentially within the department)
- Modify M&M and Legal/QI/QA constructs to be as supportive as possible, while still functioning to identify systems-based and modifiable safety concerns

Organizational Strategies for Burnout Prevention:

As appreciation for the impact of burnout increases and requirements from credentialing boards, such as the ACGME, emerge, departments are striving to create cultures of wellness. Recently, at Beth Israel Deaconess Medical Center in Boston, MA, Hale et al published their adaptation of Maslow's Hierarchy of Needs (physiologic, safety, love/belonging, esteem, self-actualization)[32] in order to create a framework to promote resident wellness.[33] This very granular paper offers a pragmatic approach to a broad range of wellness related aspects and can serve as an excellent resource for departments seeking to improve their group's culture of wellness.

Taking a similar approach of putting more of the responsibility for physician wellness on the department and institution, a "Charter on Physician Well Being" was recently published in the Journal of the American Medical Association and is also an excellent framework from which to approach wellness from both a macro and micro level. Importantly, in the more prescriptive section of the paper, few suggestions are targeted at the individual physician, with leadership styles and organizational structure remaining the focus.[34]

One final model for wellness comes from Stanford's WellMD initiative,[35] which seeks to create a culture of wellness through predominantly institutional, organizational and leadership modifications, with individual skills and behaviors taking a minority role. The 3 main realms of promoting wellness are the:

- Culture of Wellness ("Organizational work environment, values and behaviors that promote self-care, personal and professional growth, and compassion for ourselves, our colleagues and our patients.")
- Efficacy of Practice ("Workplace systems, processes, and practices that promote safety, quality, effectiveness, positive patient and colleague interactions, and work-life balance.")
- Personal Resilience ("Individual skills, behaviors and attitudes that contribute to physical, emotional and professional well-being.")

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Finally, in this author's opinion, the most critical aspect of a culture of wellness is in fostering an environment where a physician gleans meaning from their work and feels unfettered in their ability to best care for their patients. Aptly, Dr. Francis Peabody is quoted as saying "the secret of physician well-being is in caring for the patient".[36]

Conclusions:

Burnout is a clear and present issue in our profession – one that will require innovative leadership to address in order to safeguard our patients and own ranks. Burnout is a safety issue: for our patients and for ourselves. The American Society of Anesthesiologists has long been a leader in patient safety and we are uniquely suited to be leaders in this particular arena of patient and physician safety.

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Electroencephalography in Anesthesiology Practice

Emery N. Brown, M.D., Ph.D. **Boston, MA**

What is General Anesthesia?

General anesthesia is a fascinating man-made, neurophysiological phenomenon that has been developed empirically over many years to enable safe and humane performance of surgical and non-surgical procedures. Specifically, it is a drug-induced condition consisting of unconsciousness, amnesia, anti-nociception and immobility, along with physiological stability.[1] The advent of general anesthesia first practiced in the 1840's as the administration of ether transformed surgery overnight from butchery and trauma to a humane, and in many cases, life-saving therapy. Today in the United States, general anesthesia is administered daily to 60,000 patients.[1] World wide, 250 million patients receive general anesthesia each year.

Today, general anesthesia is no longer produced by administering a single agent. The most common strategy for anesthesia care management is balanced general anesthesia which means administering a combination of different agents to produce the anesthetic state. This approach was developed to reduce reliance on only ether for general anesthesia maintenance.[2] Balanced general anesthesia uses less of each individual anesthetic than if the anesthetic were given by itself.[3] Balanced general anesthesia is thought to increase the probability of obtaining the anesthetics desired effects while decreasing the probability of having its side effects.

Significant progress has been made recently in characterizing the molecular sites that anesthetics target. In recent years, systems neuroscience research in anesthesiology has begun to define how the actions at specific molecular targets lead to the behavioral states of general anesthesia. In particular, the principal feature observed across all the anesthetics are systematic, highly-organized oscillations, which are readily visible in the electroencephalogram (EEG). Substantial evidence now suggests that these oscillations induced and maintained through the administration of anesthetics are a principal neurophysiologic mechanism of anesthetic action.

The EEG as a Read Out of the State of the Brain

The fundamental mechanism through which information is transmitted in the brain and central nervous system are through spikes or action potentials, received and transmitted.[4,5] This neural activity produces extracellular electrical potentials,[6] that consist principally of hyperpolarization of neuronal membranes and post-synaptic potentials.[6,7] Extracellular potentials are commonly termed local field potentials (LFPs). Neuronal populations often produce oscillatory local field potentials and spiking which are believed to play a fundamental role in modulating and coordination communication among and within neural circuits.[5] Cortical local field potentials can be recorded at the scalp as the electroencephalogram (EEG).

The organization of cortical pyramidal neurons favors generation of LFPs pyramidal neuron dendrites travel perpendicular to the cortical surface and parallel to each other. This geometry produces a neurophysiological transmitting antenna that yields large extracellular currents. The potentials of this antenna can be recorded through the scalp and the skull as the EEG.[6,8,9] Subcortical areas, such as the brainstem and the thalamus, generate significantly smaller potentials that are harder to detect at the scalp. This is because the electric field drops off in strength one over the squared distance from its source.[9] Because subcortical and cortical structures are highly interconnected, EEG patterns recorded at the scalp are the result activity arising from both subcortical and cortical structures.[10] Therefore, the EEG offers a readout of the oscillatory state of the brain.

EEG Signatures of the Commonly-Used Anesthetics

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The EEG signatures of the commonly-used anesthetics change systematically with anesthetic class. The structure of the oscillations can be explained in terms of the receptors where the anesthetics bind and the anatomy and the neurophysiology of the circuits connecting the brain regions where these receptors are located. For example, propofol and sevoflurane both act at GABA receptors where inhibitory interneurons synapse on to excitatory pyramidal neurons. The net effects of propofol and sevoflurane at inhibitory synapses in the brainstem, thalamus and cortex are clearly visible in the EEG of young adults as alpha oscillations (8 – 12 Hz) and slow-delta oscillations (0.1 – 4 Hz).[11] When the dose of sevoflurane or anyone of the inhaled ethers is increased above 1 MAC, there is an increased activity in the theta (4 – 8 Hz) oscillations. Theta oscillatory activity does not appear with increasing doses of propofol. This is a key difference between the EEG activity of propofol and the inhaled ethers.

The sedative anesthetic and anesthetic adjunct dexmedetomidine is an alpha-2 adrenergic agonist that acts pre-synaptically to block the release of norepinephrine from the neuronal projections from the locus ceruleus to the basal forebrain, the pre-optic area of the hypothalamus, the central thalamus and diffusely to the cortex. When dexmedetomidine is administered, EEG activity shows characteristic slow-delta and spindle (intermittent 9 to 15 Hz) oscillations with low to moderate doses, and only slow-delta oscillations higher doses.[12,13] Low to moderate doses of dexmedetomidine are commonly associated with light sedation, whereas the higher doses are associated with more profound states of sedation. Ketamine is an antagonist of NMDA glutamate receptors. At low doses, ketamine acts preferentially at NMDA receptors on inhibitory interneurons and produces characteristic gamma (25 - 35 Hz) oscillations. This state is commonly associated with hallucinations and analgesia. At higher doses, ketamine binds also to NMDA receptors on excitatory neurons and shows a pattern during which gamma oscillations alternate regularly with slow-delta oscillations.[14] The pattern of gamma oscillations alternating with slow-delta oscillations is commonly associated with profound unconsciousness and analgesia.

The EEG Signatures of the Anesthetics Change Systematically with Age

That the EEG signatures of anesthetics change systematically with age is best documented for propofol and the inhaled ethers, sevoflurane, desflurane and isoflurane.

0-3 Months of Age. For children in the age range of 0-3 months, the EEG under sevoflurane anesthesia shows only slow oscillations across the entire scalp. Unlike in adults, there are no frontal alpha oscillations and there is no anteriorization of the alpha oscillations.[15] The current working hypothesis is that the alpha oscillations observed in adults represent extracellular current flows cycling between the thalamus and cortex. This idea of thalamocortical alpha oscillations was proposed based on modeling studies and has recently been verified in experimental studies in rodents. As a consequence, it is likely that the absence of alpha oscillations in infants in the 0-3 month age group represents a lack of sufficiently robust connections between the thalamus and cortex.

4-6 Months of Age. For children in the age range of 4-6 months, the EEG under sevoflurane anesthesia shows slow and alpha oscillations across the entire scalp. Unlike in adults, there is no anteriorization of the alpha oscillations.[15]

6 Months of Age to 6 Years of Age. Anteriorization of the alpha oscillations begins when the child is between 11-14 months of age.[16] Furthermore, the amplitudes of the slow-delta and alpha oscillations observed under sevoflurane anesthesia increase from 4-6 months to their maxima amplitude at 6-8 years of age.

>6 Years of Age. From 6-8 years of age, the amplitude of the slow-delta and alpha oscillations decline monotonically with each year of life.[17-19] At the early end of the age spectrum, the changes in EEG dynamics most likely reflect changes in brain development, whereas the changes observed in the later end of the age spectrum are most likely due to normal aging. The large difference in power in the spectrogram (density spectral array) between the pediatric and adult populations makes clear why EEG-based indices are unreliable for defining states of unconsciousness in the pediatric group.

Modern Strategies for Monitoring the Brain States of Patients Receiving General Anesthesia and Sedation

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The EEG of patients receiving general anesthesia changes systematically with anesthetic dose, anesthetic class and age of the patient.[11,15,17-19] A practical implication of this observation is that by tracking the unprocessed EEG and its spectrogram anesthesiologists can reliably infer the patients level of unconsciousness. This makes it possible to use the EEG to dose anesthetics in a principled way. Furthermore, because a minimum of three factors (anesthetic dose, anesthetic class, and patient age) are required to characterize a patient's level of unconsciousness, it is readily apparent why one-dimensional EEG-based indices fail to reliably identify anesthetic state across all agents.

While a monitoring paradigm based on real-time tracking of the unprocessed EEG and the spectrogram can be applied in all age groups, it is most immediately applicable to elderly patients where the prevalence of delirium and post-operative cognitive dysfunction are the highest. Indeed, a recent study has shown that intraoperative burst suppression of a periods as short as five minutes is positively correlated with the likelihood of developing post-operative delirium.[20] Post-operative delirium is a risk factor for post-operative cognitive dysfunction.

In 1937, Gibbs, Gibbs and Lennox reported the first detailed characterizations of the EEG signatures of anesthetic drugs.[21] They identified the slow-delta oscillations alpha oscillations as characteristic of ether anesthesia. They wrote, "In ether anesthesia when a 'surgical level' is reached, the slow waves have a frequency of about 1 per second. Superimposed on these are small, faster waves with a frequency of 10 or 20 per second, so that the slow waves have a crenated appearance." In a highly prescient statement, they went on to conjecture that "a practical application of these observations might be the use of the electroencephalogram as a measure of depth of anesthesia during surgical operations. The anesthetist and surgeon could have before them on tape or screen a continuous record of the electrical activity of both the heart and brain." This EEG phenomenology could not be linked to anesthetic-induced altered states of arousal and neurophysiological mechanisms of anesthetic action until: 1) the molecular targets of anesthetic action were identified; 2) the neuroanatomy and neurophysiology of the neural circuits where these targets are located were described; 3) and the neurophysiology of how actions of anesthetics at those targets and in those circuits produced anesthetic-induced oscillations and altered arousal states.[1,11,22]

The EEG under general anesthesia has the highest signal-to-noise ratio of all of the situations in which the EEG is used clinically or for research purposes. These include characterizing sleep states, studying meditation, assessing cognitive function and tracking coma recovery. This high signal-to-noise ratio for the EEG under general anesthesia occurs because the anesthetic agents induce highly structured, systematic oscillatory activity across large regions of the brain and because once the patient becomes unconscious there is a decrease in muscle tone and most often, akinesia. It is ironic that the strongest EEG signal emanates from patients receiving general anesthesia yet, anesthesiology is the field of clinical neuroscience in which the EEG is used the least. We believe that all anesthesiologists should understand the neurophysiology of the relationship between EEG patterns of the anesthetics and the level of unconsciousness or sedation these agents produce. We further believe that real-time use of the unprocessed EEG and its spectrogram to track level of unconsciousness and to manage anesthetic drug delivery would greatly benefit patients receiving anesthesia care.

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Title: State of the Art Labor Analgesia

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Learning Objectives

At the conclusion of this activity, participants should be able to:

- Utilize the latest technical advances for instrumenting the spinal and epidural spaces
- Employ non-neuraxial analgesic techniques
- Apply newer techniques and technologies for maintaining labor analgesia
- Select the most appropriate analgesic agents and adjuncts to use with spinal and epidural techniques

Introduction

The options for providing labor analgesia have undergone continuous change over the past few decades, culminating in the current state of the art. Although the available number of topics, issues, and controversies in labor analgesia are nearly unlimited, the current discussion will be limited to the following three main topics: Maintenance of Labor Analgesia, Controversies, and Techniques.

Maintenance of Labor Analgesia

PCEA/PIEB

Once a catheter has been placed into the epidural space, several options are available to maintain analgesia. One of the first methods to be employed was intermittent bolusing on patient request. Once the effect of the initial dose of local anesthetic began to subside, contraction pain would return and the patient would request more medication, at which time the anesthesiologist would provide analgesia using another bolus dose of local anesthetic. The obvious disadvantage to this technique is the relatively large amount of manpower required. Other disadvantages include non-continuous pain relief and an intermittent increase in side effects such as hypotension and motor blockade. The natural progression in management was then to employ infusions to maintain analgesia, but early infusion pumps were relatively primitive and sometimes unreliable, and data were lacking to guide infusion rates[1]. A large volume of research was eventually published to help rectify this problem, and it was during this time that the next step in the evolution of maintenance of labor analgesia occurred: patient controlled epidural analgesia (PCEA)[2]. By this time, copious experience had accumulated with the use of intravenous PCA, and the same principles were then applied to PCEA. However, it was soon discovered that there are some important differences between opioid-based IVPCA for acute postoperative pain and local anesthetic-based PCEA for labor analgesia. Perhaps most importantly, a basal infusion was found to be very effective with PCEA[3]. Studies continued, however, and further information has emerged over the past 2 decades suggesting that even more effective methods can be employed, such as intermittent bolusing at programmed intervals[4]. Epidural catheters with multiple holes are commonly used to maintain labor analgesia, and "differential flow" occurs through epidural catheters containing multiple holes[5]. During clinically relevant continuous infusion rates, the vast majority of flow occurs through the proximal port (see figure 1). Only when pressures become significantly higher will flow begin to occur at the middle and distal holes, which is what occurs during a rapid bolus. As expected, analgesia can be improved by employing flow through all three holes. The superiority of programmed intermittent epidural bolusing (PIEB) plus PCEA over continuous infusion (CI) plus PCEA has already been demonstrated, and pumps are currently being developed in order to exploit this advantage[6,7,8]. The concept of differential flow through multiple epidural catheter ports also implies the possibility that different ports can reside in different places (epidural space, intravenous, subarachnoid) and can cause different clinical characteristics depending on whether continuous infusion or intermittent bolusing is being employed. The next step in the evolution of maintenance of epidural labor analgesia will be computerized pumps with a feedback loop that can continuously adjust basal infusion rates based on average patient requirements, allowing for automatic changes in infusion rates to match the changing analgesic needs during the course of labor. These so-called "smart pumps" are currently under development, and future research will guide the best combination of their use with basal infusions and programmed intermittent bolusing.

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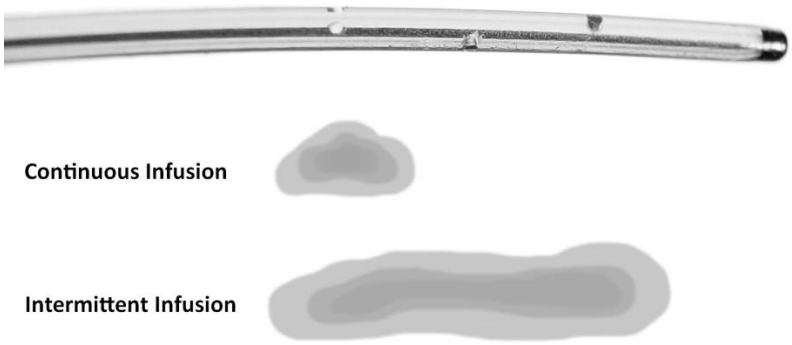

Figure 1. "Differential Flow" occurs through a multihole catheter, where at low pressures encountered during continuous infusion, the majority of flow occurs at the proximal port. Only at higher pressures encountered during rapid bolusing will flow occur at the middle and distal holes.

Intravenous Opioids

There are several acceptable opioids that can be used to provide labor analgesia. Partial agonists such as butorphanol have a ceiling effect for respiratory depression, thus making them an attractive choice in laboring women due to a theoretically lower risk of maternal side effects and neonatal depression[9]. However, the analgesic effect is likewise limited, and analgesic efficacy has been reported to range from moderate to non-existent. A commonly used dose of butorphanol is 1mg IV every hour as needed, held when delivery is imminent.

Other opioids without ceiling effect have also been used, and one of the most commonly studied is meperidine. However, as with all intravenous opioids for labor analgesia, the reported efficacy is variable and often disappointing. One report even concluded that intravenous opioids for labor analgesia are "unethical and medically incorrect"[10], but the vast majority of studies report at least a moderate effect[11]. Potential drug interactions with meperidine have contributed to its decline in popularity, including serotonin syndrome in patients taking MAOIs or SSRIs. Another potential problem with meperidine is accumulation of the metabolite normeperidine, which has been reported to cause convulsions, yet should only be an issue with chronic administration.

Fentanyl is another commonly used intravenous opioid for labor analgesia, and it has been extensively studied for this use. It rarely causes allergic reaction, and is relatively free of drug interactions, but has no ceiling effect for respiratory depression, so must be used with caution on the labor ward. It can have a cumulative effect; therefore neonatal respiratory depression is an important concern[12]. Dosage recommendations are found in figure 2.

Remifentanil is a newer opioid analgesic with a rapid onset and short duration of action, and its unique pharmacodynamic profile created early enthusiasm for its use in labor analgesia. However, even with the rapid onset, it is nearly impossible to deliver remifentanil in such a way that the analgesic effect mirrors the time course of the contraction. Doing so would require remifentanil dosing to occur about 2 minutes prior to the onset of contraction, which, of course, is difficult if not impossible to predict. One published study attempting to accomplish the goal of providing the remifentanil dose 140 seconds prior to contraction failed to improve labor analgesia[13]. In spite of this shortcoming, there are several reports of its successful use in labor analgesia, including a comparison with fentanyl, which concluded that both drugs provide moderate analgesia, with remifentanil causing more maternal oxygen desaturation, and fentanyl causing more neonatal depression[8]. Dosage recommendations for remifentanil are found in figure 3.

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Basal Rate	none
Bolus Dose	25 ug
Lockout Interval	5 minutes
1 Hour Limit	300 ug

Figure 2. Dosage recommendations for fentanyl PCA for labor analgesia

Basal Rate	0.025 - 0.05 ug/kg/min
Bolus Dose	0.25 ug/kg
Lockout Interval	2 minutes
4 Hour Limit	3 mg

Figure 3. Dosage recommendations for remifentanil PCA for labor analgesia.

Controversies

Air vs Saline for Loss of Resistance

Either air or saline can be safely used to test for loss of resistance when accessing the epidural space. Recent debates on the subject have brought to light the list of reasons to avoid air, whereas no such list exists for the argument against saline. The proponents of air correctly argue that the efficacy and overall incidence of clinically significant morbidities have not been shown to differ between the two techniques, yet case reports and clinical experience have amassed a list of reasons to avoid air. Incomplete analgesia due to air pockets in the epidural space has been reported in pediatric patients[20]. For the same to occur in obstetrics, it would presumably require large volumes of air, but this is still a potential risk that is avoided by using saline. Venous air embolism[21] and pneumocephalus[22] are more likely to occur with the use of air, and although a small amount of intravenous air is rarely a problem, pneumocephalus is the presumed reason that using air for loss of resistance is more likely to cause headache than when using saline. Finally, nerve root compression[23] and subcutaneous emphysema[24] have been suggested as additional potential complications. One historical argument against saline that is now antiquated, but deserves mention, is the theoretical possibility of confusing saline for CSF when performing a CSE. In a recent study comparing air to saline for LOR during the CSE technique, no difference was seen in failure rates, and there were no cases of saline being confused for CSF[25]. This scientific report concurs with what should be expected under these circumstances, where saline injected into the epidural space distributes amongst the tissues such as fat and blood vessels, and is then not available to subsequently be aspirated through a spinal needle.

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Accidental Dural Puncture: What Next?
The risk of accidental dural puncture (ADP) can be minimized, but not completely eliminated, and carries an overall risk of approximately 1 in 200. Once an ADP occurs, there are two basic management choices that can be made: 1) resite the epidural, or 2) insert a spinal catheter. When choosing a spinal catheter, potential complications to keep in mind include infectious risk[26], spinal cord trauma[27], neurotoxicity[28], and inappropriate injection through the catheter[29]. When choosing to resite an epidural, potential complications to consider include inferior analgesia[30] (compared to a spinal catheter), increased headache risk[31] (also compared to the spinal catheter), and the risk of unexpected high block[32]. The SCORE (Serious Complications Obstetrics REpository) Project has demonstrated that one of the highest risk scenarios for developing high spinal is when an epidural that is resited after a wet tap is being dosed for surgery. Data are mixed on whether the use of a spinal catheter after wet tap can reduce the incidence of PDPH, but no study has demonstrated an *increase* in headache risk. Whether choosing a spinal catheter or a resited epidural, perhaps the most important consideration is conspicuous labeling of the catheter at the proximal connector in order to minimize the risk of inappropriate injections.

Techniques

Combined Spinal Epidural (CSE)
Combining spinal analgesia with epidural analgesia was developed as a way of exploiting the attributes of both techniques, i.e. the reliability and fast onset of the spinal combined with the duration and versatility of the epidural. Although the CSE technique is well established, its role in labor analgesia is still in the process of being defined. For instance, the use of CSE for patients at high risk for Cesarean delivery remains controversial to some, due to the "untested" nature of the catheter immediately after placement. Once the spinal analgesic dose is administered and an epidural catheter is placed, it is appropriate to test for spinal placement of the catheter using local anesthetic, but ruling out intravenous placement is more problematic. Furthermore, even if the catheter is appropriately in the epidural space and not intravenous, its functionality is for subsequent labor analgesia and/or unexpected Cesarean delivery is unproven. The theoretical concern of higher failure rate and greater morbidity with these untested CSE catheters has not been borne out in studies, but the thought of a STAT Cesarean delivery in an morbidly obese preeclamptic parturient with an untested catheter is enough to dissuade many anesthesiologists from using a CSE technique under these circumstances. Intrathecal opioids can also cause pruritus, which is often negligible but sometimes distressing enough to cause patients to request treatment, and even to choose against a CSE with subsequent pregnancies. Nevertheless, the CSE technique has many advantages over the epidural technique alone, including rapid onset, reliability, and minimal motor block. Also, the rate of cervical dilatation has been shown to be enhanced by the use of CSE compared to both epidural[33] and systemic analgesia[34]. Figure 4 shows a typical recipe for the spinal portion of CSE labor analgesia.

Drug	Dose	Volume
Bupivacaine 0.25%	1.75 mg	0.7 ml
Fentanyl 50mcg/ml	15 mcg	0.3 ml
Total		1.0 ml

Figure 4. A typical recipe for the spinal portion of CSE labor analgesia.

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Dural puncture epidural

A recent addition to the obstetric anesthesiologist's toolbox is the "dural puncture epidural"[35]. This technique seeks to improve the quality and reliability of epidural analgesia by making a small dural puncture during epidural placement, but without the introduction of spinal medication. Then, the catheter can be fully tested for efficacy, while small amounts of the epidural drug passes through the dural puncture to improve efficacy. While still not in widespread use, this technique has been thoroughly investigated and appears to improve analgesia without increasing side effects. Additionally, it addresses the theoretical disadvantage of the CSE technique described above by "proving" the catheter to be fully functional in the event of an unexpected Cesarean delivery.

Unintended Catheter "Pullback"

Regardless of the epidural catheter technique used, the timing of securing the catheter to the skin can significantly influence the amount of catheter that remains in the epidural space (see figure 5). When the patient is in the sitting position and flexion of the lumbar spine is optimized, the distance from the skin to the ligamentum flavum is minimized. When the patient returns to a relaxed sitting position this distance increases, and the skin and soft tissues move caudad. Therefore, if the catheter were to be secured to the skin before the patient is allowed to return to a relaxed position, the catheter will be pulled back out of the epidural space by the distance that the soft tissues travel when returning to this position, even as the catheter mark at the skin stays constant. This effect can be further exaggerated by obesity, and can lead to complete failure of the epidural catheter if not recognized. To avoid this unintended catheter "pullback", the patient should be allowed to return to a relaxed position before securing the catheter to the skin. Additional consideration should be given to allowing the patient to lie in the lateral position prior to securing the catheter, as this could allow the soft tissue to move even further, especially in the obese patient.

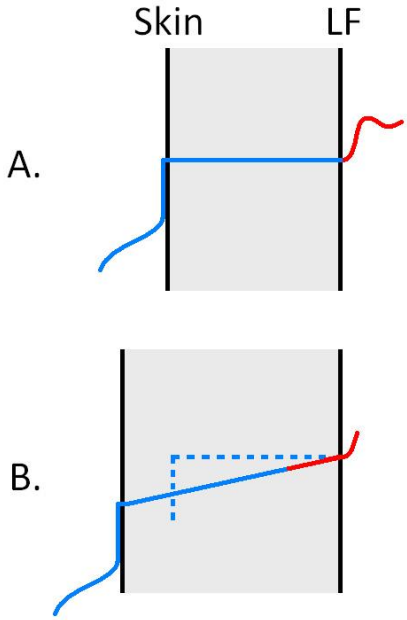

Figure 5. Unintended catheter "pullback" can occur after securing the epidural catheter to the skin while the patient is still in position for the procedure. A. With the patient in position for epidural placement, the soft tissue is compressed against the spine. B. When the patient returns to a natural sitting or lateral position, the soft tissue relaxes and the distance from the skin to the ligamentum flavum (LF) increases. If the catheter was secured to the skin while the patient was in the procedural position, then its tip will be withdrawn from the epidural space as the patient resumes a relaxed position. The solid blue/red line represents the epidural catheter, and the dotted line represents the original catheter path.

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Ultrasound guided neuraxial block

Advancing technology has made its way onto the labor ward in the form of ultrasound guided epidural placement[36,37]. Popular for many years in the practice of peripheral nerve blocks, the use of ultrasound has recently seen a flurry of activity in the obstetric anesthesia literature for use in neuraxial procedures. Traditional LOR technique is "blind" in that the anesthesiologist relies on tactile cues to determine whether the epidural is midline, which tissues the tip of the needle is passing, and when the tip of the needle enters the epidural space. Ultrasonography adds a visual tool that can be used to determine the position of landmarks and to measure a depth from the skin surface to the epidural space prior to initiating the procedure. Using ultrasound to guide a neuraxial block in *real time* is more problematic, however, due to the narrow "window" between spinous processes being shared by both the ultrasound probe and the epidural needle. Proponents of the technique hope that safety will be enhanced with the use of ultrasound. Epidural hematoma and infection are fortunately extremely rare, and so it will be difficult to ever say conclusively whether the use of ultrasound reduces the incidence of these complications by decreasing the number and duration of attempts required to access the epidural space. Similarly rare is the complication of direct trauma to the spinal cord or conus medularis, but this grave complication can be theoretically avoided by performing the technique below the terminis of the spinal cord. Previous studies have shown that even experienced anesthesiologists are frequently incorrect when predicting interspace level using manual palpation of anatomical landmarks, and when wrong, we are usually higher than predicted[38,39,40]. Ultrasound allows for precise determination of spinal interspace levels, thus avoiding unnecessary neuraxial procedures above the cauda equina[40]. Ultrasound remains less ubiquitous on the labor and delivery ward than it is in the peripheral nerve block suite, most likely due to the perception of a very high rate of success without its use, along with the limitations against its use in real time. Also, the *routine* use of ultrasound would result in an increase in the amount of time from patient request to first pain free contraction, causing some resistance to its use from both the anesthesiologist and the patient. In spite of some limitations, ultrasound is gaining in popularity as a tool for lumbar epidural placement, and in the future is likely to be widely considered an important tool for assisting in lumbar epidural placement in select cases.

Novel Approaches to Locating the Epidural Space

The use of ultrasound waves emanating from the tip of the needle has proven successful for identifying the epidural space in animal models, and is expected to reach clinical trials in the future[41]. Another similar technology uses optical spectral absorption of the different tissue planes rather than sound waves[42]. The hope is that some day, our current "blind" approach to the epidural space through loss of resistance will be replaced with advanced technology that will allow identification of the tissue planes and epidural space with real-time visualization.

Conclusion

What is "State of the Art Labor Analgesia"? The definition is constantly evolving as research and clinical experience guides changes in analgesic agents, neuraxial adjuncts, pumps for maintaining epidural analgesia, and techniques for obtaining access to the epidural and subarachnoid spaces. During this evolution, controversies will inevitably arise, and the anesthesiologist needs to be aware of the pros and cons of choosing opposing techniques such as air vs saline for loss of resistance, and whether to place a spinal catheter or resite an epidural following accidental dural puncture. Technology also provides an evolving definition of state of the art as devices are developed and perfected which allow an easier path to the epidural space while minimizing complications.

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Emergent intubation: tips, tricks, and evidence

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Learning Objectives

At the end of this lecture, the reader should be able to:

1. Describe what everyone in attendance at an intubation should know regardless of the role they are playing
2. To discuss aspects of optimizing first attempt intubation success
3. To describe a risk stratification scheme for tracheal extubation

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Introduction

Emergency tracheal intubation outside of the OR is required in patients requiring immediate assistance with oxygenation. Compared to elective intubation in the OR for general anesthesia the occurrence of difficult intubation outside of the OR is several-fold higher. In addition, airway-related complications such as hypoxemia, hypotension, esophageal intubation, and aspiration are far more common as is cardiac arrest. The Fourth National Audit Project by the Royal College of Anaesthetists (NAP4) has most recently and comprehensively highlighted this. Of the 184 reported airway events, nearly 20% occurred in either the ICU or emergency department (ED) of which nearly two-thirds directly resulted in death or permanent neurologic injury. Furthermore, factors considered to be contributory or causal were often related to communication failures or the judgment and training of the operators. In over 1/3 of events in the ICU, the quality of airway management was judged to be poor.

Patient Positioning

Appropriate positioning of the patient in preparation for airway instrumentation is an important, but often neglected aspect of airway management. Over 40 years ago, Stept and Safar reported on “Rapid Induction/Intubation for Prevention of Gastric-Content Aspiration.” As part of a multi-step process, practitioners are instructed by step 6 to “place patient in semisitting, V-position, with trunk elevated about 30 degrees…” Positioning patients in this manner may improve the efficacy of preoxygenation, maintain the airway in a more anatomic position, improve laryngeal exposure, and, of course, decrease the chances of passive regurgitation. This can be accomplished quite readily with most modern hospital beds by first putting the bed in trendelenburg position and pulling the patient up until their occiput rests on the edge of the mattress. Next the head of the bed is elevated to 30 degrees. And, lastly, if necessary to ensure that the external auditory meatus is aligned with the sternal notch, an additional headrest can be placed under the occiput. This position has reported to decrease complication rates in emergent out-of-operating room intubations. An extreme version of this, which has been recently reported, called “face-to-face” intubation, involves providing all airway management with the patient in a nearly fully seated position. Airway instrumentation is accomplished with a video laryngoscope. However, outside of the OR, only one study has examined the question of whether standard “sniffing” position is inferior to a “ramped” head-elevated position. In that pragmatically designed study, no difference in lowest oxygen saturation from induction to the first 2 minutes after intubation was noted and there were more “difficult” intubations in the “ramped” group. It should be noted that lack of experience/training in intubating patients in a “ramped” position might have affected the results, as all operators were internal medicine-based critical care fellows. A prior study of patient predicted to be a difficult intubation reported that attending anesthesiologists were more successful in intubating patients in the “ramped” versus supine position than less experienced trainees. The authors of that study suggested the result was due to having greater breadth of experience intubating in both positions.

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Pre-oxygenation/Apneic diffusive oxygenation

It is widely accepted that all patients should undergo pre-oxygenation/denitrogenation prior to induction and intubation. In emergency situations or with uncooperative patients, this may be more difficult, but is no less important. Use of trans nasal humidified rapid insufflation ventilatory exchange (THRIVE) using commercially available high-flow systems (HFNC) seems to present an opportunity to enhance safety surrounding emergency intubation procedures. In a small group of patients with a known difficult airway or who were strongly suspected to be difficult AND were likely to desaturate after induction due to high body mass index (BMI) or history of cardiopulmonary disease, HFNC at 70L/min during apnea for periods of up to 70 minutes resulted in no patients with an SPO2 of <90%! A second small study, but in shorter laryngeal surgery cases in patients with lower BMIs reported similar results. However, results in the ICU have been mixed. While a before-and-after study of HFNC in emergency intubation was largely positive, a subsequent prospective RCT was negative. The addition of non-invasive ventilation by mask to HFNC for pre-oxygenation and maintenance of apneic diffusive oxygenation during the procedure may be helpful, but requires more available equipment, logistical support, and training. The simplest of these techniques, which has been recommended, is to use standard nasal prongs at 15L/min under a facemask during the pre-intubation period and then leaving them in place during the intubation procedure after the mask is removed. However, two recent prospective RCTs failed to show any difference in lowest mean oxygen saturations during the intubation between patients receiving NC for apneic oxygenation and those who did not receive it.

Direct versus Indirect Laryngoscopy

The use of newer rigid video laryngoscopes to increase patient safety by increasing first attempt intubation success and/or decreasing time to successful intubation remains contentious. A recent meta-analysis evaluated a number of prospective randomized trials comparing direct laryngoscopy (DL) with the Glidescope (GS). The proportion of intubations taking place with a full view of the glottis (Cormack-Lehane grade 1) was significantly higher with the GS than DL. This was true for all intubations as a whole, although the effect was greater among intubations labeled as difficult. However, neither the first attempt success rate nor the time to intubation was different between techniques. This was due to, in large part, a small number of studies including novice or inexperienced operators, which did show the GS to be beneficial, having been balanced by a larger number of studies of expert operators where no benefit was reported. In addition, a recently published pilot prospective randomized trial of DL versus GS for intubation in the intensive care unit also failed to show a difference in any important outcome. It is also notable that while this study was small with 40 patients, it included what many would consider inexperienced operators, the very group that had been previously reported to benefit for the GS. At this time, there is little high quality data to support the widespread preferential use of a GS over DL by experienced personnel for initial intubation attempts. Two recent pragmatic trials of ICU intubations, which were largely attempted initially by junior trainees or staff also failed to show

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superiority of the newer technology. It should be noted that the most current version of the ASA guidelines states that "consideration of the relative clinical merits and feasibility of four basic management choices" should be made. Choice number 3 is "video-assisted laryngoscopy as an initial approach to intubation."

Extubation of the difficult airway

Extubation has traditionally been considered a routine part of the emergence from anesthesia. Anecdotally, the need to keep a patient who presented for elective non-major surgery has been considered a failure on the part of the anesthesiologist to perform their duties adequately. However, it is now recognized that some patients are at risk for extubation failure post-procedure and that failure to acknowledge this phenomena may lead to serious morbidity or death. For example, multilevel anterior cervical spine surgery with a duration > 5 hours and > 300 ml blood loss have been reported to increase the risk of upper airway obstruction post-procedure. In a retrospective review of over 2000 patients who were extubated while in the ICU of a large urban tertiary care referral hospital, nearly 1 in 5 (19%) required reintubation at some point during their hospitalization. The median time to reintubation was <24 hours with 1 in 10 of those patients needing to be reintubated within 1 hour of extubation. Additionally, the need for reintubation was associated with higher ICU length of stay, in-hospital mortality, and greater cost of care. Most recently, nighttime extubation (1900-0659 the next day) was also reported to increased mortality. On a national level, the fourth National Audit Project of the Royal College of Anaesthetists reported that more than 1 in 4 airway related events occurred at extubation or in the recovery area post procedure. The root cause of 100% of these events was judged to be due to some form of airway obstruction. Highlighting that these events are not innocuous, death or permanent brain damage occurred in 3 instances with all of the remaining patients requiring ICU level care. In response, the Difficult Airway Society of the United Kingdom has recently published extubation guidelines. As there is a dearth of literature support for any particular risk stratification or algorithm, what these types of guidelines chiefly offer is a prompt to actually consider the likelihood of extubation failure in any given patient. Underscoring the paucity of data with which to guide specific recommendations is the use of airway exchange catheters over which extubation takes place. In adults, only 430 patients contained in 3 case series have been reported, all of which were considered at high risk for extubation failure. However, extubation failure was reported to occur in only 13.4% of these patients overall (58/430) indicating that even in well selected patients, the use of the exchange catheter was unnecessary more than 85% of the time. The data for use of a SAD to bridge patients from tracheal tube to spontaneous respiration without an artificial airway is sparser still with a total of 41 patients reported to date with a 0% extubation failure rate.

Conclusion

Practitioners are likely to encounter difficulty in airway management far more

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often than they are accustomed to when performing these tasks outside the operating room. In addition, the incidence of serious complications is also higher. These complications are not simply a brief blip on the monitor screen, but rather are associated with a several fold risk of death or permanent disability. In order to optimize pre-oxygenation, laryngeal exposure, and to decrease the risk of gastric-content regurgitation, patients should be positioned in a 30 degree head up position. Currently, no new airway technology has been shown to be superior to direct laryngoscopy for initial attempts at instrumenting the airway among expert operators for critically ill patients overall. Of course, no airway management technology will be successful 100% of the time. Practitioners should familiarize themselves with alternative techniques. While literature estimates of extubation failure vary depending on the population studied and the time frame within which extubation was not considered to be a success, it occurs with some regularity in critically ill hospitalized patients. Additionally, perhaps one-in-ten of these events will occur in the first hour after extubation. Given that the consequences of a lost airway may be catastrophic, a well articulated reintubation plan should be developed for patients who possess high-risk features for extubation failure.

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CME Questions

1. All of the following are correct regarding etomidate except?
   a. Glucocorticod production may be inhibited for up to 72 hours after a single dose
   b. Hemodynamic stability is maintained better during induction of anesthesia than with other agents
   c. All-cause mortality in patients with sepsis may be negatively effected by its use
   d. None of the above

Answer: b

2. The final outcome of critical airway management can be conceptualized as being determined by the interaction of which of the following variables?
   a. Patient
   b. Personnel and equipment
   c. Time
   d. All of the above

Answer: d

3. Which of the following patients is most at risk of extubation failure?
   a. 25 year-old polytrauma with cervical spine fractures, intubated pre-hospital, in ICU. He is in a hard cervical immobilization collar and has a BMI of 41 kg/m^2. He is awake, follows commands, and has passed his spontaneous breathing trial. A cuff leak is present.

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b. 45 year-old man who has undergone a 2-level lumbar decompression and posterior spinal fusion in prone position. Blood loss was minimal and the surgery was 2.5 hours in duration.

c. 65 year-old female who has had a large left middle cerebral artery territory stroke with right sided motor deficits. She requires frequent oral suctioning.

d. 75 year-old man who has undergone a carotid endarterectomy

Answer: b

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Lipid Resuscitation: What you need to know for LAST and beyond

Guy Weinberg, MD **Chicago, IL**

Introduction

Rosenblatt et al[1] first reported the infusion of a 20% lipid emulsion (ILE) in successful treatment of severe local anesthetic cardiac toxicity in 2006. This re-purposing of a total parenteral nutrition solution has subsequently been widely adopted by the anesthesia community as an effective treatment for a potentially fatal complication of regional anesthesia – one that had traditionally been viewed as exceptionally difficult to treat. A number of professional societies in the US and abroad now include infusion of lipid emulsion in their recommendations for treating local anesthetic toxicity and such solutions are routinely stocked for rapid access at anesthetizing locations in hospitals and outpatient facilities. In 2007, Dr. Archie Sirianni[2], an anesthesiologist working at a community hospital, used ILE to save a patient with cardiovascular collapse related to a severe bupropion+lamotrigine overdose. This index case brought ILE to the attention of emergency medicine physicians and toxicologists, leading quickly to its use for treatment of many types of non-local anesthetic drug overdose and chemical poisonings. Now, a decade after the report by Rosenblatt et al, is a good time to take stock of what we have learned about ILE, its mechanisms, clinical use, controversies and future directions.

Mechanism

The formulation most commonly used in ILE is an emulsion of soy bean oil comprising mostly long chain fatty acid triglyerides as small oil droplets (average diameter, 400nm) with negatively charged (~1.2%) emulsifying egg phospholipids on the surface (z = -40mV). Glycerin (~2%) is added to make the solution isotonic and the pH is approximately 8.0. Given the size of these particles one can consider ILE a form of nano-medicine, although the goal instead of drug delivery is quenching adverse effects at targets of drug toxicity. Weinberg et al in reporting the results of an early animal model of ILE posited several possible mechanisms for the benefit observed in treating bupivacaine overdose: a partitioning effect, or 'lipid sink', based on bupivacaine's high lipid solubility; preferential shunting or redistribution; increased production of nitric oxide; and improved cardiac metabolism. Despite evidence in support of other mechanisms and perhaps because of its simplicity, the sink concept gained favor and is often cited as the chief mechanism of ILE. While it is easy to consider that the bulk lipid phase in blood could sponge offending lipid soluble drug from target tissues, the evidence is clear that other mechanisms contribute and the sink per se must be reconsidered or revised. In vitro experiments and post facto measurements from a rat model confirm that bupivacaine substantially partitions into a lipid phase, experiments reported by Litinious et al[3] in human volunteers given small doses of bupivacaine showed that ILE shortens the context-sensitive half-life of bupivacaine but doesn't alter the non-lipid bound plasma concentration – that is, no sink effect was observed at the time points measured. Moreover, Kuo and Akpa[4] used computational modeling to show that effects of a sink alone might not suffice to explain the observed clinical efficacy of ILE in rapidly reversing local anesthetic toxicity. Meantime, alternative explanations have appeared. Partownavid et al[5] showed that inhibiting mitochondrial fatty acid oxidation inhibited ILE-reversal of bupivacaine toxicity, suggesting that fatty acid metabolism likely contributes to local anesthetic toxicity and that reversing such a block could underlie in part the efficacy of ILE. Results of Li et al[6] from the same laboratory confirmed earlier observations that ILE potently attenuates myocardial stunning following ischemia-reperfusion. This occurred with activation of the RISK cytoprotective pathway, suggesting that ILE stimulates biochemical signaling pathways that could contribute to reversal of drug toxicity. Fettiplace et al[7] showed that ILE itself exerts both inotropic and lusitropic effects on cardiac function resulting in improved cardiac output and performance. The same group later found that lipid infusion activates the same intracellular kinase cascade as insulin, suggesting a common mechanism

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for insulin and ILE-induced inotropy. They also showed in a physiological study and confirmed by in silico modeling that reversal of bupivacaine toxicity in a rat model was best explained by the combination of improved contractility and a partitioning effect. Subsequently, Shi et al[8] reported in a pharmacodynamic-pharmacokinetic study of rats that ILE increased clearance of bupivacaine, resulting in pharmacokinetic effects reminiscent of those reported by Litinious et al[3]. Their most important finding is that ILE reduced concentrations of bupivacaine in both heart and brain while increasing it initially in the liver. Fettiplace et al[9] showed in more fine-grained PK analysis that bupivacaine quickly partitions (<5 min) into the infused lipid and is rapidly distributed from the blood to liver and skeletal muscle. This effect was most pronounced at high bupivacaine blood concentrations suggesting it would be most effective if given early. Moreover, since inotropy occurred only after cardiac bupivacaine concentrations declined below a threshold, high quality CPR in full cardiac arrest will aid in ILE-based resuscitation by improving the coronary perfusion needed to remove bupivacaine. In sum, a variety of mechanisms are involved in the observed benefit of ILE, including intracellular (signaling, inotropy, cytoprotection[10,11]) and intravascular (pharmacokinetic) effects. The later can be described as ILE reducing toxicity by shuttling drug from target tissues to receiver organs (e.g. liver, muscle). Further refinement of our understanding of these mechanisms will lead to optimized regimes for using ILE in treating a variety of drug overdoses. This is important since it is likely that different types of toxic exposure (eg parenteral versus oral ingestion) will require different ILE administration strategies.

LAST

Initial case reports of ILE treatment of severe cardiac local anesthetic toxicity seemed to recapitulate the laboratory experience: combining good CPR with ILE leads to very rapid recovery of heart rate and blood pressure and normalization of rhythm. Moreover, neurologic signs of local anesthetic toxicity are also reported to abate with ILE; this appears to apply to prodromal symptoms and altered mental status as well as seizure activity. The ASRA, AAGBI and AHA recommendations for treating local anesthetic systemic toxicity provide specific recommendations for administering ILE which is typically given as a large bolus (~100mL for an adult) followed by a continuous infusion (~0.25mL/kg/min lean body mass; max dose, 12mL/kg) usually given several minutes past a full recovery. These will be revised in the future to improve both efficacy and safety of ILE. Potential recurrence of toxicity requires us to monitor the patient for some time after and event and to keep materials for ILE at the ready.

Early comparisons of ILE with standard ACLS drugs in treating rat models of bupivacaine overdose showed that ILE was superior to epinephrine alone or in combination with vasopressin. ILE-treated animals had better hemodynamic and metabolic parameters (pH, lactate and pO2) than animals given the pressors. It is important to note that rats challenged with bupivacaine and treated with vasopressin alone did very poorly from the standpoint of both hemodynamic and metabolic recovery. It was also reported in the same model that epinephrine when given above a threshold dose of 10mcg/kg epinephrine impaired the efficacy of ILE in treatment of bupivacaine overdose while lower doses of epinephrine accelerated recovery. Given the normal human dose (1mg) is ~15mcg/kg, this suggests that much lower-than-usual doses of epinephrine might be more effective than the usual 1mg in treating cardiac arrest secondary to LAST. Li et al showed in a rat model that adding epinephrine to ILE improved coronary perfusion pressure but unlike ILE alone did not reduce cardiac bupivacaine concentrations. Moreover, they confirmed that adding epinephrine to ILE worsened pO2 and pH. These findings comport with mounting evidence that the standard (~1mg) dose of epinephrine does not contribute to improved survival in non-local anesthetic cardiac arrest and suggest that lower-than-usual doses of epinephrine might improve recovery in both local anesthetic and other causes of cardiac arrest compared to the standard dose. These findings inform the current recommendations for treating local anesthetic toxicity that vasopressin not be used and that epinephrine bolus doses should be reduced (e.g. ~ 1mcg/kg) especially when given with ILE.

The approach to deciding when to use ILE in treating local anesthetic toxicity has evolved over the past several years. The earliest recommendations were to use ILE only as a last resort. However, observations suggesting that ILE might

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slow or prevent progression to cardiac toxicity lead to earlier use following symptoms of toxicity. This and the difficulty predicting progression to cardiovascular compromise provide the rationale for early administration of lipid. It is worth noting that some patients appearing to have fully recovered from local anesthetic-induced seizures go on minutes later to full cardiac arrest. It seems reasonable to call for the materials necessary for ILE as soon as the diagnosis of local anesthetic toxicity is considered, then decide whether to treat based on the patient's clinical picture and physician judgement. This decision should also factor in the potential for adverse effects of ILE which are discussed below. While there are no commonly encountered scenarios where ILE should be given before regional anesthesia, it is interesting to consider an accidental Bier block with bupivacaine as one situation where 'pre-treatment' makes sense – that is, ILE could be given before (incrementally) deflating the cuff.

Non-LAST Overdose

Sirianni et al reported a very dramatic save using ILE after more than an hour of CPR using standard ACLS guidelines had proven unsuccessful in treating an adolescent with combined bupropion+lamotrigine overdose. Emergency physicians and toxicologists have subsequently adopted this approach to treat a variety of lipophilic drug overdoses and chemical exposures including calcium channel blockers, beta blockers, tricyclic and atypical antidepressants, anti-psychotics, an anti-helminth, anti-arrhythmics and herbicides. The key difference compared to treating local anesthetic (parenteral) toxicity is that most drug overdoses are oral ingestions (enteral toxicity) so that blood levels are therefore far less predictable and drugs linger in the GI tract so that toxic levels are likely to persist over long (and sometimes very long) timeframes. Thus, optimizing the timing and dose of ILE treatment becomes very challenging. Most emergency physicians use the standard treatment regimen for LAST while recognizing the lipid dosing limits (~12mL/kg lean body mass) but some reports indicate much larger doses are being infused (>3L over 2 hours; see below). This approach cannot be condoned since it runs a risk of the patient developing fat overload syndrome if the infusion continues for long periods of time, as might be seen when the patient has a positive response to lipid and physicians are reticent about stopping it. One possible approach was outlined by Fettiplace et al[12]; they used computer simulation to establish a regimen that allowed rapid attainment of ~1% triglyceride blood (1000mg/L) levels while infusing for a prolonged period of time (up to ~6 hours): 1.5mL/kg bolus followed by infusion at 0.25mL/kg/min for 3 minutes then reducing the infusion to 0.025mL/kg/min. Moreover, there is the theoretical concern that lipid infusion could increase absorption of drug residing in the gut and thereby accelerate early toxicity. There is no clinical evidence for this phenomenon and a recent series of cases reported to a registry suggest this is not a common problem. This study indicated improvement in blood pressure and Glasgow coma scale after ILE use for a variety of intoxications and survival in 5 of 8 patients with cardiovascular collapse secondary to non-local anesthetic xenobiotic overdose who were treated with ILE. Notably, there was no control group; however, the results are better than expected for patients in cardiovascular collapse. Nevertheless, given that accidental and intentional drug overdose result in tens of thousands of fatalities annually in the US (nb: the scope of the problem worldwide, particularly suicide by organophosphate ingestion in the third world, is absolutely staggering) it is clear that much work needs to be done in optimizing treatment for oral ingestion. The key issues are: when and how fast to deliver ILE, for how long and what is an acceptable dosing limit.

Controversies and Caveats

The most commonly used formulation for ILE (20% Intralipid) has a very favorable safety record in its fifty years of clinical use as TPN. While the rate of infusion as a rescue agent is more rapid than for TPN, there is little indication of consistent, clinically problematic adverse drug reactions for ILE in overdose, when the total dose is less than the accepted limit of 12mL/kig. Furthermore, when the patient has received large doses of pressors (which also cause

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pulmonary and metabolic dysfunction) and may have low output state and, by definition, toxicity from the offending drug, there are generally too many confounders to confidently ascribe any particular complication specifically to ILE.

The most common anticipated effect is lipemia, which can potentially interfere with laboratory studies; this effect can be circumvented by spinning the blood samples before chemical analysis. Chemical pancreatitis has also been reported following ILE but these cases lacked confirmatory imaging studies; moreover, these chemical abnormalities are not specific given that lipase assays often measure release of glycerol which is expected to increase with triglyceride infusion. Pulmonary fat overload has been reported in neonates receiving large doses of TPN so it is clear that volume and fat mass delivery have upper limits. Nevertheless, the LD50 for 20% Intralipid delivered to rats over 30 minutes is ~67mL/kg, which exceeds the typical volume used in treating local anesthetic toxicity (~4mL/kg) even accounting for allometric scaling. However, as noted above, the volume delivered in treating oral ingestion can be much larger given that the infusion is likely to continue for extended periods of time. Given that potential complications of ILE are related to the total volume of lipid administered, it is important to be mindful of the dosing limit (12mL/kg) and that if you start a lipid infusion, remember to turn it off!

Models for studying ILE are context sensitive insofar as parenteral and enteral toxicity differ clinically and their models aren't mutually applicable; one doesn't apply to the other. There is further controversy over the best animal for studying ILE. While porcine models are often used for studying CPR and ischemic arrest because of the anatomic and metabolic similarities with human cardiovascular physiology, pigs are sensitive to liposome infusions including lipid emulsion. Bedocs et al[13] showed that standard ILE infusion induces the generalized cutaneous mottling and discoloration previously reported by others and as well as significant pulmonary hypertension. This systemic sensitivity should disqualify pigs as a useful model for ILE.

Future Challenge

The pharmacokinetic mechanism for ILE-based rapid reversal of LA-induced cardiovascular toxicity is now reasonably well-established. This understanding will help inform optimized treatment of severe LAST – a potentially catastrophic event. However, the same cannot be said yet for treatment of enteral intoxications, a public health hazard of much greater proportions. Determining what specific drug intoxications are most susceptible to ILE reversal and identifying the best treatment regimes in terms of timing, dose and duration are the greatest challenges for the future clinical application of ILE in treating drug overdose.

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Myocardial Injury After Non-cardiac Surgery (MINS)

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In recent decades, intraoperative mortality has decreased by a factor-of-ten, even though we now care for much sicker and older patients.[1] Preventable anesthetic-related intraoperative mortality is now so rare that it is hard to quantify.[2] Postoperative mortality, in contrast, remains substantial. Overall 30-day postoperative mortality after non-cardiac surgery is about 1% in the United States, and about 2% amongst inpatients (outpatients rarely die).[3,4] To put this mortality in perspective, if the postoperative period were considered a disease, it would represent the third leading cause of death in the United States.[5]

Myocardial infarction is by far the leading cause of attributable post-operative death, accounting for a quarter of all mortality, far exceeding major bleeding (14%) and sepsis (9%). About 4% of surgical inpatients over the age of 45 years will have a myocardial infarction meeting the American Heart Association's 3rd Universal Definition, and 4% of those who do die within the month. More than 90% of myocardial infarctions within the initial 30 postoperative days occur within two days after surgery.[6]

Detecting myocardial injury

Worldwide, 8% of surgical inpatients >45 years of age sustain postoperative myocardial injury as defined by a troponin elevation that is due to an ischemic etiology, with only 42% of these events fulfilling the diagnostic criteria of the universal definition of myocardial infarction.[7] Only 14% of patients experiencing a perioperative myocardial infarction will have chest pain, and 65% are entirely clinically silent which means that they will go detected without routine troponin screening.[8-10]

Most postoperative myocardial infarctions are clinically silent, and are only identified by routine troponin screening. More than 90% of patients who have troponin elevations apparently due to cardiac ischemia have no symptoms whatsoever. Most also do not have electrocardiographic or echocardiographic evidence of ischemia, and thus do not meet criteria for myocardial infarction specified in the 3rd Universal Definition. While it is tempting to dismiss asymptomatic troponin elevations as "troponitis," mortality is almost as high without symptoms as with symptoms — indicating that isolated troponin elevations should be taken seriously.[6] Because troponin elevation with or without symptoms has comparable prognostic significance, it is referred to as Myocardial Injury after Non-cardiac Surgery, abbreviated MINS.[11]

MINS is defined by postoperative troponin elevation that is apparently of cardiac origin. The thresholds for MINS depend on the type of troponin. For fourth-generation troponin T, for example, MINS is defined by a postoperative concentration ≥0.03 ng/ml. For fifth-generation (high sensitivity) troponin T, the threshold is: 1) a postoperative concentration ≥20 ng/L with an increase from baseline of at least 5 ng/L; or, 2) a postoperative concentration ≥65 ng/L. Two days of postoperative monitoring will identify 90% of MINS and is thus usually sufficient. Unlike troponin T which is a branded product that is similar worldwide, troponin I is generic and there are many versions, each with corresponding thresholds.

Troponin screening is appropriate for most surgical inpatients ≥45 years of age, and certainly those who also have even a single cardiovascular risk factor. Troponin analysis can be included with routine morning blood sampling on the first and second postoperative mornings while patients remain hospitalized. For 5th-generation, high-sensitivity troponin, a preoperative value should also be obtained. Screening thereafter is unnecessary since about 94% of postoperative myocardial infarctions occur within 48 hours after surgery[10] and because at least half of all 30-day mortality occurs during the initial hospitalization.[12] That said, blood should immediately be sent for troponin analysis in any patients who has cardiovascular symptoms such as chest pain or shortness-of-breath. Non-ischemic causes of troponin elevation include end-stage renal disease, sepsis, and pulmonary embolism[7]; preoperative plasma troponin assays might help clinicians interpret subsequently elevated values.

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Troponin testing is inexpensive and available worldwide. Compared with so many low-value perioperative tests, troponin has a number-needed-to-test <25 for a condition with a 4% 30-day mortality. That the cost is justified thus seems obvious, a conclusion supported by formal analysis.[13] In contrast, many common preoperative risk-assessment tests such as stress echocardiograms are expensive and provide little prognostic value.[8]

Non-operative myocardial infarctions result largely from coronary plaque rupture. The etiology of postoperative myocardial infarctions remains poorly delineated, but supply-demand mismatch and coronary thrombosis appear to be important causes — although they rarely causes non-operative infarctions. As with non-operative infarctions, most do not display ST-segment elevation.[8]

There are not currently published randomized trial results suggesting specific treatments for MINS. Nonetheless, potential benefits of troponin screening include cardiology consultation and patients: 1) being informed that they had myocardial injury and are thus at risk for future heart attacks; 2) potentially starting aspirin; 3) consideration for statin and/or ACE inhibitor therapy; 4) improved hypertension control, as necessary; and, 5) use of a "teachable moment"[14] to encourage lifestyle changes including smoking cessation, sensible diet, and enhanced exercise.

Preventing myocardial injury

Because myocardial infarctions are the leading cause of attributable postoperative mortality, there have been substantive multi-national efforts to test various prophylactic treatments. The first major double-blinded randomized trial was POISE which compared extended-release metoprolol and placebo in more than 8,000 surgical inpatients patients at high cardiovascular risk.[15] Metoprolol 100 mg or placebo was given shortly before surgery, and was followed by 200 mg/day or placebo for 30 days. The beta blocker reduced the incidence of myocardial injury by 30% which was highly statistically significant, and of course clinically important. However, beta blocker administration also caused serious hypotension and strokes which increased overall mortality. Acute treatment with metoprolol thus failed to *safely* prevent postoperative myocardial infarctions. It is, of course, possible that lower doses or different beta blockers would work better, but such theories remain entirely speculative.

A second major randomized trial, ENIGMA-2, tested the hypothesis that avoiding nitrous oxide reduces the risk of cardiovascular complications. The basis for this theory is that nitrous oxide impairs vitamin B12 and folate metabolism, resulting in increased plasma homocysteine concentrations and impaired endothelial function. The assessor-blinded trial randomized 7,000 high-risk surgical inpatients to 70% nitrous oxide or 70% nitrogen. There was no effect whatsoever of nitrous oxide on the primary composite of cardiovascular complications either in the entire population or in any pre-defined subgroup. There was also no toxicity observed, except a modest increase in severe nausea and vomiting. Nitrous oxide thus appears to have neither positive nor negative effects on any substantive outcome.

The last major trial of prophylaxis for myocardial infarction was POISE-2, a double-blinded factorial trial of aspirin and clonidine.[16] Aspirin was included because its anti-platelet activity might reduce coronary thrombosis, and because of its unquestioned role in preventing secondary infarction. (Whether aspirin is effective for primary prevention of myocardial infarction is less established.) Clonidine was included because many previous studies indicated that central alpha receptor agonists control heart rate without causing nearly as much hypotension as beta blockers. The trial randomized 10,010 multi-national non-cardiac surgical inpatients who were at high cardiovascular risk. Aspirin did not reduce the risk of myocardial infarction or death within 30 days, but did increase the risk of major bleeding (Fig. 1A).[17] Clonidine also failed to reduce the risk of myocardial infarction or death, while provoking clinically important hypotension and bradycardia (Fig. 1B).[18]

Beta blockers, avoiding nitrous oxide, aspirin, and clonidine all failed to reduce risk, and three of the four drugs caused serious complications. There is thus currently no documented way of safely preventing myocardial infarction after surgery.

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Intraoperative hypotension

General anesthesia was discovered about 170 years ago, and controlling intraoperative hemodynamics is among the major tasks for anesthesiologists. One might thus assume that how best to manage blood pressure has long been well established, but it is not. Furthermore, much previous work focused on cerebral perfusion although the brain is probably less sensitive to hypotension than the heart and kidneys. One difficulty has been that until the relatively recent development of cardiac troponin, clinicians lacked sensitive biomarkers for myocardial injury. A second difficulty is that reliably estimating associations between degrees of hypotension and various relatively rare outcomes requires accurate minute-by-minute details from tens-of-thousands of cases which were unavailable until electronic anesthesia records became routine. Associations between pressure and consequent outcomes will obviously depend on how blood pressure is characterized. However, simple characterizations such as mean and time-weighted average may be less useful than measures that quantify duration and severity of pressures at the extremes which is where injury apparently occurs.

There is a strong association between intraoperative hypotension and mortality.[19] Risk increases substantially when the minimum mean arterial pressure maintained for ten minutes is less than about 70 mmHg.[20] There are similarly strong associations between hypotension and myocardial and kidney injury.[21] The threshold for myocardial injury is a mean arterial pressure of about 65 mmHg, maintained even just for a few minutes. The threshold for renal injury appears to be even greater, perhaps near 75 mmHg.[21] There are also strong associations between hypotension and myocardial and renal injury when mean arterial pressure is expressed as a percentage of baseline clinic pressures. But changes from baseline are not more predictive than an absolute threshold of 65 mmHg which is easier to use clinically.

In an analysis of adults having non-cardiac surgery at the Cleveland Clinic, a full third of all hypotension, defined by mean arterial pressure <65 mmHg, occurred between anesthetic induction and surgical incision. Furthermore, hypotensive minutes were significantly and comparably associated with both myocardial and kidney injury before and after incision (unpublished data). Aside from the occasional contribution of patient positioning, hypotension before incision results exclusively from anesthetic drugs. It is also largely preventable — and probably should be. One way to reduce intraoperative hypotension is to hold angiotensin converting enzyme inhibitors and angiotensin receptor blockers on the day of surgery.[22] In contrast, tachycardia is either not associated with myocardial injury (unpublished data), or only associated at rates exceeding 100 beats/min.[10]

Observational analyses routinely adjust for known confounders. But there are always residual confounding factors that are unknown or poorly quantified, making it hard to estimate the extent to which confounding contributes to apparent associations. The distinction is important because associations that result from confounding will not be amenable to intervention. Most likely, intraoperative hypotension is both a marker of underlying illness and a mediator of organ injury. The only reliable way to distinguish the relative contributions of each mechanism is with an interventional trial. Fortunately, at least some randomized data are now available.

Futier and colleagues compared tight vs. minimal intraoperative blood pressure control (n=298).[23] High-risk patients were randomized to minimal blood pressure control (ephedrine for systolic pressure <80 mmHg or <40% below baseline) vs. a norepinephrine infusion to maintain systolic pressure within 10% of baseline values during and for four hours after surgery. The primary outcome, a composite of systemic inflammatory response syndrome and/or at least one organ failure, occurred in 56/147 patients in the norepinephrine group vs 75/145 patients in the minimal control group: relative risk 0.73 [95% CI: 0.56, 0.94]. The investigators also reported that there were fewer sepsis cases and that the duration of hospitalization was shorter with tight blood pressure control.

Available data suggest that even brief periods of mild intraoperative hypotension are harmful. Harm appears to start at mean arterial pressures near 65 mmHg. Myocardial and renal injury depends on the duration and severity of hypotension, with only a few minutes being required once mean pressure reaches 55 mmHg.[24] Of course hypotension-induced harm is not distributed randomly among surgical patients; harm is by far most likely in patients with pre-existing risk factors — especially cardiovascular disease.

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Ward and critical care hypotension

Intraoperative hypotension is often profound, but tends to be short because anesthesiologists intervene. In contrast, ward hypotension — while usually less severe — is often sustained for hours because vital signs are measured only infrequently. A recent analysis of hypotension on surgical wards at the Cleveland Clinic identified the magnitude of the problem. Arterial pressure was continuously recorded non-invasively in postoperative patients; the continuous values were blinded to the clinical team that relied on routine nursing vital signs. Fifteen percent of patients had continuous episodes of mean arterial pressure <70 mmHg for at least 30 minutes; 10% had continuous pressures <65 mmHg for at least 15 minutes. Nursing records failed to identify any hypotension at all in 70% of these patients (unpublished data).

A sub-analysis of the POISE-2 trial evaluated the independent contribution of intraoperative hypotension, hypotension during the remaining day of surgery, and during subsequent hospital days. During each period, hypotension was significantly associated with the composite outcomes of myocardial infarction and death within 30 days. For example, during the remaining day after surgery, each 10 minutes of hypotension increased the odds 3% (95% confidence interval 1, 5%, P<0.001). While 3% per 10 minutes may seem unimportant, postoperative hypotension often persists for hours, resulting in considerable cummulative insult (Fig. 4).[25]

Acute kidney injury is far more common than cardiac injury in critical care patients, and the severity of AKI is independently associated with in hospital mortality.[26] In the same study of 2,918 postoperative critical care patients,[27] there was a linear relationship between hypotension and acute kidney injury over the entire range of from 110 to 50 mmHg, with an adjusted overall hazard ratio of 1.16 per 10-mmHg reduction in the lowest recorded mean-arterial pressure. When analysis was restricted to stage 2-3 injury, the hazard ratio increased to 1.29.

In patients with septic shock, Badin et al. showed that a mean pressure exceeding 72-82 mmHg was needed to prevent acute kidney injury.[28] Others have also concluded that a similar MAP >73 mmHg is needed to prevent progression to kidney injury in patients with severe sepsis.[29] Both duration and severity of hypotension matter: for example, it takes an hour of exposure to 80 mmHg to equal even a few minutes below 70 mmHg.[27] Interpretation of sepsis studies is complicated by the fact the sepsis *per se* causes hypotension, and worse sepsis presumably causes most hypotension and has the worst outcomes.[30] Distinguishing sepsis severity from the independent effects of hypotension is challenging and it is likely that all such analyses suffer a degree of residual confounding.

There are clearly many causes of delirium in critical care patients,[31] but hypotension may contribute. For example, patients recovering from colorectal surgery in an intensive unit were more likely to experience delirium in the ICU if they had been hypotensive during surgery.[32] Tognoni and colleagues similarly reported that delirious patients were more likely to have had intraoperative systolic pressures <90 mmHg.[33] Another study reported that intraoperative blood pressure variability was associated delirium during the initial two critical care days, whereas relative or absolute decreases in mean arterial pressure were not.[34] There is less information about the associations between hypotension in critical care units and delirium. But Aldemir and colleagues screened 818 critical care patients daily for 10 days and reported an association between systolic pressure <80 mmHg and delirium.[35] Delirium is difficult to assess and reported differences from one study to another may in part be explained by how and when delirium was evaluated.

An association between hypotension and mortality has been reported in a mixed population, without specifically assessing risk of myocardial injury. Dunser et al concluded from their work on 274 septic patients that a MAP <60 mmHg nearly tripled the risk of death.[36] Varpula and colleagues, in a similar but smaller cohort of septic patients, identified an association between mean pressures <65 mmHg and 30-day mortality.[37]

In most units, care of septic patients is generally guided by the Surviving Sepsis Guidelines. A strong recommendation, based on moderate-quality evidence, is to titrate vasopressors to an initial MAP target of 65 mmHg during resuscitation of septic shock.[38] The largest trial supporting these guidelines randomized 776 patients to high (80-85 mmHg versus low (65-70 mmHg) MAP targets in patients with vasodilatory septic shock.[39] The investigators had difficulty obtaining the targeted pressures, but did maintained good inter-group separation (85-90 mmHg vs. 70-75 mmHg). A further limitation is that clinical myocardial infarctions were only observed in only 9

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patients which precluded reliable assessment of this important outcome. Atrial fibrillation was more common in patients assigned to higher blood pressure, possibly consequent to greater catecholamine exposure. There was no significant overall difference in renal injury but in a pre-planned sub-group analysis, patients with chronic hypertension who were assigned to the lower pressure target had more renal injury and more often required renal replacement therapy. Other smaller randomized trials also report that higher blood pressure targets are associated with more cardiac arrhythmias, more vasopressor use, and similar lactate, regional blood flow, and mortality than lower blood pressure targets.[40-43]

Available data suggest that mean-arterial pressures well above 65 mmHg are needed — perhaps as high as 90 mmHg — to prevent hypotensive organ injury in critical care patients, including those who are septic. In contrast, 65 mmHg or slightly greater appears sufficient during surgery.[21,44] The most likely explanation is that general anesthesia reduces metabolic rate about 30%,[45] which presumably also reduces perfusion requirements. Furthermore, intensive care patients have coexisting insults including extreme sympathetic stimulation, fluid shifts, and often pre-existing and subsequently superimposed organ system injury. The harm threshold on surgical wards remains unknown, but may well prove to be somewhere between the pressures required during surgery and those required in critically ill patients.

Summary

Postoperative myocardial injury — the major attributable cause of death after surgery — is rarely accompanied by symptoms — meaning that more than 90% of cases will be missed without troponin screening. Mortality is 4% at 30 days, making myocardial injury a leading cause of short-term postoperative death, and mortality is similar with and without symptoms. Asymptomatic troponin elevation is thus highly prognostic and cost effective. Fourth-generation troponin T concentrations ≥0.03 ng/ml should prompt a cardiology consult and interventions that might include aspirin, angiotensin converting enzyme inhibitors, and statins; blood pressure and heart rate control; and lifestyle enhancements including smoking cessation, exercise, and a healthful diet. How to safely prevent perioperative myocardial injury remains unknown. But in the mean time, avoiding intraoperative hypotension (i.e., mean-arterial pressures <65 mmHg) seems prudent. Postoperative hypotension should similarly be avoided.

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I Can Be Sued for That? Navigating the Legal Morass Beyond Medical Malpractice: Preventing Data Breaches – Balancing Usability, Security and Liability

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Introduction

Data is a valuable asset and theft is becoming routine.[1, 2] Data breaches represent a growing concern for all businesses. Medical databases, such as Electronic Medical Records (EMR), are especially vulnerable to cyber attacks.[3, 4] From an institutional perspective, medical data breaches create legal risk, are time consuming to recover and are subject to civil penalties. From a patient perspective, medical identity theft can negatively impact both health and financial wellbeing. Institutions must continually deploy and enforce innovative "cyber hygiene" strategies to protect their data. Preventing data breaches has introduced the operational need to balance usability, security and liability.

HIPPA, PHI and Data Breaches

The US Department of Health and Human Services (HHS) issued the Standards for Privacy of Individually Identifiable Health Information, or "Privacy Rule", to implement the requirement of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The Privacy Rule established national standards for the use and security of "Protected Healthcare Information" (PHI).[5, 6] Within HHS, the Office for Civil Rights (OCR) implements and enforces the Privacy Rule.

Under HIPPA, a data breach is defined as an impermissible use or disclose of PHI.[7] All such instances are presumed to represent a data breach unless the healthcare entity, or business associate, can show a low probability of PHI compromise based upon a four factor risk assessment. HHS defines a limited number of exceptions to the breach rule. All incidents of data breach require mandatory reporting as stipulated under HIPPA.

Healthcare organizations are considered relatively easy cyber-theft targets secondary to their need to regain data access and willingness to meet hackers' demands.[8] Additionally, healthcare records are financially lucrative. Illegally obtained credit card numbers, valued at approximately $1 each, pale in monetary comparison to medical records that can garner up to 50 times the return. From 2009 to 2016, hospitals accounted for approximately one-third of all PHI data breaches involving 500 or more records.[9] Healthcare record theft continues to rise. Between 2009 and 2017, 2,181 healthcare data breaches involving more than 500 records resulted in a compromise of 176,709,305 healthcare records.[10] In 2017, healthcare accounted for 58% of all cyber threats.[11] Ransomware, a type of malware that locks most or all usable data until a ransom is paid, represents the most common attack.

Data Breach Risks and Costs

Medical record theft potentially subjects patients to financial and physical impairment. Although large data breaches occur in many industries [12, 13], healthcare breaches have unique attributes. Healthcare breaches involve demographic, medical, financial and insurance coverage data. Stolen demographic information can leave patients subjectively vulnerable. From a financial aspect, patients can be held financially liable for fraudulently acquired medical goods and services.[14] Medical information may be the most difficult aspect to recover and correct. Unlike financial data, EMR data does not have centralized reporting agencies for ongoing monitoring and accuracy verification.

From an institutional perspective medical data breaches create legal risk, are time consuming to recover, are subject to civil penalties and negatively impact the institution's brand value.[2] In 2015, Anthem Insurance Company was involved with the largest reported data breach to date.[12] The widely publicized 80 million record breach (including patient names, dates of birth, physical/email addresses, medical record/social security numbers) resulted in a record $115 million dollar settlement to the class action lawsuit.[13] In addition to payments and legal fees, HHS settlements and fines can enter into millions of dollars.[10]

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Data Breach Sources

Data breach sources can be classified in many ways. Generically, breaches are a result of 1) unauthorized access, 2) hacking (example, data theft), 3) hardware theft or 4) improper disposal (example, paper records).[9]

Unauthorized Access

Small scale data breaches commonly involve inappropriate medical record access by family or healthcare professionals.[15] A pattern of repetitive data breach behaviors is common among some physicians and hospital employees. The risks can include information theft or data manipulation. Although typically small in record volume, these events compromise patient privacy and create legal risk for the institution.

Email

Phishing, the fraudulent practice of impersonating a trustworthy email source, remains the most common technique for gaining personal information for malicious reasons.[16, 17, 18, 19] According to a 2018 report of 40 million emails by approximately 1,000 world-wide users, 91% of cyber-attacks start with a phishing email. The most commonly reported reasons for end users responding to questionable emails are curiosity, fear and urgency.

During the first quarter of 2018, the most common phishing exploits disguised themselves as DocuSign, Office365 or Dropbox.[20] Additionally, other attempts involved Amazon Prime and Apple Services. Larger organizations were most commonly targeted. Once the end user shares their credentialing information, the hacker can readily gain access to the real account and all associated information.

Websites

Even seemingly innocuous websites present risk. Websites present ads, news feeds and other external content on contained areas of the webpage called iframes. Clicking on an iframe can result in unintended outcomes including downloading any number computer viruses or redirecting to a malicious site.

External Hardware

Sophisticated malware can reside on external hardware. Thumb drives, for example, can contain applications masquerading as hardware, emulating a temporary operating system or directly acquiring information supplied by the end user.

Data Protection

As data breach strategies have become progressively more sophisticated, so have approaches to data protection. Strategically balancing usability and data protection is a highly effective approach. Forward-thinking organizations hire professionals who create, implement and oversee the holistic approach to protecting data assets.

Industry experts and HHS agree that active end user education and adhering to “cyber hygiene” are key elements in mitigating data breaches.[11] Recurring education on safe use of email and websites allow more liberal institutional cyber-security policies. Information services departments will commonly send random, leading emails teaching key elements of potentially infected or risky attachments.

At the institutional level, tools such as web filtering software, two factor authentication and secure messaging assist in protecting user identities and PHI.[21] Additionally, complex passwords routinely changed on a scheduled basis promote security. Antivirus applications are classified as static (signature based) or dynamic (behavior based). Signature based applications, similar to those commonly used on a home computer, look for malicious code

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sequences and block potentially infected files. Behavior pattern based programs use sophisticated techniques to identify malware threats. This type of virus detection monitors for suspicious program behaviors.

Data Breach Management

Despite good "cyber hygiene" and security practices, data breaches transpire. In the event of a breach, HHS recommends steps to mitigate risk including -[8]

1. Isolate the infected computer
2. Isolate all affected devices
3. Take back up data or systems off line
4. Contact law enforcement
5. If available, collect and secure partial portions of ransomed data
6. If possible, change all passwords solicit
7. Promptly gain IT professional assistance

The HIPPA Breach Notification Rule requires hospitals, surgical outpatient centers and medical practices to appropriately report data breaches.[22, 23] HHS publicly reports data breaches on a website.[24] In the case of medical practices, a physician must take an active role in evaluating the extent of the breach. HHS reporting rules include -

1. Unless meeting a "low probability of compromise" threshold, any PHI disclosure is presumed to be a breach
2. Notify patients and The US Department of Health and Human Services (HHS) of any PHI-related breach
3. All involved parties must be notified as soon as possible and no later than 60 days following the date of discovery
4. While all breaches must be reported, breaches of < 500 records only require HHS reporting
5. If the breach involves more than 500 individuals, the entity must notify a prominent media outlet serving the state or jurisdiction

Conclusion

Data breaches can present a significant risk to both patients and healthcare institutions. As data breach threats rise, Information Services departments deploy advanced cyber threat techniques to manage the potential risk. The most effective methodology to mitigate data breaches are meticulous "cyber hygiene", recurring end user education and up-to-date technology to protect data assets. Finding a balance between usability and security is a challenging and ongoing task.

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I Can Be Sued for That? Navigating the Legal Morass Beyond Medical Malpractice: Sexual Discrimination, Sexual Harassment and Hostile Work Environments

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Introduction

In this day of the #MeToo movement, 6- and 7-figure dollar payoffs, equally expensive legal judgements, high-profile arrests, at least one conviction of a well-known individual, and a general increase in the awareness of both the pervasive nature and potentially severe consequences of what in the past may have been considered merely "bad behaviour," it is important to understand what behaviours may result in charges of sexual discrimiation, sexual harassment and/or a hostile work environment.

Legal Elements

Sexual discrimination is prohibited under Title VII of the Civil Rights Act of 1964 ("Title VII"). Although there are a number of statutory and regulatory provisions regarding sexual discrimination, the two most important ones can be found in Sections 703 and 704 of Title VII. The first relates to employment practices involved in hiring, firing, promotions, and other employment oppportunities:

Employer practices

> It shall be an unlawful employment practice for an employer -
>
> (1) to fail or refuse to hire or to discharge any individual, or otherwise to discriminate against any individual with respect to his compensation, terms, conditions, or privileges of employment, because of such individual's race, color, religion, sex, or national origin; or
>
> (2) to limit, segregate, or classify his employees or applicants for employment in any way which would deprive or tend to deprive any individual of employment opportunities or otherwise adversely affect his status as an employee, because of such individual's race, color, religion, sex, or national origin.[1]

The second prohibits retaliation against individuals who complain of, testify about, or in any way participate in enforcement proceedings relating to sexual discrimination:

Discrimination for making charges, testifying, assisting, or participating in enforcement proceedings

> It shall be an unlawful employment practice for an employer to discriminate against any of his employees or applicants for employment, for an employment agency, or joint labor-management committee controlling apprenticeship or other training or retraining, including on—the-job training programs, to discriminate against any individual, or for a labor organization to discriminate against any member thereof or applicant for membership, because he has opposed any practice made an unlawful employment practice by this subchapter, or because he has made a charge, testified, assisted, or participated in any manner in an investigation, proceeding, or hearing under this subchapter.[2]

The Title VII definition of "sex" now includes preganancy, childbirth or related medical conditions. As originally passed, Title VII prohibited discrimination "because of sex" but did not explicitly include pregnancy, childbirth or other related medical conditions. In 1976, the US Supreme Court held that discrimination based on pregnancy was not unlawful discrimination under Title VII.[3] In response to this decision, Congress passed the Pregnancy Discrimination Act in 1978 to amend Title VII, explicitly making discrimination based on pregnancy, childbirth or related medical conditions a violation of Title VII.[4]

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Prohibited Activities

Title VII does not prohibit all conduct that is sexual in nature in the workplace—only unwelcome sexual conduct that is a term or condition of employment is a violation of Title VII. Under Equal Employment Opportunity Commission (EEOC) regulation 29 CFR 1604(a), "Unwelcome sexual advances, requests for favors, and other verbal or physical conduct of a sexual nature constitute sexual harassment when: 1) submission to such conduct is either explicitly or implicitly a term or condition of an individual's employment, 2) submission to or rejection of such conduct by an individual is used as the basis for employment decisions affecting that individual, or 3) such conduct has the purpose or effect of unreasonably interfering with an individual's work performance or creating an intimidating, hostile, or offensive working environment."[5]

The EEOC recognizes two types of sexual harassment: 1) "quid pro quo" and 2) hostile work environment. "Quid pro quo" harassment typically violates one or both of 29 CFR 1604.11(a)(1) and 1604(a)(2) whereas the creation of a hostile environment violates the third type of harassment identified in 1604.11(a)(3). The issue of whether sexual harassment violates Title VII reached the U.S. Supreme Court in 1986.[6] In that case, the Court held that sexual harassment does violate Title VII and affirmed the EEOC's Guidelines and definitions. The Court also explicitly recognized that a hostile work environment is sufficient on its own to find a violation of Title VII even if there are no "economic" or "tangible" injuries, holding that:

"Sexual harassment which creates a hostile or offensive environment for members of one sex is every bit the arbitrary barrier to sexual equality at the workplace that racial harassment is to racial equality. Surely, a requirement that a man or woman run a gauntlet of sexual abuse in return for the privilege of being allowed to work and make a living can be as demeaning and disconcerting as the harshest of racial epithets."[7]

On its way to the Supreme Court, the *Vinson* case was heard by the D.C. Circuit Court of Appeals. The one area in which the Supreme Court disagreed with the D.C. Circuit Court of Appeals was that an employer is absolutely liable for sexual harassment committed by a supervisory employee, regardless of whether the employer actually knew or reasonably could have known of the misconduct or would have disapproved of and stopped the misconduct if aware of it. The Supreme Court reversed that part of the D.C. Circuit's findings, holding that the appelate court had erred in finding absolute liability for sexual harassment by a supervisory employee.

Evaluating Sexual Harassment Claims

The first step in evaluating a sexual harassment claim is to determine whether the complained of actions were, in fact, "unwelcome." In many cases this may be difficult to determine because the distinction between invited, uninvited-but-welcome, offensive-but-tolerated-and flatly rejected sexual advances may well be dificult to make. However, it is important to make this distinction because only behavior that is unwelcome is unlawful. When confronted with conflicting evidence as to whether the "alleged conduct constitutes sexual harassment, the Commission will look at the record as a whole and at the totality of the circumstances, such as the nature of the sexual advances and the context in which the alleged incidents occurred. The determination of the legality of a particular action will be made from the facts, on a case by case basis."[8] A number of factors may be considered when making this determination, including: 1) did the individual subjected to the harassing behavioir make any complaints; 2) did s/he tell any co-workers about the unwelcome behaviors; 3) did others observe changes in the person's demeanor following the alleged incidents, even if they did not witness the incidents themselves; 4) did the person alleging harassment behave in a manner that **clearly** indictated that the behavior was, in fact, welcome and even more importantly, welcome from the alleged harasser; and 5) in cases where the person clearly welcomed the behavior previously but no longer does, did s/he make it clear that such behavior is no longer welcome. These are all individual facts that must be evaluated when determining whether harassment occurred.

Evaluating Evidence of Sexual Harassment

Sexual conduct may be private and unacknowledged, with no witnesses to the alleged harassing behavior. Even when the incidents occur publicly, the behavior may appear to be welcome, even when it is not. When the EEOC investigates alleged sexual harassment, it looks for as much evidence as possible to determine whether the offending

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behavior should be viewed as "welcome" or "unwelcome." This investigation is likely to involve interviews with not only the victim and perpetrator, but with a number of other individuals, including co-workers, management, physicians, counselors, family members, friends, etc. This can be a significant number of individuals.

Determining Whether a Work Environmnet is "Hostile"

The Supreme Court said that for sexual harassment to violate Title VII, it must be sufficiently severe or pervasive to alter the conditions of the victim's employment and create an abusive working environment.[9] Since a hostile work environment takes many forms, a number of factors must be considered when determining whether a specific work environment is "hostile", including 1) whether the conduct was verbal, physical or both; 2) how frequently it occurred; 3) whether the conduct was hostile or patently offensive; 4) whether the harasser was a co-worker or supervisor; 5) whether others joined in perpetrating the harassment; and 6) whether the harassment was directed at more than one individual.

Whether unwelcome sexual conduct rises to the level of a "hostile environment" in violation of Title VII, the question is whether the conduct "unreasonably interferes with an individual's work performance" or creates "an intimidating, hostile, or offensive working environment."[10] According to the EEOC, sexual flirtation, innuendo, or vulgar language that is trivial or merely annoying, would probably not establish a hostile environment.

When determining whether harassment is severe or pervasive enough to create a hostile environment, the harasser's conduct must be evaluated from the objective standpoint of a "reasonable person." According to several court cases, Title VII does not serve "as a vehicle for vindicating the petty slights suffered by the hypersensitive." If the conduct would not substantially affect the work environment of a reasonable person, no violation should be found.

The "reasonable person" objective standard is applied in a vacuum. Consideration should be given to the context in which the alleged harassment took place and should consider the perspective of a reasonable person's reaction to a similar environment under similar or like circumstances.

A "hostile environment" claim generally requires a showing of a pattern of offensive conduct. A single incident or isolated incidents of offensive sexual conduct do not usually create a hostile environment. But a single incident may be sufficient when the harassment is physical, especially if it involves intentionally touching intimate parts of the victim's body, because this is sufficiently offensive to alter the condition of the working environment. In addition, a single incident of a "quid pro quo" involving a single sexual advance may constitute harassment if it is linked to granting or denial of employment benefits.

It is important to understand the although many, or even most, sexual discrimination cases involve sexual activity, the offending actions need not involve sexual activity or language. Disparate treatment based on the gender of the individual subjected to that treatment is enough to create a sexual discrimination or sexual harassment suit. Such activity need not be directed at a specific individual. For example, different work rules for men and women, may give rise to such allegations, even if the purpose of that disparate treatment was not meant to be discriminatory. Also, different opportunities may also result in sexual discrimination charges. In this day of the #MeToo movement, some male supervisors are responding by not meeting with female subordinates, not traveling with them for work-related activities, or generally keeping a greater distance between themselves and their female associates. This may seem to be a safer way to interact with members of the opposite sex, but could, in fact, result in charges of sexual discrimination because that distance may be perceived as making it more difficult to learn from male superiors or to perform the the types of duties that would typically lead to advancement.

Preventive and Remedial Action

Prevention is the best tool for the elimination of sexual harassment. Employers should take all steps necessary to prevent sexual harassment from occurring, such as affirmatively raising the subject, expressing strong disapproval, developing appropriate sanctions, informing employees of their right to raise and how to raise the issue of harassment under Title VII, and developing methosds to sensitize all concerned.[11]

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Since Title VII affords employees the right to work in a non-discriminatory environment, an employer is liable for failing to remedy known hostile or offensive environments. When an employer receives a complaint or learns of alleged sexual harassment, the emloyer should investigate promptly and thoroughly, take immediate appropriate corrective action to end the harassment, make the victim whole by restoring lost employment benefits or opportunities, and prevent the misconduct from recurring. The employer should follow-up to make sure the harassment has not resumed and the victim has not suffered retaliation.

When an employer asserts it has taken remedial action, the EEOC may investigate to determine whether the action was appropriate and effective. If it finds that the harassment has been eliminated, all victims made whold, and preventive measures put into place, then the EEOC will usually close the case because of the employer's prompt remedial action.[12]

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I Can Be Sued for That? Navigating the Legal Morass Beyond Medical Malpractice: Employment Issues

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Introduction

With the ever-increasing consolidation in health care, anesthesiology groups are more often being forced by market pressures to merge into larger single or multi-specialty groups. These larger groups become at risk for various claims because of the decrease in personal relationships, perception of deeper pockets, and the more complex regulatory environment. For example, two groups of 35 anesthesia providers covering facilities 10 miles apart merge. That new entity now falls under the Family and Medical Leave Act (FMLA).[1] Independent anesthesiologists may form a group to help with negotiations and economies of scale and find that they are no longer independent contractors and have employees (billing staff, office managers) to manage. Knowledge of basic employment issues can help avoid costly litigation.

Who is an employee?

This seemingly straightforward question can be difficult to answer. For example, the Occupational Safety and Health Act (OSHA) provides the redundant explanation that an employee is "an employee of an employer who is employed in a business of his employer which affects commerce."[2] The FMLA defines an employee in greater detail, including any person who is on an employer's payroll and including individuals who are laid off, on leave, or on suspension but expected to return to work for that employer. If a group of anesthesiologists form a group and employ others, do they count as employees or directors/owners? They may be considered employees for the purposes of taxes (income tax and FICA withholding), but not under other regulations. In Clackamas Gastroenterology Associates v. Wells, 123 S. Ct. 1673 (2003) the issue was whether or not shareholders and directors of a professional corporation counted as employees under the Americans with Disabilities Act (ADA).[3] The Court held that the question should be resolved according to common-law elements of control, including whether the person has the ability to hire and fire; reports to or supervises others; and shares in profits, losses, and liabilities of the company. While this case turned, in part, on the specifics of Oregon professional association law, it illustrates the difficulties one may have in identifying employees. Importantly, the mere existence of a document styled "employment agreement" does not lead inexorably to the conclusion that either party is an employee.

Independent Contractors

Can a group of anesthesiologists avoid the regulatory morass by simply engaging other providers and staff as "independent contractors" and avoid the liability of having them as employees? The Fair Labor Standards Act (FLSA) offers a broad definition of "employee": to employ is "to suffer or permit to work".[4] Under the FLSA, courts use the multi-factorial "economic realities" test, which focuses on whether the worker is economically dependent on the employer or in business for him or herself. This issue often comes into play when hiring staff. For example, a group of physician anesthesiologists forms a limited liability company (LLC) to provide anesthesia services to several clinical sites. They engage a nurse anesthetist to provide anesthesia services at one or more of those sites two or three days a week, as their staffing needs vary. They would like to classify this person as an independent contractor to avoid the burden of employment tax filings, benefits, etc. Would they be correct, especially since that anesthetist works on other days for someone else? This determination requires analysis under three broad categories: Behavioral Control, Financial Control, Relationship of the Parties.[5]

Does the LLC exhibit behavioral control (does the company control or have the right to control what the worker does and how the worker does his or her job?)? In this case, the LLC sets the working days and start/finish times of providing services. It may even have clinical protocols that can be interpreted as controlling how care is provided. How about financial control (are the business aspects of the worker's job controlled - these include things like how the worker is paid, whether expenses are reimbursed, who provides tools/supplies, etc.)? In this scenario the LLC

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pays the anesthetist an hourly wage, requires that all clinical income from services provided at their facilities be turned over to the LLC (i.e. the LLC does the billing and collecting), and provides, directly or indirectly, the anesthesia equipment, supplies, etc. That certainly sounds a lot like financial control. Finally, what is the relationship of the parties (are there written contracts or employee-type benefits, is the relationship expected to continue, and is the work performed a key aspect of the business)? In this case there is a written document stating that the relationship is that of an independent contractor, but simply stating that does not make it so, rather, one must examine not "the label put on the relationship by the parties or the contract controlling that relationship, but rather focuses on whether the work done, in its essence, follows the usual path of an employee".[6] Also important in this setting is that there is expected to be an ongoing relationship between the LLC and the anesthetist and that the work performed (provision of anesthesia services) is a key aspect of the LLC's business. Lastly, either the LLC or the anesthetist can end the relationship at any time. The ability to fire someone and the corresponding ability to quit generally indicates employment status. When examining the balance of the facts, one can only include that this anesthetist is indeed an employee.

Common Employer Errors

One pitfall that employers make is misunderstanding the concept of employment at will. Almost all states (except Montana) recognize the employment at will doctrine as the basis for employment. The doctrine means that either party is free to end the employment relationship at any time with or without cause as long as the cause is not illegal (such as age or ethnicity). There are exceptions that states have made for "public policy" which would include court decisions, administrative policies, or statutes. Another exception is an actual or implied contract. Written contracts are easy to demonstrate, but verbal contracts, while enforceable, may have disagreements about what the agreement actually is. While the employer may intend to follow the "at will" doctrine, contracts can be implied from employee handbooks, policies, or even verbal assurances of continued employment as long as performance is satisfactory. Thus, even when an employee appears to be "at will", there may be company documents or actions that suggest otherwise.

Employers can also run afoul of labor laws generally referred to as the National Labor Relations Act (NLRA). Employers dealing with unions typically understand these statutes, but those with nonunion employees may unwittingly violate them. Efforts to discourage unionization or even the discussion of forming a union can be problematic. If two or more employees act together for the common good or one employee serves as spokesperson for a group of employees, adverse action taken against such employees can trigger intervention by the National Labor Relations Board, which can be expensive and prolonged. Firing the junior associate anesthesiologists who is speaking on behalf of the new hires could trigger such action.

Another potential pitfall is with wage and hour issues. Salaried employees are not automatically exempt from overtime and minimum wage requirements. They must fall into one of five categories (professional, executive, administrative, outside sales, or some computer technologies) and meet other strict criteria, including a minimum weekly salary.[7] Anesthesia providers would typically fall into the learned professional employee exemption, but might not if only paid for when they work (no base salary) as is seen for "PRN" staff. Importantly, allowing non-exempt ("hourly") employees to do work outside of normal business hours invites claims of Federal Labor Standards Act (FLSA) violations. These activities may vary from allowing employees to come in early or stay late "off the clock", answering emails, phone calls, or texts outside of scheduled work hours, or accumulating "comp time" instead of paying them overtime.

Hiring and firing employees can be fraught with risk, and giving references is often problematic. Employers need to be careful in developing and following policies to ensure that potential employees are not discriminated against and that termination decisions are not made for any prohibited reason. Therefore it is crucial to carefully document the reasons for hiring one applicant over another and the reasons for terminating an underperforming employee. After an employee leaves, there is often a request from potential future employers for a reference. Because of the risks of defamation claims from former employee or claims of failure-to-warn from the future employer, many companies have all such requests funneled through their Human Resources departments where only basic information is given such as confirming dates of employment. Writing a favorable letter when the former employer knows that the employee is problematic creates a duty that would not exist for a neutral or strictly factual letter. This was seen in

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the Kadlec Medical Center versus Lakeview Anesthesia Associates case.[8] In that case, Lakeview Anesthesia Associates (LAA) fired an anesthesiologist for cause, specifically his abuse of opioids. Subsequently, shareholders of LAA provided positive letters of recommendation to Kadlec including statements that he was an "excellent clinician, and that he would be an asset to any anesthesia service" and "recommended him highly as an anesthesiologist" but did not note his illicit drug use or dismissal. When the anesthesiologist had an adverse patient outcome while working at Kadlec while under the influence of diverted narcotics, Kadlec was sued and settled the claim for $7.5 million. Kadlec then sued LAA and other related parties for intentional and negligent misrepresentation and won with an $8.24 million award that included legal fees. The 5th Circuit Court of Appeals concluded that "there was not an affirmative duty to disclose" but that "if an employer makes a misleading statement in a referral letter about the performance of its former employee, the former employer may be liable".

Claims of discrimination or harassment based on protected classes can plague employers. Federally protected classes include: gender, race, color, national origin, age, disability, religion, veteran status, pregnancy, citizenship, familial status, genetic information. States may add other protected classes such as sexual orientation and marital status. Unless there is direct evidence such as a written statement (including email) that the employee is being fired for being Swedish, the employee must prove four elements for the claim to be successful. These are that the employee is a member of a protected class, is qualified and performing his/her job satisfactorily, has suffered an "adverse action", and the "adverse action" was the result of the employee's membership in a protected class. The employer has to then prove that the adverse action was the result of legitimate business reasons and not based on a protected status. This emphasizes the need for formal, documented performance reviews and not just when preparing to terminate someone. Joel Meyers notes "in many organizations, performance appraisals only occur when management is building a case to terminate someone.[9] However, claims of discrimination can result from other actions besides hiring and firing. For example, if an anesthesiology group gives a holiday bonus to the office staff in its Pain Medicine clinic but not to the clerical staff in the administrative office, misperceptions about the reasons for that could result in claims of discrimination. Many practices allow physicians over a certain age to be excused from some or all overnight call requirements. Could this violate the Age Discrimination in Employment Act (ADEA) by unfavorably treating younger physician employees? Probably not under the U.S. Supreme Court ruling in General Dynamics Land Systems v. Cline, 124 S. Ct. 367 (Apr. 21, 2003), that the ADEA "does not mean to stop an employer from favoring an older employee over a younger one."[10]

Privacy concerns at work can lead to claims against the employer. In general, a private employer has the right to examine email on work-provided accounts, monitor business (but not personal) phone calls, install security cameras (video only) in work areas (but not areas where there is an expectation of privacy such as locker rooms and rest rooms), require drug tests, and search lockers, desks, handbags, and the like. Keep in mind that the Fourth Amendment prohibition against unreasonable searches applies only to governmental action.[11] The simplest way of preventing such claims is to inform employees during the hiring process that monitoring, testing, or search may occur and to reinforce that information in the employee handbook and posted notices.

Insurance

As clinicians, physicians are used to dealing with medical liability issues and insurance, but are less familiar with coverage needed as they form groups and have employees. General liability insurance is needed not only for injuries that occur on the groups premises, but injuries or damages as a result of their employees' actions wherever they occur. That is because of the doctrine of respondeat superior (Latin for "let the master answer") that a party is responsible for (has vicarious liability for) acts of its agents. Forming a legal entity such as a corporation may offer protection against personal liability for such claims depending on the exact structure of the corporation. Sole proprietorships or "doing business as" arrangements do not offer such protection. Corporations should also have Director & Officers liability insurance (D&O). Such insurance indemnifies directors and officers against alleged wrongful acts in their capacity as directors and officers. Keep in mind that insurance would not cover damages due to breach of contract or claims of discrimination. Depending on the exact wording of the policy, the defense costs may be covered, but awards for breach of contract or discrimination are not covered because they are the result of intentional acts.

Conclusion

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Modern medical practice continues to evolve from independent physicians and small groups to employed physicians and large groups. The increased size of these groups makes them fall under additional regulatory scrutiny. Paying close attention to these rules and developing sound policies in conjunction with qualified Human Resources and legal advice can help practices avoid many of the pitfalls of the employer-employee relationship.

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I Can Be Sued for That? Navigating the Legal Morass Beyond Medical Malpractice: Physician Non-Compete Agreements

Brian J. Thomas, JD **Overland Park, KS**

Introduction

Nearly every anesthesiologist practicing in the United States is aware of the potential liability exposure of being sued for medical malpractice. However, there are other areas of the law that may create legal exposures many anesthesiologists face in addition to medical professional liability. This Refresher Course will provide an overview of physician non-compete agreements and examine potential legal exposures created by these contracts. Additionally, we will provide an update regarding the evolving legal enforceability of these agreements and how some states and the federal government have carved out limitations and exceptions to enforceability based upon public policy and antitrust concerns.

Legal Elements

A non-compete agreement (also known as a restrictive covenant or covenant not to compete) is a contractual promise made by an employee, or the seller of a business[1], not to compete in the same type of business in the same area for a certain time period, typically after employment terminates. A primary purpose of a non-compete agreement is to protect a business interest by limiting competition.[2]

The advantages of non-compete agreements for employers is to ensure that when physician employees leave a practice they do not take patients, patient information or other confidential business information to compete against the practice. From the employed physician's vantage point, non-compete agreements may upon termination of employment significantly limit employment opportunities, necessitate moving to another city or state to practice medicine, or result in defending costly litigation by the employer to enforce a non-compete agreement.

In order for a non-compete agreement to be enforceable, basic principles of contract law require that it must be supported by consideration (something of value – e.g. an offer of employment, increase in compensation or bonus, or sale of a business). There must also be a protectable legitimate business interest. State courts typically recognize the following legitimate business interests: (1) confidential business and proprietary information; (2) return on investment of specialized training; and (3) customer or client relations.[3] In the context of physician practices, legitimate business interests might also include patient lists, patient health information and patient goodwill associated with a professional practice.[4]

Finally, the restriction must be "reasonable" (determined on a case-by-case basis and can vary widely depending on the state) with regard to activity (type of business or practice specialty), geographic area (often defined as radius in miles from physical location of business) and duration (typically defined in months or years). Overly broad restrictions on activity (e.g. "practice of medicine"), geographic area (e.g. "within an entire state") or duration (e.g. "five years") may not be enforced by the courts.

Breach – Legal Consequences

Several legal remedies may be available to an employer if a physician attempts to breach or breaches a non-compete agreement. Those remedies include, but are not limited to, liquidated damages[5], attorneys' fees and all costs incurred by the employer to enforce a non-compete agreement. Additional legal remedies might include obtaining a court-ordered injunction[6] against the physician to enforce the non-compete agreement or prevent a violation of a restriction (e.g. taking patients from the employer's practice or joining a competing practice within a restricted geographic area). Alternatively, as noted below, if the employer materially breaches the employment agreement, some state courts may not enforce the non-compete agreement.

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Enforceability

Generally, employment non-compete agreements are disfavored as a matter of law and public policy as a "restraint of trade" at the federal and state level.[7] Therefore, while employment non-compete agreements are enforceable in nearly every state with a few exceptions[8], courts will often try to identify reasons not to enforce them.

The American Medical Association (AMA) code of ethics strongly disfavors physician restrictive covenants (i.e. non-compete agreements) stating covenants not to compete restrict competition, can disrupt continuity of care and may limit access to care. The AMA code of ethics states that physicians should not enter into covenants that do not make reasonable accommodation for patients' choice of physician.[9]

Due to the unique nature of the practice of medicine and public policy considerations, many states apply additional rules by statute or case law to limit physician non-compete agreement restrictions. Some state courts have recognized the importance of preserving the patient-physician relationship and access to critical goods and services, such as health care, by not enforcing or modifying physician non-compete agreements. Other factors courts will consider when determining the enforceability of non-compete agreements include whether the employer materially breaches the agreement or the physician-employee is terminated without cause.[10]

Several states have enacted statutes that generally prohibit the enforcement of employment non-compete agreements.[11] Other states restrict enforcement and impose additional factors to determine reasonableness by statute.[12] Some states apply stricter standards to ensure physician non-compete agreements meet specific statutory restrictions.[13]

States typically take three approaches to address non-compete agreements that are deemed overly broad or otherwise unenforceable:

1. "Equitable Reform" - The majority of states utilize this approach and courts allow employers to rewrite non-compete agreements to bring those contracts in compliance with state law.
2. "Blue Pencil" Doctrine – Other states apply the "Blue Pencil" Doctrine that allows courts to strike or remove overly broad restrictions from non-compete clauses if the remaining language and restrictions are enforceable under state law.
3. "Red Pencil" Doctrine – Some states refuse to enforce and make void overly broad the entire non-compete contract that contains any unenforceable clauses or provisions.[14] The application of this doctrine serves to incent employers to draft non-compete agreements that are enforceable under state law from the outset.

Acquisitions of physician practices might also affect the enforceability of non-compete agreements. Whether existing non-compete agreements survive an acquisition likely depends on whether it is a stock purchase or an asset purchase agreement. In a stock purchase agreement where the acquired company continues to operate the existing non-compete agreements would likely not be affected.[15] However, if the acquisition is an asset purchase agreement where the acquired physician practice merges into the acquiring practice or practice management group, some state courts and the Federal Trade Commission (FTC) have refused to enforce or modified non-compete agreements.[16,17]

Conclusion

Statutes and case law governing the enforcement of physician non-compete agreements vary from state to state and continue to evolve. Recent enactment of several state statutes, developing case law and FTC antitrust scrutiny of physician practice acquisitions reflects a trend to limit the enforceability of physician non-compete agreements. The significant and ongoing changes in healthcare delivery - including mergers and acquisitions of private practice anesthesia groups with large practice management groups and hospital systems - increase the

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likelihood that anesthesiologists have been or will be asked to enter into non-compete agreements. Anesthesiologists and anesthesia practice groups should be fully informed and advised by legal counsel, financial advisors and other resources when negotiating or renewing any non-compete agreement, including the restrictions, state and federal law regarding enforceability and the overall value of the contract.

References

[1] Non-compete agreements in the context of a sale of a medical practice are often viewed more favorably by state courts. Additionally, there may be other legal remedies included in the non-compete agreement, including liquidated damages, "claw back" provisions, legal fees and court costs. Non-compete agreements in the context of a sale of a medical practice are beyond the scope of this article.
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[11] *See, e.g.,* Alabama, California, Montana, North Dakota and South Dakota.
[12] Colorado statute states, in relevant part, "Any covenant not to compete provision of an employment, partnership, or corporate agreement between physicians which restricts the right of a physician to practice medicine, as defined in section 12-36-106, C.R.S., upon termination of such agreement shall be void…" (Colo. Rev. Stat. §8-2-113(3)).
[13] Texas Code allows non-competes to be enforced against physicians only in narrow circumstances. Among other factors, the covenant must (1) allow the physician access to his/her list of patients seen or treated within one year of termination of the contract or employment; (2) allow the physician access to patient medical records upon authorization of the patient; and (3) provide that the physician will not be prohibited from providing continuing care and treatment to a specific patient or patients during the course of an acute illness after the contract or employment has been terminated. (Tex. Bus. & Com. Code §15.50 (b)-(c).
[14] *See, e.g., Lanmark Tech., Inc. v. Canales, 454 F. Supp. 2d 524, 529 (E.D. Va. 2006); Better living Components, Inc. v. Coleman, 620005 WL 771592, at *5 (Va. Cir. Ct. Apr. 6, 2005)* (these Virginia courts declined to blue pencil non-compete agreements); *see also Lasership Inc. v. Watson, 2009 WL 7388870, at *9 (Va. Cir. Ct. Aug. 12, 2009); Pace v. Ret. Plan Admin. Serv., Ltd., 2007 WL 5971432 (Va. Cir. Ct. Sept. 28, 2007),* (finding that blue pencil

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provisions permitting judicial modification in non-compete agreements are invalid or discouraged under Virginia law).

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[17] In December 2012, Renown Health agreed to settle charges brought by the FTC and the Nevada attorney general that its acquisitions of two local cardiology groups reduced competition for the provision of adult cardiology services in the Reno area. Renown Health, based in Reno, Nevada, operates general acute care hospitals and commercial health plans serving the Reno area. Before the acquisitions, virtually all of the cardiologists in the Reno area were affiliated with two medical groups – Sierra Nevada Cardiology Associates and Reno Heart Physicians. To settle the charges, Renown Health released its staff cardiologists from "non-compete" contract clauses, allowing up to 10 of them to join competing cardiology practices. Available at: https://www.ftc.gov/enforcement/cases-proceedings/1110101/renown-health-matter

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Echocardiographic Assessment of the Right Ventricle

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Anatomy and Physiology

Under the normal loading conditions geometry of the right ventricle (RV) resembles a crescentic-shaped structure wrapping around the left ventricle (LV) when looked at in the short axis (or triangular when looked at medial-to-lateral). However, in conditions of volume and pressure overload the RV remodels to a more circular or spheroid shape structure.[1] Morphologically, the RV can be distinguished from the LV by more apical position of the tricuspid valve (TV) septal leaflet compared to the anterior mitral valve leaflet, trileaflet atrio-ventricular valve, presence of three or more papillary muscles, the moderator band and more prominent trabeculations.[1] The RV mass is about 1/6 of the LV and its free wall is much thinner than the LV because of the significantly lesser pulmonary vasculature afterload.[1] Understanding normal physiology of the RV function relies on histological orientation of the myocardial fibers. The RV contains two layers of fibers: 1) deep subendocardial longitudinal layer responsible for the base-to-apex motion (predominant pattern during the contraction) and 2) superficial circumferential fibers responsible for the inward contraction and are continuous with the ones from the LV. Notably, the continuation of superficial fibers is responsible for the ventricular interdependence and traction of the RF free wall by LV contraction.[1] However, spiral fibers present in the LV, responsible for its "wringing" systolic motion, are missing in the RV.

Echocardiographic Evaluation of the RV Size and Function

RV dysfunction is frequently present in various cardiovascular states and is associated with increased mortality in patients with acute myocardial ischemia, pulmonary hypertension, congenital heart disease and chronic heart failure. Notably, the RV dysfunction, but not significant tricuspid regurgitation (TR), is shown to be independently associated with survival late after LV valve procedures,[2] while acute RV failure following cardiotomy is a predictor of worse outcome.[3] However, accurate assessment of the RV is challenging given its complex 3D anatomy and variable physiologic response to different loading conditions. In addition, guideline-recommended measurements are derived from the transthoracic echo (TTE) imaging views introducing many limitations when adopted for perioperative transesophageal (TEE) imaging. Table 1 provides abnormal measurement values.

Assessment of RV Size

RV size measurement is guideline-recommended and is an integral part of the comprehensive approach to the RV evaluation. The visual assessment by the "eyeball" method is adequate if interpreted by the experienced echocardiographer, however quantification methods improve accuracy and reliability.[4] Importantly, RV dimensions should be assessed and measured in the RV-focused mid-esophageal view with the LV apex in the center of the sector. Retro-flexion of the probe is sometimes needed to avoid foreshortening. (Figure 1) Tip of the non-dilated RV reaches to about 2/3 of the interventricular septum (IVS), mildly dilated between 2/3 and the LV apex while moderate and severe dilation is seen when RV tip is at or beyond LV apex, respectively. Based on the studies using TTE imaging RV is severely dilated when mid-diameter (approximately 1/2 of the base-apex length at the level of papillary muscle in end-diastole) is >4.2cm, and length >9.2cm.[5] Having a smaller mass than LV, the RV functions efficiently as a volume-loaded chamber and in the chronic volume overloaded states (severe pulmonic regurgitation or left-to-tight shunts) RV will enlarge. Changes in RV dimensions also affect LV size and function via ventricular interdependence. This interaction stems from the shared IVS, superficial myocardial fibers and the pericardium. Thus, with chronic RV volume overload the LV diastolic filling is impaired due to the leftward movement of the IVS. In chronic RV pressure overload t systolic leftward shift of the IVS and decreased LV preload from diminished RV stroke volume lead to decreased LV function. Although not as important for normal systolic function, the pericardium affects normal diastolic function and may potentiate ventricular interdependence. LV eccentricity index (EI), defined as the ratio between LV antero-posterior to latero-septal diameters in the short axis is normally about 1 during both end-systole and -diastole. In chronic RV volume overload states ratio will be >1 with the LV being D-shaped towards end-diastole. Conversely, in chronic RV pressure overload states such as pulmonary hypertension and pulmonic valve stenosis, RV compensates primarily by hypertrophy (dilatation develops later in the process) and the EI >1 with the LV being D-shaped towards end-systole. Of note, the aberrant ventricular conduction (particularly left bundle branch block) makes EI evaluation challenging. Beside 2D measurements 3D volume

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measurements can be obtained as well. Although LV and RV stroke volumes are the same, RV end-diastolic volume is 17ml larger resulting in smaller calculated ejection fraction compared to the LV. A 3D echo enables measurements of RV volumes during systole and diastole. 3D imaging surpasses the limitations of the RV's geometrical complexity but requires superb image quality. Compared to cardiac magnetic resonance 3D echo tends to underestimate volumes due to suboptimal resolution leading to imprecise tracing of the trabeculated endocardium.[6] Currently available commercial 3D echo volume measurement packages are designed for TTE with the accuracy of the TEE imaging being limited by the RV's far-field location. In addition, commonly seen decrease in spatial resolution of the RV is a result of the shielding artifacts from the strong reflectors laying in the path of the ultrasound beam (mitral and tricuspid valve annuloplasty ring and prosthesis or mitral valve calcifications).

Assessment of RV Function

The visual assessment, i.e. "eyeballing", of the RV function is guideline-recommended method even though it lacks accuracy and reliability.[4] It is due to complex 3D geometry of the RV that visual assessment is still used by many physicians in evaluation of its function. In addition, quantitative imaging modalities used have limitations resulting in recommendation to use two different modalities during the evaluation.[7] Currently recommended modalities can be divided into: 1) assessment of global systolic function using RV fractional area change (FAC), RV ejection fraction (RVEF), strain and right-sided index of myocardial performance (RIMP or Tei index) and 2) assessment of regional function predominantly assessing longitudinal performance of RV using tricuspid annular plane systolic excursion (TAPSE), tricuspid annular plane velocity by tissue Doppler and regional strain and strain rate. Usefulness and validity of modalities used for assessing regional RV function stems from longitudinal muscle fiber orientation responsible for predominant base-to-apex RV systolic movement.

FAC is the ratio of the difference between end-diastolic and end-systolic areas divided by end-diastolic area, obtained by tracing the endocardial border in the mid-esophageal focused 4-chamber view (normal 32%-50%) excluding papillary muscles and trabeculations. The FAC correlates well with the RV EF obtained by cardiac magnetic resonance imaging. Although it encompasses both longitudinal and radial components of the contraction it cannot evaluate RV outflow tract performance.[7]

EF is calculated from tracings of the end-diastolic and end-systolic volumes (normal >44%). It is not obtainable by 2D but rather 3D imaging with the software designed for TTE imaging. EF measured with 3D echo has been validated against cardiac magnetic resonance imaging although calculated volumes tend to be underestimated due to the lack of spatial resolution and tendency to include trabeculations into the tracings.[6] Being load dependent measurement, EF may not truly represent RV contractility. It may overestimate RV function in conditions leading to chronic increase in preload such as left-to-right shunts or TR. Indeed, TR serves as a "pop-off" valve for the relatively dysfunctional RV generating smaller end-systolic volume but also diminished forward stroke volume despite normal EF values. In contrast, EF may underestimate true contractile function in conditions associated with chronic afterload increase such as pulmonary hypertension.[8] In addition, normal preoperative RV EF does not predict normal function following cardiac surgery as a result of pericardial disruption and/or interventricular septum dyssynergy.[9]

2D peak systolic longitudinal strain measures a percentage of systolic myocardial deformation, i.e. shortening, and it is considered a negative value (normal <-25%). Strain rate is the rate of deformation over time. Currently, both strain and strain rate are predominantly measured using speckle tracking technology which is independent of translational geometric changes. Global longitudinal strain (GLS) of the RV is a useful measurement of contractility that is less load dependent and correlates better with the magnetic resonance-derived EF than other modalities.[10] Both measurements can be obtained from the RV mid-esophageal 4-chamber view adopting software package aimed for the LV. Lack of normative data and standardization of the platforms makes for inconsistent utility of strain measurements. Currently only longitudinal deformation of the RV as an average of the longitudinal deformations of the free wall and septum is being measured and sometimes only the RV free wall which may not accurately assess overall function. Limitation includes exceptional image quality required for accurate measurement which may not be possible with TEE imaging due to decreased resolution in the far field and shielding artifacts.

RIMP is a non-volumetric measurement of the global RV function measured by either pulsed-wave Doppler (PWD) or tissue Doppler and calculated as (intraventricular contraction + relaxation time) / ejection time. For the simplicity of measurements this formula can also be restated as (TV opening to closing time – ejection time)/ejection time. (Figure 2) TV opening to closing time duration represents TR period obtained with the continuous wave Doppler (CWD) while the ejection time is the same as the period of pulmonary artery systolic flow obtained with PWD.[11] RIMP measurement using PWD and CWD is limited by two time-point measurements while the accuracy is assured

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by having similar R-R intervals.[5] RIMP obtained with TV annulus tissue Doppler measurement requires angle adjustment but provides simultaneous time period recordings.[11] RIMP can be falsely low in conditions that increase right atrial pressure, such as RV myocardial infarction, by shortening of the intraventricular relaxation time.[5] Although recommended as a measure of RV function perioperative utility of RIMP has been questioned.[12] Best TEE views include transgastric RV inflow-outflow view (80-110 degrees) or modified deep transgastric views (at 120 degrees) used for the TV annulus tissue Doppler measurement. Also, TV opening to closing time can be measured by aligning CWD beam with the TR in the mid-esophageal 4-chamber view or modified bicaval view (preferred for the centrally directed jets). RV ejection time can be obtained with PWD by measuring the opening to closing time of pulmonic valve in the mid-esophageal aortic short axis view or upper-esophageal aortic arch short axis view. TAPSE and tricuspid lateral annular velocity (S') reflect distance (velocity over time) or the velocity of the lateral TV annular plane movement, respectively. Thus, both modalities assess function of the RV basal segment ignoring rest of the free wall and septum thus potentially leading to oversimplification of the complex RV functionality.[13] Both are measurements of the regional longitudinal function with the accuracy highly dependent on the overall heart motion relative to the transducer.[5] Importantly, experience and recommendations for use of both modalities evolved from the TTE imaging with significant limitations of TEE imaging questioning its clinical utility and accuracy.[14] TAPSE is commonly obtained in the mid-esophageal 4-chamber view using M-mode with less than adequate incident angle orientation. An anatomical M-mode enables orientation of the analysis line to be parallel with the TV annulus motion.[15] Similarly, accurate measurements may prove to be challenging with transgastric RV inflow view or modified deep transgastric view due to foreshortening of the RV systolic motion. TAPSE can also be calculated as a difference in a distance between TV annulus and apex at end-diastole vs end-systole. The S' represents the velocity of TV annular plane systolic movement assessed with tissue Doppler. Like with TAPSE, S' measurement is highly dependent on parallel incident angle alignment to avoid inaccuracy. A novel method of tricuspid annulus distance measurement using speckle-tracking demonstrated validity and reliability compared to standard M-mode measurements.[16] Indeed, speckle-tracking-derived TAPSE might be a more accurate modality to quantitatively assess RV function during perioperative TEE imaging.[14] However, decrease in both TAPSE and S', despite normal FAC and EF findings, suggest significant geometrical rather than functional changes seen in post-cardiotomy patients.[17] It is speculated that the post-cardiotomy decrease in contractility, despite normal EF and forward stroke volume echocardiographic measurements, may be unmasked following pericardial disruption.[9] Furthermore, significant TR may be responsible for overestimation of the RV contractile function by exaggerating systolic inward and longitudinal motion of the TV annulus measured by the TAPSE, EF and FAC.[18]

Assessment of RV diastolic function

RV diastolic function can be assessed by measuring hepatic vein profiles, dimension of the inferior vena cava, tricuspid valve inflow profile and tricuspid annulus diastolic velocities.[7] Although part of the assessment in patients with congenital heart disease or heart failure the importance of the RV diastolic is still questionable during the perioperative assessment. However, assessment of the RA pressure becomes important as it reflects both systolic and diastolic RV condition. The hepatic venous flow pattern obtained via PWD is easily obtained from the proximal hepatic vein. Contrary to the predominant systolic flow pattern seen in patients with normal RA pressure (high hepatic vein to RA pressure gradients), diastolic flow predominance is seen with increase in RA pressures (gradient decreases).[19] Hepatic venous systolic filling fraction (calculated as the ratio between the time-velocity integral [TVI] of the systolic flow and sum of systolic and diastolic TVI's) predicts RA pressure >8 mmHg if the filling fraction is <55%.[19] Atrial flow reversal velocity greater than systolic velocity also predicts elevated RA pressure. (Figure 4) However, atrial compliance and severe TR may influence accuracy of these measurements. Similarly, irregular heart rhythms, like atrial fibrillation, decrease normal systolic flow pattern leading to diastolic predominance regardless of the RA pressure.[19]

RV function is an independent determinant of major outcomes in non-surgical and cardiac surgical patients. Despite improvements in imaging technology accurate assessment of the RV geometry and function remains challenging. Majority of echo modalities used for RV assessment have limitations and multi-modality evaluation is necessary. This in particular holds true during the perioperative TEE assessment given the adoption of TTE-derived modalities. Hopefully, evolution of new imagining modalities overcomes those challenges and enables more consistent and reliable RV assessment.

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Table 1: Normal values for parameters of RV function

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RV function measurements	Abnormal values
RV FAC	<17 %
3D RV EF	<44 %
Pulsed tissue Doppler TV annulus velocity	<9.5 cm/s
TAPSE	<1.7 cm
Pulsed-wave Doppler RIMP	>0.40
Tissue Doppler RIMP	>0.55
2D speckle global strain (free wall)	Limited data: >-20%
RV dp/dt	<400 mmHg/s
RV diastolic function	E/e'>6

Figure 1: An illustration demonstrating variability of the RV chamber linear dimension based on the TEE plane position. Note that the RV linear dimension may be over- or under-estimated (line 2 represents mid-esophageal RV focused 4-chamber view). LV= left ventricle; RV= right ventricle

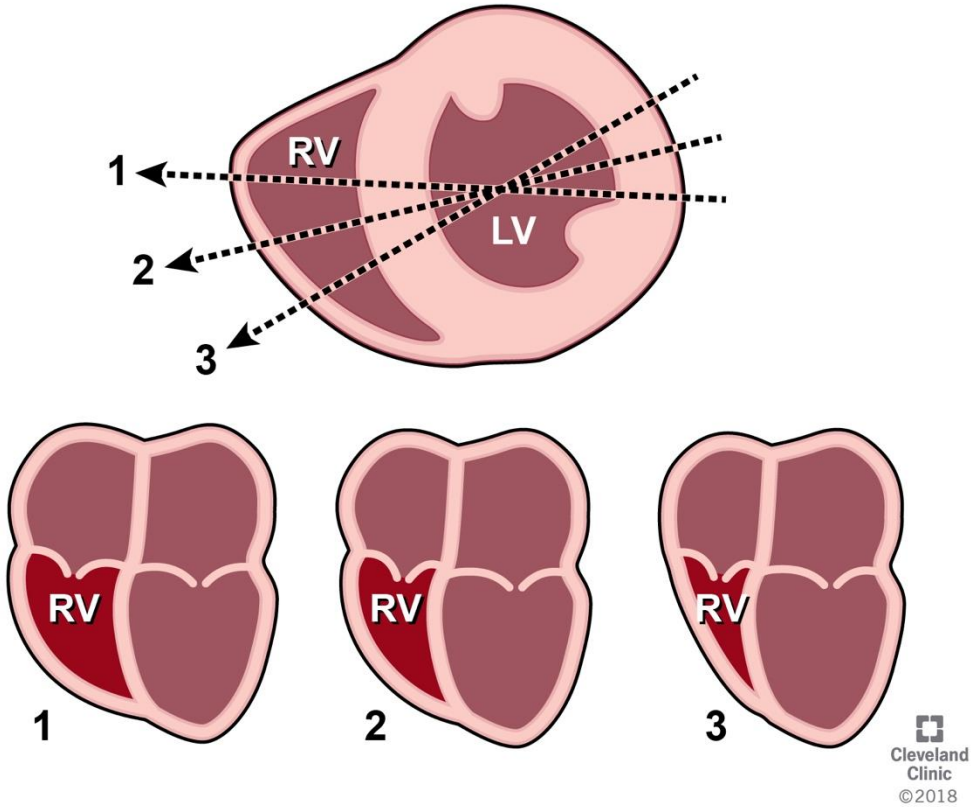

Figure 2: An illustration representing a measurement of the right ventricular index of myocardial performance (RIMP) based on the time measurement of the tricuspid regurgitation (TR) time (consisting of contraction, ejection and relaxation times) and ejection time (ET).

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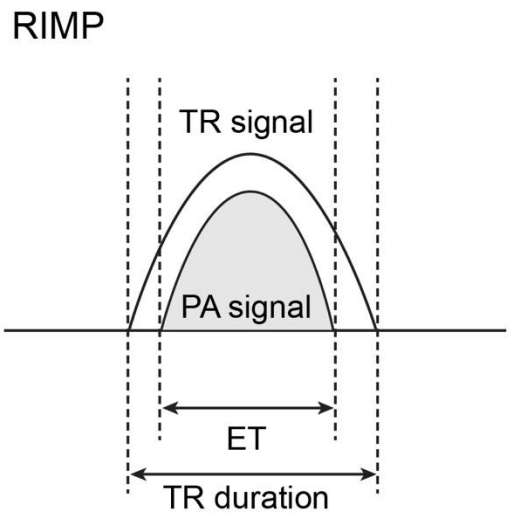

$$\text{RIMP} = \frac{(\text{TR duration} - \text{ET})}{\text{ET}}$$

Figure 3: A lateral tricuspid annulus deformation (TAD) obtained with speckle tracking echocardiography. Note, lateral annulus in blue and medial annulus displacement (mm) in light brown.

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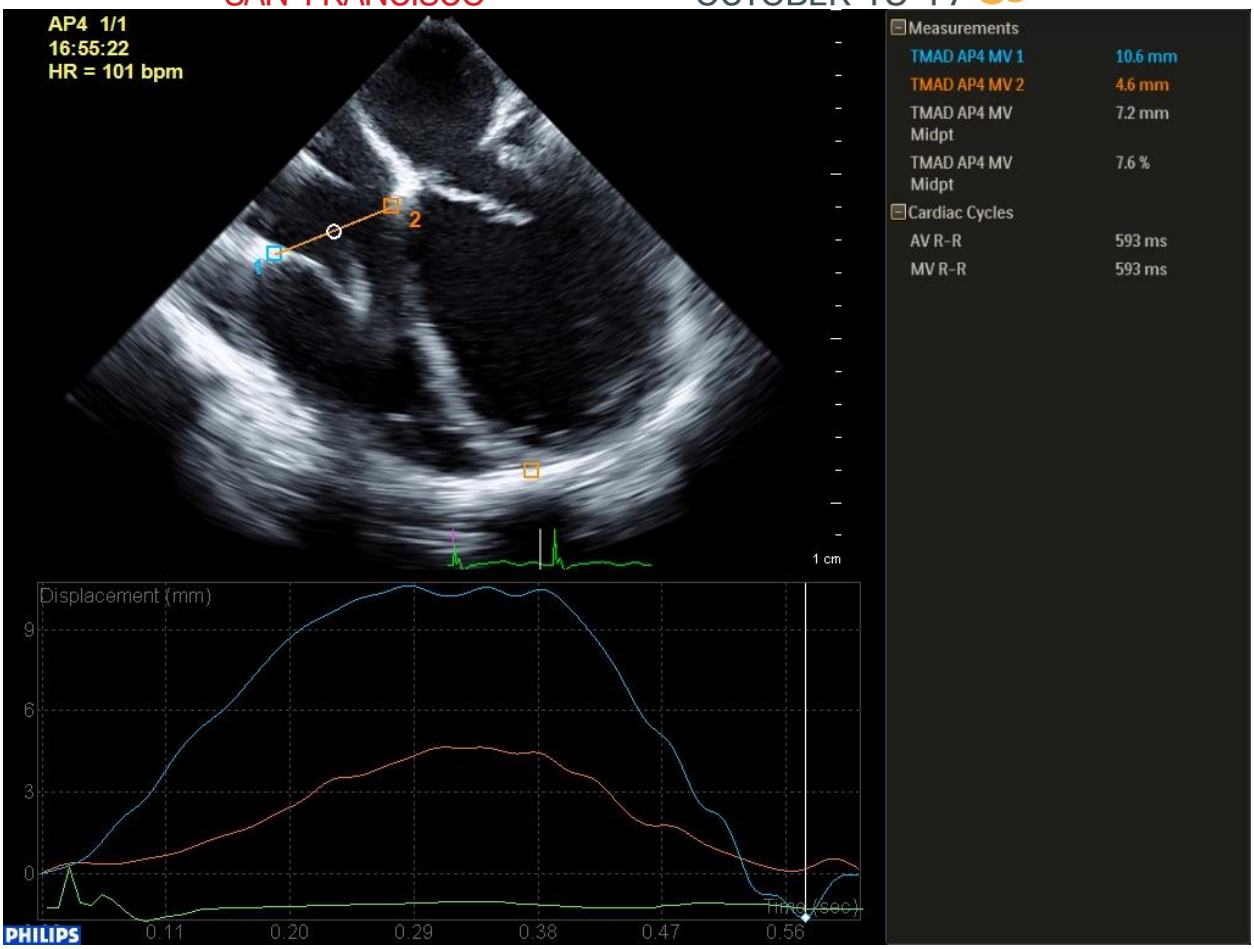

Figure 4: Pulsed-wave Doppler of the hepatic venous flow. Note predominance of the diastolic flow with the atrial reversal velocity greater than the systolic velocity indicating an increase in right atrial pressure. S-systolic wave; D-

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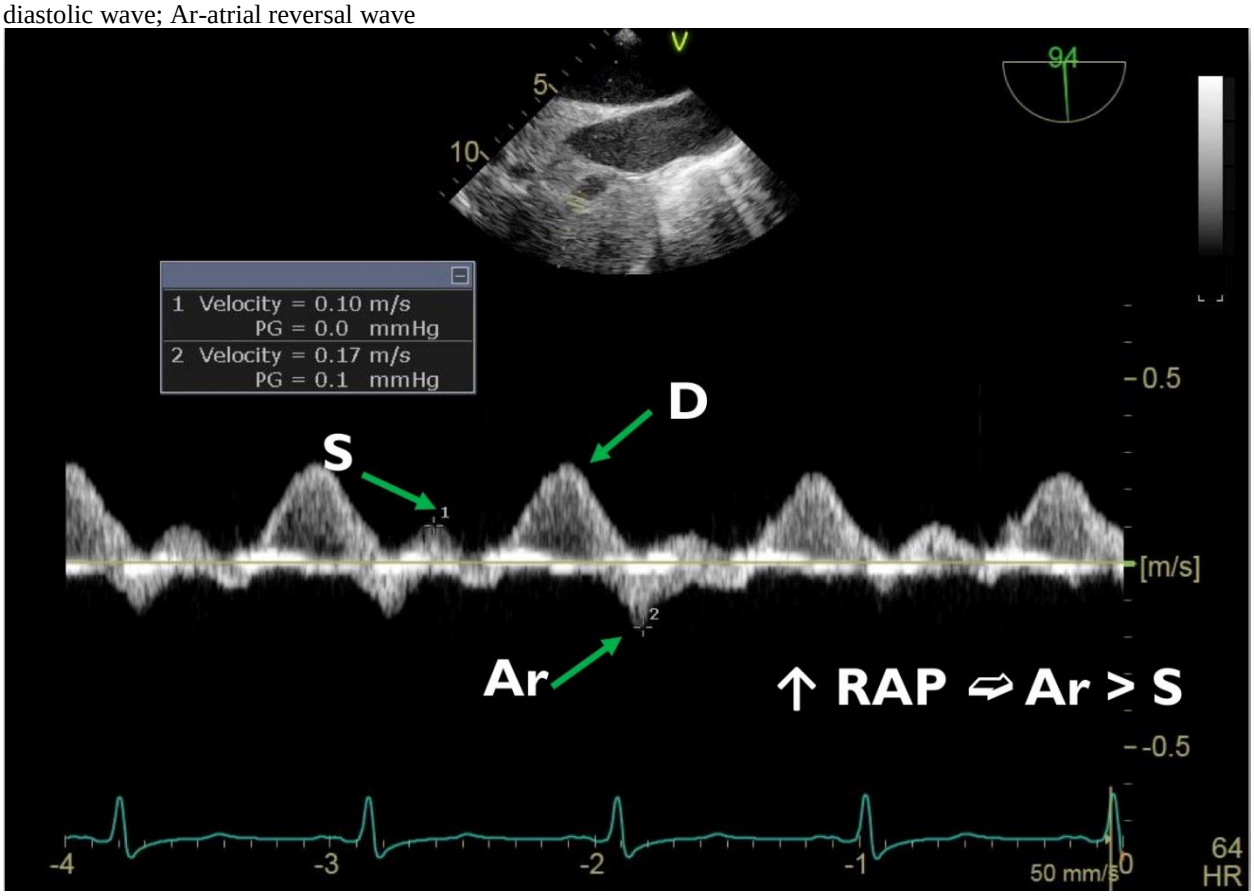
diastolic wave; Ar-atrial reversal wave



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Definition, Risk Scores and Prediction of Right Ventricular Failure

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Introduction: Right ventricular failure (RVF) occurs from a multitude of etiologies. For many years, emphasis was placed on the left ventricle (LV), and the right ventricle (RV) was considered a mere conduit for the flow of blood into the pulmonary circulation. Impairment of RV function may occur in patients for many reasons, including pulmonary hypertension, congenital heart disease, and coronary artery disease (CAD) or valvular heart disease. The commonest cause though is from left sided heart failure. The cardinal signs and clinical manifestations of RVF include fatigue, decreased exercise tolerance from diminished systolic reserve, low cardiac output from atrial or ventricular arrhythmias, fluid retention, peripheral edema, ascites and anasarca[1]. The present review focuses on RV function, dysfunction, and failure from left sided heart failure.

Definitions: RVF is defined as a complex clinical syndrome as a result of any structural or functional cardiovascular disorder that impairs the ability of RV to fill or eject blood[2]. On the other hand, RV dysfunction (RVD) refers to abnormal filling or contraction without reference to signs or symptoms of heart failure (HF).
The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)[3] has characterized acute RVF as documented elevations of central venous pressure (CVP) and its clinical manifestations such as edema, ascites, worsening hepatic or renal dysfunction. Elevated CVP can be documented by right heart catheterization with a right atrial pressure greater than 16mmHg or via echocardiography showing a significantly dilated inferior vena cava or clinically with an elevated jugular venous pressure. It is important to remember that the definition of RVF includes both elevated CVP and its clinical manifestations. The clinical manifestations include peripheral edema ($\geq$ 2+), ascites or hepatomegaly upon examination or by diagnostic imaging or laboratory evidence of hepatic dysfunction (total bilirubin > 2mg/dL) or renal dysfunction (creatinine > 2mg/ dL).

INTERMACS also has categorized RVF based on severity into mild, moderate, and severe forms. In the mild form, following VAD implantation, patients should meet both the criteria for RVF and need for inotropes, vasodilators, or nitric oxide less than 7 days. RVF is considered moderate post implant with the need for inotropes, vasodilators, or nitric oxide for 7 to 14 days. Severe form exists when inotropes, vasodilators or nitric oxide are needed beyond postoperative day 14 or a need for right ventricular assist device (RVAD) anytime post LVAD implantation.
It is crucial to review micro and macro anatomy such as size, shape, composition, geometry, motion, similarities and differences between the RV and LV in this context.

Distinguishing anatomic features and the architecture of the RV: Embryologically**,** the RV and LV originate from different progenitor cells. Cardiac morphogenesis has shown that RV originates from anterior heart field and the primary heart field gives rise to atrial chambers and the LV[4].The discovery of transcription factors such as HAND1 and HAND2, and recognition of chamber specific gene expression from knock out mice and different transcriptional events in the formation of RV and LV have led to the idea that different patients react differently due to genotypic differences[5].

The RV is the most anteriorly situated, thin walled cardiac chamber located behind the sternum. When viewed from front, it is more triangular in shape and in cross section, the cavity appears like a crescent. The superficial layer of myocardial fiber is arranged more or less circumferentially, initially parallel to the atrioventricular groove, then they turn obliquely toward the cardiac apex in the subcostal region[2, 6]. Deep myofibers in the RV are aligned longitudinally. The normal thickness of the RV is 3-5mm, excluding the trabeculations.
In contrast, LV is near conical in shape and has circular myocardial fibers sandwiched between the obliquely arranged superficial fibers, and longitudinally arranged deeper fibers of the sub endocardium[7]. The normal thickness of LV is 7-11 mm. During systole, these contractile bundles change the shape of the heart and generate force to pump blood from respective chambers. The superficial layer of RV and LV are in continuity with each other, wind around both ventricles, and functionally bind both ventricles together. Both ventricles are surrounded by the pericardium that prevents and protects from sudden expansion. Both ventricles share an interventricular septum (IVS), the composition of which is similar to the LV. Contraction generated by the superficial layer of circumferential fibers result in inward thickening (radial thickening) and contraction by the deep layer of longitudinal fibers result in longitudinal (base to

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apex) shortening[8]. Longitudinal shortening provides a greater contribution to stroke volume in the case of the RV than the circumferential (short axis) shortening. Ventricular interdependence plays an important role in RV function due to a shared wall (IVS) and mutually encircling epicardial fibers. Under normal conditions, the thinner RV is suitable for the low impedance and highly distensible pulmonary vascular system. The septum and free wall contribute approximately equally to right ventricular function[9].

Perfusion of the RV: CAD may predispose the RV to ischemia and/or infarction. It is important to remember the blood supply to RV and IVS in this regard and correlate intraoperative findings and changes from existing findings. The anterior 2/3rd of IVS receives blood supply from anterior interventricular artery which is a septal branch of the left anterior descending artery. The posterior 1/3rd of IVS is supplied by the posterior interventricular artery, also known as posterior descending artery, which is a branch of right coronary artery. The right coronary artery also supplies rest of the RV, right atrium, SA node and AV node. Thus, RV performance is influenced by the rhythm and synchrony of ventricular contraction. Bradycardia, tachyarrhythmia and subsequent suboptimal preload may precipitate RV dysfunction. The perfusion of the RV occurs during both diastole and systole with adjustable oxygen metabolism and extraction creating extended tolerance to ischemia; therefore it is considered to be more resistant to ischemia[10].

Assessment of the RV: The measurement of RV function is difficult because of the interplay between intrinsic myocardial performance and loading conditions. The RV pumps the same amount stroke volume as the LV but only with 25% of stroke work because of the low resistance of the pulmonary vasculature. Therefore, by virtue of Laplace's relationship, the RV is thin walled and more compliant. In contrast to acute pressure overload, under most circumstances, the RV develops adaptive hypertrophy to chronic pressure overload.

Assessment of the RV Structure: The measurement of RV dilation and degree of RV dilation compared with LV dilation and right atrial size can be easily performed using echocardiography. Functional anatomy includes assessment of the mechanical aspect of ventricular contraction. The contraction of the RV is sequential, which begins with the inlet, followed by the trabeculated myocardium, and ends with the infundibulum, resulting in shortening of the RV, drawing the tricuspid annulus towards the apex and causing inward movement of free wall.

Measurement of the RV function: Both invasive and noninvasive methods are used to assess RV function such as cardiac magnetic resonance imaging (CMR), cardiac computed tomography (CT), cardiac catheterization, transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), speckle-tracking echocardiography (STE). CMR is considered the gold standard for evaluating RV size and function[11].CT is accurate for volume assessment.

Hemodynamic Parameters: Right heart catheterization provides hemodynamic parameters such as central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP). From catheterization data, it is easy to calculate parameters such as pulmonary vascular resistance (PVR), cardiac output (CO), pulmonary artery pulsatility index (PAPi), right ventricular stroke work index (RVSWI) and trans-pulmonary gradient (TPG). Catheterization is used in the diagnosis of pulmonary hypertension and responsiveness to vasodilator treatment. Commonly adapted hemodynamic (Table1 & Table 2) and echocardiographic parameters (Table3) are summarized below.

Table 1: Measured Hemodynamic Parameters

	Normal values	RVD	RVF
CVP mmHg	2-6	≥ 16	>18
Systolic/Mean/Diastolic PAP mmHg	<30/18/15		≥50/25
PCWP mmHg	6-12	≤ 18	≤ 18

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Table 2: Derived Hemodynamic Parameters:

Assessment	Formula	Normal Values	RVD	RVF
Pulmonary vascular resistance (PVR) dynes-sec/cm^{-5}/m^2	80 x (mPAP - PCWP)/CO	<250	>250	
Pulmonary artery pulsatility index (PAPi)	(PASP-PADP)/RAP	>3.5	1.5-2.0	<1.5
Right ventricular stroke work index gm-m/m^2/beat	(mPAP-RAP) x (0.0136 x SV/BSA)	5 - 10	<5	<4.4
Trans pulmonary gradient mmHg	mPAP-PCWP	≤12	>12	
Cardiac filling pressure	CVP/PCWP	<0.5	>0.63	>1

mPAP= mean pulmonary artery pressure; PCWP= pulmonary capillary wedge pressure; CO= cardiac output; PASP= pulmonary artery systolic pressure; PADP=pulmonary artery diastolic pressure; RAP= right atrial pressure; SV =stroke volume= CO x heart rate; BSA= body surface area

Table 3: Echocardiographic Parameters for RV[12, 13]

Assessment of right systolic ventricular function:	Normal values	RVD	RVF
Fractional area of change (FAC)	49% (35-63)		<35
DTI-derived tricuspid lateral annular systolic velocity wave (S')	>10 cm/sec	5-10	<5
Tricuspid annular plane systolic excursion (TAPSE)	23 mm (16-30)	10-15	<10
RVEF	57% (45-69)	30-44	<30
Lateral Longitudinal strain (STE) %	-26 (-20 to -32)	-9 to-20	>-9
RV basal diameter	33 mm (24-40)	40-45	>45
RV mid-cavity diameter	28 mm (20-35)		>35
RV longitudinal diameter	71 mm (56-86)		

RV: right ventricle; EF: ejection fraction; DTI: Doppler tissue imaging; STE: speckle tracking echocardiography All references validated with transthoracic echocardiography RVD: RV dysfunction RVF: RV failure

Predictors of RVF: Identifying patients that are high risk for RVF is crucial in the setting of LVADs. Multiple scoring systems exist that use various biochemical, echocardiographic, and hemodynamic parameters to predict risk of RVF. These scores do not take into account intraoperative events such as air embolism, disruption of grafts that supply RV with resultant ischemia, or injury to previously functioning RV. Many groups have developed risk scores to predict RVF (summarized in table 4). From the table, it is evident that RVF is a common complication after LVAD implantation. Many indices have been used to describe RV dysfunction and there is no single risk score that reliably distinguishes patients that would develop RVF or successfully tolerate isolated LVAD implantation without RVF.

Table 4: Risk Predictors of RVF

Risk predictor	Assessed parameters [points]	Definition of RVF (based on post op therapy)	RVF Incidence
RVFRS[14] Michigan score/Matthews Score	4 variables: 1. Vasopressors [4] 2. AST ≥ 80 IU [2] 3. Bilirubin mg/dl ≥2.0 [2.5] 4. Creatinine ≥2.3mg/dl [3]	1.Inotropes (>14days) 2.NO (≥48h) 3.RVAD 4.Discharged on inotropes	35%
Penn score[15]	6 variables: 1. CI≤2.2 l/min/m2 [18] 2. RVSWI ≤ 0.25mmHg l/m2 [18] 3. Severe pre RV dysfunction [16]	RVAD	37%

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	4. Creatinine ≥1.9mg/dl [17] 5. Redo surgery [16] 6.SBP≤96mmHg [13] Max 98 ≥ 50 (RVA)		
Utah Score[16]	7 variables: 1. DT [4] *2.* Inotropes [2.5] 3.*PVR (Wood unit)* a. ≤1.7 [1] b. 1.8-2.7 [2] c. 2.8-4.2 [3] d. ≥4.3 [4] 4. Obesity [2.5] 5. ACE/ARB's [2.5] 6. IABP [4] 7. Beta blockers: [2]	1. Inotropes (>14days) 2. NO(≥48h) 3. RVAD	44%
Pittsburgh decision tree[17]	Decision tree with 8 variables: 1. TPG 2. Age 3. RAP 4. INR 5. HR 6. WBC count 7. ALT 8. # Of inotropes	RVAD	14.8%
Penn score[18]	5-point risk score Multivariable logistic regression analysis: CRITT 1. CVP>15mmHg 2. Severe RV dysfunction 3. Pre-operative intubation 4. Severe TR 5. HR>100 (tachycardia) Score of ≥2 predictive	RVAD	23%
HM2 BT trial[19]	Independent risk factors: 1.CVP/wedge >0.63 2. BUN >39ml/dL 3. Mechanical vent	1. Inotropes >14 d 2. RVAD 3. Inotropes after 14 days	20%
Right to left ventricular end-diastolic diameter ratio[20]	Right to left ventricular end-diastolic diameter ratio (R/L ratio) Cut off ≥0.72	Occurrence of 2 of the following criteria in the absence of tamponade within 48h postoperatively: 1. MAP<55mmHg 2. CVP>16mmHg 3. Mixed venous saturation <55% 4. CI <2 l/min/m2 5. Inotropic support>20 units 6. RVAD	
Michigan score Expansion[21]	Usage of Michigan score + 5. RVLS > -9.6% [2.5]	1. Inotropes >14 d 2. RVAD	40%

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Bayesian Model Pittsburg[22]	Bayesian model with 3 sets of variables (33 or 34) for RVF: 1. Acute (<48h), 2. Early (48h -14 days) 3. Late (>14days)	INTRERMACS definition prior to 2014 (appendix A, www.intermacs.com) 1. Findings/ symptoms of RVF 2. Differentiation of mild, moderate, severe and severe acute 3. Use of inotropes and inhaled/or intravenous vasodilators (7 or =/>14 days), RVAD or RVF related death	18.5% Acute: 2.7% Early: 9.5% Late 6.4%
EUROMACS score; Model[23]	9.5 point score model 1. INTERMACS class 1-3 [2] 2. >3 inotropes [2.5] 3. Severe RV dysfunction* [2] 4. RA/PCWP >0.54 [2] 5. Hgb ≤10 g/dl [1] *Semiquantitave ECHO finding	1. RVAD (Short/long-term) 2. Continuous inotropes ≥14days 3. NO≥48h	21%

RVF: right ventricular failure;RVFRS: right ventricular failure risk score; AST: aspartate aminotransferase; NO: nitric oxide; RVAD: right ventricular assist device; Cl: clearance; RVSWI: right ventricular stroke work index; RV: right ventricle; SBP: systolic blood pressure; PVR: pulmonary vascular resistance; ACE: angiotensin converting enzyme; ARB'S: angiotensin receptor blockers; CVP: central venous pressure; BUN: blood urea nitrogen; RVLS: right ventricular longitudinal strain; HR: heart rate; EUROMACS: European Registry for Patients with Mechanical Circulatory Support; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; PCWP: pulmonary capillary wedge pressure; Hbg: hemoglobin; TPG: transpulmonary gradient; RAP: right atrial pressure; INR: international normalized ratio; WBC: white blood cells; ALT: alanine aminotransferase; MAP: mean arterial pressure.

Summary and Conclusion: The RV differs from the LV in both anatomy and physiology. It is critical to determine the prognosis and understand that RVF is distinct from LVF. The study of the RV is challenging due to its complex shape and marked load dependence. Severe RVF after LVAD implantation is associated with increased perioperative morbidity and mortality. RVF also causes liver, gastrointestinal, and renal congestion, which can lead to coagulopathy, altered drug metabolism, diuretic resistance, malnutrition and overall poor quality of life. There is no agreement on what meaningfully defines RV function or dysfunction. Multiple interactions exist between myocardial injury, neurohormonal activation, altered gene expression, and ventricular remodeling. In recent years, many studies have demonstrated the prognostic value of RV function in cardiovascular disease. It is unclear at what stage in failure, the RV could completely recover. Understanding the mechanism of RVF, progression from asymptomatic RV dysfunction to symptomatic RVF and triggering factors that transition into refractory RVF, is still a work in progress.

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Pharmacological Management of Acute Intraoperative Right Heart Failure

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Acute right heart failure (ARHF) occurs due to maladaptive changes in preload, afterload, and contractility. Intraoperatively, its presentation can be dramatic and life threatening. This condition is characterized by right ventricle (RV) dilation which in turn causes a change in the ventricular septum's contribution to right ventricular forward flow and leads to systemic venous congestion and hypotension. The etiologies of ARHF are many, but common causes of intraoperative RV failure include: acute left ventricular failure, RV ischemia, left ventricular assist device (LVAD) implantation, pulmonary embolism (PE), pulmonary hypertension exacerbation, sepsis, and volume overload. Each condition presents a unique physiological challenge to the right ventricle (RV) and treatment must be tailored to the specific condition. While individualized treatment to salvage the RV is the ultimate goal, general pharmacological support principles described below should be considered to temporize these critically ill patients.

When managing an acutely decompensated right ventricle, myocardial oxygen supply-demand is compromised and administering oxygen with a saturation goal of 92% or greater is a simple first step to improve delivery. Increased myocardial wall tension is a barrier to effective myocyte perfusion and systemic hypotension adversely impacts coronary perfusion pressure, further compromising oxygen delivery. Hypoxia will also increase pulmonary artery pressure in a ventricle that is intolerant to increases in afterload. Presuming the patient is intubated, the early use of paralytics should be considered to optimize ventilator synchrony and chest wall compliance. The change in preload caused by a patient struggling against the ventilator can precipitate cardiac arrest. Finally, sedative and analgesic agents should be carefully titrated to avoid endogenous catecholamine release and abrupt changes in pulmonary vascular resistance (PVR). It is this author's opinion that it is beneficial to administer total intravenous anesthesia (TIVA) and avoid inhalational anesthetics. The reasoning for this is patients will not require changes in anesthetic modalities from inhaled to intravenous agents when moving from the operating room to the intensive care unit, introducing additional risk of hemodynamic perturbations. The inhaled agents' deleterious effects on systemic vascular resistance (SVR) hypoxic pulmonary vasoconstriction (HPV) can also be minimized. Further, if an inhaled pulmonary artery vasodilator such as epoprostenol or nitric oxide is to be administered, a ventilator separate from the anesthesia machine is usually required.

Fluids and vasoactive medications should be carefully administered in ARHF patients. Failing to utilize the utmost caution in resuscitation can precipitate a pharmacologically non-salvageable situation. Clear treatment goals should be established early on, although no there is no consensus on which goals to use. Mixed venous oxygen saturation (SvO2) may be used an indicator of resuscitative responsiveness[1]. Improvement in systemic or right sided pressures pressure may be another. An arterial line is needed because of the profound hemodynamic changes, the use of vasoactive medications, and regular arterial blood gas sampling. Central venous and pulmonary artery catheters can be informative in guiding resuscitative efforts if the etiology is uncertain or if the patient is hemodynamically unstable and resistant to treatment[2]. An advantage of invasive monitoring is that is can continue to be used intraoperatively in the intensive care unit (ICU); transitioning care should be an early consideration in the access and monitoring strategy since these patients will likely be critically ill at the end of the procedure. Transesophageal (TEE) or transthoracic (TTE) echocardiography is also very helpful in establishing a cause of RV dysfunction as well as the response to volume management and vasoactive therapies[3]. In a hyperacute or code situation, TEE can be rapidly deployed and aid in resuscitative efforts until the patient is stable enough for the placement of invasive monitors.

Hypotension complicating right ventricular failure may be initially addressed with a small fluid bolus (250-500cc) if contractility is not severely impaired since there is preload-dependence to the RV and it may be operating on the ascending portion of the Frank-Starling curve. Autotransfusion via the passive leg raise is a simple and reversible measure to test volume responsiveness[4]. The Trendelenburg, or head down position, will briefly augment right heart filling but abdominal contents will push the diaphragm cephalad and decrease thoracic volume and

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ultimately reduce preload and increase intrathoracic pressure and PVR, adding additional strain to the right heart. Pulse pressure variation is not an accurate indicator of volume responsiveness in these patients[5].

The commonly held belief that a failing RV should be volume loaded is not accurate and aggressive fluid administration should be discouraged. Excessive RV preload will cause further cavitary dilation and subsequent diastolic leftward deviation of the interventricular septum as RV stroke volume decreases. This will increase RV transmural pressure, decreasing myocardial perfusion as well as increasing coronary sinus pressure and negatively affecting venous drainage of the heart[6]. A central venous pressure (CVP) of greater than 15-20mm Hg may warrant diuresis, however CVP should not be considered an accurate metric of preload[7]and the CVP value on which to treat is arbitrary. Intraoperative administration of furosemide should be considered early but drug resistance may be encountered due to renal congestion, low cardiac output, and evolving acute kidney injury[8]. If resistance to a loop diuretic is encountered, the addition of a thiazide diuretic, such as chlorothiazide, may be helpful. Diuretics should not be held in the context of hypotension and blood pressure augmentation should be instituted as needed. Because diuresis is a relatively slow and potentially futile process, this therapy should be used in conjunction with other therapies. Potassium, magnesium, and calcium should be carefully monitored with diuretic therapy since dysrhythmias are poorly tolerated. Aggressive pharmacologic treatment of dysrhythmias is of high importance as they can exacerbate a low output syndrome or precipitate a cardiac arrest. Amiodarone, magnesium, and lidocaine are reasonable choices given their favorable therapeutic index and are chosen based on the presenting dysrhythmia. Digoxin should be used with caution due to its narrow therapeutic index, sensitivity to electrolyte levels, and likely evolving multisystem organ dysfunction. Beta blockers should be used with extreme caution if at all given the negative ionotropic effects on the RV.

The normal right ventricle is perfused throughout systole and diastole. However, with pressure overload, most coronary perfusion will occur during diastole. Systemic hypotension will result in inadequate perfusion of the right coronary system and ignite a lethal cycle of RV failure. In patients with depressed RV function, vasopressor therapy has been shown superior to treatment with ionotropes and fluids[9]. Thus, the first step in salvaging a failing RV is increasing coronary perfusion pressure. Norepinephrine is potent α1 and modest β1 agonist and improves cardiac index and RV-PA coupling in addition to systemic vascular resistance (SVR)[10]. At doses less than 0.5mcg/kg/min, norepinephrine has been shown to increase SVR, reduce pulmonary vascular resistance (PVR), and decrease the PVR/SVR ratio[11]. Arginine vasopressin is a V1 agonist and its pressor effects preferentially increase SVR relative to PVR. Traditional dosing is 0.02-0.04 IU/min is recommended although doses of 0.06 IU/min have been described[12]. At higher doses there is concern of increased PVR along with myocardial effects and coronary vasoconstriction[13]. Vasopressin may be an ideal first line agent for hypotension due to its low serum level during shock, but the β1 effect from norepinephrine is often required and the two drugs appear to act synergistically[14]. Phenylephrine improves right coronary perfusion pressure in RV failure but increases PVR in and may worsen RV function[15,16]. The reflex bradycardia and lack of β1 may be beneficial in patients with serious dysrhythmias. While phenylephrine can aid in correcting RV failure, consideration should be given to other agents first. Methylene blue inhibits guanylate cyclase and nitric oxide synthase and blocks the vasodilatory action of nitric oxide. Its use is associated with decreased and persistent vasoconstrictor requirements and serum lactate levels[17]. The use of this drug has not shown a survival benefit and furthermore the risk of severe pulmonary hypertension should not be under estimated. In patients with RV dysfunction it can cause immediate hemodynamic collapse and its use is not supported.

Treatment of metabolic acidosis in the context of ARHF is highly controversial. Metabolic acidosis can impair ventricular systolic and diastolic function, increase pulmonary artery pressure (PAP), decrease SVR, pre-dispose to dysthymias, and reduce responsiveness to catecholamines. Correcting metabolic acidosis ultimately requires restoration of right heart function and systemic perfusion. As a temporizing maneuver, sodium bicarbonate is often administered as a temporizing agent. The outcome benefit of sodium bicarbonate is at best unclear and its use is de-emphasized in ACLS guidelines[18] and not recommended in the treatment of sepsis[19]. The accumulation of carbon dioxide is of particular concern due to increased PVR, paradoxical intracellular acidosis, decreased ionized calcium, and coronary vasospasm. Administering THAM is not well-defined but may be considered as an alternative therapy to reduce some of sodium bicarbonate's deleterious effects. If a practitioner chooses to administer sodium bicarbonate, careful attention must be given to ventilation and arterial blood gasses should be regularly obtained with a focus on correcting the ultimate problem of RV dysfunction.

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Ionotropic RV support is typically necessary during periods of acute decompensation, but the choice of agent must be made with great consideration. Common ionodilators include dobutamine, milrinone and levosimendan. Dobutamine is often considered a first line agent in treating RV dysfunction. It will augment contractility while decreasing PVR at lower doses (5mcg/kg/min) although at higher doses (10mcg/kg/min) may cause tachycardia and systemic hypotension[20]. It is common to incorporate a pressor with its use. Milrinone is a phosphodiesterase III inhibitor that prevents degradation of cyclic AMP and increases myocardial calcium influx and thereby increases contractility. PVR is reduced but milrinone has a profound effect on SVR, more so than dobutamine, and this severely limits its use. There is occasionally a role for low dose milrinone (0.125mcg/kg/min) to help support the RV if hypotension is an issue and a state of quasi-stability is encountered. In an acute intraoperative situation with marginal systemic prefusion pressure, milrinone boluses should be avoided. There is some evidence showing that inhaled milrinone provides preferential pulmonary vasodilation with minimal systemic hypotension, but robust data on this is lacking[21]. Levosimendan is an inotrope that increases calcium sensitivity of myocytes by binding to troponin C and increases contractility while afterload. Interestingly, levosimenden may increase myocardial oxygen supply via coronary artery vasodilation and does not appear to increase myocardial oxygen consumption, a distinction from other ionotropes[22]. While indicated for acute heart failure (class of recommendation IIa, level of evidence B)[23], it is not approved for use in the United States at this time and its role in treating ARHF in the intraoperative setting is not defined. Common ionopressors used for RV support include dopamine and epinephrine. Dopamine is not typically used because of its tachycardic and arrhythmogenic properties[24]. Epinephrine is used in decompensated situations because it increases systemic pressure and contractility owing to its intense α and β agonism. However, epinephrine also increases PVR and heart rate and can precipitate further decompensation. Interestingly, patients in septic shock with RV dysfunction refractory to other therapies have been shown to have an increase in RV systolic function despite an 11% increase in PVR with epinephrine treatment[25]. Although controversial, in patients with severe or refractory RV failure, or nearing cardiac arrest, epinephrine is a reasonable first choice for intraoperative rescue despite its numerous risks. It can be dosed in small (10-20mcg) bolus doses to test response in a struggling patient and is the ACLS recommended drug during cardiac arrest[18].

RV afterload reduction is another important intervention in supporting a failed right ventricle. Non-specific intravenous PA vasodilators, such as sodium nitroprusside or nitroglycerin, can cause systemic hypotension and subsequent cardiac arrest and should not routinely be used in an unstable intraoperative setting. Inhaled agents such as epoprostenol and nitric oxide work locally and specifically to reduce PA pressure without causing systemic hypotension and can be administered in the most acute of patients. Before these agents are considered, isolated pulmonary venous hypertension should be excluded since elevated transpulmonary flow against a left sided obstruction can cause pulmonary edema. Nitric oxide is administered at 5-40ppm and ability to lower PAP and improve RV function and oxygenation, coupled with its rapid onset of action and short half-life, make it an ideal agent to for use in the most critical of patients[26]. This drug is generally well tolerated but patients must be monitored for methemoglobinemia. Inhaled epoprostenol is a less expensive alternative to inhaled nitric oxide that activates cAMP and dilates the pulmonary arteries. It may be similarly efficacious[27]. It is initiated at 1-2ng/kg/min and has a half life of 3-6 minutes. While there is no risk of methemoglobinemia, epoprostenol inhibits platelet aggregation[28]. As a note on intraoperative use: if administering this medication in the operating room, the heat and moisture exchanger (HME) should be removed since it will interfere with drug delivery. Also, prolonged ventilator holds can result in accumulation of the drug and a subsequent unintentional bolus resulting in hypotension. The is evidence that combining inhaled epoprostenol and inhaled milrinone have additive effects on right heart support while minimizing systemic hypotension[29]. Inhaled agents should be considered early in the management of acute RV dysfunction give their favorable hemodynamic profile and relatively benign side effects compared to intravenous agents.

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Mechanical therapy for Right Heart Failure

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Right heart failure (RHF) describes a spectrum of contractile dysfunction ranging from mild-to-severe, whereby the forward flow or right-sided cardiac output is increasingly reduced. The resulting reduction of left-sided filling will limit left-sided output, ultimately leading to systemic circulatory failure. The right ventricle (RV) is a thin walled structure designed to work in a low-pressure system. Right ventricular muscle mass is ~ 1/5th of its left sided counterpart. While the right ventricle's thin wall allows dilation in response to increases in volume, acute pressure changes are poorly tolerated. Primary right-sided myocardial disease and volume or pressure overload due to pre- or post- capillary pulmonary hypertension are contributing mechanisms to RHF. Etiologies include right-sided ischemia, right-sided endocarditis, left heart failure, left-sided valvular disease, pulmonary embolus, and pulmonary arterial hypertension. RHF leading to circulatory failure is associated with a high mortality rate [1]. Perioperatively, the anesthesiologist might observe acute RHF following a pulmonary embolus, after prolonged cardio-pulmonary bypass, or after placement of a left ventricular assist device. Treatment should identify and address the primary etiology of RHF, while treating dysfunction through optimizing preload, reducing afterload, and augmenting right ventricular contractility. If pharmacologic therapy including diuretics, vasoconstrictors, pulmonary vasodilators, and inotropes fail to improve circulatory failure, mechanical circulatory therapy (MCS) is indicated.

MCS used to support the RV includes intra-aortic balloon pump (IABP), veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and temporary right ventricular assist devices (RVAD). Though IABP are being placed to provide reduction in left ventricular afterload and to augment diastolic pressure to improve perfusion, studies have shown limited efficiency in RHF [2, 3]. VA-ECMO has been successfully used for cardiogenic shock, as it unloads the right ventricle and increases systemic perfusion. The blood return to the arterial system increases left ventricular afterload, which is poorly tolerated by a dysfunctional left ventricle (LV), leading to increases in pressure, thereby offsetting RV unloading. Decompression of the left ventricle using temporary left-sided MCS, placing a left ventricular vent or advancing a venous cannula into the pulmonary artery (venous AV ECMO), has been described to improve worsening pulmonary edema [4].

Conceptually, MCS can provide direct temporary and prolonged support to a "failing ventricle" by draining its blood and providing perfusion to its circulatory system, either pulmonary or systemic. The approximately six million heart failure patients in the USA drove the development of short- and long-term left ventricular assist devices (LVAD's), and 2-year survival of patients with end stage heart failure improved from 20% to 80% due to contemporary durable devices [5, 6].

The development of right-sided MCS progressed much slower. To date, the US Food and Drug Administration (FDA) approved RVAD's are limited to temporary support only. It is generally accepted that ventricular recovery after failure occurs more likely in the RV due to its perfusion timing (systole and diastole), and adjustable oxygen extraction and metabolism [7]. Hence, temporary right-sided support provides time to recovery or transplantation if indicated. A VAD consists of a pump, an inflow and an outflow cannula. Current RVAD's drain blood from the right atrium through an inflow cannula, and return it to the pulmonary artery through an outflow cannula. Most devices use two venous cannulas placed either peripherally or centrally. Peripheral cannulas are placed through the femoral veins, whereas central cannulation is possible after sternotomy directly into the atrium and pulmonary artery. Recently, a dual lumen cannula (Protech®) was developed, that allows the use of a single cannula positioned through the right internal jugular vein, with a draining orifice in the right atrium and the proximal tip in the pulmonary artery. Numerous pumps with continuous flow technology can be utilized to provide right-sided mechanical support (e.g. CentriMag™, Bio-pump™, RotaFlow™, or TandemHeart©), but they differ in approved duration of use. With the exception of the CentriMag™ pump, all above-mentioned pumps (Bio-pump™, RotaFlow™, or TandemHeart©) are FDA approved for support up to 6 hours [8]. The Thoratec CentriMag™ has FDA approval with humanitarian device exception for up to 30 days, therefore being the only pump for extended

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temporary support. A recent addition to percutaneous RVAD's is the Impella RP® (right percutaneous). This device is a catheter-based micro-axial pump placed through a femoral vein. The cannula is positioned with its inflow portion located in the inferior vena cava, and its outflow into the pulmonary artery. A clinical trial demonstrated the safety and efficacy of the Impella RP® in 2015 [9]. In 2017, the Impella RP® was FDA approved for the temporary support of a failing RV for up to 14 days under humanitarian device exemption. The combination of lower demand for RVAD's and the unique anatomy and physiology of the RV left the development of durable RVAD's in its infancy. To date, no long-term devices are approved for use in the RV. Treatment options of non-resolving severe RHF include the placement of a total artificial heart as bridge-to-transplant or heart transplantation if indicated. The off-label use of small durable devices designed for the left ventricle (HeartWare HVAD®, Jarvik 2000®) has been described in the literature [10-14]. Modifications of the devices were necessary, as anatomy and physiology of the ventricles are different enough, that the use of a LVAD for the right ventricle creates problems. Anatomical challenges relate to the significant protrusion of the inflow cannula into the right ventricular cavity, while physiological problems arose from high device flows as a consequence of lower pressure in the pulmonary system. The lack of a true broad muscular apex makes position and angulation of the RV inflow cannula difficult, with potential misdirection towards the free wall or interventricular septum, thereby setting the stage for a suction event. The shorter length of the RV in combination with a protruding cannula allows for close proximity to the sub-valvular tricuspid chordae with the potential to cause structural distortion and the development of regurgitation. Off–label use describes the use of felt spacer on the epicardial surface to avoid significant protrusion of the cannula into the RV cavity, or cannulation of the right atrium [11, 15].

The optimal performance of LVAD's is described using pressure-flow (HQ) relationships at a given speed [16]. H represents the differential pressure between outflow (aorta) and inflow (ventricle), also called pressure head, while Q describes the flow. Clear relationships of pressure and flow are described by the manufacturers in HQ-curves. Due to the fact that the pressure difference on the right side is much lower, device flows at a given speed are going to be higher, clinically leading to pulmonary edema and bleeding in the pulmonary system [17]. Though these complications would be avoided by lowering the speed of the device, lower pump speed is associated with blood stasis and increased risk clotting [18]. Off-label modification includes reducing the size of the outflow cannula by 50 % giving the ability to utilize device appropriate flows without causing pulmonary edema [13]. HeartWare® is currently seeking approval for its HVAD® as RVAD.

Three devices are currently being evaluated for long-term use on the right side, while another two devices are undergoing development for short-term use [19]:

Long-term:
1. HeartWare MVAD®
2. DexAide Blood pump©
3. CircuLite® Synergy system®

Short term:
3. Deltastream DP3©
4. PERKAT©

None of these devices are tested in clinical studies yet, precluding them from being a solution any time soon. To date, treatment options of RHF beyond temporary support include the placement of a total artificial heart as bridge-to-transplant or heart transplantation if indicated.

In conclusion, RVF has a high mortality if left untreated. Treatment options include pharmacology, short-term MCS and transplantation if indicated. Short-term support includes a variety of devices differing in approved support duration. To date, no log-term VAD is approved for use on the right side, though development is ongoing.

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The Brain's Glymphatic System: Role in Sleep and Anesthesia

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Peri-operative brain health

An increased focus on peri-operative 'brain health' has emerged with reports of increasing prevalence of post-operative delirium and cognitive dysfunction with the rising number of elderly patients undergoing anesthesia and surgical procedures [1]. Minimally invasive surgical approaches to reduce tissue damage and implementation of 'early recovery and enhancement from surgery' (ERAS) protocols have reduced post-operative pain, facilitated rapid ambulatory function and early discharge and also helped ameliorate post-operative delirium [2-4]. Additional interventions to further investigate cognitive morbidity in the elderly have highlighted: anesthetic depth as defined by electroencephalography (EEG) monitoring [5,6], attention to intraoperative hemodynamic control in the elderly [7], adherence to drug dosing recommendations in the geriatric population [8], rapid emergence with stimulant drugs [9,10], pharmacologic enforcement of peri-operative sleep architecture [11,12] and routine use of opioid-sparing multi-modal analgesia. Nevertheless, delirium and the associated morbidity and mortality remains a clinical concern especially in the geriatric population [1,13,14]. The essential cerebral hemodynamic parameters (i.e. cerebral blood flow, perfusion pressure, oxygen delivery and extraction, cerebral bioenergetics), cerebral oximetry, intracranial pressure, EEG, self-reports of pain, psychometric agitation-sedation scoring and assessment for stroke remain the principal readouts of most clinical studies addressing peri-operative brain health and morbidity. However, a unique and recently discovered feature of the central nervous system (CNS) which might also play an important role for preserving brain health peri-operatively is the brain's need for continuous metabolic waste clearance.

The brain is one of the most metabolically active organs in the body and to maintain homeostasis continuous removal of metabolic waste is necessary. For decades scientists were puzzled by the fact that the brain unlike the rest of the body, lacked conventional lymphatic vessels, which are part of the immune system outside the central nervous system, and facilitate drainage of metabolic waste to lymph and the systemic circulation to be expelled from the body. A few years ago, scientists made the surprising discovery that the brain does indeed have a system which functions analogous to the lymphatic circulation, but it is constructed in a completely different way and governed by different physical forces. In the following, the various anatomical and functional components of this new system – so-called "glymphatic system" - will be reviewed. Controversies and gaps in the knowledge of the glymphatic system will also be highlighted, as well as evidence for its existence in the human brain. General understanding of the glymphatic system is becoming increasingly important clinically in the context of new reports of its potential causative physiological role in sleep and anesthesia; and might in the near future become a novel physiological parameter – a '6th vital sign' - to monitor and control peri-operatively to preserve brain health.

Lymphatic system, interstitial fluid and waste drainage

The lymphatic system which is part of the immune system is present in most body organs outside the central nervous system and responsible for tissue fluid homeostasis, removal of cellular waste products and absorption of fatty substances from the digestive system [15]. The lymphatic system is comprised of blind-ending lymphatic capillaries imbedded in the interstitial space of tissues which drain to larger transporting lymph vessels and lymph nodes which again connects to efferent larger lymph vessels that converge into greater 'trunks' which empty into blood. Lymph is created by the microcirculation and is a representation of interstitial fluid including waste solutes. Studies show that because hydrostatic and oncotic pressure differentials between blood and the abluminal side of glycocalyx on endothelial cells an efflux of plasma (with solutes) is being driven through leaky capillaries via transendothelial pores and junctions. This ultrafiltrate is propelled into the interstitial fluid space of the surrounding tissues and partly reabsorbed by the lymphatic circulation. The lymphatic system is a network with a remarkable fluid volume capacity. For example, a human body of 70 kg produces approximately 8-12 l of lymph each day, with the major portion produced at the level of the microcirculation and 50% or more of lymph is reabsorbed by the level of the lymph nodes and only the remaining 4 l is returned to the systemic circulation.

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Brain tissue has no lymphatic vessels - how is waste cleared?

The brain cells and interstitial fluid is separated from the systemic circulation by the blood brain barrier (BBB) and the blood-cerebrospinal fluid (CSF) barrier at the level of the choroid plexus. The brain's capillary tight junctions make the BBB essentially impermeable to water and it has been argued therefore that there is no need for a lymphatic system because the BBB prohibits generation of an ultrafiltrate. However, the brain generates a massive amount of metabolic waste all of which cannot be recycled, therefore other processes to clear waste evolved in place of a classical lymphatic system. Immediate byproducts of brain activity, such as ammonia and lactate, are rapidly eliminated, however, recycling of cytosolic proteins require more extensive breakdown via ubiquitination and autophagy. In most neurodegenerative diseases waste protein aggregates are present in brain cells and the interstitial space: Alzheimer's disease (Aβ, tau), Parkinson's disease (alpha-synuclein), Huntington's disease (huntingtin) and Amyotrophic Lateral Sclerosis, ALS (TDP-43 and others), and most of these (except for Aβ) lack specialized BBB transporters and cannot easily be removed. It has been hypothesized that impairments at the level the vascular bed (inflammation, BBB leakage) and decline in recycling and waste breakdown processes with age are involved in the pathogenesis of neurodegeneration and cognitive decline but the mechanisms are still incompletely understood.

For decades it has been assumed that CSF formation transport functions as a 'third circulation' involving waste clearance in place of a lymphatic system. Dr. Heinrich Quincke was the first to inject cinnabar dye directly into CSF of live animals and documented its transport pattern in relation to the CNS post-mortem [16,17]. He discovered that CSF at the level of the spinal cord communicated with CSF covering the brain, and also that the dye leaked out along cranial and peripheral nerves and large vessels and drained to lymph nodes, but he did not observe dye within the brain and spine tissues. In the 1850's fluid-filled channels along the cerebral vasculature was discovered - the "Virchow-Robin" spaces – and postulated to serve as conduits for CSF and ISF 'bulk' flow currents. Several decades later Helen Cserr and colleagues injected small molecular weight (MW) solutes into the brain parenchyma and documented rapid movement suggesting transport by bulk flow rather than by diffusion [18,19]. Another important study by Rennels and Grady used horseradish peroxidase as CSF tracer, and reported rapid (10 min) transport of horseradish peroxidase from the subarachnoid space into a brain-wide peri-vascular network [20]. Unfortunately, this data was never reproduced and the concept of rapid, peri-vascular CSF transport in the brain was abandoned.

The glymphatic system

In 2012, Iliff and Nedergaard [21] introduced novel data describing a hitherto overlooked system in the brain that facilitated waste (including soluble amyloid beta and tau) clearance from the interstitial fluid (ISF) space. The experiments were extensive and implemented state-of-the-art in vivo techniques to track transport of the dyes in brain in real time. Fluorescent dyes with different MW were injected into CSF via the cisterna magna in a series of live, anesthetized transgenic mice and their transport from CSF into brain was visualized through a cranial window with two-photon optical microscopy and by ex vivo optical imaging [21]. Below is a brief description of the major results that led to the formulation of the brain's 'glymphatic system'.

a. **Rapid peri-arterial CSF and solute influx**: Small MW dyes moved rapidly (<5-10 min) from the subarachnoid space into peri-arterial conduits (but not peri-venous conduits) and crossed into ISF.
b. **Astroglial endfeet:** Larger MW dyes (2000 kDa) remained stuck in the peri-vascular space and did not pass into ISF indicating the presence of barrier to solutes between the two compartments. This 'barrier' is composed of astroglial endfeet. The gap between the astroglial endfeet is only ~20 nM which, is why large MW solutes cannot pass into ISF. The blood vessels and peri-vascular spaces can be viewed as a coaxial system: The inner tube is the blood vessel itself, and the outer tube the astroglial endfeet which, envelop nearly all the cerebral vasculature.
c. **AQP4 water channels facilitate rapid perivascular CSF transport and CSF-ISF exchange**: The astroglial endfeet are remarkable in the context of peri-vascular CSF transport because they are characterized by a high density of aquaporin-4 (AQP4) water channels (which do not transport solutes but only water). Using AQP4 knockout mice they demonstrated that the AQP4 water channels facilitate rapid fluid transport from the peri-vascular into astrocytes and ISF.
d. **ISF waste including Aβ is cleared via peri-venous channels and dependent on AQP4:** Solutes including fluorescently tagged Aβ was administered directly into the brain parenchyma and showed to drain along perivascular spaces of large central veins. This process was also dependent on AQP4 water channels. Note that in studies where waste solutes were administered directly into parenchyma it is

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assumed that their clearance from brain is also reflective of CSF transport via peri-vascular AQP4 channels. In other words, it is assumed that transport of the waste parallels mobility of ions and other molecules driven by the water flux via AQP4 channels.

e. **Vascular pulsatility increases CSF transport**: The peri-arterial transport of small and large MW solutes was dependent on arterial pulsation and therefore assumed to be bulk-flow driven [20,22]. There is currently debate in the literature regarding the mix of physical forces driving solute transport within the glymphatic system. While some studies support pressure-driven bulk motion of fluid referred to as 'advection' (independent on the solute's MW) others claim that diffusion forces (dependent on MW) govern.

Collectively all of these results led to the formulation of the 'glymphatic' system. The designation of the system as the 'glymphatic system' was based on its dependence on glial cells and its functional role analogous to lymphatic system. As such the glymphatic system can be viewed as a brain-wide perivascular 'connectome' which via AQP4 water channels allows for CSF to be rapidly transported into ISF. The continuous high-volume perivascular CSF transport, arterial pulsatility and APQ4 channels enable CSF-ISF mixing and ISF waste solute removal. The CSF-ISF fluid mixed with interstitial waste solutes is thought to clear via the peri-venous compartment of the larger central veins from where it eventually exits into lymphatic vessels and the systemic circulation.

Visualizing and measuring glymphatic transport in the brain

Using in vivo MRI or other imaging modalities such as positron emission tomography (PET) in combination with MR contrast or radioactively labeled solutes the glymphatic transport process can be described 'macroscopically' in the whole rodent, non-human primate brain or human brain in vivo [23-26]. Typically, MR contrast is administered into CSF and tracked over time using dynamic-contrast enhanced MRI. Parametric readouts describing transport from such in vivo studies includes 1) peri-arterial influx representing the front-end of the glymphatic process; 2) tissue uptake of the tracer representing the glymphatic CSF-ISF exchange process as well as 3) tissue clearance of contrast over time. The clearance of contrast from the tissue represents peri-venous and peri-neural efflux out of the skull. Each of these processes can be quantified using simple curve fitting, compartmental kinetic modelling, or more complex algorithms.

Drivers of glymphatic transport

Given the anatomical and functional features of the glymphatic system described above the following physiological parameters can be inferred as paramount for its function: 1) normal, continuous CSF production assuring constant CSF volume and pressure for transport, 2) normal cardiac output and vascular pulsatility, 3) respiratory force (Ref), 4) normal perivascular space anatomy, 5) high density of AQP4 water channels on astroglial endfeet, 6) normal and intact intracranial pressure, 7) downstream connection to authentic lymphatic vessels outside the brain tissue and 8) magnitude of the ISF volume fraction. It is beyond the scope of this write-up to describe in detail each of these factors influence the efficiency of glymphatic transport and waste. Briefly, the main 'controllers' for the glymphatic system are summarized below:

- **CSF production and transport:** If CSF production is reduced pharmacologically, or CSF is leaking (e.g. dural tear or cisternotomy) glymphatic transport and waste clearance is reduced.
- **Pulsatility:** Increased pulsatility (e.g. dobutamine) enhances glymphatic transport and decreased pulsatility (e.g. ligation of the carotid artery) decreases glymphatic transport.
- **Breathing/ventilation**: In humans forced inspiration has been shown to increase CSF transport out of the ventricles to the basal cisterns but there is a gap in knowledge as to how other respiratory patterns (e.g. positive pressure ventilation) impact glymphatic transport.
- **AQP4 water channels**: The polarity of AQP4 water channels on astroglial endfeet are essential for CSF transport into the glymphatic pathway, and this polarity is altered in stroke and mild traumatic brain injury and is associated with dysfunctional glymphatic transport.
- **Intracranial pressure**: The importance of intracranial pressure on glymphatic transport and waste clearance is still not clear. However, ICP changes with body position and glymphatic transport including clearance of Aβ from rat brain was shown to be reduced in prone compared to supine or lateral body position [27]. In addition, since the glymphatic system appears to be a 'low-pressure system' any condition

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that leads to open skull (brain collapses over time in atmospheric pressure) will have impact on glymphatic transport.

- **Downstream efflux to lymphatics** outside brain: The downstream connection of the glymphatic system with authentic lymphatics on the neck has been documented but the exact anatomical constructs which merge the two systems and how it affects the glymphatic transport are still debated. However, new data on the downstream lymphatic network and how it interconnects with the glymphatic pathway has recently emerged. First, authentic lymphatic vessels (LV) were confirmed at the level of the dural meninges [28] and more recently shown to be functionally capable of absorbing macromolecules from brain tissue and drain these to the deep cervical lymph nodes [29,30]. Second, lack of dural lymphatics in transgenic mouse models was shown to impede clearance of macromolecules from the brain to cervical lymph nodes [29,31]
- **Interstitial space volume fraction**: The ISF is connected to the glymphatic system and waste solutes are cleared via this mechanism by the CSF-ISF exchange and then proceed to drain to the exits of the glymphatic pathway, that is, conduits along central veins and cranial nerves. The volume of the ISF space is only 15-20% of brain volume and it is a complex compartment which provides a 'resistance' to fluid and solute transport. The ISF volume fraction has been shown to expand during sleep when compared to wakefulness and this increases glymphatic transport and waste clearance which is one of the most intriguing factors with potential big implications for several disease states [32]

Glymphatic system function during sleep and anesthesia

One of the most exciting studies related to the glymphatic system was the observation that slow wave sleep greatly enhanced influx and clearance of waste solutes including Aβ from brain. Specifically, Xie et al. showed in mice that glymphatic influx was increased by 95% and Aβ was cleared 2-fold faster during slow wave sleep (or anesthesia with ketamine/xylazine) when compared to wakefulness [32]. This study was met with excitement because maintaining efficient brain waste drainage across the lifespan – possibly by preserving normal sleep architecture or inducing sleep - emerged as a novel therapeutic target for preventing cognitive dysfunction and decline in aging and possibly in many other neurodegenerative disease states. It was inferred from this study that all drug-induced states of unconsciousness will promote brain waste clearance. However, the basis for sleep-induced enhancement of glymphatic transport appears to be closely linked to expansion of the ISF volume fraction and central norepinephrine tone/activity. In agreement with this concept, we recently showed that rats receiving dexmedetomidine (which blocks norepinephrine release from the locus coeruleus) in combination with low-dose isoflurane exhibit a 30% higher glymphatic transport function relative to rats receiving isoflurane alone [33]. This finding may be important for clinical practice because dexmedetomidine or other drugs that reduce central norepinephrine signaling could have the added benefit of improving 'brain waste removal' in the context of peri-operative patient care. For example, glymphatic transport enhancement might explain why the use of dexmedetomidine sedation in the ICU decrease the incidence of postoperative delirium[34].

Does a glymphatic system exist in the human brain?

It is currently unknown if a glymphatic system for waste drainage as described in rodents exists in humans. Clearly, fundamental anatomical and physiological differences exist between the two species which need to be considered. For example, the cerebral metabolic rate of glucose utilization in young adult rat is twice as high as that of adult human inferring that waste production will change in proportion to overall metabolic rate in rodent brain when compared to humans. Further, the much larger brain mass, greater ratio of white-to-gray matter, and surface area in human brain compared to rodent brain regarding CSF transport and existence of a glymphatic system would also have impact on a glymphatic system. From the point of view of vascular pulsatility the much higher resting heart rates in rodents (mice ~500 bpm; rats ~300 bpm) compared to humans (~60-70bpm) which theoretically lower overall glymphatic transport rates humans compared to rodents. Evidence of a glymphatic system for solute waste removal in human brain would need to include: 1) CSF influx from subarachnoid space into peri-arterial space, 2) AQP4-dependent CSF transport from the peri-arterial space into the parenchymal ISF space, 3) peri-venous drainage of brain interstitial waste products and most importantly an association between ISF space changes, EEG (%delta power) and sleep states.

Ringsted et al. recently characterized CSF transport in normal human brain using the same MRI technique used in rodents to visualize and measure glymphatic system function [25,27,35]. In this study in humans CSF was observed to

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penetrate along arteries as well as into brain parenchyma, however the superior sagittal venous sinus was not enhancing at any time point suggesting that dural sinuses are not major drainage pathways for interstitial solute waste, or that the rate of drainage in to the venous sinuses was too slow to show up as an increase in the blood signal. Further, there is still no direct documentation in human brain of waste clearance in relation to large central veins as described in rodent brain[21]. As mentioned, faster glymphatic transport and waste clearance during sleep in rodents was associated enhanced clearance of soluble Aβ from brain tissue [32]. Several new studies correlating Aβ levels in CSF and/or brain of humans with changes in sleep have recently emerged: 1) increases in Aβ in the thalamus and hippocampus after acute sleep deprivation [36], 2) increases in CSF Aβ with disruption of slow wave sleep [37], 3) increases in CSF as well as brain Aβ after 24 hrs of sleep deprivation [38], 4) correlation between self-reported sleep duration and Aβ accumulation in the brain [39] and 5) circadian variation in CSF Aβ and tau [40]. Although all of these studies support the existence of a glymphatic system in humans it does not provide direct proof or causative physiological links between ISF volume fraction, sleep and waste clearance.

Summary

The glymphatic system has revived the field of CSF flow dynamics and highlighted its role as a mechanism for waste drainage from the CNS. A large body of experimental evidence in rodents has emerged over the last few years suggesting that the function of the glymphatic system decline in healthy aging and is dysfunctional in animal models of neurodegeneration including AD and stroke. The implication of slow wave sleep and anesthesia with alpha agonists (xylazine and dexmedetomidine) for maximumum enhancement of brain waste drainage compared to wakefulness has escalated research efforts focused on uncovering the different mechanisms involved in maintaining and controlling this complex system. However, along with novel information on glymphatic system function, unexpected and controversial findings have also emerged. Examples of unresolved issues include the physical forces driving solute transport in brain parenchyma, that is, bulk flow or passive diffusion. Other important gaps in knowledge relates to whether waste solutes are transported from periarteriolar to perivenular conduits before exiting the head and data supporting the causative physiological relationship between glymphatic transport, sleep and neurobehavior.

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Brain Based Biomarkers for Pain: Objective Measures of Pain or a Journey Down the Rabbit Hole?

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Educational Objectives

1. Understand that no single region within the central nervous system is responsible for the brain representation of acute or chronic pain. Chronic pain is associated with altered brain structure and function occurs across many regions of the brain, brainstem and spinal cord.

2. Describe how machine learning or multivariate pattern analysis (MVPA) is a new and powerful technology allowing for a whole-brain identification of altered brain structure and function in chronic pain.

3. Understand how MVPA may ultimately help to develop brain based biomarkers of pain and advance the goal of precision pain management.

3. Be aware of how researchers are now using neuroimaging to identify brain targets for novel and effective treatments for chronic pain such as transcranial magnetic stimulation, real-time fMRI, and other neuroimaging-based therapies.

Introduction

Neuroimaging has opened a window to the brain, to non-invasively study brain structure, function and chemistry. Multiple types of neuroimaging approaches have been developed for the study of pain including:

- Positron emission tomography (PET)
- Electroencephalograpy (EEG)
- Magnetoencephalography (MEG)
- Single-photon-emission computed tomography (SPECT/CT)
- Magnetic resonance imaging (MRI)

We will focus on MRI based techniques in this review. Several different approaches or protocols using MR techniques are used to characterize structure, function and chemistry including:

- Voxel-based morphometry, cortical thickness analysis: measures the density and distribution of gray matter

- Diffusion tensor imaging, functional anisotropy: measures the density and distribution of white matter

- Functional MRI (fMRI): indirect measure of brain activity based on changes in blood oxygenation level (referred to as the BOLD signal) [13]

- Magnetic resonance spectroscopy (MRS): measures relative concentrations of metabolites [29]

- Arterial spin labeling (ASL) fMRI: measures changes in global and regional blood flow by using magnetically labeled protons in the blood as an endogenous tracer [30]

The processing and modulation of pain within the central nervous system (CNS), brain and spinal cord, and how it is disrupted in chronic pain has been increasingly elucidated using neuroimaging (for review: [11]). Multiple chronic painful conditions have been characterized using neuroimaging including:

- Chronic low back pain (cLBP) [27]
- Fibromyalgia (FM) [24]
- Osteoarthritis (OA) [12]

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- Complex regional pain syndrome (CRPS) [2]
- Phantom-limb pain, chronic migraine [5]
- Chronic pelvic pain (CPP) [10] [1]
- Peripheral neuropathy (PN) [18]

However, to date and despite hundreds if not thousands of studies using neuroimaging for pain, brain neuroimaging has provided minimal diagnostic, predictive or prognostic potential, or avenues for direct clinical application to pain.

A relatively new field of neuroimaging has developed using multivariate pattern analysis (MVPA) to assess neuroimaging data for meaningful patterns of neural structure and function. MVPA has previously been applied to research ranging from economics to social science to medicine [6; 17; 19]. MVPA is a form of machine learning technology with the potential to serve as a classification technique [23]. In contrast to conventionally used univariate MRI analysis methods, MVPA has the potential to have clinical value. For instance, MVPA techniques can be used to develop brain "signatures", "fingerprints" or patterns that could stratify chronic pain patient populations and have neuroprognostic value for treatments. However, while the future applications of this technology to clinical care are great, important limitations, ethical and legal implications are important to consider and keep in perspective.

MVPA Approaches and Advantages for the Study of Pain

The complex physiological and psychological phenomenon [16] of pain makes it inherently challenging to study and treat. Large individual variability of subjective pain perception and variability in treatment response poses additional challenges to pain assessment and treatment. Subjective report is the primary tool and gold standard to assess and rate pain. Subjective report by an individual, for example rating pain on a numerical scale from 0 to 10, is an extensively validated and useful measure in both scientific research and clinical assessment [21]. However, there are situations where the self-report of pain is not obtainable, such as in the very young, very old and infirmed populations. Further, subjective report of pain prior to injury or surgery is neither available or predictive of whether a person will subsequently develop chronic pain. Additionally, subjective report of pain is not prognostic of whether a patient will respond to a particular treatment. We need novel, safe and validated biomarkers to advance clinical care and help define new targets for treatment.

Univariate analyses approaches have been traditionally applied to brain imaging analyses [9]. Univariate methods employ repeated voxel by voxel statistical comparisons to characterize regions of significant differences within the brain. In sharp contrast, multivariate analyses perform global search and apply statistics in later steps to identify particular brain regions that contribute most to the important pattern (i.e., significance map or discriminative map) [19]. In MVPA, data from individual voxels within a region are jointly analyzed. Additionally, MVPA retain statistical power to identify brain regions that may otherwise have been missed with univariate analyses [20]. Thus, MVPA methods are well suited to analyze large complex neuroimaging data sets. MVPA methods can also handle high-dimensional data with small number of examples.

MVPA is also fundamentally a pattern oriented approach thereby promoting the classification of individual data sets. This makes MVPA particularly useful for the study of pain [23]. As has become increasingly evident, both acute and chronic pain involves distributed mechanisms that involve multiple regions throughout the brain, brainstem and spinal cord [7]. Over the last couple decades, researchers have used univariate methods to identify regions that collectively process the various components of the pain experience [8]. MVPA can advance that by similarly identifying spatial patterns (i.e., sets of distinct brain regions), and, further, to apply these patterns to classify novel data sets. Additionally, MVPA can classify data from a single individual as belonging to a particular group (e.g., pain or no pain; healthy or chronic pain; treatment responder or non-responder; likely or unlikely to develop chronic pain after surgery). MVPA classification provides clinically useful measures of classification accuracy, sensitivity, specificity, positive and negative predictive value, as well as information about misclassified subjects. Thus, the combination of classification ability and specific analysis outcome measures can inform us of the degree of direct applicability to medicine.

MVPA Applications to the Study of Acute and Chronic Pain

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We and other researchers have begun to establish reproducible and validated brain signature patterns for pain using MVPA. Several studies have classified brain activity in response to acute painful stimulation [3; 4; 15; 28]. In these studies MVPA differentiated between perceived low and high levels of painful stimuli, and between painful and non-painful stimuli [4; 15]. Wager et al. has also applied MVPA across multiple studies to define a neuroimaging brain pattern of heat pain [28] distinct from the experience of emotional pain. Together, these studies have advanced classification of acute pain response and simultaneously contributed to the collective knowledge of central pain processing mechanisms.

One of the earliest application of MVPA to the field of pain research is that of identifying a signature pattern. At its most simplistic level, the signature pattern could distinguish between individuals with chronic pain and healthy individuals. While this dichotomy can obviously be determined by a patient's subjective report, an MVPA signature pattern could validate subjective report. While admittedly not the most clinically useful first step (as we have patient self-report), it is one that is necessary in the refinement and future applications of MVPA. While not the most clinically useful, a benefit of developing MVPA patterns classifying chronic pain could be a more comprehensive description of the distributed brain regions involved in pain. These distributed patterns would serve as targets for pharmacologic, mind-body or neuromodulation approaches for treatment.

Our group has taken some of the first steps in defining MVPA signatures of chronic pain. Ung et al. applied MVPA to chronic pain populations by classifying individuals with chronic low back pain from healthy volunteers based on brain structure [27]. More recently we applied MVPA to classify patients with chronic pelvic pain from healthy volunteers based on brain structure [1]. It remains to be seen to what extent there are overlapping vs distinctive patterns of brain function and structure for different chronic pain conditions. This is an area of future research to identify signature patterns for various chronic pain syndromes and subtypes.

Future Applications of MVPA Techniques in Pain Research

The use of MVPA techniques in pain research and medicine hold great potential to develop objective biomarkers for pain. These biomarkers can be considered in the following categories:

- *Diagnostic Marker:* Identifies a disease (i.e. the presence or absence of pain)
- *Predicative Marker:* Identifies risk factors for developing chronic pain (or persistent opioid use) after surgery or injury
- *Prognostic Marker:* Predicts outcome ("Neuroprognosis")
- *Stratification Marker:* Predicts treatment response (responder or non-responder)
- *Efficacy Marker:* Measures treatment response
- *Toxicity Marker:* Detects treatment toxicity/side effects
- *Surrogate Endpoint:* Measures outcome

Furthermore, MVPA techniques offer great potential for the elucidation of pain processing mechanisms and novel diagnostics. However, this potential is not free of concern. In recent commentaries, pain researchers have debated whether chronic pain is a disease of the brain [25], whether brain-derived diagnostics of chronic pain are beneficial [22], and whether neuroimaging surrogate measures of pain are useful [14]. These commentaries highlight points that both reject [22] and support [14] the concept of a brain signature of pain. While the subjective report of pain is undeniably essential, the need for additional objective measures of pain is great and could ultimately aid clinicians in treatment selection on a per patient basis – the goal of precision medicine. This can be achieved without the replacement of self-report so crucial in the patient-clinician relationship.

As an example of the potential benefits of using MVPA derived brain imaging biomarkers for neuroprognosis, we will illustrate using a "non-pain" example. In a recent study, researchers identified a brain signature pattern that accurately predicted how much a child would benefit from math tutoring with significantly greater accuracy than subjective report and conventional aptitude tests. [26]. Thus, patterns in brain structure may provide more information than can be gathered from questionnaires or personal assessment; in the future this may be shown to be also true with pain.

Future Directions

As we continue to use and advance new technologies like MVPA, still much remains unknown. Future studies must compare MVPA derived neuroimaging results with conventionally obtained results. Great opportunities exist in the potential to combine

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various types of neuroimaging data in multimodal classification analyses (for examples, see Fig. 1). Integration of behavioral, genotype, phenotype and longitudinal data into these analyses could further increase sensitivity and specificity of signature patterns. It is hoped that by combining multiple sources of neuroimaging and big data, MVPA will advance us towards individually tailored medicine - the ability to predict drug efficacy and best treatment options for each individual patient.

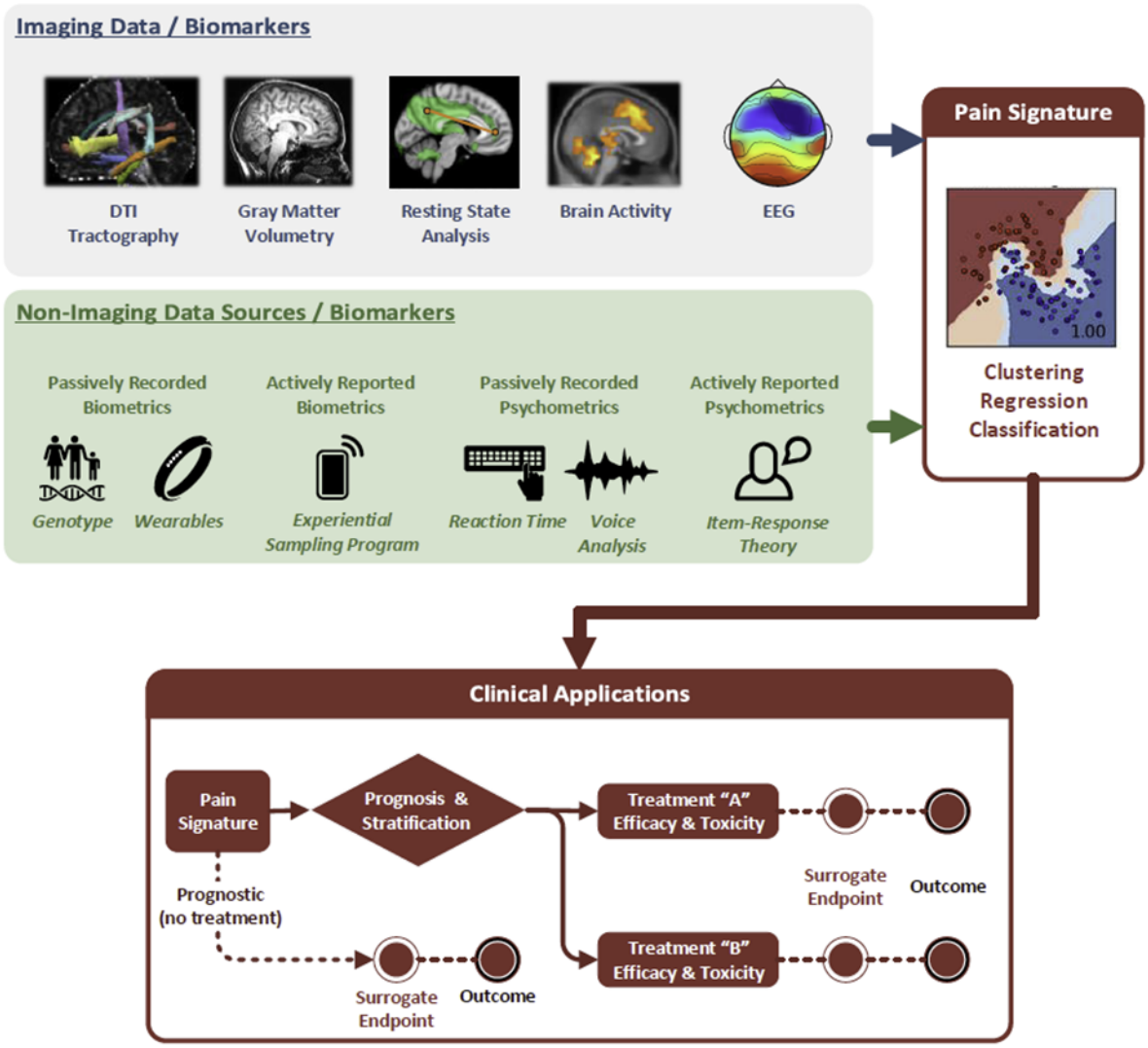

Figure 1. Schematic of Data Sources and Clinical Applications Related to Identification of Pain Signature Patterns: Imaging data can provide large sources of detailed and objective biomarkers for pain (top, gray box). Various sources of imaging biomarkers include 1) structural abnormalities measured with magnetic resonance imaging (MRI) (e.g., diffusion tensor imaging of white matter tractograpy, DTI; gray matter volumetry), 2) functional differences measured with functional MRI (fMRI) (e.g., resting state fMRI networks and functional connectivity between brain regions; brain activity in response to evoked stimulation or during a task), and 3) functional differences measured with non-MRI modalities such as electroencephalography (EEG). Non-imaging data sources can provide additional objective biomarkers (middle, green box). These include, for example, genotype information, biometrics from wearable technology (e.g., actigraphy), actively reported biometrics (e.g., via handheld devices for recording patients' symptoms throughout the day), psychometrics including reaction time tests and voice analysis (e.g., to measure emotional states such as depression or anxiety) and actively reported psychometrics (i.e., demographic, psychological and clinical questionnaires). The identified biomarkers from both imaging and non-imaging sources can be combined as input for a multivariate pattern analysis (MVPA). The MVPA uses clustering, regression and/or classification technology and is capable of identifying the most meaningful biomarkers to provide a multi-variable signature pattern of pain (right, red box). The MVPA-

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derived pain "signature" can then be used in a variety of clinical applications (bottom, red box). Starting as a complex prognostic measure, the pain signature could provide the basis for stratification of an individual to a specific treatment program ("Prognosis & Stratification"). Surrogate endpoints, follow-up measurements after treatment, could be used to evaluate the treatment as effective or non-effective for the individual patient. Ultimately, the final outcome measures would indicate the pain signature's prognostic sensitivity and specificity. Alternatively, as a more traditional clinical course of action ("Prognostic – no treatment"), the pain signature could be used simply as a diagnostic (for clinical or legal purposes) or to predict a patient's prognosis over time regardless of treatment. Figure republished with permission from Martucci KT, Mackey S. Imaging Pain. Anesthesiology Clin 2016; 34(2). [In Press].

The previously mentioned example of using brain biomarkers for neuroprognosis of math tutoring illustrated its immense potential. However, it also illustrates the extraordinary ethical issues this technology presents. Imagine MVPA as used in this example to determine which child would or would not receive math tutoring? There could be similar parallels in pain and we need to be mindful of unintended consequences. The authors are quite concerned about inappropriate uses of this technology to potentially: (1) deny treatment, (2) reject or confirm legal cases, or (3) invalidate a patient's experience of pain. As this field evolves, there needs to be continued expert discussion of the strengths and limitations, and appropriate and inappropriate applications of the technology.

In summary, MVPA analyses hold great potential to change the frontier of pain management and treatment. However, it is imperative to interpret neurological studies with caution and acknowledge the continued importance of patient self-report. MVPA offers a powerful scientific tool for elucidating the mechanisms of pain processing. Clinically, MVPA holds the potential to provide novel diagnostic, predictive, and prognostic biomarkers to help achieve the goal of precision medicine.

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ANESTHESIOLOGY 2018
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Consciousness, Anesthesia, and the Cholinergic System

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Consciousness is determined both by level (e.g., being awake vs. being anesthetized) and content (i.e., the qualitative aspects of experience). There has been ongoing debate regarding the role of the prefrontal (vs. posterior) cortex in mediating contents of consciousness but there has been relatively little exploration of how the cortex regulates level of consciousness. By contrast, subcortical areas are known to play a causal role in regulating the level of consciousness and reversing the effects of general anesthetics [**1-9**].

Various studies have been used both to support and refute a role for prefrontal and posterior cortices in the level of consciousness [**10-22**]. However, the prefrontal cortex has extensive reciprocal connections to wake-promoting centers in the brainstem and diencephalon [**23,24**], potentially rendering it a hub that could control level of consciousness. Indeed, a recent study suggested that the prefrontal cortex might be important in arousal and anesthesia [**25**] but this study did not report causal evidence and did not test more posterior sites in the cortex.

We have previously found that both propofol and sevoflurane reduce acetylcholine levels in the prefrontal cortex [Figure 1, **26**]. We have furthermore shown that increased cholinergic tone in the prefrontal cortex is associated with accelerated recovery from isoflurane anesthesia [**27**] but causal relationships were not established. Therefore, to test the hypothesis that acetylcholine in prefrontal cortex plays a role in regulating level of consciousness, we attempted to reverse sevoflurane anesthesia by cholinergic stimulation of the prefrontal cortex—as well as two areas of parietal cortex—in rat. We demonstrate that carbachol stimulation of prefrontal cortex, but not parietal cortex, restored wakefulness, despite continuous exposure to approximately one minimum alveolar concentration of sevoflurane anesthesia. Furthermore, we demonstrate that prefrontal acetylcholine levels are increased significantly in association with reversal of anesthesia; the source of increased acetylcholine in the prefrontal cortex is hypothesized to be activated cholinergic neurons in the basal forebrain.

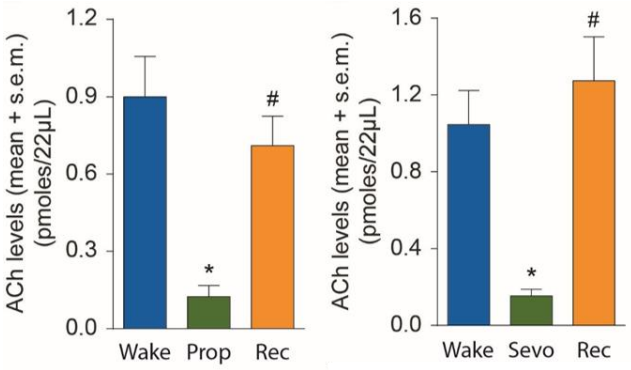

Figure 1: Acetylcholine levels in prefrontal cortex of rat are reduced by propofol (Prop) and sevoflurane (Sevo). From Pal et al, Anesthesiology, 2016.

We conclude that cholinergic mechanisms in prefrontal cortex can regulate the level of consciousness. This supports prior work suggesting that prefrontal cortex is an important contributor to consciousness and anesthesia [**25**], and also supports the prefrontal cortex as a relevant site for clinical monitoring.

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Post Dural Puncture Headache and Epidural Blood Patch

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Introduction

Post dural puncture headache (PDPH) is one of the most common adverse events to occur after neuraxial anesthetic procedures. Most of the data concerning both PDPH and epidural blood patch (EBP) comes from the obstetric anesthesia literature, although a smaller amount derives from the pain and other anesthesia literature.

Incidence, clinical features, and etiology

Meta-analysis reveals that: The incidence of accidental dural puncture (ADP) with a large bore needle during epidural anesthetic procedures is approximately 1-2%, although the range varies across different reports. In obstetric patients, PDPH follows 50-60% of ADPs. Of those patients with PDPH, 50-60% require EBP. PDPH occurs in the absence of a recognized ADP in fewer than 1% of patients (1). A typical PDPH is positional, such that headache worsens in the upright position, and abates (although perhaps not completely) when the patient assumes the recumbent position. Headache may be accompanied by neck ache and back pain, visual symptoms such as photophobia and blurred or double vision, auditory disturbances including decreased hearing acuity and tinnitus, and even cranial and upper cervical nerve dysfunction. Onset is usually within 1-2 days, and duration, 7-10 days in the obstetric population (1). Onset may lag and duration may be shorter in general surgical patients. The differential diagnosis of headache in postpartum patients includes states specific to pregnancy such as preeclampsia, venous thrombosis, and intracerebral bleeds, as well as more generic causes of headache such as tension headache; migraine may recur in the postpartum period also (2). Diagnostic neuro-imaging should be considered for postpartum patients whose headache is accompanied by focal neurologic signs or lack of response to treatment, as these can be signs of intracranial pathology (2).

Headache occurs due to leakage of cerebrospinal fluid (CSF); however correlation between headache symptoms and degree of leak/intracranial hypotension is incomplete. Some patients with small lumbar leaks develop headache, whereas some with large leaks do not report any symptoms (3). Similarly, a proportion of patients with severely depleted intracranial CSF volume may remain asymptomatic, while some with only mild CSF decreases develop severe headaches (4). When the brain loses its CSF cushion, downward displacement of the cranial contents may occur, putting traction on pain-sensitive meningeal structures. Furthermore, reflex cerebral vasodilation occurs in response to intracranial hypotension and pain-sensitive perivascular stretch receptors may contribute to headache symptoms (5).

Risk factors for PDPH

Patient-related factors. Young age and female gender are risk factors for development of PDPH after dural puncture (6). Whether pregnancy itself is an independent risk factor remains unclear. Obesity predisposes to ADP (7). The effect of obesity on headache rate once ADP occurs is less clear because retrospective studies demonstrate conflicting effects (8, 9, 10, 11), but obesity is probably protective against development of headache after ADP when confounders are controlled for (11). Obese patients may have a better response to epidural blood patch (EBP) versus non-obese patients (12).

Obstetric-related factors. Patients who have vaginal delivery are more likely to develop headache after ADP than those who undergo cesarean delivery (13). Performance of Valsalva maneuvers during pushing may cause extrusion of CSF, as headache rate is proportional to pushing time (14). Furthermore, patients often receive spinal morphine after cesarean delivery, which decreases headache pain (15).

Technique-related factors. Headache rates increase after puncture with large-gauge versus small-gauge needles, and beveled/cutting versus pencil point/non-cutting needles (6,16). One group of authors demonstrated that inserting an

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epidural needle with the bevel parallel to, rather than perpendicular to, the longitudinal axis of the spinal canal, decreased headache rate (17). They recommended holding the bevel parallel to the long axis to identify the epidural space, and then rotating the needle within the space once it had been identified, to decrease the risk of the catheter veering off to one side, resulting in unilateral blockade. Others questioned the utility of this practice, demonstrating that it was not necessary for satisfactory analgesia to rotate the needle before threading the catheter into the epidural space (18). Rotation of the needle within the epidural space may increase ADP occurrence.

The effect of loss of resistance (LOR) medium used during epidural space identification on headache development remains unclear. One author demonstrated higher headache rates in pain patients after LOR to air versus saline (19). However, the air-related headaches had faster onset and shorter duration than the saline-related headaches, and therefore may have been due to temporary pneumocephalus that resulted from injection of air into the intrathecal space during LOR. Practitioners should aim to inject the smallest amount of air possible into the epidural space during LOR in order to minimize the development of pneumocephalus should ADP take place.

Once ADP has occurred, one may elect to thread a catheter into the intrathecal space for continuous spinal anesthesia, or to withdraw the epidural needle, and re-site it into the epidural space at a different intervertebral level. Some have theorized that intrathecal catheter insertion causes inflammation near the dural tear, speeds healing, and decreases headache risk. Retrospective and other uncontrolled studies addressing this possibility are confounded, and therefore yield conflicting results, some demonstrating lower headache rates with intrathecal versus epidural catheterization and some showing no effect. Two randomized controlled trials investigating the relationship of intrathecal catheterization and PDPH risk exist. Norris used a quazi-randomization technique to assign parturients to receive intrathecal versus epidural anesthesia after ADP, and showed no difference in headache rate or severity or in need for EBP (20). In the definitive study, Russel et al randomized obstetric patients to receive intrathecal versus epidural catheterization after ADP (21). Intrathecal catheters were left in place for 24 hours post delivery to maximize the pro-inflammatory effect. Headache occurred at equal rates in both groups, as did performance of EBP. The weight of the evidence therefore does not support the notion that intrathecal catheterization decreases headache risk after ADP. A meta-analysis that drew the opposite conclusion included both randomized and non-randomized trials, and was therefore flawed (22).

Issues other than the effect on headache rate should be considered after ADP. In the Russell study, patients in the epidural group suffered more complications than those in the continuous spinal group, such as repeat ADP and failure to establish blockade (21). Therefore, the authors recommended intrathecal catheterization after ADP despite its lack of efficacy regarding headache prevention. Some caution is warranted, however, because high spinal levels may result if local anesthetic doses intended for the epidural space are accidentally administered intrathecally. High spinal level can also result through an epidural catheter after a previous ADP because local anesthetics may translocate across the large-diameter hole in the dura, particularly during bolus administration for cesarean delivery. Similarly, epidural-administered hydrophilic opioids may traverse across the dural tear, so epidural morphine is contraindicated after a prior ADP. (Lipophilic opioids such as fentanyl traverse the dura quite freely and so the presence of the tear does not affect their dosing.)

Prophylaxis and treatment

Conservative therapy. Bedrest after ADP does not prevent PDPH (23), and inactivity remains inadvisable for postpartum patients due to their risk for deep venous thrombosis. One should maintain euvolemia as dehydration results in decreased CSF production; excessive hydration, however, does not promote excess CSF production. Abdominal binders may favorably affect pressure gradients across the dural tear and decrease PDPH after ADP; unfortunately, they are not well-tolerated by most patients and are not popularly used. Practitioners commonly prescribe analgesics, particularly those combination pills that include butalbital and caffeine. Caffeine, by way of its vasoconstriction properties, may decrease headache symptoms (24), but its effect is modest and transient, and so while clinicians may encourage patients to consume extra caffeine for mild or moderate headaches, severe headaches usually warrant other treatments. Also, caffeine has a prolonged half-life in postpartum patients, and accumulation may occur after repeated dosing or infusion (25). Furthermore, reports of seizure and arrhythmia during caffeine infusion exist (26,27).

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Alternative therapies. One small trial investigating utility of sumatriptan in this clinical setting produced disappointing results (28). ACTH analogs increase aldosterone levels, and some theorize that the resultant salt and water retention may lead to increased CSF production, but studies investigating their usefulness have yielded conflicting results. One investigation indicated ACTH analogs were appropriate for PDPH prophylaxis (29), but another showed no effect of ACTH analogs on established PDPH (30). Small case series describe administration of sphenopalatine ganglion blocks for PDPH (31), but the technique has not been evaluated rigorously and further study is needed.

Epidural blood patch. EBP remains the treatment of choice for severe PDPH (32). Injection of blood into the epidural space quickly produces a tamponade effect on the intrathecal sac, increasing epidural and intrathecal pressures in both the lumbar and intracranial spaces, restoring intracranial pressure, and relieving adenosine-mediated vasodilation (33,34,35,36). In addition, clot adheres to the dura after several hours, presumably decreasing leak and promoting healing (35). MRI studies indicate that approximately 15-20 mL blood is sufficient for spread and tamponade of the sac (33). A randomized controlled trial conducted by Paech et al compared 15 versus 20 versus 30 mL blood for EBP (37). All volumes of blood were similarly effective for treatment of headache symptoms; however, the area under the time-pain curve over 48 hours was higher in patients given 15 mL of blood compared to patients in the other groups, and the authors therefore recommended the use of 20 mL blood for EBP. One group reported 100% successful response to patch when they routinely administered as much as the patient could tolerate, up to 30 mL (38).

Retrospective audits reveal that 88-100% of obstetric patients with PDPH after ADP experience some degree of relief after EBP; however, some patients have only partial or temporary relief, and symptoms often return after a few days (38,39,40). Up to 31% of patients may require repeat patching (37). Although EBP lacks perfect efficacy, complete lack of any effect at all should spur the clinician to question the diagnosis of PDPH.

It remains unclear how timing affects EBP efficacy. Studies purporting to show decreased efficacy when patches are administered within less than 24 to 48 hours of puncture are difficult to interpret because they include a mixture of patients (male, female, obstetric, non-obstetric) and needle sizes and types used for puncture (12,41,42). It is just as likely that patients at high risk (e.g., obstetric patients delivering vaginally, suffering large-bore dural punctures) experience severe symptoms early after puncture, and are therefore patched earlier than others, and are also more likely to need repeat patching. While it is certainly reasonable to offer a patient experiencing mild or moderate symptoms a trial of conservative therapy, one should not hesitate to administer EBP to patients with severe symptoms within a day of puncture. Such patients should be made aware of the possibility of repeat patch requirement. A more positive approach to early patching may result in less pain over time and a better patient experience (43).

Prophylactic EBP can be performed through the epidural catheter before it is pulled out after delivery. Two randomized controlled trials stand at odds regarding the efficacy of prophylactic EBP. One demonstrated no difference in headache incidence, peak pain scores, or need for therapeutic EBP after prophylactic EBP compared to a shame patch, although those who received the prophylactic patch had shorter duration of headache (13). A second did show fewer headaches and therapeutic EBPs performed in those patients randomized to receive prophylactic EBP versus nothing; however, this study has been criticized because the treating physician was not blinded to patient group and treatment was not standardized, leading to possible bias (44). Considering these two studies together, it is likely that prophylactic EBP provides some benefit in high risk patients, although probably not a dramatic one (45).

Backache follows epidural blood patch in 85% of patients (37). Discomfort is usually mild, although occasionally can be more severe or be associated with radicular pain. It may be advisable to limit injectate volume, particularly if the patient feels pain or radicular symptoms during the procedure. Non-steroidal anti-inflammatory agents often provide relief. Rarely, more severe complications follow EBP, including deterioration of mental status and seizures when EBP is performed for headache other than PDPH (46), neurologic deficits after accidental subdural injection (47), and arachnoiditis (48, 49).

Scope of the problem

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Postpartum PDPH increases length of hospital stay, increases hospital and emergency department visits after discharge, and interferes with activities of daily living, including childcare (50). The sixth cranial nerve may become stretched during downward brain displacement, causing nerve injury and subsequent double vision (51). Often, PDPH responds to EBP treatment, but the diplopia persists for many months during myelin regeneration, or in rare instances, is even permanent (51). Sixth cranial nerve palsy is an indication for immediate emergency EBP to affect relief of nerve ischemia. Rarely, subdural hematoma follows PDPH, as bridging veins are stretched, and subjected to increased transmural pressures (52). EBP may limit hematoma extension.

There may exist longer term consequences to ADP than has previously been thought. Investigators who compared parturients who suffered ADP to a matched cohort who had not, revealed that patients in the ADP group had increased rates of headache and backache approximately 12 to 24 months post-delivery (53,54). EBP appeared to provide some protective effect against these long-term symptoms; however, the lower headache and backache rates in patients who had received EBP versus those who had not, did not reach statistical significance, possibly because the study was underpowered for this outcome (53).

Conclusions

ADP and PDPH continue to pose vexing problems for the anesthesiologist. EBP remains the mainstay of therapy for severe headaches.

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ANESTHESIOLOGY 2018
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Clinical Hemodynamics: Assessment and Management

Jeffery S. Vender, M.D., MCCM, FCCP, MBA **San Francisco**

Anesthesiologists typically receive direct feedback when they deliver a fluid bolus to a surgical patient which, results in an increase in blood pressure and/or urine output. This process is interpreted as "fluid responsiveness" or an improved cardiac output (via a boost in preload/stroke volume). We ultimately hope this intervention leads to an improvement in end organ perfusion and subsequent favorable clinical outcomes. Realistically, this often times takes a leap of faith that in order to become a reality requires a far more advanced level of knowledge, applied science and appropriate therapeutic intervention.

Fundamental knowledge of hemodynamics is required in order to appropriately interpret physiologic responses in different clinical settings. Cardiac output (CO=SV x HR) is predicated on the heart's function and venous return function (i.e. preload). Well over 100 years ago, Frank and Starling demonstrated that an increase in end diastolic volume typically resulted in a greater cardiac force that produced an increase in cardiac output. The now famous Frank-Starling curve taught in basic physiology courses in medical school infers that afterload, heart rate and contractility are all constant (CO=MAP-RAP/ SVR). When heart rate or contractility increase or afterload decreases, cardiac output increases for any given preload (a leftward shift of the curve). However, after some point (plateau), a further increase in preload (end diastolic volume) will not result in further improvement in cardiac output. This maneuver will likely result in ventricular overdistension, overfilling and increased cardiac oxygen consumpton. The elegance of the Frank-Starling theory is echoed by "what comes in must come out."

The other vital component to cardiac output is the venous return (VR) function. Venous return is predicated on the elastic recoil of venous capacitance vessels. The mean circulatory pressure (Pms) minus the right atrial pressure divided by venous resistance equals venous return (VR=Pms-RAP/RVR). The heart controls its blood return by lowering right atrial pressure. An increase in stressed volume (volume stretching veins), results in a shift of the return function curve to the right. Venous resistance can also alter the return curve, where an increase in venous resistance leads to a decrease in venous return for a given right atrial pressure. Lastly, venous capacitance (the total venous volume for total pressure) is another component that restricts the circulatory system response. Veins have a small potential for contraction and when this threshold is reached, the so called, "unstressed volume" can no longer be utilized for improved cardiac output. This area is well discussed in a recent article by Gelman.

Plotting both the cardiac function and venous return function curves on the same graph allow for the clear depiction of the working relationship between these two important components. Physiologic and pathophysiologic states (shock) can be examined utilizing some of these premises. For instance, giving a fluid bolus to a hypovolemic shock patient will likely improve the associated cardiac output. However, giving fluid bolus to a patient who is past the plateau portion of the Frank-Starling curve could result in fluid overload and a worsened cardiopulmonary status. We will discuss the definition and pathophyisiologic explanations of shock (hypovolemic, cardiogenic, distributive and obstructive) in this talk.

Clinicians may use Goal-Directed Therapy (GDT) to address patients in shock like states (or with abnormalities in the cardiac function/return function relationship). Too often we have relied on monitoring and measurements (assessment) to alter outcome when it is actually the application of a therapeutic intervention (management) based on the information that alters outcome. Practitioners, who use goal directed therapy should recognize the following factors that most commonly will determine outcome: outcome: *appropriateness of care* (i.e interpreting data correctly and formulating the appropriate treatments), *timeliness* of care, and *responsiveness* (appropriate population targeted) to that care. **These axioms are vital to any clinician's success with goal directed therapy.**

Most GDT studies demonstrate improved clinical outcomes when appropriate physiologic end points are coupled with appropriate therapeutic measures, in a higher risk population, and *before end organ damage* occurs. The most difficult conundrum to address is which physiologic end points to use and how to accurately derive them. Endpoints of resuscitation can be divided into two categories; upstream and downstream. Upstream endpoints may include: hemodynamic (preload (CVP, PAOP, PPV)), contractility (SV), afterload (MAP, SVR)) and global oxygen delivery

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parameters (arterial oxygen saturation and oxygen carrying capacity). Downstream metabolic endpoints may include: lactate, SVO2, pH, base deficit, tissue oxygenation, inflammatory mediators, etc. The intermediary between the two is of course the microcirculation. Unfortunately, no widely adopted clinical monitoring system is available to investigate the microcirculation consistently.

Improved clinical outcomes are primarily achieved when these endpoints are appropriately monitored to derive an effective, timely therapeutic intervention. In this talk we will address various static and dynamic methods for hemodynamic monitoring. Unfortunately, monitors have not consistently been shown to improve clinical outcomes e.g. mortality (Ospina-Tascon FA). Shoemaker, Kern, Berlauk and Boyd all demonstrated that optimizing hemodynamic parameters derived from the pulmonary artery catheter (PAC) resulted in improved clinical outcomes for high risk patients if instituted before organ failure.. However, subsequent clinical studies using the invasive PAC did not show specific patient benefits. These studies are often flawed and have been criticized for their lack of adoption of the *outcome axioms* discussed above (Vender). However, the negative PAC studies promoted the development of several other less invasive devices and techniques to derive similar parameters as the PAC (i.e. esophageal doppler, pulse contour analysis, pulse pressure variation, bioimpedance, bioreactance, partial CO2 rebreathing, transthoracic echocardiography, etc). It is still unclear as to whether these less invasive devices provide the accuracy needed to aid clinicians in the development of helpful therapies. Still, recent studies have demonstrated a clinical benefit in perioperative patients when using some of these noninvasive techniques coupled with GDT. Further discussion of the benefits and liabilities of these invasive and less invasive hemodynamic monitors will be discussed in this lecture.

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MACRAs Physician-Focused Alternative Payment Model (PF-APM) Options: A 2018 Multispecialty Perspective

Asa Lockhart

NOTE:

For previous attendees to this RCL, the updates begin on page 5. For new attendees, I am including the detailed description here for a thorough discussion of the basics and foundations. The presentation will review the basics but will also concentrate on current trends and implications.

BACKDROP

The Medicare Access and Chip Reauthorization Act (MACRA) replaced the Sustainable Growth Rate (SGR), which had been renewed numerous times with a series of patches. MACRA created two options for compliance. The first path, which does not require assumption of insurance risks, is the Merit-based Incentive Payment System (MIPS) that consolidated existing quality programs and added clinical practice improvement. The other fork in the new highway is the Alternative Payment Model (APM) with one subgroup variant being Physician Focused (PF-APM) where the physician accepts some level of risk for services and expenses over which they have some control. One should be aware that another variant is the Hospital Focused (HF-APM), but this presentation is focused on PF-APMs with an emphasis on potential multispecialty models that in a particular community enable anesthesiology practices to participate; so the goal of this presentation is to increase awareness of subtle opportunities that may be developed by others in the community where anesthesia may play a role. Other presentations at this meeting will focus on more anesthesia specific options (e.g., Perioperative Surgical Home). While physicians may have a wide range of experience with the MIPS elements, most have (at a minimum) a grasp of the basic concepts and foundations. In contrast at the other end of the numerical spectrum, few physicians have any idea how APMs might apply to their practice. Some APM options such as the Patient Centered Medical Home have been around for some time yet have not penetrated the market in many parts of the country, especially in smaller practices that may lack infrastructure or feel they have too many immediate production pressures to take the time to apply the concept.

Our current system is oriented towards intervention and is often focused on the anecdotal, and what is possible, while emerging models emphasize prevention and evidence-based or experientially-based utility. Neither camp wants to harm patients; they just have a different idea of how to get there. The HMOs of the 90s were viewed as being solely focused on finances (Just say no!), and the models now under discussion are focused on balancing optimization of outcomes, costs, and patient satisfaction. While we may do a great job of diagnosing, managing, and treatment of chronic diseases, we do not do as well preventing their development, managing or preventing their complications, and differentiating the efficacy of various options. There are multiple reasons. There ae silos of care where the emphasis on focused on the part a particular physician or specialty may play. There may be disconnects between the consumer (the patient) and the producer (not limited to physicians) so questions of costs and utility are often not asked. Does the test need to be done? Before one commits to a procedure, the questions of how often it meets expectations, at what costs, and at what risks are not valued by the current system. Additionally, there is no prerequisite that the patient has an affirmative responsibility to optimize their personal health. And finally, the system itself is a barrier.

BARRIERS

The driving concepts behind APM begin with the realization that existing models do not address barriers to redesigning services that provide a higher-value of healthcare. Before one can innovate, they must have the latitude to reallocate precious, but limited, resources and have space to make the transition. Two commonly mentioned barriers are either no or inadequate payment for many high value services and financial penalties for delivering a different mix of services that result in a lower costs to society.

There are many services that may benefit patients either through enhanced personal time in an alternative

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model or the freedom to pursue lower cost options with improved or neutral outcomes. We are not paid to take the time to counsel patients on lifestyle and the various options available to them that are time-intensive or require relational databases that may not exist and would be expensive to establish. Physicians are best positioned to evaluate alternative delivery systems, optimize cost delivery settings, and different combinations of services and providers. But that takes time, requires support resources (human and financial capital) that are not made available currently, and alignment of incentives that focus more on outcome, utility, and coordination rather than component production and what is merely possible.

During the transition from the current model to the emerging models, one still has to keep the doors open; this is one laudable goal not supported by United Way! If the current transactional practice revenue decreases by delivering fewer or lower cost services, a transitional strategy will be necessary to shield operating losses since the changes will not likely be proportional and may be even be higher in a temporary dual system.

There are a number of examples where no or inadequate payment for high-value services are a barrier by both Medicare and private health plans for services that would benefit patients and help reduce avoidable spending. For example, responding to a phone call about a symptom or problem might help patients avoid a more expensive ER visit. There is no recognition for the value of coordination between primary care physicians and specialists or taking ownership for the coordination of care and time spent to avoid ordering duplicate tests and prescribing conflicting medications. There are no incentives for the time that it takes community and emergency physicians to facilitate discharge planning in emergency departments that could enable patients to be safely discharged without hospitalization. Some high-risk patients might respond to a proactive early-stage telephone call that would optimize preventive care and lower comorbidities. Deconditioned patients in particular, and many patients in general, would benefit from prehabilitation but there is no support for development of this intervention. Smoking cessation reduces respiratory complications and length of stay as well as improvement in wound dehiscence. Current paradigms do not recognize these benefits while a well-designed APM would embrace such opportunities.

There are several ways that financial penalties for delivering a different mix of services may pose a transitional risk to physicians. As the health of patients improve, they will require fewer services and may avoid developing a disease. They would be expected to have fewer complications or lower comorbidities that require intervention. Even though there may be fewer or less costly procedures, the cost of running a practice generally does not decrease; rent and utilities are not pegged to quality of care or resource utilization. Since most of the savings to the system from APMs do not come from physician payments, the savings can be realized without financially targeting and implicit penalization of physician practices for delivering a societal goal. With healthier patients, physician practices would receive less income under current approaches. This could be the greatest conflict with our current FFS system, and one essential foundation and question that must be answered if we are to make substantial progress as APM options are developed.

With these barriers, what are the prerequisites for successfully creating new options? The Center for Healthcare Quality and Reform has identified three characteristics for enabling change:

1. Flexibility in Care Delivery
   In order to overcome the barriers discussed above, an APM must provide enough innovative flexibility—with a patient centric focus—to deliver a mix of services that makes sense but is not covered within today's payment methodologies so that we can provide a new path to efficiency and effectiveness.

2. Adequacy and Predictability of Payment
   As one contemplates navigating the coming changes, this characteristic is essential so that the financial resources will be available to start the process with confidence that the return on investment (ROI) will be there. The fear at the end of the dance is that we will be out there alone. If we are successful, there is a concern that some politician will award our victory to a political crony. So the rules of engagement must deliver adequate and predictable resources to

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allow physicians to create the alternative structures that will identify high-quality service opportunities whose costs include both start-up and transitional financial risk to physicians. The exposure must be both risk-adjusted to recover their investment yet be within an acceptable financial risk corridor for small businesses and medical practices.

3. Accountability for Costs and Quality That Physicians Can Control
   The program design must be structured to assure non-provider stakeholders, (patients and payers) that the outlays will be controlled or reduced with the implicit assumption that quality will at a minimum be maintained if not improved. However, the beauty of the "Physician-Focused Payment Models" is that individual physicians should only be at risk for those aspects of spending and quality they can materially control or influence. This is similar to Activity-Based Accounting where one has to have control over the activity for it to be in that cost center.

EXAMPLES OF POTENTIAL MODELS

In the document A Guide to Physician-Focused Alternative Payment Model prepared by the AMA and the Center for Healthcare Quality and Payment Reform, they identify seven potential models. A basic graphic of the various models is shown in Figure 1 at the end of this article. Since this is an emerging concept and there are no other resources that synthesize the material as well as this publication, I will rely upon the following excerpts from that comprehensive document to stimulate your evaluation of how one of these models could benefit your practice and your community:

"APM #1: Payment for High Value Services where physicians are paid for delivering desirable services that are not currently billable in order to avoid the need for patients to receive other, more expensive services… A physician practice would bill and be paid for the time and resources needed to apply appropriate use criteria and engage in an education/shared decision-making process with patients in order to determine the most appropriate diagnostic tests to use… In contrast to a typical shared savings program, an individual physician practice's payment would not be explicitly tied to how much money that practice saved the payer. Instead, the physician practice would be paid adequately to deliver appropriate services, and the payer would save money by spending less on avoidable services (for the patients in all participating practices)." Could such a program be a component of an early stage PSH (e.g., pre-op testing protocols, prehabilitation, smoking cessation)?

"APM #2: Condition-Based Payment for Physician's Services … where a physician has the flexibility to use the most appropriate diagnostic or treatment option for a patient's condition without reducing the operating margins of the physician's practice… the practice would have the flexibility to use the payments for whatever combination of services were most effective –office visits, phone calls, emails, support from non-physician staff, etc." These would replace E&M codes limitations with monthly payments targeted to chronic conditions. For a primary care physician with global risk, potentially a seamless transition into a PSH may become an opportunity or smoking cessation achieved as a result of a PSH may enhance the management of a COPD patient.

"APM #3: Multi-physician Bundled Payment…where the goal is to give multiple physicians who are providing services to the same patient the flexibility and resources needed to redesign their services in coordinated ways that will improve quality and reduce the costs of diagnosis or treatment… Patients would benefit because the physicians delivering their care could work together in a more coordinated way and use the additional resources and/or flexibility under the bundled payment to deliver different types or combinations of services that cannot currently be provided. The payer would benefit because the new payment would enable the physicians to deliver care more efficiently, order fewer or lower-cost services from other providers, and/or reduce the number of complications for their patients. The physician practices would benefit by having the resources and flexibility to deliver the most appropriate services to patients in a coordinated way without concern about which services will generate more revenue for the individual practice." This model has a very high potential as well as likelihood for participation by anesthesiologists since it offers major benefits and aligns incentives for all stakeholders to coordinate care by virtue of shared risks and rewards. This model would allow acceptance of risks for professional services, especially in

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circumstances where the facility partner is unable or unwilling to participate.

APM #4: Physician-Facility Procedure Bundle… where the goal is to give physicians greater ability to choose the most appropriate hospital or other facility to deliver a particular procedure and to work with the facility to improve efficiency and quality in delivering that procedure...The patient would benefit by being able to receive high quality care at the lowest-cost facility and to receive coordinated and efficient care from the physician and facility staff. The payer would benefit because the Alternative Payment Entity could accept a lower payment for the bundle than the total amounts that would have been paid separately to the physician and facility under current payment systems. The physician practice could benefit by using the bundled payment to cover the costs of services that are not current billable or do not receive adequate compensation, and by receiving compensation for changes in the physician's services that reduce the costs of the services delivered by the facility." This model has a very high potential as well as likelihood for participation by anesthesiologists since it offers major benefits and aligns incentives for all stakeholders for both surgical and obstetrical management. I would note that the marked variability in hospital charges will be a significant driver and an opportunity to engage payers in many communities. Since anesthesiologists may cover multiple sites and know the inside baseball, they may be in a unique position to help select the most efficient or progressive facilities (e.g. stable facilities with good policies and procedures versus one with high turnover and poor/unenforced policies).

APM #5: Warrantied Payment for Physician Services…where the goal is to give physicians adequate payment and flexibility to redesign care in a way that will prevent complications and reduce the spending needed to treat them… In contrast to penalties that reduce payments when complications occur, the warranty approach provides greater upfront resources so that care can be redesigned to reduce complications. In addition, although no additional payment is made when complications occur, the cost of treating some complications is built into the warrantied payment amount, so the physician practice is not financially penalized when a small number of complications occur, but it is rewarded if it can eliminate most or all complications." This could be a potential variant of a monetization strategy for a PSH.

APM #6: Episode Payment for a Procedure… where the goal is to give physicians and other providers the ability to deliver all of the care during and after delivery of a particular procedure or treatment in a coordinated, efficient way… all of the costs involved in performing hip or knee surgery during an inpatient hospital admission, delivering rehabilitation services after surgery, and treating any post-operative complications. The payment amount would be higher for patients with comorbidities and functional limitations that would require more inpatient or post-acute care. The payment amount would be adjusted based on measures of quality and outcomes for the patients." This essentially takes Models 4 and 5 plus adds the post-discharge management and re-admission risk components. While optimally this might be a later more mature option after experience in Models 4 and 5, market and political pressures may make this the initial option. The current Comprehensive Care Joint Replacement (CJR) has some of the elements of this APM but it is currently limited to hospitals. It could be revised so that the episodes could be managed by physicians ; however, at the time of this draft, it is *not* on the APM list under the proposed rules!

APM #7: Condition-Based Payment… gives physicians and other providers who are delivering care to patients for an acute or chronic condition the flexibility and accountability to deliver the most appropriate treatment for the patient's condition in a coordinated, efficient, high-quality manner." One of the examples was for a Condition-Based Payment for Post-Acute Care Following a Hospitalization for spine surgery. This model may be a separate initiative, perhaps with different provider groups, as either an early stand-alone or as an independent but complementary part of Model 3 or 4, but an integral part of Model 6. The post-discharge management of a PSH patient could be a stand-alone approach in some communities and circumstances. In the procedural arena, I do not see this as a long-term option and would predict a rapid integration with one of the other models.

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CHANGES PROPOSED FOR 2019, SUMMER 2018 "SURPRISES," AND APM UPDATES

As in earlier years, most of the 2019 changes are still in the MIPS bucket, but there are some that apply to the APM realm. The earlier requirement that practices bear "more than nominal risk" for monetary losses, which was defined as the lesser of 8% of total Medicare revenues or 3% of total Medicare expenditures will be in the second year of its two-year extension. There had been earlier discussion of increasing this to 15% so this was good news, and at this time I am unaware of any current proposed changes. On June 13, 2018, HHS Secretary Azar announced none of the twelve APMs put forth by PTAC will be implemented as proposed. PTAC's comments and recommendations are the first step in the process and then provided to the Secretary for consideration and approval so this announcement was a disappointment to many and places those plans in limbo.

The ACS-Brandeis Advanced APM was submitted by the American College of Surgeons and accepted in May 2017 for limited-scale testing and is very applicable to anesthesiologists. The link to their website for a deeper dive is: https://aspe.hhs.gov/system/files/pdf/253406/TheACSBrandeisAdvancedAPM-ACS.pdf. This model has the highest potential to relate to anesthesia at this point in time. One of the four stipulations by PTAC at the time of approval was that "the algorithms and construct of the episode grouper, which is the lynchpin of the model, should be made publicly available; and a mechanism should be in place for continuous update of the grouper so that it remains current with advances in healthcare." It is my understanding that they are working to create aspects of the model as a public utility for all to use.

In May one of the prominent State Surgical Quality Collaboratives met with CMMI to promote a multi-state pilot based on PSH and ERAS principles. The meeting reportedly went well and is still in the process of evaluation. Hopefully, during the live presentation at the meeting, I will have updates, and subject to schedule changes hope to have Dr. Frank Opelka from the ACS and other project leaders join us where they can answer questions on their model in the first person.

Two summer "surprises" may impact or predict trends in the development of APMs. On July 26, CMS proposed "site neutral payments" whereby payments for clinic visits by hospital and ambulatory physicians would be paid at the Physician Fee Schedule (PFS) rate beginning in 2019. This is the most common code group paid by Medicare and will result in a 2/3 cut to hospital and ambulatory practices that will gut the primary foundation for facility-owned medical practices. Comments by one hospital-friendly consulting giant noted that this might be a mixed blessing because it would force physicians to come to the table to quit resisting ACO and bundled payment initiatives in order to stabilize the system. This comes on top of the loss of 340b pharmaceutical income and potential impact of compensation changes to E&M codes. These developments total well over $1B and will place extreme financial pressure on facilities thereby highlighting and placing pressure on compensation for service agreements as they try to rebalance their portfolio of services to achieve budgetary stability in a very narrow time frame.

On August 9, the other game-changer was announced by CMS Administrator Seema Verma, which was "Pathways to Success" for Medicare Shared Savings Program (MSSP) ACOs. She noted that it was time for the program to evolve. The evolution is the number of tracks would be consolidated from the current four to two: one "basic," the other "enhanced." The structure of the "basic" path is two years of "upside-only" shared risk followed by three years of gradually increasing two-sided risk. The fifth year in the basic track would meet the standard to qualify as an advanced alternative payment model. The current Track One option with upside-only risk in multiple three-year cycles is gone. The key factoid is that 82% of MSSP participants are Track One and wrote a letter in February 2018 to Administrator Verma that they are not ready to assume risk albeit the sixth year (second cycle) for many of them. This will call the question for many and may result in an accelerated and disruptive transition to risk products and maturation of existing ACOs since they will want to qualify as an "advanced" APM. These two developments will certainly qualify as disruptive innovation! However, now is the time to pursue one of the seven models above and evaluate your options for the future – be the leader as you offer constructive solutions to their crisis and a pathway to success.

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IN CONCLUSION

As this document is updated in August, we are in the current phase of rule-making and the ASA and AMA have several units diligently studying options to preserve your future and search for options. There may well be other surprises between this draft and our meeting in October. There are multiple system options, which may be payer-designed, facility-designed, or physician-designed. Close your eyes and make a guess; of those three options, which avenue is most likely to design an optimal system that treats our colleagues and our patients in the most equitable manner? The options presented above will in all likelihood evolve with both the final rulemaking and system adaptation. Hopefully, the ACS-Brandeis model is the first of many that will be developed in the procedural arena, and the SSQC will become a second option. I hope to have updates to share with you on both of them in October. Secretary Azar's action is slowing the process and creating ambiguity, but the summer "surprises" signal a potential escalation and alternative pathways. Although I am skeptical that many anesthesia practices will benefit, please note that the proposed rules provide for an exclusion with a neutral score (0%) update if you have less than $90,000 in *allowable* charges or less than 200 patients that are enrolled in *regular* Medicare; Medicare Advantage does not count in this deliberation. This continues in the proposed 2019 rulemaking. However, even if you qualify, I would encourage you to assess some of the options above; the market and your future are moving in that direction!

I would like to acknowledge briefing materials contained in the publication A Guide to Physician-Focused Alternative Payment Models* jointly produced by the AMA and the Center for Healthcare Quality and Payment Reform that provided the generous excerpts, direction and resources for this article. In particular, I would like to thank Sandra Marks (AMA) and Harold Miller (CHQPR) for their copyright permission in general and allowed use of generous excerpts and edits in particular. For a deeper understanding on how you can take control of your future, this excellent resource may be accessed at:
http://www.chqpr.org/downloads/Physician-FocusedAlternativePaymentModels.pdf

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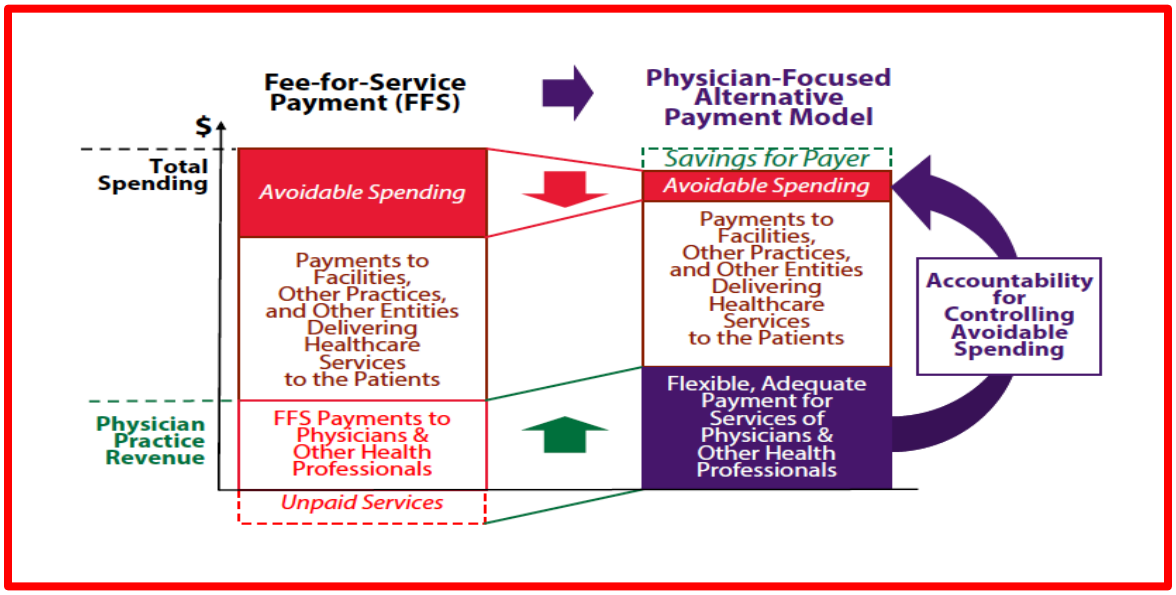
Figure 1: Basic model



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Enhanced Recovery After Surgery in Infants, Children and Adolescents (ERAS): A Multimodal Approach to Pain Management

Charles Berde, MD, PhD Boston, MA

A. Learning Objectives:

1. Outline a roadmap for pediatric ERAS based on adult outcomes research.
2. Review roles of multiple components of pediatric ERAS: pre-op preparation, regional anesthesia, adjunctive medications, opioid sparing, early mobilization, home transition.
3. Survey the status of pediatric ERAS programs for specific patient groups
4. Evaluate challenges and barriers to ERAS that are uniquely pediatric.
5. Consider the role of ERAS in the pediatric surgical home
6. Outline the tension between standardized care and personalized care.
7. Propose future directions for pediatric ERAS research.

B. ERAS in Adults

Enhanced Recovery After Surgery (ERAS) programs in adults arose from the pioneering research, vision, and advocacy of Henrik Kehlet and his collaborators. Peri-operative care is regarded as a form of acute rehabilitation aimed at accelerating recovery and preventing or diminishing patterns of disability and complications that have traditionally occurred after surgery. Disability is exacerbated by immobility, catabolism, inflammation, delayed enteral feeding, bowel dysfunction, over-hydration, and by traditional practices and dogmas. Pain treatment can be a double-edged sword. While better analgesia can accelerate rehabilitation, improve sleep, and blunt stress responses, analgesics can generate risks and side-effects that can impede recovery. In particular, opioids were identified as contributing to peri-operative disability and delayed recovery, and multi-modal opioid-sparing analgesic approaches were advocated.[1-8] The term "multi-modal analgesia" implies combinations of agents acting on different targets.

Through the 1980s-2000s, a series of prospective clinical trials challenged many prevailing beliefs and practices regarding postoperative care, and provided evidence for several individual practice changes associated with accelerated and/or improved recovery. Many traditional practices were shown to unhelpful, including routine bowel preparation, prolonged fasting, routine use of nasogastric tubes and bladder catheters, bed rest, and treatment of anesthetic induced hypotension with fluid boluses rather than vasopressors. Beginning with colorectal surgery and then extending into other adult surgical conditions, collaborating groups developed care bundles and a program for ongoing collaboration and assessment. The ERAS Society was formed to develop care bundles and foster multicenter continuous quality improvement (CQI) for multiple types of surgery, with approximately 20 elements that span preoperative, intraoperative and postoperative care.

ERAS is about more than selection of particular medications, fluid management strategies, or surgical techniques; it involves an overall team-based collaborative approach to care and CQI. The patient is an active participant, not a passive bystander.

C. Bundles: the Good, the Bad, and the Muddled

A care bundle is defined by the Institute for Healthcare Improvement (IHI) as "a structured way of improving the processes of care and patient outcomes: a small, straightforward set of evidence-based practices — generally three to five — that, when performed collectively and reliably, have been proven to improve patient outcomes." [9] Care bundles have had notable successes; commonly cited examples include: reducing central line infections, ventilator associated complications, sepsis, and obstetric / perinatal complications, improving surgical safety in developing and developed countries, and in prolonging life in patients with cystic fibrosis. As noted by IHI, care bundles should ideally involve individual components that are each supported by Level 1 evidence.

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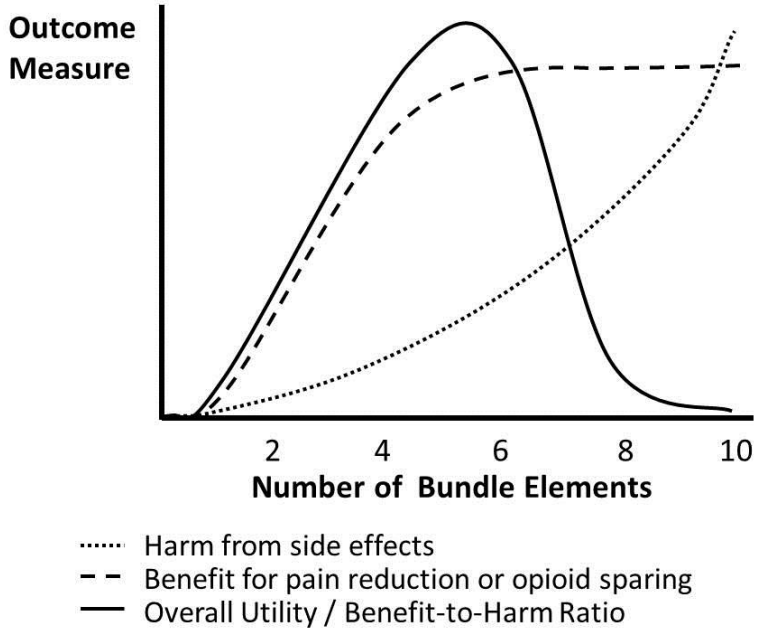
Care bundles offer great benefits. Are the potential downsides? First, even if components of a proposed bundle are supported by strong evidence, it does not necessarily follow that these components will provide additional benefit when combined. In outcomes research and implementation science, there is a crucial role for assessing balancing measures along with primary outcome measures, and this seems especially relevant when considering multi-modal analgesia. The presumption is that analgesics acting on multiple targets will provide additive or supra-additive pain relief, while avoiding some of the dose-limiting side-effects or toxicities of higher doses of each single agent, analogous to combination chemotherapy regimens for cancer. Consider the following example of a proposed multi-modal analgesic bundle.

Suppose that you are approaching a particular type of surgery for which previous single-intervention clinical trials showed level 1 evidence for meaningful benefit of gabapentin, low-dose ketamine, acetaminophen, NSAIDs, and wound infiltration on postoperative pain scores, nausea and vomiting, opioid use, length of stay, patient experience measures, and rehabilitation. (Each of these treatments showed significant efficacy in multiple single-treatment RCTs against placebo.) Based on this literature, you now propose to study a hypothetical multimodal protocol with 4 treatment groups: 1. Gabapentin alone, 2. Low dose ketamine alone, 3. Gabapentin-ketamine combination, and 4. Placebo. All 4 groups get acetaminophen, NSAID, and local anesthetic wound infiltration. Your findings might be the following: a. with acetaminophen, NSAID, and wound infiltration for everyone, groups 1 and 2 show smaller effect sizes for pain scores against group 4 than in previous single-treatment trials, due to the strong benefit of wound infiltration, NSAID, and IV acetaminophen, b. patients in group 3 have marginally better pain scores or marginally reduced opioid use compared to other groups, but MUCH greater delirium, somnolence, poor ambulation and frequent falls. Note that gabapentinoids can generate an adverse pharmacodynamic interaction with opioids, i.e. increased somnolence and respiratory depression[10], so that opioid-sparing per se does not guarantee a reduction in adverse events. Note also the general problem with studying incremental improvements: it's likely that subsequent add-on therapies will have smaller effect sizes compared to the initial "low hanging fruits". The preceding paragraph is not meant to discourage use of care bundles in general or multi-modal analgesic bundles in particular, only to point out that they can be complicated to study, and more is not always better.

Figure 1 depicts a rough heuristic model of how adding more bundle elements to a multi-modal regimen might not always result in additional benefit over harm.



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D. Standardized versus Personalized - Are They Incompatible?

The adult ERAS consortium has generally espoused the view that, for each type of surgery, best approaches can be identified, and care should be standardized. Standardization is a common theme in the quality movement, and in several "philosophies" arising from manufacturing and operations research, e.g. Toyota processes, Six Sigma, Lean, Lean Six Sigma, High Reliability….

Standardization has many advantages. Conversely, while one Toyota Corolla engine or chassis is nearly identical to the next one in the assembly line, two patients having the same operation vary in a number of clinical, genetic, and psychological domains that can dramatically influence outcome. The best bundle for one patient might not be the best bundle for another patient. Among adults undergoing surgery, a number of genetic, clinical, and psychosocial variables account for considerable variance in postoperative pain severity, opioid use, length of stay, and rehabilitation outcomes. Patients with chronic pain, longstanding opioid use, catastrophizing, anxiety, and depressed mood may benefit from some additional tailored interventions that would be unnecessary for patients without these characteristics. For example, Brummett and Clauw have described features denoted as "fibromyagia-ness" that predict greater pain severity, greater opioid use, or worse rehabilitative outcomes among adult surgical patients.[11, 12]

E. What are the Overlaps and Interrelationships Among ERAS, Primary Care/Medical Home, Perioperative Surgical Home, Acute Pain Services, Regional Anesthesia Services, and Preoperative Clinics….?

To quote the late Speaker of the U.S. House of Representatives Thomas "Tip" O'Neill, Jr., "All Politics is Local." In a word, it's complicated and controversial. [13-16] Local factors influence team composition, champions and leaders, and roles of participants. What works best for a large pediatric service in a tertiary children's hospital might not be optimal for a small pediatric service in a general hospital. Adding new layers, new teams, and more hand-offs does not necessarily add value. In the live lecture, there will be some examples and opinions.

F. **Pediatric multi-component ERAS Studies to Date**

Pediatric literature on multi-component ERAS is relatively limited and preliminary. Many CQI efforts are not formally named as ERAS-like, and may escape medical literature search under those keywords. Overall, there is support in pediatric literature for some components of the ERAS program, but much less evidence for comprehensive bundles in pediatric surgical care.

Individual components of perioperative care that have favorable pediatric studies (either alone or as part of a bundle) include: minimally invasive surgical approaches for several types of operations, limiting or omitting extensive bowel preparation, early enteral feeding, early removal of urinary catheters, prophylactic anti-emetics, several blood conservation strategies, and early mobilization. [17 -33]

An extensive body of pediatric RCTs provide support for analgesic efficacy and/or opioid sparing from a wide range of individual systemic analgesics and regional anesthetic interventions. These include studies of acetaminophen and NSAIDs by multiple routes of administration, a range of peripheral nerve blocks, single shot caudal blocks, and continuous peripheral or epidural infusions. [34, 35, 36] Opioid sparing is a useful pragmatic surrogate endpoint for pediatric analgesic trials. [34]

What about pediatric studies of multi-modal analgesic combinations? Acetaminophen-NSAID combinations have evidence for efficacy and effectiveness.[37-38] Multiple pediatric studies support additional benefit of oral, parenteral or rectal NSAIDs when combined with regional anesthesia, either via wound infiltration, peripheral block, or caudal block[39-40]. Studies of additives to caudal local anesthetics have shown mixed results. Although clonidine and other additives do prolong analgesia in multiple studies, the extent of prolongation has been quite variable, and the optimal dose remains a matter of dispute. [41] Dexamethasone has impact in prevention of nausea, but systematic reviews found modest analgesic impact after tonsillectomy. Adult studies indicate that dexamethasone prolongs peripheral nerve blocks either by perineural administration or when administered systemically. At Boston Children's Hospital, it is common practice to administer dexamethasone intravenously for many groups of patients having peripheral nerve blocks. Pediatric studies to date of gabapentin and low-dose ketamine as add-on components of a multi-modal regimen have yielded mixed results. [42-45]

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Preoperative preparation programs have demonstrated effectiveness in reducing perioperative anxiety and preventing adverse postoperative behavioral sequelae[46-49]. Preparation should be individualized in several domains, as outlined previously.[47-49] Additional studies are needed to better define roles of preoperative education, parental guidance, fear reduction, and positive coping in pediatric ERAS programs for specific types of surgery and for children of different ages and with different comorbidities. It seems plausible that web-based programs and tele-health programs will emerge as cost-effective approaches to pre-operative preparation. Recent studies suggest roles for virtual or augmented reality interventions in management of perioperative anxiety.

Recent reviews[21-22] and recent lectures[18-19] by Brockel at the Society for Pediatric Anesthesia and Society for Pediatric Pain Medicine surveyed available literature on pediatric multi-component ERAS programs. Shinnick et al included articles in which at least 4 of the 20 ERAS Society elements were implemented.[21] They found 5 such studies, including 1 retrospective and 4 prospective cohort studies. Methodologic limitations were identified.

Scoliosis Surgery

Traditionally, adolescents undergoing scoliosis surgery had a prolonged course of recovery and the highest postoperative opioid utilization among all pediatric operations. Two groups have recently reported on outcomes of ERAS programs for posterior spine fusion for adolescent idiopathic scoliosis, using slightly different care bundles. Muhly et al[33] reported on a program at Children's Hospital of Philadelphia with multiple components, including intraoperative IV methadone, addition of gabapentin and ketorolac, early conversion from PCA to oral opioids, accelerated ambulation, and early removal of tubes. Average length of stay was reduced from 5.7 days to 4 days after implementation of this pathway. Thomson et al reported on a program with different analgesic components for scoliosis surgery at Children's National Medical Center in D.C. as part of a perioperative surgical home framework.[16] Components of their care bundle included: limiting crystalloid infusion, blood conservation and minimizing transfusion, pre-operative laxative regimen, intraoperative dosing of either IV methadone or intrathecal morphine, prevention of hypothermia, early removal of tubes and lines, early conversion to oral opioids, and early mobilization. In their series, median length of stay reduced from 5.2 to 3.4 days after implementation.

Urologic Surgery [26,50]

Pediatric urology practice has increasingly emphasized minimally invasive approaches, earlier removal of catheters, earlier mobilization, and emphasis on non-opioid analgesia, including NSAIDs, regional anesthesia, and selective use of anti-bladder spasm medications. Durations of hospital stay for pyeloplasty, ureteral reimplantation and hypospadias have been steadily reduced over the past 20 years. Rove, Brockel and colleagues recently reported on implementation of ERAS for complex pediatric urologic reconstructive procedures. Notably, they found improvements overall and specifically found an association between outcomes and adherence to ERAS elements.[51]

Appendectomy[28]

Duration of hospital stay has been steadily reduced for both non-perforated and perforated appendicitis. There is support for non-opioid analgesia, avoidance of nasogastric tubes, and early feeding[28]. Hospital stays of 1 day are now common for uncomplicated appendicitis. A majority of children with uncomplicated appendicitis can be comfortable postoperatively with very sparse opioid dosing; recent records at Boston Children's Hospital recording a median of 1 prn opioid dose.

Colorectal Surgery[17, 20-24, 29-31,52]

Traditionally, children undergoing colorectal surgeries at many pediatric centers had extensive bowel preparation, prolonged fasting, prolonged use of naso-gastric tubes and bladder catheters, and little emphasis on early mobilization or early enteral feeding. Several groups in Europe and in the U.S. have reported on multi-component programs for accelerated recovery after pediatric intestinal surgeries.[17, 20-24, 29-31,52] Much of the emphasis in these reports has been on nutrition, removal of tubes, fluid management, mobilization, and minimally-invasive surgical approaches. Opioid sparing analgesia has been a common theme.

Orthopedic Surgeries on the Extremities

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Regional anesthesia has an increasingly central role in facilitating accelerated recovery for pediatric extremity surgeries. As an example, at Boston Children's Hospital, with a very pro-active regional anesthesia program, over the past 15 years, anterior cruciate ligament repair has changed from routine overnight admission to > 95% day surgery.

Pectus Excavatum

Muhly et al[53] surveyed analgesic practices following Nuss operations. Pediatric centers vary widely in their analgesic practices. Thoracic epidural analgesia remains a common approach, though its use appears to have declined in recent years. Prospective studies of multi-component analgesic regimens are in progress.

G. Should ERAS Efforts Focus on Healthy Children or Medically Complex Children?

My view is "both". Common operations in relatively healthy children afford opportunities for standardization, and small increments in length of stay can have significant impact on overall health care costs. Care bundles for tonsillectomy, adenoidectomy, ureteral reimplantation, pyeloplasty, and hypospadias repair have resulted in meaningful reductions in length of stay and costs, generally without incremental increase in readmissions or risk. Studies of outcomes after tonsillectomy found that young age and comorbidities were associated with increased risks after early discharge, and suggest a safety benefit from more prolonged observation.[54]

Children with medical complexity, especially those with neuromuscular and developmental conditions, have frequent and prolonged hospital admissions for both medical and surgical diagnoses, especially following scoliosis surgery.[55] Comorbidities such as chronic respiratory dysfunction, epilepsy and bladder dysfunction were associated with prolonged hospital stay and increased costs. Overall, hospital readmissions are relatively infrequent following most pediatric operations. Structured follow-up interventions might prevent some pediatric readmissions.[56] Children and adolescents with psychiatric illness have longer than expected hospital stays, higher opioid use, and higher pain scores following surgery.[57]

H. How Should Pediatric ERAS be Implemented and Studied?

Progress is likely to come from both "bottom-up" and "top-down" efforts, i.e. a blend of innovative pilot projects from single institutions with highly integrated multidisciplinary teams along with larger multicenter efforts with backing and funding from national or international organizations. In my view, it will be helpful for our national and international organizations (a partial list includes: Society for Pediatric Anesthesia, Society for Pediatric Pain Medicine, American Academy of Pediatrics Section on Anesthesiology and Pain Medicine, European Society of Paediatric Anaesthesiologists, Association of Paediatric Anaesthesiologists of Great Britain and Ireland, …) to dedicate resources to support partnerships with the ERAS Society and with a range of national and international pediatric surgical societies. Some of these collaborations are in progress already; for example, between the American Academy of Pediatrics Section on Anesthesiology and Pain Medicine and the American College of Surgeons National Surgical Quality Improvement Project Pediatric (ACSNSQIP-P). A Pediatric Perioperative Outcomes collaborating group has recently published recommendations for core outcomes for pediatric CQI efforts.[58]

I. Conclusions

Pediatrics ERAS programs are in early stages of development but are likely to make progress by following the basic principles described by Kehlet and other pioneers of ERAS in adults. There are age-related differences in physiology, in metabolic and inflammatory responses to surgery, in diseases, comorbidities, and surgical diagnoses, and in the child's understanding and ability to participate actively in their recovery. Implementation, research, and measurement should follow best practices. It will be crucial to understand how better to engage the family and the child as partners in these efforts, and to measure success both in terms of costs, resource utilization, and consensus outcome measures, but also in terms of the child's and family's experience of care.[59]

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Is it Time to Ask the Burning Question:What is the Fire Risk?

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In the days when flammable anesthetic agents were frequently used, fire and explosion hazards were of paramount importance to the anesthesiologist. Although most operating room personnel do not consider fires a major safety hazard, in reality many fires occur in the operating room every year. It has been estimated by the ECRI (Emergency Care Research Institute) that there are approximately 500-600 operating room fires every year in the United States. About 10% of these produce serious injury to patients or operating room personnel. Therefore, it is incumbent upon all those who work in the operating room to be aware of how to prevent fires and what to do if one should occur.

The Fire Triad

In order for a fire to occur, three elements must come together at the same time. These elements are known as the fire triad. They include; (1) heat, or an ignition source; (2) fuel; and (3) an oxidizer. In the operating room, the heat source is commonly the electrosurgical unit (ESU), a laser, or a fiberoptic light cord. There are many elements that can provide fuel for an operating fire. These include paper drapes, plastics, gauze dressings, endotracheal tubes, the patient's hair, linens and gel mattress pads. The common oxidizers in the operating room are oxygen, air and nitrous oxide.

A fire is actually the chemical reaction of fuel rapidly combining with oxygen with the resultant release of heat and light energy. Prevention is clearly better than extinguishing a fire. Fires can be prevented by isolating the various legs of the fire triad. This can be done by minimizing the amount of oxygen or nitrous oxide that is delivered to the patient. It should be remembered that oxygen and nitrous oxide support combustion equally well. Therefore, a mixture of 50% nitrous oxide and 50% oxygen is virtually the same as 100% oxygen. Oxygen and nitrous oxide are oxidizers and not explosive gases. Examples of explosive gases are cyclopropane, hydrogen and methane.

Keeping heat sources away from flammable materials is another important safety precaution. It should be remembered that an ESU tip remains hot for a few seconds after the instrument has been deactivated. Similarly, ends of fiberoptic cables can retain significant amounts of heat after being disconnected from their light source. Therefore, it is important to be careful where one places the end of a fiberoptic cord. Lasers should be immediately placed in standby mode and ESUs placed in an appropriate holder when they are not in use. Finally, volatile liquids must be allowed to dry since the vapors can be quite flammable.

There are many dangers from a fire. Obviously, heat can cause burns to the patient or operating room personnel. Of great importance is that smoke from the fire can necessitate that the room be evacuated. Depending on what is burning, toxic products can be given off by the combustion of various materials. Many of these products such as carbon monoxide, ammonia, cyanide, isocyanates and hydrogen chloride are quite toxic. They can cause chemical and physical irritation to the tracheal-bronchial system but more important, they can cause asphyxia.

Being prepared for a fire and knowing what to do if one should occur are key elements of a fire safety program. Knowing the location of fire extinguishers and having fire drills will enable all operating room personnel to become familiar with proper procedures. Operating room personnel should be familiar with the location of alarm boxes, gas shut-offs, and fire extinguishers. People should realize that it is important to immediately call for help, decide who is going to fight the fire, when it will be appropriate to leave the room and how to care for the patient during the fire. If drapes are burning, they must be removed as most OR paper drapes are impervious to water. Therefore, the fire will burn on the underside and dousing them with water will not extinguish the fire. Having sources of battery powered portable lighting available is also extremely important.

Types of OR Fires

Operating room fires can be classified into two types: those that occur in the patient and those that occur on the patient. Fires that occur
in the patient would include airway fires such as ignition of an endotracheal tube or a fiberoptic bronchoscope or an intra-abdominal fire. Fires occurring on the patient include ignition of drapes or surface fires that are fueled by supplemental oxygen.

One of the ignition sources in the operating room is the laser. Laser is an acronym for Light Amplification by Stimulated Emission

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of Radiation. The laser light is produced when energy is aimed at the "lasing medium". The lasing medium then becomes the name of the laser. For instance, electrical energy aimed at carbon dioxide molecules is a carbon dioxide laser. The light produced by a laser is known as coherent radiation. Coherent light can be focused into very small spots with a very high power density.

There are a number of different types of lasers. These include the argon laser which is used in eye and dermatologic procedures. The energy produced by this laser is absorbed by hemoglobin and melanin and has a tissue penetration of 0.5 to 2.0mm. The KTP (frequency doubled YAG) laser produces energy that is absorbed by hemoglobin and has a tissue penetration of 0.5 to 2.0mm. The dye laser has wave lengths that are tunable for different applications. The Nd:YAG laser has tissue penetration of 2-6mm and can be used for tumor debulking particularly in the tracheal-bronchial tree. Its energy can be transmitted through a fiberoptic cable which enables it to be used in a "contact" mode. The CO_2 laser produces energy that is absorbed by water. It is used where precision is needed and has negligible tissue penetration. Also there is minimal heat dissipated to the surrounding tissues. The helium neon laser (He-Ne) is a very low power laser. Its red light is used for aiming the CO_2 and the Nd:YAG lasers.

Fires in the Patient

The most serious fire in the patient is an endotracheal tube fire. Although the ET tube can be ignited by electrocautery, it is more common for a fire to occur as a result of it being struck by a laser. Wolf and colleagues showed that the red rubber, the polyvinyl chloride (PVC), and the silicone endotracheal tubes all have a flammability index of less than 25% oxygen. Therefore, these tubes are not appropriate when doing surgery in and around the airway.

Before specific laser resistant tubes were developed, many practitioners wrapped endotracheal tubes with various kinds of foil or copper tape. Today, this is a dangerous practice and should be avoided. There are many complications associated with wrapping tubes which include kinking of the tube and having unprotected parts of the tube exposed where layers of tape fail to overlap. In the event that an endotracheal tube should be set on fire, it is important to immediately disconnect the tube or the inspiratory hose from the anesthesia machine. This will usually result in the fire going out since the oxidizer has been removed from the fire. Simultaneously the surgeon should remove the ET tube, and saline or water poured into the airway. The patient is mask ventilated and then reintubated. Next, bronchoscopy is performed so that the airway can be inspected and any pieces of foreign material removed. These fires can be quite devastating as an endotracheal tube ignited by a laser with high concentrations of oxygen essentially turns into a "blow torch" with resultant burns to the lungs, trachea, and esophagus.

Upper Airway Surgery

When anesthetizing patients for upper airway surgery, a number of anesthetic techniques are possible. One can use jet ventilation either through a metal bronchoscope or a catheter inserted through the cricoid membrane. In this circumstance, there is no tracheal tube in the airway to burn. However, the FIO_2 is not controllable as it is dependent on a venturi mechanism that entrains room air which is delivered to the patient. Complications of this technique include hypoventilation, barotrauma and aspiration. The surgery can also be performed using an endotracheal tube that is specifically resistant to the type of laser being used. The tube should have two cuffs and they should be filled with saline that has been colored with methylene blue. This allows the surgeon to know when one of the cuffs has been ruptured.

If the carbon dioxide laser is being used, then the LaserFlex™ (Mallinkrodt) ET tube is an excellent choice. The tube consists of a double cuff and a flexible metal shaft that is highly resistant to the CO_2 laser. This tube, however, is not resistant to the Nd:YAG laser. If the Nd:YAG laser is to be used in the upper airway, then a special laser resistant tube called Lasertubus™ (Rusch, Inc.) can be used. The Lasertubus™ consists of a soft rubber shaft that is covered by a corrugated silver foil which is then covered by a Merocel™ sponge covering. The Merocel™ when moistened with saline will consume laser energy if it is struck. It also dissipates the laser light and the silver foil prevents the laser light from penetrating the shaft of the tracheal tube. It is critical that the Merocel™ covering be kept moist at all times. This tube also consists of a double cuff design. Only a portion of the tube is laser resistant and it is important that this part of the tube always remains in the surgical field.

The electrocautery can also be a source of ignition during upper airway surgery. A typical example would be during a tonsillectomy on a child with an uncuffed tracheal tube. The anesthetic mixture, which may contain oxygen and nitrous oxide, can readily leak around the tracheal tube and be present in sufficient concentrations that the electrocautery could cause a fire at the operative site. In these cases, it is recommended that oxygen be mixed with air and the FIO_2 be kept as low as possible. The surgeon can also put wet pledgets around the tracheal tube; however, it must be remembered that if the pledgets dry out they can also be a source of fuel for a fire.

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Lower Airway Surgery

When doing surgery on the lower airway, the Nd:YAG laser is frequently employed. The surgeon usually passes a laser fiber through the suction port of the fiberoptic bronchoscope. This bronchoscope may then be passed either through a PVC tracheal tube or through a rigid metal bronchoscope. If the fiberoptic bronchoscope is passed through a tracheal tube a PVC tube can be used. There is no special tube for this type of surgery. Indeed the fiberoptic cable passes through the inside of the tracheal tube. Therefore, it is essential to keep the inspired oxygen as low as possible (preferably <30%) and titrate the oxygen saturation to between 90-95%. Also, the endotracheal tube should be placed just below the vocal cords so that the tip is as far away from the operative site as possible.

If the rigid metal bronchoscope is used, then obviously there is no tracheal tube in the airway. The patient is then ventilated with a form of venturi which will entrain room air. Therefore, the inspired oxygen is not precisely controllable. The FIO_2 will usually vary between 40-60%. It should be remembered that in either circumstance, the cover of the fiberoptic bronchoscope is plastic and can easily burn especially in an oxygen enriched environment.

Laser Safety

There are other safety considerations when using the laser. Reflected laser light can cause retinal damage. The patient's eyes should be covered with wet eye packs and all personnel in the room must wear goggles that are specific for the laser being used. These goggles frequently have a color tint, which may make it difficult to monitor skin color changes. Also, all windows should be covered with black window shades and warning signs should be posted on all doorways to the operating room. There is also potential damage to the respiratory track from vaporized tissue which may contain chemical toxins or virus particles in the laser "plume". It is recommended that special (high filtration) masks be worn by OR personnel during these types of procedures.

Another place where a fire could occur in the patient is during laparoscopic surgery. Even though the abdomen is inflated with CO2, after about 30 minutes of nitrous oxide anesthesia, the N2O can diffuse into the abdomen and reach levels that could support combustion. Neuman et al studied this phenomenon and found that at 30 minutes the mean nitrous oxide concentration was 36%. However, in certain patients, the nitrous oxide concentration was as much as 47%. Bowel gas contains two potentially flammable gases. These are methane and hydrogen. The reported maximum concentration of methane in bowel gas is 56% and hydrogen 69%. 56% methane would require 47% nitrous oxide in carbon dioxide to support combustion. Since that was the maximum concentration found in the study, this presents a relatively small hazard. However, 69% H_2 will burn in concentrations of nitrous oxide of 29% or greater. Therefore, if the surgeon should accidentally enter the bowel during laparoscopy which contained a high percentage of hydrogen, a fire could occur. The nitrous oxide would support combustion, the hydrogen would be the fuel, and the electrocautery would provide the heat source. Greilich et al reported a fire in which a tank of 14% carbon dioxide and 86% oxygen was accidentally used to inflate the abdomen instead of pure carbon dioxide. When the surgeon activated the electrocautery, a fire ensued. The pin index for tanks with 100% CO_2 is the same for any tank with greater than 7% CO_2.

Another kind of fire that occurs in the patient is the ignition of a tracheal tube during a tracheostomy. A critically ill intubated patient will be receiving supplemental oxygen. A surgeon may use the electrocautery to enter the trachea. This is an extremely dangerous practice since the tracheal tube is frequently in the field while supplemental oxygen is being delivered to the patient. The ESU then provides a source of heat and a number of fires have resulted. Decreasing the inspired oxygen would obviously be a safety factor; however, this may not be possible in this patient population. Also, unless the patient is ventilated with decreased inspired oxygen content for at least a minute, the higher concentration of oxygen will continue to be present in the trachea. It is far better that the surgeon use a scalpel or scissors to enter the trachea, instead of the ESU. This will greatly reduce the risk of a tracheal fire.

Fires on the Patient

The other type of operating room fire is one that occurs on the patient. Most commonly these are associated with monitored anesthesia care (MAC) for head and neck cases where the patient is administered supplemental oxygen either by a face mask or a nasal cannula. The surgeon then drapes the field such that there is a build up of 100% oxygen under the drapes and in close proximity to the operative site. This oxygen, in certain circumstances, can then diffuse directly into the operative site so that when the electrosurgery pencil or the laser is used, a fire can be started. There are many potential objects that could provide fuel for the fire. These include paper drapes, gauze sponges, plastic tubing from the oxygen mask, and even the patient's facial hair. It is important to remember that oxygen is a drug. Therefore, the need for supplemental oxygen as well as the concentration of oxygen needs to be titrated in each patient. Frequently, by reducing the amount of sedation given to the patient, the use of supplemental oxygen can be eliminated. The oxygen can be diluted with room air and titrated to keep the patients oxygen saturation between 90-

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95%. The drapes should be arranged so that the oxygen does not build up underneath the operative site. The drapes should be arranged in a fashion that forms an open tent so that the oxygen will be diluted with room air. Since oxygen is slightly heavier than room air, as long as there is some way for the oxygen gas to get in and out, it will tend to flow towards the ground.

Another potential strategy to minimize the risk of fire is to discontinue the use of supplemental oxygen several minutes before the surgeon uses the laser or the ESU. This will give any oxygen that has built up time to dissipate which would greatly reduce the risk of fire. However, this may be difficult to do if there is frequent use of the ESU or laser. Also, it is difficult to predict how long it would take for the oxygen to dissipate. Therefore, the newest recommendation from the Anesthesia Patient Safety Foundation and the ECRI Institute, is to secure the airway with an LMA or endotracheal tube when the patient needs supplemental oxygen for a head and neck procedure. There are a few exceptional cases when there is a need to communicate with the patient (i.e. awake craniotomy or carotid endarectomy). In these cases the FiO_2 should be less than 30 percent.

Volatile prep solutions provide another potential source of fuel for a fire. Solutions such as isopropyl alcohol are frequently used by surgeons as skin prep. These solutions could pool in certain areas and remain liquid for a considerable period of time. Additionally, these solutions will vaporize and the resulting vapor, especially in an oxygen enriched atmosphere, is highly flammable.
DuraPrep™ is a skin prep that is very popular in many hospitals. It consists of Iodofor and 74% isopropyl alcohol. It appears that the very high concentration of alcohol is not appreciated by many surgeons and operating room personnel. If the solution is not allowed to dry completely before beginning surgery, then the alcohol will provide a potential fuel for a fire. In 2001, Barker & Polson reported on just such a case. A patient was having a burr hole craniotomy under MAC anesthesia. The patient was receiving supplemental oxygen and the head was prepped with the Iodofor and alcohol solution. When the surgeons made the skin incision, the electrosurgical unit was activated and a "pop" sound was heard. In very short order, smoke and a ball of flames engulfed the patient's head and shoulders. The fire was quickly extinguished, but the patient suffered burns to the face and neck area. In a laboratory re-creation of the event, Barker and Polson discovered some interesting facts. By duplicating the setup in the operating room, they were able to re-create the fire. However, if there was no flow of supplemental oxygen, there was no fire. If the alcohol-based prep solution was not used, again there was no fire and finally, if the closed space where the oxygen was allowed to build up was not present, again there was no fire. This illustrates an essential fact, that although operating room fires are a rare event, when the key elements come together at precisely the same time, a fire is easily started. Also, in the presence of an oxygen enriched atmosphere, the fire will spread almost instantaneously.

In 2004 four cases of fires in the CO_2 canister of the anesthesia machine were reported. These canisters have melted or actually caught on fire. In at least one case there was a serious patient injury. The common elements included use of a CO_2 absorbent that was desiccated (Baralyme™), Sevoflurane™, and low O_2 flows. Apparently a breakdown of Sevoflurane™ occurred, and there was a very exothermic reaction, which caused a fire. Laster et.al. demonstrated that when desiccated Baralyme™ interacts with Sevoflurane™ there is a sustained temperature increase to 200 degrees C, and in one case to over 300 degrees C. In contrast, with Isoflurane™ and Desflurane™ there was only a transient increase in temperature to 100 degrees C. Amsorb™ is a newer CO_2 absorbent that does not contain strong alkali, and does not react with Sevoflurane™. Therefore, it would not pose a fire hazard.

In 2010 Laudanski and colleagues reported two cases of a ventilator circuit that caught on fire. This was associated with a wire that was used to heat the gases in the circuit. In this type of circuit this is a risk of melting wires, insulation, and/or tubing that can lead to a fire.

Extinguishing a Fire

If a fire should develop, it is important to know how to extinguish it as rapidly as possible. Breaking the fire triad is extremely important. Therefore, removing the oxidizer by disconnecting the oxygen or the circuit from the patient, will frequently extinguish the fire. Burning drapes should be removed as quickly as possible and once on the floor, they can then be extinguished. It should be remembered that impervious paper drapes will repel water and the fire will actually burn on the underside of the drapes. Therefore, attempting to throw water on these burning drapes would be useless. Although most operating rooms have a sprinkler system, the sprinklers are usually not activated in cases of OR fires. This is because the sprinklers are rarely located over the operating room table, and they are also heat activated. OR fires tend to give off a lot of smoke and toxic products of combustion, but not necessarily enough heat to activate the sprinklers.

It is important that all operating room personnel are familiar with fire extinguishers. They are classified into three basic types. Class A is used for wood, paper, cloth and plastics. Class B is used to extinguish flammable liquids or grease, and Class C are used

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for energized electrical equipment. Many fire extinguishers are classified to be used in two or all three types of fires. Halon is a fire extinguisher commonly found in operating rooms. It is a bromofluorohydrocarbon and can be used on Class B & C fires and on many Class A fires as well. It is a highly effective fire extinguisher and can be used safely around electronic equipment. However, because it is a fluorocarbon, it is no longer being manufactured. Newer, environmentally friendly substitutes are now available. Carbon dioxide fire extinguishers are useful for Class B & C fires and can also be used in Class A fires. The blast of carbon dioxide gas has liquid and solid components that rapidly vaporize, which leads to a cooling and smothering of the fire. Carbon dioxide extinguishers do not leave a residue which could damage electronic equipment, but the cold may cause freezing if it came into contact with exposed skin. Pressurized water can be used in hand held fire extinguishers or from the large fire hoses located in the operating room corridors. If a corridor fire hose is used, it can deliver up to 50 gallons of water a minute. These devices are best used by the fire department unless a patient or OR personnel is in need of immediate rescue. Obviously, these devices would cause extreme damage to electronic equipment. All fire extinguishers have advantages and disadvantages. When considering all of these factors, the CO_2 fire extinguisher is probably the best for an operating room fire, although the water mist extinguisher is also acceptable.

When using a fire extinguisher, the acronym "PASS" should be remembered. This stands for Pull the pin to unlock the handle of the fire extinguisher; Aim the nozzle of the fire extinguisher at the base of the fire; Squeeze the handle to activate the fire extinguisher and release the agent; Sweep the stream of the extinguisher over the base of the fire.

Case Studies

A couple of case scenarios of actual OR fires will help to illustrate some of the points that have been made. In one instance during a neurosurgical procedure, the laser and the electrosurgery unit were both in use during the case. The surgeon picked up the ESU while the laser was lying on the drapes. He mistakenly stepped on the laser pedal which immediately ignited the drapes and subsequently the mattress and gel pad. A fire was started which produced very toxic smoke and forced all of the OR personnel to leave the OR. They subsequently had to crawl back into the room, disconnect the patient from the anesthesia circuit and pull the patient and the table out of the room. This case illustrated the value of being absolutely certain of which pedal activates which device. Also, when a laser is in use, once it is set down, the laser should be put in the standby mode immediately. Similarly, when an electrosurgery unit is not in use, the pencil should be placed in a plastic holder.

Another case involved a trauma patient for an exploratory laparotomy. The electrosurgical pencil became draped over the side of the table and the button was inadvertently activated. This immediately set the drapes on fire. Although initially the fire appeared small, within a few seconds the flames had engulfed the left side of the patient. Attempts by the OR staff to extinguish the fire were unsuccessful and the fire department arrived approximately 15 minutes later and extinguished the fire. A review of the incident revealed that the OR staff had no plan for dealing with the situation, they couldn't find the fire extinguishers, the fire cabinets were blocked by equipment and the OR sprinkler system was not activated. Once again, the fact that the ESU pencil was not placed in the holder contributed significantly to this fire.

ASA Practice Advisory Recommendations

The ASA practice advisory makes a number of recommendations on the prevention of OR fires. First the OR team must determine if a high risk situation exists. If there is a high fire risk then each person is given a specific task on how to prevent a fire, and what they will do in the event a fire occurs. All fire management equipment must be readily available. Prevention is the most important part of the equation. The anesthesiologist and the surgeon must collaborate during the procedure to minimize an oxygen rich environment. The drapes must be configured to avoid oxidizer buildup, and flammable skin preps must be dry before draping. Many institutions have instituted a “prep time out” to insure that all flammable solutions have dried and there is no pooling of prep solutions. This must be completed prior to draping the patient. The surgeon should be notified if an oxidizer and ignition source are in proximity, and time allowed for the oxidizer to dissipate before using the ESU or laser.

The team should be aware of early signs of a fire such as a pop, flash, or smoke. If these occur, the surgery must be stopped immediately, and everyone carries out their assigned task. If it is an airway fire, then simultaneously stop the flow of gases and remove the ET tube. Saline is poured in the airway and burning materials are removed. If the fire is on the patient, then the fire is extinguished with water or saline, and the burning drapes are removed and thrown on the floor. The patient is then given supportive care, and the degree of injury is assessed. Finally, the scene is preserved, and hospital and local regulatory reporting requirements are followed.

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All OR personnel must be vigilant to potential operating room fires. Clearly, prevention is better than trying to deal with an established fire. It is however, incumbent upon OR personnel to be prepared. This includes fire drills, being familiar with the type and location of fire extinguishers, having an evacuation plan, knowing where gas and electrical shutoffs are located, and being able to rapidly call for help, sound a fire alarm and communicate with other OR personnel. Only by working together to keep all three legs of the fire triangle from coming together, can OR fires be prevented.

Although relatively rare, an Operating Room fire can be devastating for the patient, their family, and the OR personnel involved. A fire frequently leaves the patient with severe burns, which can be very disfiguring. The OR personnel are traumatized, and the institution will have to explain to regulatory bodies why this fire occurred. This is a perfect example where an institutional culture of safety will go a long way to making this a never event. Many groups have resources that are extremely valuable to the individual and the hospital to establish fire safety guidelines. These include the ASA, APSF, AORN, ECRI Institute, and the FDA.

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Social Media for Physicians: Why You Must, How You Should, and Easy Strategies for Risk Mitigation

Marjorie Podraza Stiegler, M.D. **Chapel Hill, NC**

Like it or not, the internet is a rapidly growing repository of indelible information about you. Patients, professional colleagues, future employers, and many others are reading about you online. Ignore your digital footprint, and you're missing opportunities to learn from others, share your expertise, grow your practice, network with colleagues, and influence your own online reputation.

Why create and manage an online presence? This RCL will address the following possibilities:

1. Find collaborators
2. Keep up to date with medical news – both from academic journals, and the news that patients are reading
3. Contribute to health literacy by posting educational content. Otherwise, most of what patients, journalists, and policy-makers find online is low quality and often not written by medical professionals.
4. Recruit the best and brightest colleagues and trainees to your institution
5. Reach more people with the healthcare messages you feel are important
6. Make your work easy to find, which leads to opportunities for professional advancement

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7. Learn from others
8. Network far and wide
9. Protect your reputation from misinformation, bad reviews, or auto-populated digital noise
10. Professional medical social media usage is increasing by several thousand percent each year. Get out in front, or get left behind.
11. Curate your library by keeping online "favorites" of journal articles, news coverage, and opinion pieces
12. Help patients find your practice (particularly relevant for pain medicine docs, but perhaps applicable to us all)
13. Influence public policy by engaging in professional advocacy. "preaching to the choir" does not advance your cause.
14. Create an entirely new set of performance metrics for promotional purposes. Being able to share statistics about the reach of your work represents a new academic currency.
15. Make your bigger projects easier. Experiment with small ideas that will be the basis for your next research project, quality improvement effort, article, book chapter, or presentation.

There are many more applications for social media, personal websites, and online activities. As well, there are many options for platforms on which to participate. Understanding the differences and having a clear agenda will help you select the right one for you. This need not be onerous.

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If you aren't already taking charge of your online presence, get started today with these tips:

1. **Give yourself a checkup.** Especially if you are not active on the web with a blog, website, or social media, most content about you will not have written or posted by you. Routinely check your own internet presence to ensure that information about you is accurate and appropriate. A search of your name is likely to lead to pages of healthcare rating sites (there are more than 75 such websites, and counting), including healthgrades.com, vitals.com, doximity.com, betterdoctor.com, and so on. While they could contain a negative review, most often these sites are nothing more than a sparse profile of publically available information. However, this kind of digital clutter obscures content you might prefer to showcase, such as your departmental profile page, presentations, manuscripts, and press releases.
2. **Share your expertise.** Patients find an abundance of both information and misinformation online. If patients are searching for answers, shouldn't you be providing them? As a physician or other healthcare provider, you have unique expertise. You also have the ability to translate sophisticated material and years of experience into easy-to-understand language. You can help only one patient at a time in the hospital or clinic, but you can help thousands by disseminating education online and improving health literacy. When the Mayo Clinic tweets, for

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example, over one million followers listen. Social media outreach is a key strategic initiative for many major medical centers.

3. **Be professional, always.** Regardless of your intention for online content to be private, anything has the potential to become public and permanent. This is true for private Facebook or Instagram accounts, just as it is with email. Privacy policies are continually evolving, and a simple click of a button is all that is needed to "forward" or "share" your content to a public domain. Select your words and photos carefully; even in casual settings, there is a professional standard expected of healthcare professionals. Be aware of family and friends who "tag" you in photos and posts on their own accounts, and how that information may be more public than you wish. And of course…
4. **Don't post about patients.** Never post any content about patients, and certainly do not post any identifying information. HIPPA violations, whether egregious or unintentional, can have serious professional consequences. As well, health care professionals sometimes use dark humor as a way of coping with stress, and to some degree, may become desensitized to illness and injury. Cases that are "great" for trainees and conferences are often linked to really bad news for patients. Consider seriously how you present content online, including your tone, use of slang, use of humor, and controversial or private topics.
5. **Influence your web presence.** Just as inappropriate posts can portray you unfavorably, the right kind of posts put your best image forward. Start with a short

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biosketch and professional photo on your departmental website. Use videos to tell your personal and departmental story. Provide educational content. Link to awards, press releases, faculty CVs, and current activities. Finally, consider maintaining a professional account on LinkedIn. This kind of content, as well as any blog or social media activity, is likely to outrank random healthcare ratings sites and push them to the distant pages of an online search. Therefore, by creating and publishing your own content, you can effectively curate digital search results.

Basic tips for beginners

Start with a good bio. It is always best practice to set up account(s) with a professional user name, and ideally keep this consistent across the platforms. For example, my user name is @drmstiegler on Twitter, Facebook, and Instagram. Include an image in your profile. You will have very little credibility until you replace that blank spot with a decent headshot.

Listen first. Regardless of platform, spend a little time poking around and observing how others use it. Familiarize yourself with the etiquette and norms. Follow other accounts to get a sense of how communication and conversations flow.

Measure twice, post once! Although the digital landscape moves quickly, you should give some careful thought to your posts. Ask yourself whether you would want your parent, child, spouse, or boss to see the post. If not, resist the urge. Ask yourself

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whether your post might be perceived as offensive or disrespectful – and if so, ask whether that is your intention. Some people post controversial or inflammatory content specifically to get a reaction, and if that's consistent with your goals, go for it. If not, keep in mind that consequences (usually social, but potentially related to your employment status) can be real. Consider whether your post is representing the best side of yourself, and maintains your intended 'personal brand' voice.

Respond. If someone replies to your post, reply to them! This is not only polite and engaging, but it also increases the likelihood your post will be seen by more people. Replies, comments, and shares help the search engines and the social media platforms know that your post is worth a read, so they will serve it to more readers. However, avoid the 'trolls' – never get into an argument online. If someone is aggressive, you can choose to ignore, block, or report them.

Remember, it's not all about you. In fact, it should be only 20-30% about you, and less than 10% about your personal life. Spend roughly 60-80% of your posting efforts on content that others have generated. It's fine to add your commentary, but be generous in sharing the great work others have done. This is key to building a community, in contrast to creating a unidirectional stream of information about yourself.

Strategies for increasing engagement and building your community :

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Share great content	Share press releases, research papers, timely headlines, and announcements. Include your brief opinion, or simply that the content is thought-provoking.
Add a link	Share the full story or webpage related to the your commentary.
Use interactive features	Most platforms have options for sharing live video and polls/surveys – these are best for driving engagement
Add an image	Posts with images and links get up to 40% more engagement than those without.
Tag other relevant users	Tagging (including a person's "@" name) is similar to email, bringing your posts to the tagged person's attention. Don't spam, but do use tags to communicate and credit the work of others.
Use appropriate hashtags	Hashtags organize conversations and topics, helping others find keyword topics of interest. Popular hashtags in medicine include #meded and #ptsafety. Conferences often use a hashtag as well, such as #ANES18

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"Perioperative Imaging and Pain Medicine: Patient Safety and the Biological Effects of Ultrasound and Fluoroscopy"

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Biological Effects of Ultrasound

Ultrasound imaging for needle guidance is now commonplace among anesthesiologists. Ultrasound related biological effects had been recognized in animals since the 1970s. The fact that ultrasound has a demonstrated safety profile in obstetrics may have been the reason for the bioeffects of ultrasound receiving little attention in the anesthesiology and pain medicine literature.

Historical perspectives

In 1917, Langevin first reported that fish in a small tank died when exposed to ultrasound. Fry examined the effects of focused ultrasound on nerve damage including reversible and permanent impairments in nerve conduction. When the lumbar enlargement of intact frogs was exposed to ultrasound, a second 4.3-second exposure of the ultrasound beam produced complete paralysis with destruction of neurons. Because of these and other reports of the potential adverse bioeffects of diagnostic ultrasound in experimental animals the Safety Standard for Diagnostic Ultrasound Equipment was formally adopted in 1983 by the American Institute of Ultrasound in Medicine (AIUM) and the National Electrical Manufacturer's association (NEMA). In 1992, the Output Display Standard (ODS) was developed which led to the FDA removing the restrictions on the upper limits for the acoustic output. The FDA then required that the end user utilize the ODS displayed on the ultrasound machines for assessing for potential damage to tissues.

Thermal Effects

The potential for ultrasound to cause temperature increase is dependent on both the ultrasound characteristics (e.g., intensity, beam width, exposure duration), and the physical properties of the tissue (e.g., density, protein content, heat capacity, perfusion). The thermal effects of ultrasound are more likely in the lens, cornea, tendon, and adipose tissue. Absorption coefficients of tissues which is directly related to protein content, vary between 1 (skin, tendon, spinal cord) and 10 (bone) dB/cm MHz.

Mechanical Effects

Non-thermal or mechanical effects are most likely in air-filled cavities and have been the center of multiple investigations. Acoustic cavitation causing lung hemorrhage has been studied in a variety of animal models including mice, monkeys, and rabbits, besides neonatal and young pigs. In the lungs, it produces hemorrhage and alveolar injury. This is determined by tissue characteristics at pleural interface with lung, magnitude of lung deflation and the peak ultrasound rarefactional pressure. Despite these data in experimental animals, it has not been demonstrated in humans. Similarly, intestinal walls develop petechial hemorrhages on the mucosal surface after ultrasound exposure at or above typical diagnostic frequencies. This has been utilized in therapeutic release of various chemicals including thrombolytic agents using microbubbles.

Neural Effects

Animal studies have demonstrated histological changes including pyknosis and myelin and neuronal destruction following ultrasound exposure leading to hind limb paralysis. As the lesions occur in a short time, it is most likely

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secondary to cavitation. Myelin is very sensitive to ultrasound bioeffects. Impairment of myelin could alter nerve conduction. Animal studies on conduction are difficult to validate as multiple factors which alter nerve conduction are modified. The changes in conduction velocity and amplitude in these studies have been shown to be reversible.

Limitations of these data

As the core temperatures of experimental animals are vastly different from humans, translation of such data to humans may be not accurate. Most of these data on teratogenicity have not undergone rigorous validity studies.

Ultrasound Bioeffects in Humans

With the long history of ultrasound use in obstetrics, most of the reported studies are on the effects in fetus. Having said that, longitudinal follow up over decades have not shown and increased propensity for any damage or long-term effects in children. Potential reasons for the lack of bioeffects in humans could be the cold ultrasound gel, frequent movement of the transducer and conduction of the heat by the needle and blood flow.

Thermal Index

Ultrasound being a form of mechanical energy, when absorbed by tissues as they traverse, it tends to increase the local temperature. Heat related injury has been variously demonstrated in animals from genetic, cellular, and ion channel damages.

The thermal index is determined by the ratio of the system power to the power required to increase the temperature by 1^0C. Thermal index is calculated for soft tissue, bone and cranium and is displayed as TIs, TIb, and TIc. Present day ultrasound machines have the capacity to increase local tissue temperature upwards of 4^0C especially when using power Doppler. Limiting the exposure time is the most crucial factor for ensuring safety.

Mechanical Index

Cavitation is a process by which ultrasound waves when bombarded against gas bubbles produce rapid changes in the size of the bubbles with expansion and contraction. This produces rapid increase in temperature, mechanical stress, fluid micro jets and short-lived free radical production. Short wavelengths, as seen with higher frequencies, do not provide sufficient time for significant bubble growth and hence cavitation is less likely at higher frequencies. Acoustic cavitation may be inertial or non-inertial. With inertial cavitation, there is inrushing of surrounding fluid after a rapid contraction of a bubble, and may be symmetrical or asymmetrical. Symmetrical inertial cavitation may lead to temperature rise as high as 1000^0C leading to internal thermal derangements or facilitating the formation of reactive chemicals. Asymmetric inertial cavitation by producing high velocity jets of liquid cause direct mechanical damage.

The mechanical index is the ratio of the peak rarefactional negative pressure adjusted for tissue attenuation and square root of the frequency and was developed to describe the relationship between cavitation formation and acoustic pressure. The mechanical index is frequency dependent.

79% of regular ultrasound users in the United States were unable to identify the display location of thermal or mechanical indices in their equipment.

Regulatory requirements

Comparison of ultrasound output of equipment manufactured between 1995-1999 compared with earlier equipment confirmed significant increase in acoustic outputs. Newer machines have been manufactured with the image quality as the main focus and hence have higher outputs. This could lead to the physician being held responsible for controlling for the bioeffects of ultrasound. The ODS, the only required monitoring method, requires display of a Thermal and a Mechanical index. Although acoustic power is the primary determinant of thermal and mechanical injury, alterations in ultrasound modes, color flow, area of interest, transmission frequency, pulse repetition frequency and focal zone also have significant effects.

Based on review of all published literature on ultrasound related bioeffects, the AIUM concluded that there is no direct bioeffects of ultrasound in humans unless exposure occurs over an extended period. The required temperature increase that could lead to damage in non-fetal tissues was calculated as 18^0 C with a 0.1-second exposure. When

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the temperature increase is less than 2^0C, even a 50-hour exposure does not cause damage. Hence the recommendation to follow the ALARA principle.

Conclusion

Further investigations in humans are required to establish the bioeffects of ultrasound in humans as there appears to be clear evidence of damage in animals. In the interim adhering to the limits of TI and MI is prudent.

Biological Effects of Fluoroscopy

Everyone on Earth is exposed to background radiation such that if you combine cosmic radiation with medical, industrial and commercial sources, the average American will be exposed to 6.2 mSv/year. As anesthesiologists, we are increasingly asked to care for patients in the radiology suite or in orthopedic operating rooms, where radiation exposure is a hazard. While pain physicians, over the last two decades, have used imaging guidance, primarily fluoroscopy, for pain procedures. The majority of the published studies focus on the exposure of surgeon or proceduralist, but very few publications address the exposure of the anesthesiologist.

Definitions

Absorbed dose is the amount of energy deposited in the tissues at a specific point. It is measured in Gray (Gy) or Rads (1 Gy=100 rads).

Equivalent dose is a dosimetry metric that attempts to quantify biologic damage by different types of radiation. It is primarily used for radiation protection purposes and are only “approximate indicators” of potential harm. Equivalent dose is expressed in Sievert (Sv) (1 Sv = 100 rem). For example, alpha particles emitted in radiation therapy can do more damage than electrons emitted by x-ray imaging.

Effective dose is used to deal with the non-uniform dose distribution in the body and whether radiation is absorbed by a specific tissue. You need to take into account the type of radiation and the variable sensitivity of the organ (tissue weighting factors). Effective dose is expressed in Sieverts (Sv). The tissue-weighting factor is the fractional contribution of each organ to the total whole-body radiation. (Tables 1 and 2)

Absorbed Dose ----------> Equivalent Dose ----------> Effective Dose

Radiation weighting factor

Tissue weighting factor

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Table 1: Organ relative radio-sensitivity (Tissue weighting factors) used by ICRP.

Tissue Weighting Factor	Organs	Detriment
0.12	Bone marrow; colon; lung; stomach; breast; adrenals, etc	Cancer
0.08	Gonads	Hereditary
0.04	Bladder, liver; esophagus, thyroid	Cancer
0.01	Skin; bone; brain	Cancer

Table 2: Organ dose (mGy) or Equivalent dose (mSv) for radiographic examinations.

Organ	Lateral Skull	PA Chest	AP Abdomen
Bone marrow	0.05	0.02	0.2
Lungs	<0.01	0.06	0.02
Stomach	<0.01	0.01	1.3
Colon	<0.01	<0.01	1.3
Breast	<0.01	0.01	0.01
Gonads	<0.01	<0.01	0.60
Effective Dose (mSv)	0.03	0.015	0.5

Radiation Biology - Interactions of radiations with tissue

Biologic effect of radiation depends on the total energy deposited in the cell (absorbed dose). The primary variable is that inherent to the cells at the time of irradiation, but there are other variables related to the radiation itself (type of radiation, absorbed dose, etc.). Damage to biologic systems always occurs first at the molecular level. Loss of molecular function will ultimately lead to cellular dysfunction and organ damage.

Direct vs. Indirect Ionizing Radiation

Direct action occurs when Compton electrons and photoelectrons ionize DNA molecules. It is responsible for less than 1/3 of the biological damage by ionizing radiation.

Indirect action occurs when Compton and photoelectrons interact with water in the cell to produce free hydroxyl radicals. These radicals can diffuse and damage target molecules, such as DNA. About 2/3 of the biologic damage

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by x-rays is caused by indirect action.

Deterministic vs. Stochastic Effects

Deterministic effects are harmful tissue reactions that occur above a threshold dose (D threshold). For doses above the threshold dose, deterministic effects are expected to occur in all exposed individuals and are generally a direct result of cell destruction. Severity of these effects may increase with increasing dose. Examples of deterministic effects include skin burns, epilation, eye cataracts, and sterility.

Skin: High skin doses generally occur at the point where an x-ray beam enters the patient. Below skin doses of 2 Gy, no effects are observed. Between 2 and 5 Gy erythema may occur, and above 5 Gy erythema will occur, so patients should be advised to perform self-exam in the following 2-10 weeks.

Epilation: The loss of hair can occur following irradiation of the scalp in high-risk procedures. Below 3 Gy no loss of hair is expected. For scalp doses 3 to 6 Gy, temporary epilation may occur, with an onset at 2-3 weeks and complete regrowth at 6-12 months. At scalp doses of 7 Gy or above, epilation is likely to be permanent.

Cataract: As of 2011, the International Commission of Radiological Protection (ICRP) considers the threshold dose for cataract induction at 0.5 Gy. The latency period for the development of cataracts may be of several years and as the doses increase, the latency period may get shorter.

Sterility: Doses as low as 0.2 Gy can result in low sperm count and doses above 0.5 Gy can result in azoospermia. Permanent sterility in men requires a single dose of 6 Gy, and fractionated exposure to the gonads produce more damage than acute exposure. In females, doses for sterility (permanent ovarian failure) are dependent on age. Whereas 10 Gy can result in permanent sterility in prepuberty, only 2 Gy will do so in in premenopausal females.

Stochastic effects are random tissue reaction that have no threshold dose and the severity of these reactions are also independent of the radiation dose. In stochastic effects, the radiation dose only affects the probability of the event occurring. Examples of stochastic effects are carcinogenesis and hereditary effects.

Carcinogenesis: It is generally accepted that at higher (therapeutic) doses, radiation may result in cancer (i.e. radiation therapy for breast cancer and Hodgkin's lymphoma). Although there is still some uncertainty, growing evidence suggest that lower dose, such as those encountered in diagnostic applications, may result in increased carcinogenic risk (i.e. increased in leukemia and brain tumors in children who underwent CT in the UK).

Hereditary effects: these are based on animal data. Studies of children born to the A-bomb survivors have not shown any significant increased effects. In a population that excludes children, the hereditary risk is about 0.1% and in the entire population, the ICRP hereditary risk estimate is 0.2% per Gy. For conceptus deterministic risks, please see the ACR Practice Guidelines for Imaging Pregnant Women.

Radiation Safety for patients and staff

Approximately 400 million diagnostic exams are performed in the United State each year (table 3). Average exposure of the US population has increased from 0.6 mSv in the 1980s to 3 mSv in 2006. CT scans now account for 17% of all diagnostic x-ray examinations and half the population medical dose. Practitioners need to understand the magnitude of risk to benefit ratio of x-ray exam or x-ray guided procedure.

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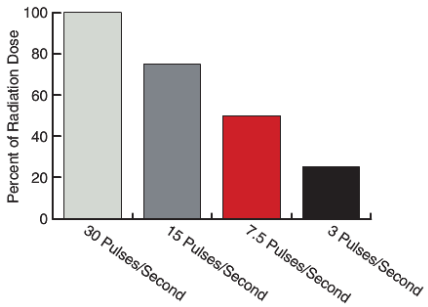
Table 3: Radiology exams performed in the United States in 2006

Type of exam	# performed (millions)	Average effective dose/patient exam (mSv)	Per Capita dose (mSv)
Radiography & Fluoroscopy	290	0.3	0.3
Interventional Radiology	20	8	0.4
Computed Tomography	70	7	1.5
Nuclear Medicine	20	13	0.8
Total	400	2.5	3.0

Radiation protection aims at preventing deterministic effects and minimizing risk of stochastic effects. As a rule, the scatter dose at 1 meter is about 0.1% of the entrance skin dose. Methods to control radiation dose are decreasing exposure time, increasing distance from the source and shielding.

Exposure time should always be minimized. Fluoroscopy units have a 5-minute alarm that reminds operators of increasing exposure. Pulsed fluoroscopy should be used rather than continuous fluoroscopy whenever possible. Table 4 shows how using pulse fluoroscopy can reduce radiation dose.

Table 4: Pulse fluoroscopy and effect on radiation dose



Distance: Radiation intensity is inversely proportional to the square of the distance from the source, such that doubling the distance reduces the doses fourfold. Increasing the distance from a source is more effective at reducing operator doses than reducing the exposure time.

Shielding: x-ray attenuation by lead is high due to its high density and atomic number. Lead aprons should have 0.25 – 0.5 mm of lead and should be worn at all times. Lead aprons are expected to attenuate at least 90% of an incident x-ray beam. Lead aprons can crack when folded improperly so they should be tested annually. Lead neck shield should be worn to reduce thyroid exposure and leaded glasses reduce eye lens exposure. (Figure 1) The table should have a lead curtain to protect the staff in the room. Leaded gloves may be used to minimize extremity doses

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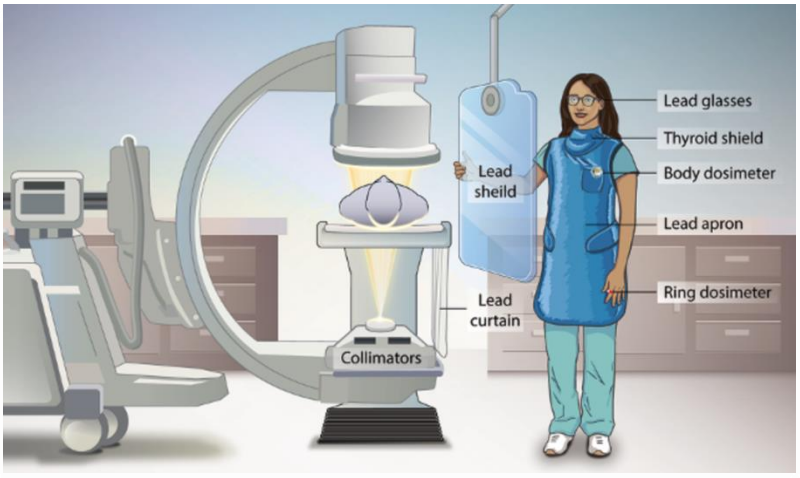
Figure 1: Devices available for operator and staff protection.



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Upper Extremity Regional Anesthesia: Essentials for Your Practice

Joseph M. Neal, MD **Seattle, Washington**

Dr. Neal has no conflicts of interest related to this presentation and receives no financial support from any entity other than his employer

Learning Objectives:
Upon completion, participants will be able to:
1. Distinguish those techniques that can improve block success
2. Recognize the nuances of local anesthetics and additives used for upper extremity blocks
3. Identify the prevention and treatment of block-related complications

Regional anesthesia for shoulder and arm/hand ambulatory surgery improves early outcome measures such as better analgesia, decreased opioid-related side effects, earlier readiness for discharge, and reduced frequency of unplanned hospital admission. After single injection blocks, these advantages do not exceed 24 hours and initial analgesia may be accompanied by significant rebound pain upon block resolution. Continuous perineural catheters consistently improve analgesia, and may facilitate earlier hospital discharge and rehabilitation after major shoulder surgery. This information is important, because it provides objective data that brachial plexus regional anesthesia can positively affect outcome in patients undergoing upper extremity surgery.

This refresher course lecture focuses on the selection of approaches to the brachial plexus, techniques to improve block quality, important pharmacologic considerations, and complications associated with upper extremity neural blockade. Because of time and space constraints, actual techniques of performing upper extremity blocks will not be discussed. Participants are referred to classic textbooks and atlases for this information.

APPROACHES TO THE BRACHIAL PLEXUS

Knowledge of surgical site and brachial plexus anatomy combine to determine one's approach to the brachial plexus. The interscalene approach is ideally suited for shoulder surgery, but less appropriate for surgery distal to the elbow because of its propensity to spare the lower trunk (ulnar distribution). The supraclavicular approach is appropriate for most upper extremity surgery, although shoulder surgery may require supplemental supraclavicular nerve (C3-C4) block. The infraclavicular approach provides anesthesia distal to the shoulder and is consistently superior to the axillary approach for hand and arm surgery, in part because it more efficiently anesthetizes the musculocutaneous nerve. The axillary approach provides anesthesia for surgeries of and distal to the elbow, but specific blockade of the musculocutaneous nerve is advised if the surgical field involves the volar radial forearm.

TECHNIQUES THAT IMPROVE BLOCK SUCCESS

Nerve Localization

Despite over a century experience with brachial plexus blockade, studies have failed to identify a superior method to localize nerves. Indeed, block success (a term that unfortunately encompasses multiple definitions) plateaus at 90-98% regardless of whether nerves are localized using peripheral nerve stimulation, paresthesia, or in the case of axillary block, perivascular techniques. When compared to peripheral nerve stimulation, randomized clinical trials variably show that the use of ultrasound-guided regional anesthesia (UGRA) improves block onset, reduces block performance time and the number of needle passes, and results in more reliable blockade of the lower trunk via the interscalene approach. However, rates for surgical readiness and block success are similar. With the exception of reduced local anesthetic systemic toxicity (LAST), studies of UGRA have yet to prove increased safety as compared with other localization techniques.

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Ideal Number of Injections
Regardless of how a nerve is located, the ideal number of injections to optimize block quality is block- and localization technique-specific. Ultrasound-guided blocks are typically multiple injection techniques that surround the nerves with local anesthetic. Nerve stimulator-guided interscalene and supraclavicular approaches to the brachial plexus achieve reliable blockade after a single injection. As the brachial plexus architecture begins to diverge into more widely spaced components, the value of increasing the number of local anesthetic injections becomes evident. Double or triple ultrasound-guided injection leads to faster supraclavicular block onset. Infraclavicular brachial plexus block is improved with double rather than single injection, particularly when one of the stimulations involves the posterior cord. A single posterior injection appears adequate for UGRA techniques. Landmark-based axillary blocks are improved by using three, but not four, injections. Injecting near the radial nerve is most important for attaining optimal anesthesia using the axillary approach, while injecting near the ulnar nerve is least important. Recent studies suggest that a two-injection ultrasound-guided technique (injecting at the musculocutaneous nerve and at the 6 o'clock position below the axillary artery) may be equally efficacious to a triple- or quadruple-injection nerve stimulation technique.

Continuous Perineural Catheters
Extended analgesia can be accomplished with continuous perineural catheters. Particularly for painful shoulder surgeries, continuous perineural catheters provide superior analgesia, limit opioid-related side effects, and improve patient satisfaction and sleep. This technology has proven useful and safe for outpatients. There is less evidence that perineural catheters improve economically-sensitive parameters such as earlier return to work, long-term rehabilitation, or other health-related quality of life measures.

PHARMACOLOGIC CONSIDERATIONS

Local Anesthetics
Local anesthetic selection for upper extremity regional anesthesia is determined primarily by the desired anesthetic and analgesic duration. There is no inherent advantage of one local anesthetic over another with regard to block quality, although limited data suggest that ropivacaine infusion preserves motor function better than bupivacaine. For single-injection brachial plexus blockade, bupivacaine 0.5% is equipotent to ropivacaine 0.75%, which implies that the advantage of reduced cardiotoxicity with ropivacaine may be offset if an increased mass (concentration x volume) of ropivacaine is required to overcome its reduced potency. There is no advantage to mixing a long-acting and an intermediate-acting local anesthetic—block onset is similar, but duration is shorter than would be achieved with the long-acting local anesthetic alone.

While it is intuitive to increase local anesthetic mass to optimize block characteristics, existing evidence suggests that doing so does not provide clinically relevant improvements when using traditional volume techniques, i.e., 20 mL or greater. Indeed, increasing local anesthetic concentration, volume, or total dose does not hasten block onset, improve quality, or prolong analgesia. Instead, increased concentration correlates with neurotoxic injury, while increased mass worsens LAST. Thus, modifying local anesthetic characteristics to facilitate neural blockade is ineffective, but conceivably places the patient at increased risk should nerve injury or LAST occur. Ultrasound-guidance further supports this concept, as excellent block characteristics are attainable using lower volumes of local anesthetic. However, there is emerging evidence that block duration may be reduced when extremely low volumes (less than 10 mL) are used. In the setting of continuous perineural analgesic techniques, evidence suggests that initial bolus dosing can be accomplished with relatively low volumes and concentrations of local anesthetic, e.g., 20 mL of 0.375% ropivacaine for interscalene block, followed by 0.1-0.2% ropivacaine infusion.

Additives
In the absence of continuous perineural techniques, limited prolongation of analgesia is achievable with local anesthetic additives. Yet despite a myriad of choices, only epinephrine, clonidine, and buprenorphene reliably prolong blockade from intermediate-acting local anesthetics. Those adjuvants do not significantly affect long-acting local anesthetics, whereas **dexmedetomidine** 150 mcg has been shown to increase the duration of ropivacaine interscalene blockade by about 4 hours. Dexmedetomidine as a perineural additive is an off-label use in the United States and has received limited human study; in one study its perineural effect was similar to that associated with intravenous administration. Perineural dexmedetomidine extends analgesia (by about 20%) as compared to clonidine

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for supraclavicular block, but does so at the expense of sedation and transient bradycardia. **Epinephrine** prolongs peripheral nerve blockade by reducing clearance of the local anesthetic, in addition to serving as a marker of intravascular injection. Epinephrine 2.5 mcg/mL (1:400,000) achieves nearly the same block prolongation as 5 mcg/mL (1:200,000), but with less tachycardia and less reduction in peripheral nerve blood flow. **Clonidine** 0.5 mcg/kg prolongs anesthesia and analgesia by 50% for intermediate-acting local anesthetics, but <20% for long-acting agents (~2 hr. prolongation for either epinephrine or clonidine). However, clonidine can cause sedation (NNH 5) or hypotension (NNH 10) and lacks epinephrine's ability to signal intravascular injection. Clonidine is significantly more expensive than epinephrine; it is unclear if one is superior to the other or if indeed their actions are synergistic. Neither epinephrine nor clonidine improves sensory block quality when used during continuous infusion. **Buprenorphene** 0.3 mg prolongs duration of analgesia after axillary block. **Dexamethasone** has been shown to prolong the duration of mepivacaine analgesia to a degree similar to epinephrine or clonidine (~50%). Within the last year, neurotoxicity concerns related to perineural dexamethasone have been discounted, although diabetic patients may be at increased risk. Recent meta-analyses conclude that if perineural dexamethasone results in greater block prolongation as compared to systemic administrative, the effect is limited (<4 hrs). Perineural dexamethasone is effective at 1 mg. Perineural doses in excess of 4 mg are no more effective than intravenous administration of a similar dose. Other additives—opioids, neostigmine, hyaluronidase, tramadol, and calcium channel blockers—serve no useful purpose in brachial plexus blockade, are reported without comparison to a systemic control group, or are incompletely studied with regard to neurotoxicity. **Alkalinization** of intermediate-acting local anesthetics does not accelerate brachial plexus block onset, despite its usefulness in hastening the onset of epidural block. Moreover, alkalinization has been shown in animals to actually reduce block duration and intensity. In the last year, based on limited clinical studies, **liposomal bupivacaine** has been approved by the FDA for interscalene analgesia. When compared to bupivacaine alone, the effect on worst pain during the first postoperative week of additional interscalene liposomal bupivacaine was modest (<2 numeric rating scale points).

COMPLICATIONS OF BRACHIAL PLEXUS BLOCKS

Local Anesthetic Systemic Toxicity

Two unique circumstances related to brachial plexus blockade affect LAST. First, seizures associated with local anesthetic injection are five times more likely to occur with peripheral nerve block than with epidural block. Second, brachial plexus approaches are particularly prone to systemic toxicity because they are often placed near arteries that directly supply the brain, thus seizures can occur after remarkably small doses of local anesthetic, e.g., 2.5 mg bupivacaine injected into the vertebral artery during the interscalene approach. Case reports document episodes of LAST despite the use of UGRA, although recent studies report ~65% decrease in the incidence of LAST when ultrasound-guidance is used rather than peripheral nerve stimulation. In accordance with the ASRA Practice Advisory on Local Anesthetic Systemic Toxicity, lipid emulsion should be readily available to treat local anesthetic toxicity wherever upper extremity blocks are performed.

Pneumothorax

Pneumothorax can occur with the supraclavicular approach; less so with the interscalene and infraclavicular approaches. Importantly, symptoms may not become noticeable for 8-12 hours following the block, particularly in the absence of positive pressure ventilation. Pleuritic chest pain is the most common presenting symptom, not dyspnea. Development of techniques designed in part to avoid the pleura, such as the plumb bob or subclavian perivascular approaches, or UGRA, have likely reduced the incidence of pneumothorax significantly, although no large studies confirm this impression. Based on reported cases, the risk of pneumothorax associated with ultrasound-guided supraclavicular block is 1:1000 (calculated upper limit, 95% confidence interval).

Vascular and Muscle Injury

Minor bruising occurs in up to a quarter of patients after axillary block. Serious vascular conditions—compressing hematoma, vasospasm, or arterial dissection—are rare, but should be considered in patients with postoperative neurologic impairment. The ASRA Consensus Conference on Anticoagulation and Regional Anesthesia suggests that deep brachial plexus blocks, e.g., supraclavicular or infraclavicular, not be undertaken in anticoagulated patients. Temporary myotoxicity can happen when local anesthetic, particularly bupivacaine, is infused into muscle.

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Unintended Destinations of Local Anesthetics

Needles can be placed unintentionally near the neuraxis during interscalene block by advancing too far medial into the epidural, subdural, or subarachnoid space. The distance from the skin overlying the interscalene groove-to-the neuraxis is 23-35mm. Local anesthetic can also enter the subarachnoid space if a needle (seemingly placed at the proper depth) punctures a particularly long dural root sleeve. (Figure 1) When local anesthetic reaches the neuraxis, high spinal anesthesia or massive epidural anesthesia develops, which may be particularly difficult to diagnose in an anesthetized patient. If this happens, patients may present with unexpectedly high, and bilateral, sensory and motor block, bradycardia, hypotension, or asystole. Treatment is the same as for hypotension / bradycardia following spinal anesthesia, and includes early epinephrine to increase heart rate, contractility, and coronary perfusion pressure.

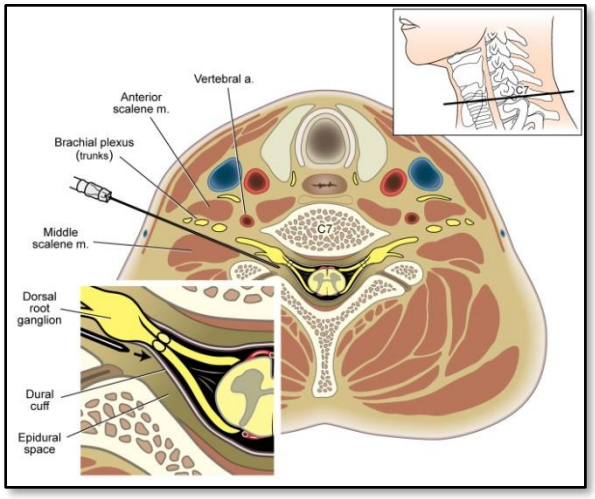

Figure 1. Neal & Rathmell, 2013

Unintended destinations of local anesthetics can also result in nuisance symptoms such as Horner's syndrome from blockade of the cervicothoracic sympathetic trunk, or hoarseness from blockade of the vagus and/or recurrent laryngeal nerves. These symptoms dissipate with resolution of local anesthetic blockade.

Hypotension / Bradycardia

Awake or mildly/moderately sedated patients who undergo interscalene brachial plexus block and are placed in the beach-chair position are reported to develop sudden hypotension and bradycardia in 13-24% of cases. These hemodynamic changes typically occur about an hour after block placement. The etiology of this condition is unclear, but is believed to involve relative preload deficit (from the sitting position) plus increased ventricular contractility (from exogenous and endogenous epinephrine), both combining to (arguably) activate the Bezold-Jarisch reflex. (Figure 2) Incidence can be reduced with metoprolol pre-treatment, but not glycopyrrolate.

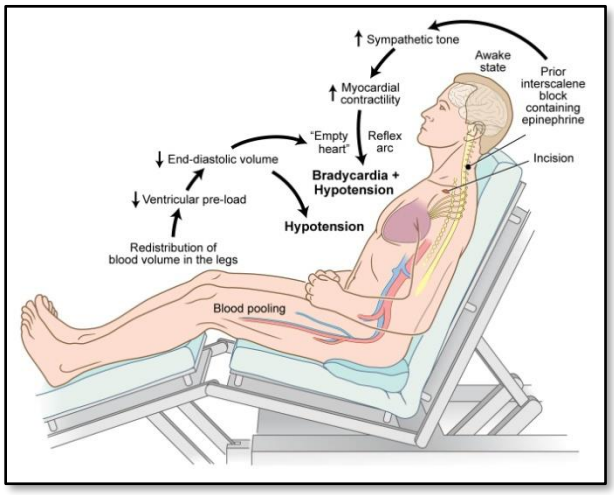

Figure 2. Neal & Rathmell, 2013

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Inadequate Cerebral Perfusion

Rare cases of cerebrovascular accident have been reported in patients undergoing shoulder surgery in the beach chair or upright position. Although not specifically a complication of upper extremity regional anesthesia, practitioners should be aware of this complication, the etiology of which is not entirely certain, especially with regard to its association with hypotension. Nevertheless, issues of particular concern include measuring blood pressure at the appropriate site or performing hydrostatic calculations to accurately reflect pressure at the level of the brain (1.33cm from cuff to brain = 1mmHg reduced pressure at the brain). (Figure 3) Some experts argue that patients in the beach chair position should maintain mean arterial pressures of at least 75 mmHg (measured at the arm).

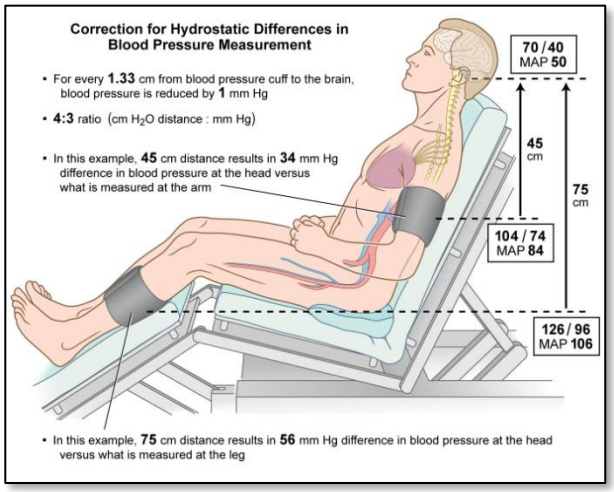

Figure 3. Neal & Rathmell, 2013

Complications of Continuous Perineural Blocks

Continuous perineural catheters do not appear to consistently increase complication rates as compared to single-injection techniques. Within the limitations of relatively few published studies, nerve injury does not appear to be increased. Similar to single-injection interscalene block, nerve injury has been associated with catheter placement in anesthetized patients. While the incidence of bacterial colonization is high (~39%), actual abscess formation is low (0.07%).

Hemidiaphragmatic Paresis

All landmark-based interscalene blocks and ~50% of supraclavicular blocks result in temporary hemidiaphragmatic paresis (HDP) secondary to anesthesia of the phrenic nerve. During interscalene anesthesia, a small subset of patients experience 25-32% reduction in pulmonary spirometric values. Pulmonary function is unaffected in healthy volunteers whose hemidiaphragm is paretic following supraclavicular block, but this may not be the case in patients with compromised pulmonary function. The incidence and severity of HDP can be reduced, but not completely and predictably eliminated, when local anesthetic volumes are decreased to 5-10 mL using UGRA. The ultrasound-guided approach probably blocks the phrenic nerve because of its proximity to the C5 nerve root. (Figure 4) Above the clavicle blocks are relatively contraindicated in patients unable to withstand a ~30% reduction in pulmonary function. Hemidiaphragmatic paresis following infraclavicular block is rare with the coracoid approach, but ~25% of patients who undergo the (more medial) vertical infraclavicular approach develop HDP with an accompanying 30% reduction in spirometric values.

Recently investigators have described novel techniques to reduce the incidence of HDP or grip strength diminution without sacrificing analgesia after major shoulder surgery. Such approaches include using the anterior approach to suprascapular nerve block for either single injection or continuous techniques. Less well studied is the combination of suprascapular nerve block with the infraclavicular approach to reduce HDP.

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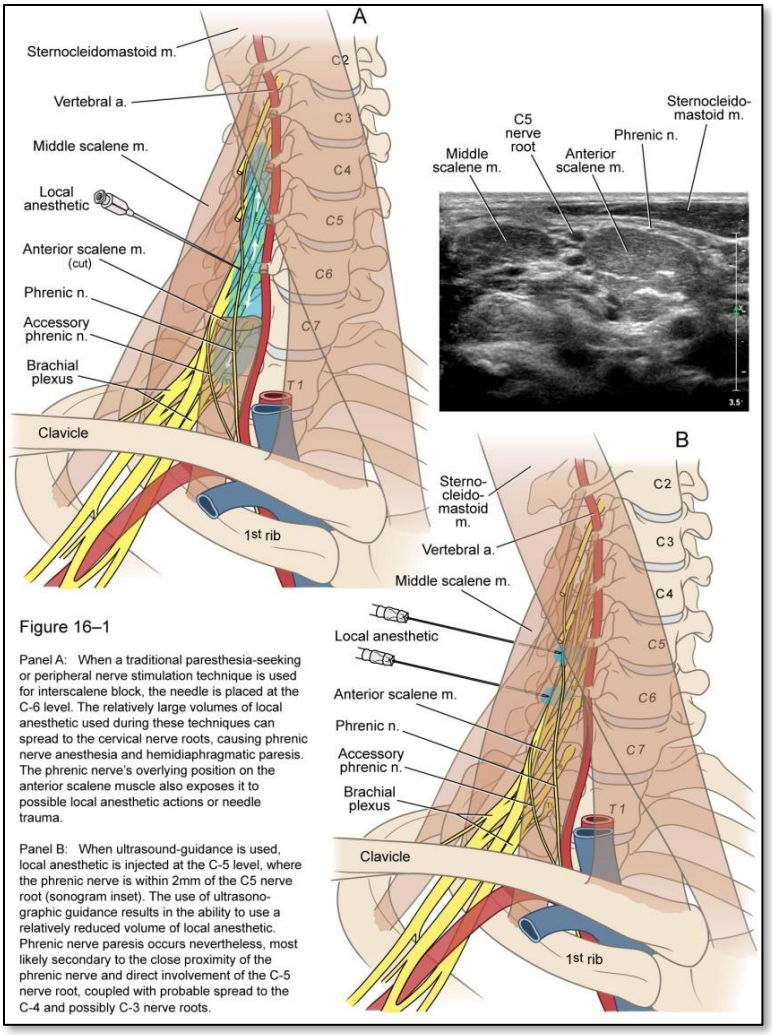

Figure 4. Neal & Rathmell, 2013

Peripheral Nerve Injury

The use of an interscalene block does not increase the baseline risk of nerve injury associated with total shoulder arthroplasty. Permanent peripheral neuropathy associated with brachial plexus block is a decidedly rare event (95% confidence interval, 0–16 / 10,000 patients). Depending on how it is defined, temporary nerve dysfunction in the early postoperative period may occur in up to 19% of patients and typically presents within the first 48 hours. Most symptoms resolve by 6 weeks; well less than 0.1% remain after a year. Up to 10% of upper extremity elective orthopedic surgery patients will experience a transient (or rarely, permanent) injury inherent to the surgical procedure itself. When a patient sustains a peripheral nerve injury after brachial plexus block it is crucial the anesthesiologist recognize that the vast majority of these incidents are related to surgical factors—direct nerve trauma, positioning injury, stretch injury, or compressive etiologies from hematoma, edema, or the application of constrictive tourniquets, casts, or dressings. When motor function is impaired, the injury appears to be progressive, or improvement is not obvious after a few postoperative days, early neurological consultation is advised. Although abnormalities on neurophysiologic studies (EMG, nerve conduction studies) are most apparent 2 to 3 weeks after injury, earlier evaluation may be beneficial when injuries meet the above noted criteria. Early, bilateral neurologic evaluation may establish baseline, document pre-existing conditions, or identify reversible lesions.

Factors associated with anesthesia-related peripheral nerve injury are poorly understood. No human data exist to guide our choice of short- vs. long-beveled needles in preventing injury. The relationship of paresthesia elicitation to peripheral nerve injury is equally unclear. Pain on injection of local anesthetic is generally regarded as a sign of

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potential nerve damage, but case reports suggest that this is an inconsistent warning sign. Not all pain on injection is associated with clinical injury. In contrast, there are reports of injury occurring when pain on injection was immediately followed by discontinuation of injection, implying that even if a warning occurs, the damage may already be done. There is no evidence that using UGRA reduces the incidence or severity of nerve injury, but there are case reports of injury despite the use of ultrasound. Two risks specific to brachial plexus regional anesthesia deserve comment. Reports of intramedullary spinal cord injection during interscalene block under general anesthesia while using the classic interscalene groove approach suggest that this practice may be dangerous. Furthermore, reports of peripheral nerve injury after supplemental selective nerve block performed at the elbow or wrist in patients with incomplete proximal brachial plexus blockade suggest that this practice too may be risky. There are no data to confirm or refute the contention that UGRA can reduce these risks.

In the absence of those rare instances when a needle fully or partially transects a nerve, anesthesia-related nerve injury is believed to result from a combination of factors. First, harmful needle contact or intrafascicular (subperineurium) injection damages the nerve-blood barrier. Once this protective barrier is breached, normally innocuous local anesthetics can cause neurotoxicity, which in turn can be worsened if epinephrine impairs clearance of local anesthetic from the perineural area and/or causes ischemia to the injured nerve. (Figure 5) Peripheral nerve injury may also occur in the setting of a 'double crush' phenomenon. This theory suggests that when nerves already compromised by an existing subclinical injury, e.g., cervical disc disease, diabetes mellitus, or neurotoxic chemotherapy, are then exposed to a second relatively minor injury, e.g., surgical positioning or a minor needle injury, significant clinical injury becomes manifest. There is clinical evidence to both confirm and refute the role of "double crush" in peripheral nerve injury. Finally, the brachial plexus is particularly prone to inflammatory neuropathies such as neuralgic amyotrophy. We inadequately understand these rare and usually temporary, but occasionally devastating, peripheral nerve injuries associated with brachial plexus regional anesthesia.

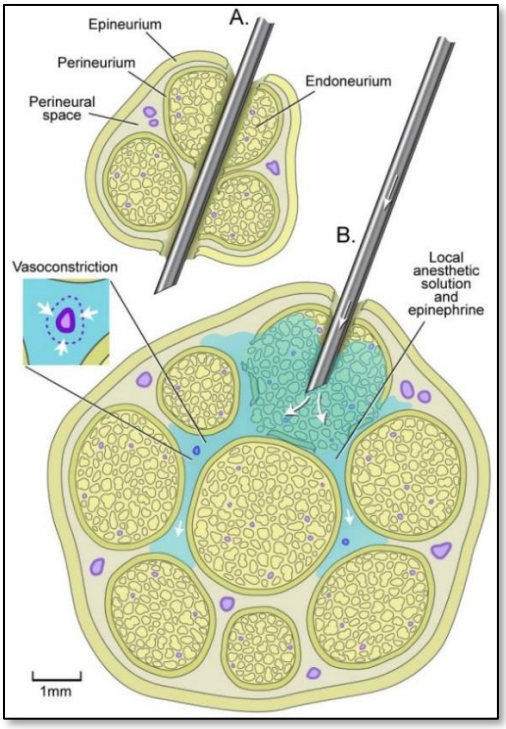

Figure 5. Neal & Rathmell, 2013

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Radiofrequency Ablation of the Spine and Major Joints, Updates on Technology and Outcomes

Maxim Eckmann, MD **San Antonio, TX**

Introduction

Chronic pain of the spine and major joints is a significant source of pain and disability in the world and the United States. Numbers of spine surgery and joint replacement are expected to increase substantially in the next several decades, reflecting tremendous direct and indirect medical costs. Radiofrequency ablation (RFA) for palliative denervation of nerve tissue has been available since the 1950s since the discovery that alternating high frequency electric fields can cause controlled tissue heating[1]. This technique has been applied to a widening variety of chronic pain conditions in an attempt to palliate painful joints and nerves. Current practitioners in interventional pain medicine must be versed in the relevant neuroanatomy, selection criteria, technology, and complications around RFA to include applications in the lumbar spine, thoracic spine, cervical spine, sacroiliac joint, hip joint, knee joint, and possibly the shoulder joint in the future.

Science of Radiofrequency and Determinants of Lesion Geometry

Tissue Effects

Rapidly oscillating electromagnetic field delivered by the RF probe results in ionic movement within tissue and secondary heating through friction[2]. This method is much more predictable and safe for the cardiac conduction system than direct current heating. Tissue factors[3] therefore have a strong effect on determining the size and shape of lesions, as does radiofrequency active tip geometry. Key factors include regional differences in tissue electrical conductivity and impedance, tissue thermal conductivity, heat losses from circulation, and current density[3]. Monopolar lesion shape is generally ellipsoid around the active tip of the RFA cannula, as this is the where the formed electrical current has the greatest density. The radial center of the RF lesion is slightly cooler than the peak temperature achieved. Bipolar lesions can be formed between two cannulas placed in close approximation, with electrical return path oscillating in the form of alternating current between the two electrodes. Over time, bipolar lesions can connect to form a strip of coagulation if the distance is not too great[4]. The presence of adjacent tissue layers, namely bone, may also influence lesion geometry due to changes in impedance and electrical return paths[5].

Augmentation

Several methods to augment the size of RFA lesions have been used, in an attempt to increase the chances that the coagulation zone successfully encompasses the target. Saline enhancement has been shown to increase lesion size; this technology was originally employed in the ablation of tumors[6]. Recent ex-vivo investigations[7] show that hypertonic saline can cause the most lesion size augmentation in monopolar lesions for lesion duration approaching 180 seconds. Increasing the contact of active electrical tips through needle geometry design can increase lesion size. Multipolar probes[8] and probes with protruding tines grant options that may improve efficiency of lesion matching with neuroanatomy; however whether these devices improve outcomes is unproven. Cooled radiofrequency ablation (CRFA) differs from standard radiofrequency ablation (SRFA) in that the tip of the probe is actively cooled to reduce central peak temperature somewhat while still achieving thermocoagulation. This allows for increased power delivery without charring or steam formation, driving the peak temperature further radially away from the central axis of the probe. CRFA lesions can encompass 8 times more volume and double the diameter of SRFA lesions. CRFA can also be applied in a bipolar fashion. Larger lesion sizes may confer slightly increased risk of complications, including reported skin burns in thin patients[9].

Lumbar Zygapophyseal Joint Ablation for Chronic Low Back Pain

Anatomy and Technique

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Zygapophyseal (a.k.a. facet or Z) joints are innervated by medial branch nerves from the spinal nerve above and at the level of the articulation. For example, an L4/5 facet joint is innervated by a descending medial branch from the L3 nerve root and a local medial branch from the L4 nerve root. Medial branch nerves are small in diameter and lumbar branches lie in the junction between the superior articular process and transverse process[10], deep to the mamillo-accessory ligament. RFA of the lumbar medial branch nerve, described by Shealy in 1976, is used as a denervation procedure for facetogenic low back pain, although technically the medial branch also innervates other structures like the multifidus muscle. Current procedural guidelines recommend maximal ablation contact zone with the course of the nerve while remaining posterior to the neuroformen to avoid spinal nerve injury. Patients are candidates for RFA if they have had a good response to a precise and fluoroscopically guided nerve block of the medial branch nerves innervating the painful segment in question, and if they do not have contraindications to the procedure.

SRFA

Currently available SRFA probes and cannulas have a linear geometry and active tips of curved or straight angulation. Active tip lengths generally vary from 5-10mm. Lesion size with SRFA depends on the gauge of the cannula used[11]; 18 gauge cannulas can generate a maximal lesion diameter of about 4-5 mm. Best practices include placement of the active tip along the expected anatomic course of the medial branch nerve for the best chance of successful lesion generation. Multiple fluoroscopic views to include anterior/posterior (AP), lateral, and oblique views are recommended for precise and safe guidance of the needle toward the target. The approach may use a declined angle and some obliquity for the optimal vector toward and over the nerve target. Motor testing and lateral fluoroscopic landmarks assist the physician in avoiding over-advancement and possible injury to the spinal nerve. Multiple passes in slightly different paths may increase the chance of a successful nerve lesion. Motor response will often demonstrate multifidus twitch but should not recruit lower extremity muscles.

CRFA

The fundamental concept of using CRFA for treatment of lumbar facetogenic pain does not substantially differ from that for SRFA. However, CRFA has the potential to create a 1cm diameter spherical lesion that protrudes distally a few millimeters from the active tip. Theoretically there is a greater probability of creating a successful lesion of the medial branch nerve in a single approach than with a single SRFA approach. Superior rates and amplitudes of positive outcomes are thought to be possible with this new technology in the setting of lumbar medial branch ablation but so far this assumption is unproven[12].

Evidence

Metanalysis of outcomes for lumbar medial branch RFA report that there is moderate quality evidence for short term improvement in pain and function vs. placebo[13,14,15], while on the whole there is weak evidence for longer duration of benefit (>1 month). Analysis of subgroups[15] suggests that outcomes are improved in cases where there is very good response (>80%) relief to diagnostic nerve block is used as a selection criteria for proceeding to RFA. A sham controlled study by Nath[16] did show improved pain back pain scores at 6 months (by 2.1 NRS points compared to 0.7 for placebo), back movement, hip movement, and quality of life variables in treatment group; included subjects had responded over 80% in a concordant duration of action with blinded diagnostic blocks containing lidocaine and bupivacaine, and RFA was performed parallel to the anatomic course of the medial branch nerves using a 22g cannula with 5mm active tip.

Thoracic Zygapophyseal Joint Ablation for Chronic Thoracic Spine Pain

Anatomy and Technique

Thoracic medial branch nerves demonstrate variable course depending on which portion of the thoracic spine is considered[17]. Lower thoracic nerves at the T11-T12 levels appear to be close to the base of the superior articular process. At mid-thoracic levels (T5-T8), the nerve may lie in the intertransverse space superior and medial to the tip of the transverse process, then courses over a portion of the transverse process, to move medially and

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caudally toward the facet joint. At other thoracic levels (T1-4, T9-10) the nerve is close to the tip of the transverse process.

SRFA and CRFA

Multiple techniques have been proposed for ablation of the thoracic medial branches[18]. Multiple passes along the transverse process with an SRFA probe, or a cooled RFA lesion at the superior border of the transverse process are both theoretically appropriate methods. Incidental intercostal or spinal nerve injury at these levels is not optimal but confers less functional deficit than would be seen with lumbar nerve roots.

Evidence

Evidence for thoracic RFA is very weak and consists primarily of case series[19], though theoretically the same diagnostic and treatment paradigm should apply. Augmented RFA has been proposed as a method to increase chances of successful denervation. Considering the lower prevalence of thoracic facetogenic pain and the variable course of the medial branch nerves, outcomes in this region of the spine are much less proven than for other applications of RFA in chronic pain.

Cervical Zygapophyseal Joint Ablation for Chronic Cervical Spine Pain

Anatomy and Technique

Cervical medial branch nerves generally lie in the waist of the articular pillars of the cervical spine as they emerge from the nerve root and course posteriorly to the facet joint[20]. The vertical distribution of medial branches varies with spine level; best lesions may be achieved somewhat more cephalad at the C7, C6, and C3 levels; while other levels have a relatively central target. However, due to individual variability, multiple locations can potentially increase the chances of success. Motor testing may result in local spine muscle twitch, but where applicable there should be no upper extremity movement. Care is taken for the lesion not to encompass the spinal nerve. A small number of patients may have dysesthesias or burning sensation in the overlying skin after the procedure. Severe but rare complications include dropped head syndrome and progressive kyphosis[21,22].

SRFA

Lateral, oblique, and posterior approaches to the medial branch nerves are all possible. Posterior approaches require a declined view in order to place the active tip along the course of the nerve. Curved tips may facilitate steering and close approximation to the waist of the articular pillar; alternatively several angles with a straight tip can be used. Lateral approaches may be more comfortable for the patient but may have drawbacks to include potential for spinal cord injury and non-optimal matching of lesion geometry with the course of the medial branch.

CRFA

CRFA of the cervical spine is an emerging technique which requires more posterior placement of final tip position. There is no significant literature for guidance on outcomes or complications. Injury to nearby cervical vasculature is a theoretical complication.

Evidence

A sham controlled RCT was performed using 100% pain relief from dual controlled diagnostic blocks and lack of response to a placebo block as the criterion progression to RFA. In a meticulous technique with multiple approaches, levels below C2/3 were treated. Patients did achieve durable pain relief with median time of at least 50% pain relief = 263 days vs. 8 days for sham group[23]. Paraspinal tenderness has been a physical finding associated with greater chance of improved outcome[24]. Opioid use, conversely, is associated with less chance for benefit[24]. There is additionally on the whole level II evidence for greater than 50% pain relief at 12 months following intervention when other available studies are analyzed[25].

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Sacroiliac Joint Ablation for Chronic Sacroiliac Pain

Anatomy and Technique

Chronic sacroiliac (SI) joint pain remains a challenge for diagnosis and treatment for several reasons. Physical exam maneuvers are notably non-specific in the identification of sacroiliac joint pain. Portions of the innervation of the sacroiliac joint are dorsal and accessible to block or RFA[26], yet some are ventral and not accessible with current techniques. Lateral branch nerves emerge from the sacral foramina and course over the sacrum in variable depths, laterally to the sacroiliac joint. The concentration of neural innervation appears to be near S1 and S2, but can include S3 and the dorsal ramus of L5[26]. Controlled diagnostic blocks are believed to be the best method to prognosticate suitability for lateral branch RFA.

SRFA, CRFA, and Multipolar

SRFA using multiple lesions near the lateral, lateral superior, and lateral inferior aspect of the dorsal foramen can be performed. Bipolar palisading strip lesions can also be made using SRFA probes[4]. CRFA can be applied in a similar fashion. A custom multipolar probe technology can apply a strip lesion using combined monopolar and bipolar lesions in one single pass between the foramens and the sacroiliac joint.

Evidence

Outcomes for SRFA of the SI joint show low evidence for intermediate term improvement in pain[14]. Recent meta-analysis including 7 cooled RFA trial of mixed retrospective and prospective or placebo controlled design spanning follow-up of 3-24 months demonstrated mean reduction in pain of about 3.8 points on NRS and Modified Oswestry Disability scale improvement of 18 points after treatment, though more high quality prospective study is likely needed to improve the power of the findings[27]. Multipolar RFA has observational data and requires more prospective study[8].

Genicular Nerve Ablation for Chronic Knee Pain

Anatomy and Technique

Genicular nerves are articular sensory nerves that innervate the knee capsule and emerge from several branches of both the femoral and sciatic nerves[28,29]. In analogous fashion to the treatment paradigm for lumbar and cervical facet ablation, it has been discovered that innervation to portions of the knee joint, particularly anteriorly, can be interrupted without compromising motor strength. Genicular RFA is an emerging technique for management of intractable pain from osteoarthritis, and may show promise for palliating pain prior to total knee preplacement surgery.

SRFA, CRFA, Evidence

Two early randomized, sham controlled RCT's applied RF lesions near the lateral and medial distal femur, and medial proximal tibia. In patients with advanced OA, pain relief of up to 12 weeks was seen in a significantly higher proportion of patients for the treatment group. The technique is applied in a posterior to anterior approach, with the needle tip being advanced adjacent to the periosteum slightly past the midway depth of the shaft of the femur and tibia in the lateral view[30]. CRFA has been adapted to this application, and prospective long term studies currently show a 19% chance of complete pain relief, as well as a 35% chance of minimum clinically important difference to include at least "improved" global perceived effect, >= 50% NRS pain improvement, and avoidance of surgery[31]. Using a cutoff of >80% relief from diagnostic block markedly increases the odds of success, as does having pain under 5 years in duration. More data is needed to confirm the effectiveness of RFA for chronic knee pain, to include patient selection characteristics, diagnostic block standards, anatomically based approaches, and perioperative/postoperative applications.

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Obturator and Femoral Articular Nerve Branch Ablation for Chronic Hip Pain

Technique

The obturator and femoral nerve send articular nerve branches to the anterior hip joint. The posterior hip is innervated by the nerve to quadratus femoris and the superior gluteal nerve. The anterior nerves have been ablation targets in an attempt to palliate severe, non-operable hip pain. Analogous diagnostic paradigms for diagnostic nerve blocks are applied and theoretically should confer a chance for improvement with RFA. Hip flexor and adductor muscle strength should be preserved.

SRFA, CRFA, Evidence

Several case series of SRFA suggest some promise for ablation over the superior portion of the acetabulum and inferomedial portion of the acetabulum. Approach can be performed in an anterior, caudal, and oblique fluoroscopic view or vector. Femoral nerve and arterial injury have occurred with this technique[32]. No randomized controlled trials are available as of the time of this review. CRFA has been developed for this procedure in an attempt to increase lesion success, but outcomes differences are unproven.

Shoulder Radiofrequency Ablation

Anatomy and considerations

The shoulder is the most complex major joint with a high degree of mobility, many contributing muscles, and many innervating nerves. Chronic shoulder pain may stem from a variety of causes including rotator cuff disease, osteoarthritis of the glenhumeral joint (GHJ), nerve injuries, capsulitis, and others. The suprascapular, axillary, lateral pectoral, subscapular, and musculocutaneous nerves, are known to innervate the GHJ[33]. Other nerves may also contribute theoretically by Hiltons Law of joint innervation. Articular branch nerves have been described and may be future clinical targets[35].

Evidence

Anatomic studies suggest access to articular branch nerves is probably practical and safe. Case series exist of main suprascapular nerve ablation to palliate shoulder pain in patients with limited functional use of the shoulder[35]. While weakness of the shoulder is a logical complication, patients tend to retain or improve function due to reduced pain and compensation from other muscles.

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Radiofrequency: Adapting Recent Technical Advancements RFA options of the Spine and Sacroiliac Joint

Ricardo Vallejo, M.D., Ph.D.

Bloomington, IL, USA.

Radiofrequency lessoning of the medial branches to treat facet joint pain was introduced by Shealy in 1975. Four years later, Bogduk, described the anatomy of the region and the basic principles that govern the percutaneous use of radiofrequency ablation. Before considering the recent advances in the use of radiofrequency and potential considerations to improve clinical outcomes is important to discuss the conditions relevant to this presentation.

The prevalence of Lumbar facet joint and sacroiliac pain increases with age with peak between 50 and 75 years of age for facet and over 60 years of age for sacroiliac pain.

An important consideration relates to the challenges to obtain the correct diagnosis, as there is no specific finding on clinical history or physical examination, or association between imaging and diagnostic blocks. Furthermore, diagnostic blocks of the medial branches have a high rate of false positive results. Because of this, a double differential diagnostic block is recommended to increase diagnostic accuracy. While double dual diagnostic blocks may improve clinical results, is important to avoid the use of radiofrequency in patient incorrectly diagnosed with the condition. Possible causes of false positive results include leakage of injectate into adjacent structures (epidural space, intervertebral foramina, posterior paraspinal muscles-multifidus/longissimus), inappropriate use of sedation (muscle relaxation), excessive use of superficial local anesthetic, and placebo. Ways to reduce false positive response include, performing placebo-controlled/confirmatory blocks, aim at lower target on the transverse process, reduce the volume of injectate, and judicious use of superficial local anesthesia. The accuracy of diagnostic blocks increases when patients report > 80% relief after them. Furthermore, because of the low prevalence of lumbar facet pain the certainty of the accuracy in the diagnosis may require the use of placebo blocks, which may have some ethical considerations, which are beyond the scope of this presentation,

The sacroiliac joint is a true synovial joint, with a minimal passive movement (4 degrees) and an average volume of 1.6 ml. The joint receives innervation by the lateral branches of L4 to S3. Out of this innervation L4 contributes in 4% of patients, L5 in 8% , S1 and S2 100%, and S3 in 88% respectively. Regarding the prevalence, it represents 15 to 30% of axial low back pain patients, although is more common in patients with fail back surgery syndrome. It is bilateral in 20% of the cases and when unilateral, more common in the right than the left side. Common causes of sacroiliac joint pain include motor vehicle accidents, fall on the buttock, sudden lifting and twisting, and repetitive shear or torsion.

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The diagnostic algorithm is based initially on a solid history and clinical examination focused on the Fortin finger test, tenderness over the SI joint sulcus, and provocation maneuvers (Distraction, thigh Thrust, FABER, Compression, and Gaenslen's maneuver). The sensitivity and specificity of 3 or more positive provocation maneuvers for SIJ pain is 85 and 76% respectively. Differently from facet joint arthropathy, intra-articular SIJ diagnostic injections are the current standard.

Radio waves delivered at certain intensity via an electrical probe, into conductive tissue, generate a current due to ionic flow. The ionic friction resulting from the current flow increases the temperature of the tissue around the active electrode. From the active electrode, the current travels towards a grounding pad located far from the radiofrequency probe to close the electrical circuit. When the temperature of the tissue exceeds 45 °C, biological changes start to occur in cells. Temperatures above this critical value have an increasingly larger impact. At temperatures above 55 °C, irreversible damage is caused, generally referred as an ablation lesion. Radiofrequency (RF) based ablation has been developed as a therapy that is utilized in interventional pain medicine for denervation of neural tissues and oncology to destroy cancerous tumors, while protecting the integrity of neighboring structures. Current understanding and focus within the art aims to provide the largest lesions safely possible through manipulation of RF probe configuration, size of probe introducers, ablation time, ablation temperature, and injection of conducting fluids in the lesion site. Another important technical consideration is the angle the radiofrequency needle in reference to the target, for ablation, considering that the lesion is developed along the axis of it.

Based on this considerations, placing the electrode perpendicular to the nerve has the risk to miss the nerve altogether, or creating no more than a spot lesion on the nerve.

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The Wave of the future: Rescue Transthoracic Echocardiography for Non-Cardiac Anesthesiologists

Josh Zimmerman, MD, FASE **University of Utah**

Presentation 1 – Give me the Basics : Transthoracic echocardiography image acquisition and interpretation

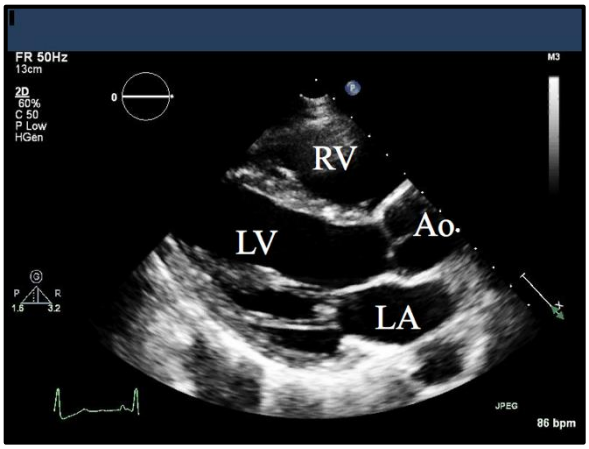
Introduction

This lecture will cover the basics of bedside transthoracic echocardiography for the assessment of the unstable patient by the non-cardiac anesthesiologist. This is a complex topic and one that obviously cannot be mastered during a single lecture, however the new bedside sonographer will be given a basic introduction as a starting point. During our discussion the techniques required to obtain the basic two-dimensional images will be described, the anatomy of each view will be discussed, and the findings that are likely to be identified in the unstable patient will be described. For readers interested in a more detailed discussion, this topic has recently been reviewed.[1]

Basic Views – Image Creation, Anatomy, and Assessment

Parasternal Long Axis

The parasternal long axis view is made with the ultrasound probe placed just to the left of the sternum generally in the 3rd to 5th intercostal space with the indicator pointing toward the patient's right shoulder. The view shows a portion of the right ventricle (RV), the aortic valve, proximal ascending aorta (Ao), left atrium (LA), mitral valve (MV), and left ventricle (LV.) This view should be assessed for chamber size, global left ventricular systolic function, and function of the aortic and mitral valves.



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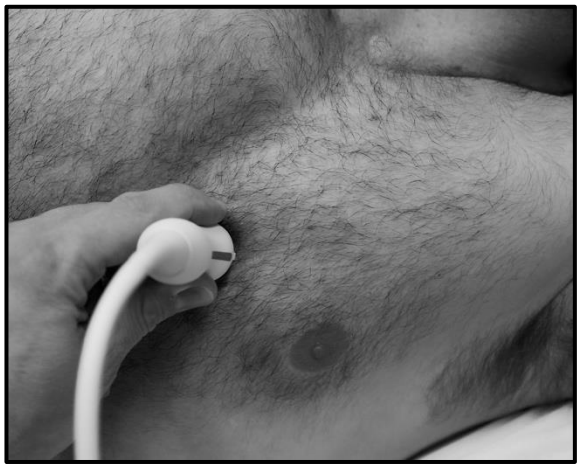
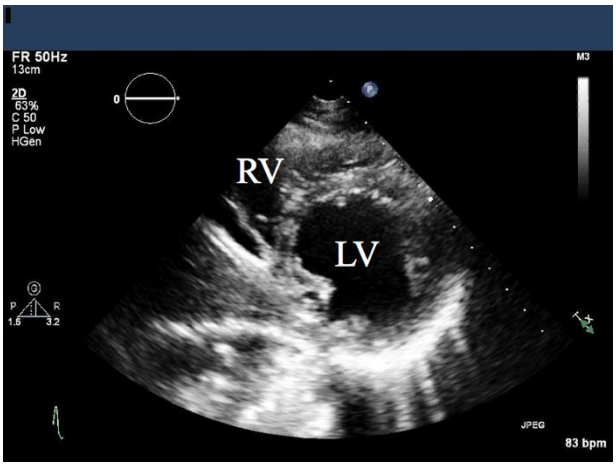
Parasternal Left Ventricular Midpapillary Short Axis

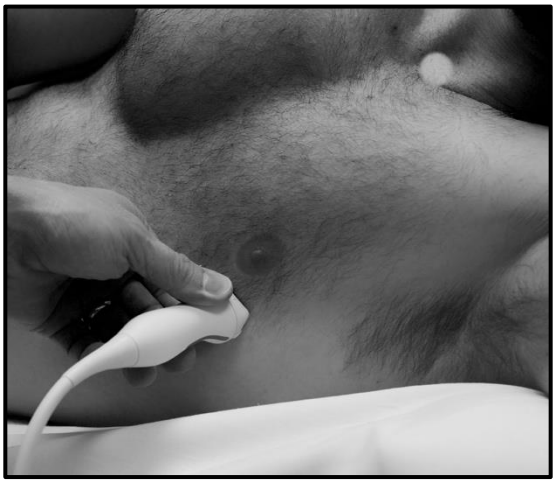
The parasternal short axis view is created by rotating 90 degrees from the long axis, with the indicator pointing toward the patient's left shoulder. This view shows the mid portion of the left and right ventricles at the level of the papillary muscles. It shows 6 segments of the left ventricle representing all 3 coronary distributions. This view should be assessed for global and regional left ventricular systolic function and left ventricular filling.

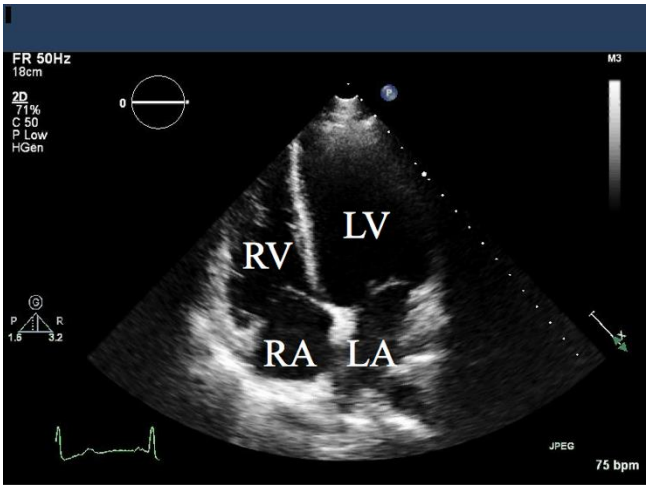




Apical Four Chamber

The apical four chamber view is created by moving the probe the LV apex, which can be identified by palpating the point of maximal impulse (PMI.) The indicator will point toward approximately 5 o'clock when viewed from above. This view shows the left and right ventricles, the mitral and tricuspid valves, and the left and right atrium. This view should be assessed for left and right ventricular systolic function and filling, chamber size, and mitral and tricuspid valve function.





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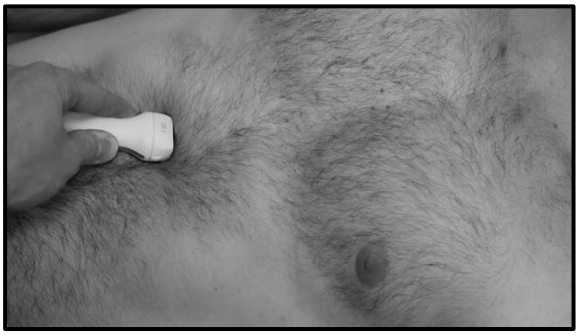
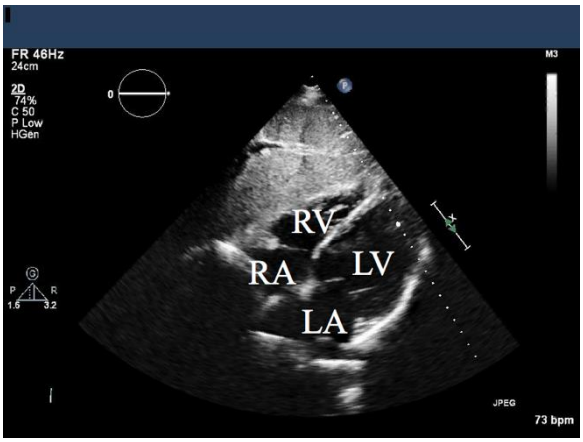
Subcostal Four Chamber

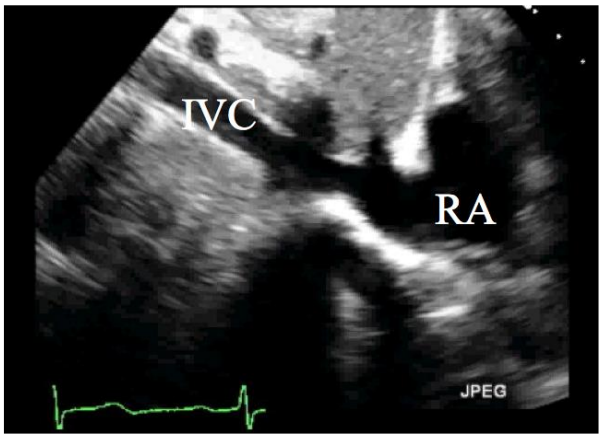
The subcostal four chamber is made by placing the probe below the xiphoid process or slightly toward the patients right, nearly perpendicular to the skin, angled slightly down and toward the patient's left. This view shows the left and right ventricles, the mitral and tricuspid valve, and the left and right atria. This view should be assessed for left and right ventricular systolic function as well as for the presence and significance of pericardial effusion.





Subcostal Inferior Vena Cava (IVC) Long Axis

The subcostal IVC long axis is created from the four chamber view by keeping the right atrium in view and slowly rotating the probe clockwise until the IVC is seen entering the right atrium. This view shows the size and behavior of the IVC with ventilation which gives information about right atrial pressure and volume status.



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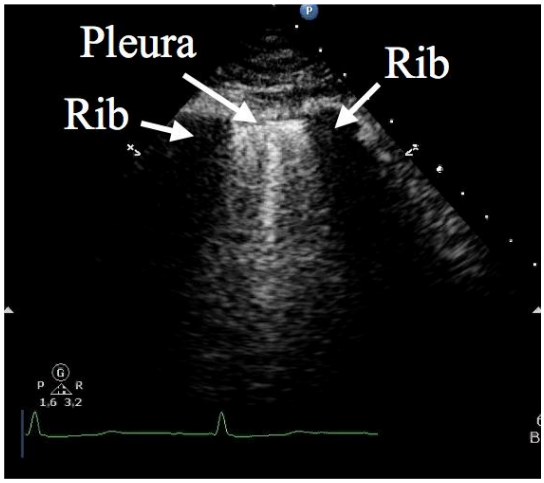
Lung Windows

Each lung should be imaged in at least 6 locations, both superior and inferior locations in the midclavicular line, the midaxillary line, and as far posterior as the patient's position will allow. The probe should placed perpendicular to the skin, with the indicator pointing cephalad. The non-dependent lung fields should be assessed for lung sliding (the presence of which excludes significant pneumothorax), the posterior lung fields should be assessed for evidence of significant effusion, and all lung fields should be assessed for the presence of 3 or more B-lines (lung rockets, comet-tail artifacts) which suggest increased lung water.



Presentation 2 - Now How do I use it? Preoperative Risk Stratification for Urgent and/or Emergent Surgery

Yuriy Bronshteyn **Duke University**

This lecture will describe several specific applications of diagnostic point-of-care ultrasound (POCUS) in the peri-operative period. Diagnostic POCUS broadly refers ultrasound that is performed and simultaneously interpreted at the bedside using simple equipment to qualitatively answer time-sensitive clinical questions. POCUS can be performed by someone with focused training in ultrasonography. This lecture will focus on two subsets of POCUS: focused cardiac ultrasound (FoCUS) and focused lung ultrasound. Notably, FoCUS is distinct from echocardiography: a quantitative evaluation of the heart using advanced equipment by someone with comprehensive knowledge of cardiac ultrasound views and pathology.

Clinical trials randomizing patients to POCUS or control in the perioperative period may never be deemed ethical because of evidence from other clinical contexts showing the value of this skillset in the management of acute organ failure. Further, there is a lack of data showing that any diagnostic tool (including even the pulse oximeter) improves patient outcomes. Thus, for the time being, the evidence supporting perioperative use of POCUS is limited to (1) case series and (2) POCUS studies conducted by other specialties such as emergency medicine and critical care.

The potential perioperative value of POCUS can be separated into two broad applications: (1) pre-operative planning and (2) intra-/post-op crisis management. In the pre-operative setting, FoCUS can be used to screen patients for anesthesia-relevant cardiac conditions that are routinely missed and/or misdiagnosed by the physical exam. Specifically, pre-operative FoCUS can be used to screen for any of the following: (1) gross left ventricular dysfunction; (2) gross right ventricular dysfunction and/or dilatation; (3) gross hypovolemia; (4) the presence of a pericardial effusion; and (5) gross valvular disease. In terms of valvular disease, providers with minimal training can be taught to identify aortic valves that are grossly stenosed and those that clearly open widely. Ambiguous cases of any finding on FoCUS exam can always be referred to providers with advanced training in echocardiography (e.g., echo-cardiologists and cardiac anesthesiologists).

Intra- and post-operatively, POCUS is most useful for crisis management. In patients who develop shock/hypotension and/or pulmonary insufficiency, POCUS can help narrow the differential diagnosis and potentially expedite treatment. Specifically, in that setting FoCUS can help to identify the same five pathologies listed in the pre-operative evaluation above as well as (6) dynamic left ventricular outflow tract (LVOT) obstruction. Further, the addition of lung ultrasound can help screen for at least three additional conditions: (7) mainstem intubation, (8) pneumothorax, (9) pulmonary edema. Mainstem intubation and pneumothorax should be suspected whenever ultrasound reveals a loss of lung sliding unilaterally. In this scenario, the presence of something called a "lung point" can help: "lung point" rules in pneumothorax with reported 100% specificity. Pulmonary edema is identified by the presence of multiple ring-down artifacts ("B lines") emanating from the pleural line.

Notably, the ASA is currently developing a framework both to help anesthesiologists learn POCUS and to assess competency in this skillset. A resulting certificate may empower increasing numbers of qualified anesthesiologists to use POCUS to improve patient care.

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Title: Safety and Efficacy of Regional Anesthesia in Infants, Children and Adolescents

Santhanam Suresh, MD **Chicago, IL**

Introduction: Regional anesthesia is experiencing rapid growth in pediatric anesthesia. The use of ultrasound guidance has increased the variety for blocks that can be performed in infants, children and adolescents. The increased safety of performing blocks with US guidance has allowed the practitioner to attempt to perform more difficult blocks compared to previously described using landmark techniques [1–4]. The use of ultrasound guidance can also allow minimal use of local anesthetic solutions thereby decreasing the risk of toxicity[5]. In this lecture, a variety of regional anesthesia techniques will be described that you can use in your everyday practice. Central neuraxial as well as peripheral nerve blocks will be described with clinical techniques as well as images for reference while performing these blocks.

Equipment: As the field of regional anesthesia is exploding, the use of ultrasound imaging is undergoing constant improvement. Several ultrasound imaging machines with the capability of offering a variety of applications including echocardiography have entered the market with greater emphasis on user-friendliness and portability. This may be of greater importance in the pediatric population since most of these blocks are performed in the operating room under general anesthesia. In children, it may be easier to perform regional anesthesia with deep sedation or under general anesthesia[6]. Recent multi-center reports demonstrate regional anesthesia under general anesthesia is safe in children[7]. US probes commonly used in children include a high frequency hockey stick probe and a linear 25 mm high frequency probe. Since most of the neurovascular structures are located superficially in children, visualization of neural structures is easier with a high frequency probe. The physics and equipment descriptions can be found in textbooks on US guided regional anesthesia. US guidance can be used for central neuraxial blocks as well as for peripheral nerve blocks. A brief description of each of these blocks will be provided at this refresher course. In general, the use of curvilinear probes is limited to the use in older children and obese individuals.

Dosing: Recent attention has been focused on the dosing of local anesthetics and adjuvants in regional anesthesia. Significant dose variability was found in a multi-center report of over 40,000 peripheral nerve blocks, with 5- to 10-fold spread in dosing depending on the block type. Albeit this, only two patients developed local anesthetic systemic toxicity, with no short- or long-term sequelae[8]. Since then, the European Society of Regional Anesthesia (ESRA) and American Society of Regional Anesthesia (ASRA) have released joint recommendations on local anesthetic and adjuvant dosing[9]. Similarly, the European Society for Paediatric Anaesthesiology (ESPA) has released guidance on dosing in pediatric regional anesthesia as part of a pain management initiative[10]. The topic remains controversial and requires further pharmacokinetic and pharmacodynamics evidence[11].

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Central neuraxial blocks:

Epidural Analgesia:
Ultrasound imaging seems promising for use either pre-procedurally (prior to puncture) or during block performance (US aided), although the latter may be most suitable in infants. The largely cartilaginous posterior vertebral column of neonates and infants enables good US beam penetration to view the spinal structures and can in some cases enable a view of the needle tip trajectory. Acceptable safety of neuraxial catheters in neonates has been demonstrated[12].

Epidural Analgesia:
- US-guided technique does not preclude continuous testing for loss of resistance.
- The limitation of the technique is that the needle shaft and tip may be hard to localize with the tangential relationship of the needle (midline) and the probe (paramedian longitudinal).
- An assistant (2nd set of hands) is required during catheter placement in order to perform the imaging real-time for US aided catheter placement. It is important to use saline for LOR to facilitate US imaging.

Techniques
Sonoanatomy:
A moderate-high frequency probe (hockey stick, 13-6 frequency probe) is utilized using a paramedian longitudinal view. The 'window' between the two spinous processes will allow the operator to visualize the anterior complex (anterior duramater, and the posterior longitudinal ligament), the posterior duramater and the ligamentum flavum. Our preference is to visualize the neuraxis using a paramedian approach. In a paramedian longitudinal view at the thoracic spine, the spinous processes are represented by slanted hyperechoic lines beneath the homogeneous-appearing paravertebral muscle mass. Dorsal shadowing will be apparent deep to the spinous processes and other posterior vertebral elements. The highly hyperechogenic ligamentum flavum and dura mater are captured lying in the alternate 'windows', and the underlying spinal cord appears largely hypoechoic with an outer bright covering of the pia and a central line of hyperechogenicity (median sulcus)[2]. In the first report of US imaging in central blockade, Chawathe et al. performed a pilot study in 12 patients (1 day old to 13 months) to evaluate the possibility of detecting catheters, and verifying their placement, within the epidural space after placement (within 24 hours) via the direct lumbar route[13]. The important point from this paper is that US imaging (specifically using the midline approach) of static structures such as catheters can be performed, yet only reliably in very young patients where much of the posterior bony elements of the spinal column may exist as cartilage, thus allowing good US beam penetration. An optimal angle of probe alignment needs to be evaluated in children and surrogate markers for viewing needle and catheters may be necessary to facilitate a dynamic technique. Willschke et al placed epidural catheters under real-time US guidance using the paramedian longitudinal imaging plane in 35 neonates[14]. Needle tip entry and the injection of local anesthetic solution within the epidural space were used to confirm epidural placement; these parameters could be viewed in all neonates. Epidural catheters could only be identified via surrogacy through tissue movement (i.e., anterior movement of the duramater) and fluid injection.

Caudal Needle Placement

- Initially use a transverse plane of imaging to identify the sacral hiatus located between the cornua; the sacral hiatus is located between an upper hyperechoic line representing the sacrococcygeal membrane/ligament and an inferior hyperechoic line representing the dorsum of the pelvic surface (base) of the sacrum.
- Rotate the probe to the longitudinal plane (a paramedian plane may be required in older children) to capture the sacrococcygeal membrane, a relatively thick linear hyperechoic band, sloping caudally.
- Insert the needle under either plane of view, although a longitudinal view may allow for optimal viewing along the needle. A transverse view can be used after needle placement within the epidural space, in order to view the spread of local anesthetic(as dilation of the caudal space and localized turbulence).

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Caudal Epidural Block
Caudal blocks, including both single-shot caudal and lumbar or thoracic epidural catheters advanced from the caudal epidural space (thus avoiding the spinal cord), is a commonly practiced regional anesthesia technique in children. Although this technique is practiced with the identification of landmarks, there is a small, but not insignificant chance for failure.

Sonoantomy: Ultrasound imaging at the midline using both transverse and longitudinal alignment of the probe should be performed prior to needle placement in order to appreciate the patient's anatomy and to identify the sacrococcygeal ligament, dural sac and cauda equina. A linear high-frequency small footprint or hockey stick probe is a suitable choice, although a larger footprint may be used when viewing the longitudinal axis to allow an adequate field of view. Placing the probe initially in a transverse plane at the coccyx and scanning in a cephalad direction can help with landmark identification particularly during training in sonoanatomy. This view allows a good delineation of the sacral hiatus; the sacral cornea are viewed laterally (as "humps") and the sacral hiatus is located between an upper hyperechoic line representing the sacrococcygeal membrane/ligament and an inferior hyperechoic line representing the dorsum of the pelvic surface (base) of the sacrum. Placing the probe longitudinally between the sacral cornua will capture the dorsal surface of the sacrum, the dorsal aspect of the pelvic surface of the sacrum and the sacrococcygeal ligament. The sacrococcygeal ligament covers the sacral base beyond the end of the dorsum of the sacrum. It appears as a relatively thick linear hyperechoic band, sloping caudally. The sacral hiatus is identified as a hypoechoic space located between the dorsum of the sacrum and the dorsal side of the pelvic surface of the sacrum. In older patients where the structures may be ossified at the midline, the paramedian longitudinal view may be necessary since it will allow the US beam to penetrate the spaces on either side of the spinous processes. This paramedian view would allow appreciation of the ventral movement of the duramater during fluid injection, but would not allow a real-time view of the needle along its axis.

Technique: During or after skin puncture with the needle, both transverse and longitudinal sonographic planes can be used for confirming caudal epidural needle placement. Roberts at al. published a prospective observational study of 60 children, in which they determined whether a saline test bolus could be reliably imaged with US in order to confirm cannula placement in the caudal epidural space[15]. While transverse imaging was performed in the pre-puncture scan to help visualize the neuraxial structures (there was no mention of measurements or skin markings), longitudinal imaging (approximately 1 cm above the cannula insertion site) was used during the saline test bolus of 0.2-0.3 ml kg^{-1} to view the anterior displacement of the posterior duramater. The longitudinal plane may allow a view of the long axis of the needle as it penetrates the sacrococcygeal ligament. This technique may be particularly beneficial to allow adjustments in needle angle to ensure adequate length of advancement and depth of penetration without intraosseous placement. The optimal angle for needle insertion during caudal block has been evaluated using US, since many of the previous recommendations include multiple angles, necessitating needle manipulations, including a steep initial angle, which may increase the incidence of bony puncture. When introducing a catheter into the caudal space to reach the lumbar or thoracic spine, similar technique to the above is used for cannula placement and the catheter is viewed during advancement using US imaging at the level of the spine above the sacrum. The above section describing intervertebral epidural catheter placement can be referred to for imaging techniques when viewing the spinal column.

Head & Neck Blocks: Head and neck blocks are often performed in infants and children for managing pain in the postoperative period. Although these blocks are simple and easy to use, the prevalence of their use has been lower than expected due to inexperience as well as the need for education of surgeons regarding their use. Two common blocks that we use in our practice are the infraorbital nerve blocks and the superficial cervical plexus block.

Infraorbital nerve blocks: The infraorbital nerve is the terminal branch of the trigeminal nerve (V1). This nerve, as it exits the maxillary foramen supplies the sensory innervation to the upper lips, the maxillary sinus area and parts of the nasal septum. We have used it successfully for infants undergoing cleft lip repair as well as in sinus surgery[16].
Technique: The upper lip is everted, using a 27_G needle, it is advanced towards the infraorbital foramen, after careful aspiration 1 mL of 0.25% bupivacaine is injected. The area is gently massaged to allow easy spread of the local anesthetic solution.
Adverse effects: The upper lip remains numb after the block and some children may find it distressing. In addition, a small hematoma can develop at the site of injection.

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Superficial cervical plexus block: The superficial cervical plexus is derived of the cervical nerve roots and supply the pain fibers for the neck, the pinna and the mastoid area. The superficial cervical plexus wraps around the belly of the sternocleidomastoid to supply the anterior neck as well as the mastoid area with its branches, the great auricular, the lesser occipital, the transverse cervical and the supraclavicular.
Technique: Using a sterile technique, the sternocleidomastoid is identified at the level of the cricoid cartilage(C6), a 27- g needle is inserted along the posterior border of the sternocleidomastoid, after careful aspiration, 2 mL of 0.25% bupivacaine is injected to provide pain relief. We have used this technique for children undergoing mastoid surgery repair as well as for cochlear implants[17].
Adverse effects: Serious adverse effects can be seen from injection into a blood vessel but with superficial injection, there is little chance for major problems.

Suprazygomatic Maxillary Nerve Block: This block has been demonstrated to be very effective in the management of cleft palate repair in children[18]. The suprazygomatic approach from the frontozygomatic angle is one of the safest recommended approaches to the foramen rotundum, which limits needle insertion trajectory to avoid inadvertent puncture of the intraorbital contents through the infraorbital fissure.

The advent of US imaging has resulted in rapid development of different US guided approaches in recent years, including the suprazygomatic maxillary nerve block. Real-time ultrasound guidance minimizes the risks of nerve damage or vascular puncture, but allowing direct localization of the internal maxillary artery, needle positioning, and spread of LA solution. The US probe is placed over the maxilla and under the zygomatic bone, inclined at 45° in the frontal and horizontal planes. Visualization is of the pterygopalatine fossa, with the maxilla at the anterior, and greater wing of the sphenoid posteriorly.

Following puncture at the frontozygomatic angle, located at the junction of the upper edge of the zygomatic arch and the frontal process, the needle is advanced perpendicular to the skin to reach the greater wing of sphenoid at approximately 20 mm of depth, then withdrawn several millimeters and redirected toward the nasolabial fold in a 20° forward and 10° downward direction, progressing in the direction of the pterygopalatine fossa.

To produce effective anesthesia in the maxillary area, the needle is introduced through the pterygomaxillary fissure to the fossa. The needle is advanced using an out-of-plane approach while visualizing the needle under US. Under US the pterygopalatine fossa is bounded by the root of the pterygoid plates, the inferior surface of the greater wing of the sphenoid bone, and the posterior surface of the maxillary bone. It appears on US as a funnel limited by these surrounding structures. The internal maxillary artery is readily visualized in most patients, with a two-dimensional pulsing. Advancement through the temporalis muscle is acknowledged with a loss of resistance and marks appropriate puncture depth. Following performance of a blood aspiration, US can be used to see the spread of local anesthetic in the pterygopalatine fossa and should be clearly observed in >90% of cases.

Upper Extremity Blocks
The most common approach to the brachial plexus in infants and children is the axillary approach and the supraclavicular approach. With the advent of US guidance, the interscalene approach has resurfaced as a viable technique for placement of a catheter. Peripheral catheter use is increasingly used, following good safety data[19].

Interscalene Block
Sonoanatomy: A small footprint hockey stick probe will allow optimal recognition of the superficial structures in this region for infants and small children. In a transverse oblique plane at the level of the cricoid cartilage and at the posterolateral aspect of the sternocleidomastoid muscle, the superficially-located sternocleidomastoid muscle appears triangular in shape and overlies the internal jugular vein and common carotid artery. In small infants, the US probe footprint is wide enough to capture the great vessels along the brachial plexus in the same image screen. Lateral to the vessels and deep to the sternocleidomastoid muscle lies the anterior scalene muscle, and more posterolaterally, the middle and posterior scalene muscle (the latter two often appearing as a single mass). The hyperechoic (bright)-appearing tissue forming a lining around the muscles is presumably the fibrous tissue of the interscalene sheath. Brachial plexus trunks and/or roots in this sagittal oblique section are usually visualized as three (or more) round or oval-shaped hypoechoic (grey or dark) structures, lying between the scalenus anterior and medius muscles[20]. Continuous interscalene blockade was performed for a 10-year old girl in the Philippines during a plastic surgery medical mission with an intravenous catheter[21]. Without the availability of perineural catheters as well as stimulating needles, a 22 gauge angiocatheter was used for the block, utilizing an in-plane alignment to the posterior

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edge of the probe using the US equipment from the obstetric suite. This case demonstrates the ubiquitous nature of US equipment in most medical centers across the globe.

Supraclavicular Block

Sonoanatomy: The probe is placed along the upper border of the clavicle. The carotid and the internal jugular vein are recognized. The probe is moved laterally while looking for the pulsation of the subclavian artery. The supraclavicular brachial plexus is located lateral to the artery and appears hyperechoic mixed with hypoechoic shadows in a grape like fashion surrounding the artery.

Technique: The supraclavicular block is performed using a high frequency hockey stick or linear probe. The subclavian artery to identified, inferior to it is the dome of the pleura and lateral and inferior to it is the 1st rib. The plexus can be accessed using an in-plane approach from laterally. Nerve stimulation can be used in conjunction with US guidance for this block.

Comment: When performing a supraclavicular block there is a greater risk of pneumothorax as the cupola of the lung lies just medial to the first rib, not far from the plexus; the distance of the plexus from the lung being especially short in children. It is critical to ensure that clear visibility of the needle shaft and tip is obtained by aligning the needle in-plane to the ultrasound probe at all times. Single injection techniques are generally sufficient; however multiple injections of local anesthetic can be performed if needed with the needle redirected to ensure sufficient

circumferential spread around the plexus. However, care should be taken to avoid intravascular injection of the surrounding vessels (including the transverse colli artery located cephalad to the plexus). Auscultation of the lungs should be performed before and after performance of the block as well as prior to discharge to detect clinical signs of pneumothorax. A simple method to
recognize the viability of the radial median and ulnar nerve can be performed by a 'thumbs up sign' radial nerve; flexion of PIP (median nerve) and scissoring of the fingers (ulnar nerve) prior to performance of the block to recognize prior injury[22].

Clinical Pearls - Supraclavicular block

- Place a linear probe superior to the clavicle scanning lateral to the great vessels
- Notice the 1st rib and the subclavian artery
- The supraclavicular plexus is seen surrounding the subclavian artery as a 'bunch of grapes'
- Using an in-plane approach, place the needle below the plexus, injection of 0.3mL/kg of local anesthesia will produce adequate analgesia.
- Stay away from using a medially positioned needle due to close proximity to the pleura.

Axillary Block

Sonoanatomy: With the probe placed perpendicular to the anterior axillary fold, a short-axis view of the neurovascular bundle can be obtained; the biceps brachii and coracobrachialis muscles are seen laterally; the triceps brachii muscle is medial and deep to the biceps brachii muscle. The anechoic and circular pulsating axillary artery lies centrally, adjacent to both the biceps brachii and coracobrachialis muscles, and is surrounded by the nerves. The *median* nerve is typically located superficial and between the artery and biceps brachii muscle, the *ulnar* nerve is commonly located medial and superficial to the artery, and the *radial* nerve often lies deep to the artery at the midline. At this level, the musculocutaneous nerve is located between the biceps brachii and coracobrachialis muscles.

Technique: The terminal nerves are visualized in an axial plane, the probe is placed in the axillary fold. A needle is placed in an in-plane approach to access the median, radial and ulnar nerves individually. Local anesthetic solution is placed to surround the plexus in its entirety to provide an adequate blockade. We feel that the use of ultrasound may allow reduction in dosing for the block although further studies are required to prove the pharmacodynamic ability of US guidance with lower volumes for axillary blocks in children.

Comment: Multiple injections and needle redirections are commonly required to ensure circumferential spread of the local anesthetic around each of the individual nerves. Since there is an abundance of vessels in this region, complete avoidance of vessel puncture can be a challenge even when utilizing ultrasound imaging. It is important to understand that the plexus remains very close to the surface and hence the needle should be directed cautiously while this block is attempted. Smaller doses can be used to provide an adequate blockade of this plexus in infants and children.

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Axillary Block
- Place a hockey stick probe or a linear small footprint probe in the axilla as proximal as possible.
- The needle is directed from superior to inferior using an in-plane approach.
- The structures are superficial and hence are located fairly superficial and can be easily identified.
- Color Doppler can be used to recognize the vascular structures.
- Local anesthetic solution is injected to surround the cords.

Lower Extremity Block

Femoral Nerve Block:

Sonoanatomy: Similar to using conventional technique, arterial pulsations of the femoral artery is the key landmark when using US guidance for femoral nerve blockade. With the probe placed at the level of and parallel to the inguinal crease, the nerve appears lateral to the large, circular and anechoic femoral artery (color Doppler may be used to identify the femoral artery and vein). The nerve often appears triangular in shape and may be variable in size. The fascia

lata (most superficial) and iliaca (immediately adjacent to the nerve and in fact separating the nerve from the artery) are seen superficial to the femoral nerve and often appear as bright and longitudinally angled echogenic signals[23].
Technique: A linear high frequency US probe is placed at the level of the inguinal crease and using an in-plane approach, the femoral nerve is accessed from the lateral aspect. Once the needle enters the fascia iliaca compartment, local anesthetic solution is injected to envelope the nerve entirely. If a nerve stimulator is used adjunctly, quadriceps contraction is elucidated. Although one cannot be sure about intraneural injection while using US guidance, it may be prudent to place the needle in the fascia iliaca compartment and not place it directly into the neural plexus.

Femoral Nerve Block
- Place a linear probe along the inguinal/femoral crease.
- Place a needle in an in-plane approach.
- The local anesthetic is injected to surround the nerve.
- The needle has to be placed inside the fascia iliaca compartment and the local anesthetic is seen surrounding the nerve bundle.

Lateral Femoral Cutaneous Block:

Sonoanatomy: The lateral femoral cutaneous nerve is located at the lateral aspect of the insertion of the Sartorius and medial to the tensor fascia lata. The nerve is located between the fascia lata and the fascia iliaca. This supplies the lateral aspect of the thigh and can be used for providing analgesia for surgery to the lateral aspect of the thigh including muscle biopsies[24] and for percutaneous hip pinning.
Technique: A finger is placed to identify the ridge between the tensor fascia lata and the Sartorius. A linear probe is placed straddling the tendinous ridge. The fascia between the tensor fascia lata and the Sartorius houses the lateral femoral cutaneous nerve. After sterile preparation, a 22-G needle is inserted through the fascia lata , after aspiration, 5 to 10mL of local anesthetic solution is injected.
Complications: Rare, bruise at the site of injection.

Sciatic Nerve Block:

Sonoanatomy: The sciatic nerve block is commonly used in children for providing analgesia for lower extremity surgery. We use it in combination with a femoral nerve block for providing analgesia for knee surgery. The sciatic nerve is usually scanned at the level of the popliteal crease. The biceps femoris tendon is identified. The popliteal artery is identified with the popliteal vein on top of the artery. Immediately above that is the tibial nerve. On scanning further laterally, the common peroneal nerve can be located.
Technique: In the supine or prone position, the popliteal fossa crease is identified, a linear US probe is placed at the level of the popliteal crease. The popliteal artery is identified, the popliteal vein deeper to it and deep to that structure is the tibial nerve. The US probe is moved laterally to visualize the common peroneal nerve. The probe is advanced cephalad to where the common peroneal and tibial nerves coalesce to form the single sciatic nerve. A

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needle is placed in an in-plane orientation; the sciatic nerve can be stimulated if a stimulating needle is used to elicit inversion or eversion of the foot.

Sciatic Nerve Block at the Popliteal Fossa

- Place a linear probe in the popliteal fossa at the crease at the knee.
- Look for the popliteal artery.
- The popliteal vein is noted above the artery.
- The tibial nerve is often located in close proximity to the popliteal artery.
- The common peroneal nerve is located lateral to the tibial nerve.
- A linear probe is gently moved cephalad until the two branches confluence; the nerve will diverge from the vessels.
- Using an in-plane approach, a needle is placed in close proximity to the sciatic nerve and local anesthetic solution is injected to surround the nerve.

Blockade of the Anterior Trunk

Among many blocks performed at the anterior trunk, ilioinguinal/iliohypogastric nerve blockade is one of the most commonly performed blocks for surgery in the inguinal region and may be one of the most common peripheral nerve blocks in children[19]. Various other nerve blocks are also becoming popular to provide analgesia for procedures in the umbilical or epigastric regions. Ultrasonography can be particularly beneficial for truncal blocks in children due to the close anatomical relations between the nerves and various critical abdominal structures.

Ilioinguinal/Iliohypogastric Nerve Block

Sonoantomy: A linear high frequency probe is placed immediately medial to the superior aspect of the anterior superior iliac spine (ASIS) to capture a short-axis view of the ilioinguinal nerve sandwiched between the internal oblique abdominal and transverse abdominal muscles. The ASIS appears hypoechoic (due to dorsal shadowing beyond the highly-reflective periosteum) and nodular-shaped at the lateral edge of the screen. The lateral abdominal muscles will appear with multiple hyperechoic dots within a hypoechoic background. The nerve can be identified as an elliptical-oval shaped structure with a hyperechoic film surrounding a hypoechoic core[25,26].
Technique: A hockey stick probe will be suitable for many infants and younger children, since the nerves are closely situated beneath the skin (8 mm on average) and medial (7 mm on average) to the ASIS. The probe is placed with the direction pointed towards the umbilicus. A needle is inserted in an in-plane approach to place in between the internal oblique and the transversus abdominis muscle. Local anesthetic solution is injected to hydro-dissect between the two layers thereby providing a blockade of the L1 nerve root. We use a volume of 0.1mL/kg with a total maximum volume of 5mL for this blockade.

Ilioinguinal Nerve Block

- Place a linear probe or a hockey stick probe along the ASIS with the probe oriented towards the umbilicus.
- The three layers of the abdominal wall muscles can be recognized.
- The ilioinguinal nerve and iliohypogastric nerves are seen as 2 hypoechoic structures between the internal oblique and transversus abdominis muscles.
- Using an in-plane approach, a 27-Gauge needle is advanced and placed between the internal oblique abdominal and the transversus abdominis muscle.
- After aspiration, 0.1mL/kg of local anesthetic solution is injected.

Rectus Sheath Block

Sonoantomy: The rectus sheath is located between the rectus abdominis muscle and the posterior rectus sheath. A small footprint probe will be suitable for viewing unilateral anatomy. The anterior and posterior aspects of the rectus sheath and the enclosed rectus abdominis muscle are visualized. The sheath appears hyperechoic with multiple linear layers, lying on the anterior and posterior aspects of the rectus muscle.
Technique: A linear high frequency probe is placed on the abdominal wall lateral to the umbilicus. Using an in-plane approach and coming in from laterally, a needle is inserted posterior to the rectus abdominis muscle but anterior to the posterior rectus sheath. Superior displacement of the rectus abdominis muscle is seen with injection

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of the local anesthetic solution. This block can be used for umbilical hernia repairs as well as most midline abdominal surgeries involving the T10 distribution

Rectus Sheath Block

- A linear high frequency probe or a hockey stick probe is placed at the level of the umbilicus.
- The rectus abdominis muscle is identified along with the anterior and posterior rectus sheaths.
- Using an in-plane technique, a 27-gauge needle is advanced until it penetrates the space between the rectus abdominis and the posterior rectus sheath.
- 0.1mL/kg of local anesthetic solution is injected into the potential space between the posterior rectus sheath and the rectus abdominis muscle.
- Hydro-dissection can be used to find the exact plane since the space is small and may need exact localization.

Transversus Abdominis Plane (TAP) Block

Sonoantomy: The layers of the abdominal wall can be easily distinguished using ultrasonography. The thoraco-lumbar nerve roots (T10 to L1) provide the sensory supply to the abdominal wall. The nerves run in a plane between the internal oblique and transversus abdominis muscle, hence referred to as the transversus abdominis plane or TAP. A linear probe placed along the lateral aspect of the abdomen can distinguish the various layers of the abdomen including from superficially, fascia/fat, external oblique, internal oblique and the transversus abdominis muscle. A blockade at this level can provide analgesia for anterior abdominal wall surgery. This may be especially useful in infants and children who may have underlying coagulopathy, spinal dysraphism or as a rescue block following a failed neuraxial blockade. The block has been demonstrated to be effective for abdominal surgery in the adult population[27] and safe in children[28].

Technique: A simple step by step approach to this block has been recently described[29]. A linear high frequency probe or a hockey stick probe is used for the procedure. Recognize the various layers of the abdomen. A needle is inserted in the in-plane technique to enter the plane between the transverses abdominis and the internal oblique. Local anesthetic solution (0.2mL/kg) is injected. The downward movement of the transverses abdominis signifies correct placement of the needle in the TAP plane.

Paravertebral Block

Sonoanatomy and Technique: Paravertebral technique has been described in children[30] and various approaches in adults[31]. After positioning the patient in the lateral position for single PVNB or full prone for bilateral PVNB, the desired thoracic level is identified using surface landmarks. Traditionally, T7 has been thought to be the lower

Transversus Abdominis Plane Block

- A high frequency linear probe or a hockey stick probe is placed lateral to the umbilicus.
- Sliding the probe laterally, the three muscle layers of the abdominal wall are recognized (external and internal oblique abdominal and transverse abdominal).
- In the mid-axillary line, using an in-plane approach, place a needle between the internal oblique and the transverse abdominal muscles.
- As local anesthetic is injected, the plane is seen to expand with posterior movement of the transversus abdominis muscle.

border of the scapula whereas C7 is the vertebral prominence. A linear ultrasound probe is placed in a transverse orientation over the midline of the spine and desired dermatome. Characteristic hyperechoic inverted v shapes with an acousting shadow beneath are used to identify the spinous process. The spinous process is identified and moving the probe laterally and with slightly oblique rotating, reveals the tip of the transverse process, in the same view as the parietal pleura. The internal intercostal membrane is identified as a hyperechoic structure connecting the edge of the internal intercostal muscle to the lower edge of the transverse process.

A needle is then introduced in-plane several centimeters from the lateral edge of the US probe and advanced at an angle from lateral to medial until the needle tip is through the internal intercostal membrane, between the parietal pleura and acoustic shadow of the transverse process. It is visualized at all times and correct position within the

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paravertebral space is confirmed by downward depression of the pleura with minor injection of several milliliters of saline and followed by verifying negative aspiration for blood and/or CSF, or air.

Conclusion: US guidance for peripheral and central neuraxial blocks are becoming the mainstay of regional anesthesia in children. As equipment improves and becomes more cost-effective, the use of US guidance may become the norm rather than the exception. Multiple hands-on workshops offered by the ASA, ASRA and SPA may shed greater insight into some of the common techniques. The steep learning curve for US guidance can be offset by offering it as routine curriculum for training residents and fellows in anesthesia training programs. A block-rotation (as offered by the fellowship program at the Ann & Robert H Lurie Children's Hospital of Chicago) can improve and reinforce the use of regional anesthesia in infants, children and adults. Ongoing data is being collected prospectively by the Pediatric Regional Anesthesia Network (PRAN)[32], a consortium of Children's hospitals in North America as well as international efforts in Europe[33]. As more data is collected, we will be able to provide a more meaningful insight into adverse effects, dosing and pharmacodynamics of regional anesthesia in infants, children and adolescents.

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Figure: Ilioinguinal N Block

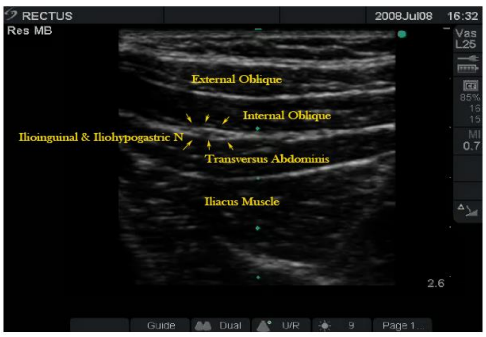
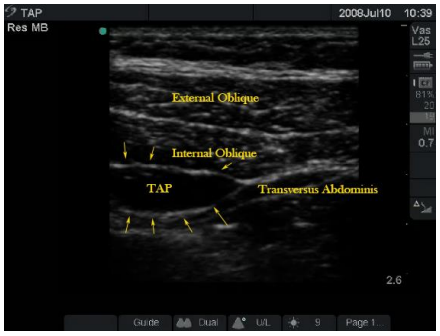


Figure: TAP block



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Trauma Anesthesia for Special Populations: Obstetric Trauma Patient

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Trauma Anesthesia for Special Populations:

Obstetric Trauma Patient

Incidence and Outcomes of Trauma During Pregnancy
Traumatic injury is a relatively common reason for medical evaluation and treatment of a pregnant woman with the estimated incidence of up to 4% and rate of fetal loss up to 19.1% [1]. Most common reasons for injury during pregnancy are falls (usually resulting in minor injuries) but motor-vehicle accidents(MVAs) and violence are most likely associated with severe injury or death.[1,2] Abusive behavior and a suicidal attempt may also be associated with any trauma mechanism in pregnancy and clinicians should maintain a high index of suspicion while treating those women.

Physiologic Changes of Pregnancy: Implications for Trauma Care
There are several physiologic changes of pregnancy that are relevant for resuscitation and anesthetic care. Plasma volume and cardiac output are increased by 50 and 20% respectively by 34 weeks, which may mask or delay timely the recognition of hypovolemia. On the other hand, baseline HR is increased up to 90-100 bpm, and systolic blood pressure is decreased giving a false impression of mild hypovolemic shock. The venous return may be decreased due to compression of inferior vena cava by gravid uterus, which may be exacerbated by hypovolemia.

Mild hypocapnea ($PaCO_2$ =30mmHg) produced by an increased tidal volume and minute ventilation lead to a compensatory decrease in bicarbonate to 20-21 mEq, but base excess (BE) remains in the high -normal range of 2. “Normalization” of $PaCO_2$ around 40-45mmHg range may indicate impending respiratory failure. Decreased functional residual capacity, intrapulmonary shunt and increased cardiac output may lead to rapid and profound desaturation during anesthesia induction and endotracheal intubation. Gastric emptying is delayed, and tone of the lower esophageal sphincter is decreased that is further exacerbates the ever so increased chance of aspiration already present in general trauma population. Edema of the airway warrants uses of smaller endotracheal tubes and avoidance or very cautious use of nasogastric tubes.

Pregnancy, in general, is a hypercoagulable state with significantly increased levels of fibrinogen, factors VII, VIII, IX, and von Willebrand factor. This may have somewhat protective effect against trauma-induced coagulopathy, and “normal” fibrinogen level may indicate disseminated intravascular coagulation (DIC). Conversely amniotic fluid contains many anticoagulant factors including plasminogen, which may lead to profound DIC in cases of amniotic fluid embolism.[3]

Maternal and Fetal Assessment
The most important message for providers caring for a pregnant trauma patient is that the presence of the fetus should not distract them from the conventional framework of ATLS guidelines and indicated radiographic imaging. Risk of missed injuries in the mother due to incomplete work-up far outweigh the small chance of congenital malformation or neoplasm (doubling baseline risk of childhood leukemia) in the fetus. Radiation exposure is more likely to cause congenital malformation very early in pregnancy (4-10 weeks) and mental retardation up to 25 weeks, while the risk of any biologic injury is greatly diminished after 26 weeks of gestation. Observational studies demonstrated significant delays of care and deviations from diagnostic protocols in work up of the injured pregnant patient. Due to a paucity of evidence-based guidelines on this subject, which can be "looked up" at the moment, simulation training and drills are essential so when the need arises caregivers less likely to speculate about risk-benefits between mother and the fetus, delaying important work up and intervention.[4]

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In the context of trauma, pregnant patient following obstetric complications should be assessed: placental abruption (especially in rapid deceleration injury), uterine rupture, preterm delivery and emergent need for cesarean delivery. Fetal-maternal hemorrhage complicates up to 30% of maternal traumas and can be diagnosed by Kleihauer-Betke (KB) test, which detects fetal blood cells in maternal circulation and can provide a general estimate of hemorrhage volume.
After stability of the mother has been ascertained fetal assessment should be performed. Fetal heart rate (FHR) and uterine activity generally should be monitored when gestational age is >24 weeks (minimum survivable age for the fetus) by a qualified person, usually nurse from labor and delivery. Some advanced centers have a higher survival rate of premature infants and monitoring may be warranted earlier, at the gestational age of >22 weeks. Duration of initial FHR monitoring should be 2-6 hrs.[5]

Airway Management, Positioning, and Vascular Access
ATLS guidelines have only slight modification for pregnant trauma victims including a provision of supplemental oxygen, left uterine displacement (LUD) position if possible or manual side shift of gravid uterus and preference for intravenous access above the diaphragm due to a possibility of utero-caval compression.
The utility of LUD has been questioned recently in the settings of a neuraxial block with concomitant vasopressor use, but it is still recommended for hypotensive pregnant trauma patients.[6]

The incidence of difficult tracheal intubation in obstetrics is four times higher than in general surgical population which in combination with cervical spine precautions, decreased FRC, and full stomach makes airway management potentially very challenging. Head-elevated positioning should be considered for intubation to decrease complications by improving pre-oxygenation and laryngoscopy view. Endotracheal intubation should be performed by most experienced person available at the time.[7]

Intravenous access in lower extremities should be avoided because of the possibility of a vena cava compression by gravid uterus and likely need of lithotomy position in case of vaginal exams/delivery or hysterectomy.

Damage Control Resuscitation for Pregnant Patient
The concept of hemostatic resuscitation with a high ratio of PRBC/FFP/PLTs has been adopted from trauma literature into massive obstetric hemorrhage protocols and similarly should be applied to the pregnant trauma patient. Early administration of tranexamic acid (TXA) should be considered for all pregnant trauma patients as it is shown to improve survival in both traumatic and peripartum hemorrhage.[8]

Amniotic fluid embolism may occur with rapid deceleration injury and presents itself as profound hemodynamic instability and disseminated intravascular coagulation. It should be considered in the cases of hemodynamic instability out of proportion to sustained injuries and estimated hemorrhage.

Traumatic Maternal Cardiac Arrest
Perimortem cesarean delivery (PMCD) should be considered within 4 minutes of a maternal arrest of any cause (including traumatic). It should be done mainly for fetal salvage if gestational age is >20 -24 weeks, depending on the local survival rates. The benefit of PMCD for the return of spontaneous circulation (ROSC) in the mother in traumatic cardiac arrest remains controversial. Earlier reports claimed an association of PMCD and successful ROCS, likely due to relieving of vena cava obstruction, but later analysis questioned such relationship.[9]

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Trauma Anesthesia for Special Populations: Geriatric Trauma Patient

Olga Kaslow, MD, PhD. **Milwaukee, Wisconsin**

Trauma Anesthesia for Special Populations

Geriatric Trauma Patient

Trauma is now the seventh leading cause of death for those age 65 years and older.

Older patients also have the highest case-fatality rate following trauma and are up to four times more likely to die than similarly injured younger adults.

The most common causes of trauma among elderly are falls and motor vehicle collisions. Each year, one in three adults over age 65 falls, and an average of 586 older adults are injured daily in car crashes.

Age-related physiologic changes contributing to trauma
Visual loss: Cataract formation decreases vision and increases requirements for bright light; impaired pupillary response affects eye accommodation to light and darkness; peripheral vision is also decreased.
Cognitive dysfunction: Due to decline in memory, thought processing, there is a high prevalence of depression and dementia.
Unsteady balance and gait: Caused by degenerative changes of visual, vestibular, and proprioceptive sensory systems.
Slowed reaction time: Time between perception of a hazard and avoidance behavior becomes longer.
Syncope: The most common causes are cardiac dysfunction, cerebrovascular disease, and orthostatic hypotension.

Anesthetic implications of age-related changes in physiology
Cardiovascular function: Acute blood loss is poorly tolerated in the elderly as cardiac output cannot be improved by the increase in heart rate. Fluid boluses into a stiff heart with diastolic dysfunction and arrhythmias place the elderly trauma patient at risk for heart failure. The aging myocardium is less responsive to circulating catecholamines.
Respiratory function: Preoxygenation prior to induction of anesthesia may not be sufficiently effective due to decreased vital capacity and increased residual volume; abdominal or chest surgery compounded by opioid requirements for pain control and the elderly's baseline increased work of breathing may lead to early respiratory failure.
Renal function: Impaired excretion and conservation of water and electrolytes lead to a predisposition to hyper- or hypovolemia, and hyper- or hypotension; hypovolemia and medication-induced nephrotoxicity make elderly patients susceptible to postoperative renal failure.
Central nervous system function: Postoperative delirium occurs in 5–50% of the elderly; possible etiologies include alteration in cellular proteins by potent inhalational agents, central cholinergic insufficiency, preexisting subclinical dementia, infection, altered electrolytes, anemia, pain, and sleep deprivation.
Physiologic reserve
There is a continuous decline in all organ functions each year with age. However, individual decline remains unpredictable, in part due to concomitant coexisting disease and associated organ dysfunction. A physiologic reserve is a difference between baseline functioning and function required in the face of trauma and severe illness. In elderly, it is narrowed, leading to rapid decompensation, multiple organ dysfunctions, and ultimately death. Age alone should not be a sole reference for clinical decision making in injured geriatric patients. Knowledge of functional status prior to injury can also help to determine the risks of morbidity and mortality that are usually increased in patients with poor functional capacity.
Pre-injury physical frailty
Frailty is defined as a syndrome of decreased physiological reserve across multiple organ systems leading to an impaired ability to withstand physiologic stress. Frail patients are at higher risk of poor outcomes following even

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minor injuries, including postoperative complications. There are multiple models for measuring frailty; one of them is the frailty index (FI) which has been shown to be an independent predictor of in-hospital complications in geriatric trauma patients.

Evaluation of the Trauma Patients

The Eastern Association for Surgery of Trauma and the American College of Surgeon's Trauma Quality Improvement Program developed practice management guidelines regarding the evaluation and management of the geriatric trauma patients. Elderly patients are often undertriaged; age alone should prompt the highest level of trauma activation. A high index of suspicion for concomitant injuries must be maintained even with seemingly innocuous trauma mechanisms. Preexisting conditions could alter the clinical symptoms and increase the risk of poor outcome in elderly patients. Hypoperfusion is often underestimated in the elderly. Normal blood pressure may signify hypotension in a patient who has baseline hypertension. Base deficit and lactate should be assessed to identify patients in occult shock. Knowledge of the trauma victim's medication list is of paramount importance since these medications can significantly alter the response to resuscitation and hospital course. The most common medications taken by geriatric patients are antihypertensives (including beta-blockers and vasodilators), oral hypoglycemic agents or insulin, statins, thyroid hormone replacements, steroids, and anticoagulants. Recent studies demonstrate that 11% to 20% of trauma patients 65 years or older were being treated with anticoagulants at the time of injury. Availability of products for reversal is changing rapidly. Rapid anticoagulation testing and reversal protocol are suggested to be in place in the trauma centers.

Intraoperative Anesthetic Concerns

Airway: C-spine injury such as C1-C2 and odontoid fractures may frequently occur in falls, even from the standing height.

Breathing: Osteoporosis makes an older patient susceptible to rib fractures, pneumo- and hemothorax, flail chest, and pulmonary contusion.

Circulation: Doses of induction agents such as etomidate, ketamine or propofol should be reduced in the elderly by 20%. In the case of hypovolemia and bleeding, doses of induction agents should be decreased even further. Elderly are more likely to develop shock than younger patients with similar injuries. Recognition of early shock might be difficult since both the blood pressure and the heart rate response to hypovolemia and circulating catecholamines is unreliable in a geriatric patient.

The following issues should be taken into consideration when addressing circulation in a geriatric patient:

- Base deficit (−6 mEq/L or less) on the admission arterial blood gas is a marker of severe injury and significant mortality and requires ICU admission.
- Elevated lactate (> 2 mmol/L) along with a delayed rate of clearance suggest occult hypoperfusion and are also associated with increased mortality.
- Significant reduction in coronary perfusion and subsequent myocardial infarction may occur even in the absence of coronary artery disease in elderly patients, revealing a strong association between hypovolemic and cardiogenic shock
- Patients on warfarin, clopidogrel or new oral anticoagulants (NOACs) may result in significant hemorrhage even in the presence of a minor injury.
- Early administration of blood has been advocated to improve oxygen delivery. No clinical benefit has been shown with the use of a restrictive transfusion strategy (transfusion threshold of hemoglobin <8g/dL) in elderly patients when compared to a liberal strategy (transfusion at hemoglobin <10g/dL)

Hip fractures

Worldwide, 1.6 million patients suffer from hip fracture every year, and this number is increasing by 25% every decade. Hip fracture is associated with a poor outcome in elderly patients which markedly contrasts with the relatively simple surgery needed for its repair.

Collaborative care models

Trauma centers that care for a high number of older patients have better outcomes. At these centers, elderly patients are managed by a specialized multidisciplinary team, have the protocols that promote early operative intervention, early ambulation, and daily physical therapy. Various approaches have been proposed to integrate orthopedic and geriatric care for elderly patients with hip fracture, an initiative also known as orthogeriatrics. The anesthesiologist's role in orthogeriatric service includes early alert from the emergency department (ED), prompt preoperative

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anesthesiology evaluation, perioperative pain management, careful resuscitation and facilitating a prompt surgical repair.

Timing of surgery

Surgical repair of a fractured hip is not an elective procedure. A preoperative assessment and optimization of coexisting medical conditions should be expedited and not delay the surgery. Literature shows that early surgery (24 to 48 h) was associated with significantly lower risk of death and pressure sores.

Anesthetic choice

Patients with hip fractures benefit from adequate multimodal analgesia with acetaminophen, opioids and regional nerve blocks that can also be easily performed in the ED. It has been reported that the combination of an obturator and lateral femoral cutaneous nerve blockade is likely to be the most effective against postoperative pain. Reduced opioid requirements also decrease the occurrence of postoperative delirium. There is no firm evidence supporting the superiority of any one anesthetic technique. Multiple studies comparing GA vs. NA for outcomes after hip fracture surgery provide conflicting conclusions. The institutions performing NA for a higher number of their patients with hip fractures demonstrate improved outcomes.

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Trauma Anesthesia for Special Populations
Burn Care

Jessica Lovich-Sapola MD, MBA, FASA **Cleveland, Ohio**

Trauma Anesthesia for Special Populations

Burn Care

Burn injury is considered to be the costliest and most challenging of all trauma care. The skin is the largest organ of the human body and it plays many important physiological roles and maintains body homeostasis. A large burn can alter the proper functioning of almost all organs and can significantly impact the patient's risk of infection.[1,2,3]

The initial assessment of any burn starts with history to determine the circumstances such as existence of confined space, explosion and potential injury mechanisms for associated injuries. Physical examination should begin with airway evaluation to assess whether there is any evidence of facial trauma or burns. A burn injury often directly impacts the airway. Inhalational injury, which leads to swelling, edema, and airway obstruction, is caused by direct thermal or chemical injury. It is especially important to recognize the edema is usually progressive and may require early intubation.[1,2,3]

While assessing the airway, it is important to obtain intravenous access for fluid resuscitation. All burn patients that will require excision and grafting of their skin should have at least two large-bore peripheral intravenous lines or one central line. Lines may be placed through burned skin if required. Arterial lines are helpful with resuscitation of large burns. Excision and grafting surgery often results in a significant blood loss, with an average 200 ml of blood lost for every 1% total body surface area (TBSA) excised. A typical burn without an associated trauma does not in itself result in blood loss, therefore the American Burn Association (ABA) does not recommend blood products be administered to treat the associated dilutional anemia from aggressive fluid resuscitation during the initial resuscitation. The ABA does recommend that blood products be given just prior or upon arrival to the operating room for an excision and grafting procedure. It is very easy to fall behind on resuscitation during excision and grafting surgery.[1,2,3]

A burn patient's nutritional status is of great significance. After a burn, the patient becomes hypermetabolic. The patient will have an increased requirement for energy and protein. This hyperdynamic physiologic response can last for months in a severely burned patient. Failure to satisfy this caloric and protein requirement can result in failure to thrive, loss of body mass, impaired wound healing, multiple organ dysfunction, increased infectious complications, and death.[1,2,3] The concern is that patients with significant burns will often require daily surgical procedures and dressing changes in the first few weeks of care. The current ASA NPO guidelines make it often impossible to get the patient enough nutrition to aid in healing. The Anesthesia Department at MetroHealth Medical Center in Cleveland, Ohio has modified the NPO guidelines for all patients with significant burns to address this patient population's need for high caloric intake. The new NPO guidelines increase the time that a burn patient receives enteral feeding during the peri-anesthetic period and decrease the risk of aspiration while improving perioperative nutrition. This protocol applies to all burn patients requiring operative procedures, general anesthesia, or deep sedation. The result since 2014 has been that our protocol has significantly increased the calorie intake of each burn patient with no resulting increase in complications, such as aspiration.

Severe pain is an unfortunate consequence of burn injury. The pain is often difficult to treat secondary to the multiple sites of injury involved. The burn patient often has complicating psychological and emotional issues secondary to the burn injury. Multimodal pain management is often required. The primary goal of our burn unit is the use a non-opioid pain management technique as much as possible. The Burn Unit Team and the Anesthesia

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Department/ Acute Pain Service are in early and constant communication from the time of a new burn admission. Since 2011, we have aggressively treated severe burn patients with single-shot regional blocks and block catheters, many times in multiple extremities. The only burn-related contraindication for regional anesthesia in a burn patient is that we do not place catheters through burned or infected skin. In addition to regional anesthesia, the teams also use IV lidocaine infusions, IV ketamine, Tylenol, and NSAIDS. Opioids are reserved as a last resort. The goal is to decrease narcotic exposure from the day of admission and try to aggressively treat the patient's pain while avoiding long term complications of opioid administration. Patient satisfaction with pain control in the burn unit has significantly improved with this collaborative multimodal pain treatment approach.

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Trauma Anesthesia for Special Populations: Pediatric Trauma Patient

Sam S. Sharar, MD **Seattle/Washington**

Trauma Anesthesia for Special Populations

Pediatric Trauma Patient

Caring for an injured child is challenging on several fronts, and often involves competing interests and emotions. As parents, we commit – often compulsively – to protecting, comforting, consoling, and treating our own children in life's constant exposure to a childhood injury, yet we understand we cannot anticipate every risk, prevent every accident, or eliminate all negative consequences of such injuries. Similarly, as anesthesiologists, we learn that childhood injuries are statistically commonplace and that some will inevitably require our clinical care, yet these instances in our practices are generally infrequent to rare. When they do occur, however, they are often emotional and stressful, due to their unpredictability and urgency, the care team's potential unfamiliarity with caring for an injured child (particularly a critically injured child treated in an adult-focused hospital), and the high stakes associated with pediatric anesthesia care (particularly for anesthesiologists who infrequently care for children). Readiness for such instances is best achieved by highlighting the basic epidemiology of childhood injury, understanding the key tenets of anesthesia and critical care for injured children, and considering the range of non-clinical contributions to pediatric trauma care that our specialty has to offer.

Basic Epidemiology of Pediatric Trauma

Accidental and intentional injuries account for more deaths in the US (~10,000 annually) among adolescents and young children than all other causes combined, as well as more years of potential life lost under 18 years of age than for infectious diseases, cancer, and sudden infant death syndrome combined. Furthermore, over 10 million children require emergency department care each year in the US for the evaluation and treatment of traumatic injuries. As a result of hospital and other ongoing costs related to lifelong disability and requisite skilled care in this sizeable cohort, the economic costs of pediatric trauma have been estimated at $14 billion in lifetime medical spending and $66 billion in present and future work losses. As staggering as these US numbers are, pediatric trauma is a rapidly increasing problem on the worldwide scale. The causes of this problem include the significant fraction (roughly half) of the worldwide population now younger than 25 years, the pace of economic and technologic development across the globe that has resulted in increased automobile traffic, and the ongoing presence of armed conflicts around the globe that increasingly involve children as both combatants and innocent victims of intentional trauma. As a result, the World Health Organization estimates that traumatic injuries result in almost 1 million deaths annually worldwide [1]. More specifically, the Global Burden of Disease Pediatrics Collaboration recently reported that road accident-related injuries among adolescents are the 3rd leading cause of childhood death worldwide and are the 10th leading cause of Disability-Adjusted Life Years (DALYs) [2].

Key Clinical Tenets of Pediatric Trauma Perioperative and Critical Care

Care of the injured child – identical to that of the injured adult – is interdisciplinary in nature and best delivered when all team members are guided by the same "playbook". The American College of Surgeons (ACS) Advanced Trauma Life Support (ATLS) program has served as the definitive trauma care playbook since 1980. What makes the acute, resuscitative, peri-operative, and critical care of pediatric trauma patients different from other clinical settings and populations, and therefore worthy of special emphasis here and in the ATLS program? Among the answers to this question, two deserve special mention - (1) the unique characteristics of pediatric (compared to an adult) trauma patients, and (2) the more complex interdisciplinary approach to their clinical care [3].

First, both the age-dependent anatomy and cognitive variability in children create special considerations for injury patterns, diagnosis, and treatment. As is commonly stated, children are not merely "small adults," but rather

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unique and continually evolving systems with respect to anatomic size, anatomic shape, skeletal composition, cardiovascular performance, respiratory reserve, drug metabolism and excretion, cognitive understanding, verbal maturity, and psychological coping ability. For example, the toddler's small body mass and incompletely calcified skeleton allow blunt force energy to be more widely transmitted to multiple organs, more likely resulting in remote and/or multiple organ injuries than in adults, often in the absence of obvious bony fractures on radiographic examination. In particular, the relatively soft skull incompletely protects the brain from blunt injury, resulting in a high frequency of traumatic brain injuries – the most frequent cause of death among hospitalized pediatric trauma victims, and a clear target for specific evidence-based clinical management guidelines [4]. Similarly, the small child's fixed stroke volume makes cardiac output almost exclusively heart rate dependent, while their reduced functional residual capacity and increased basal oxygen consumption significantly reduce apneic oxygenation time and gas exchange efficiency in the presence of a lung injury. As a result of these two critical physiologic differences from adults, hemorrhagic shock and respiratory failure can present abruptly and be immediately life-threatening. Hepatic metabolism and/ or renal excretion of anesthetic and analgesic medications in the very young child are frequently prolonged due to organ immaturity, resulting in increased drug potency, prolonged duration of action, and increased incidence of unwanted side effects. Lastly, the stress, pain, and perceived threat associated with accidental or intentional injury may induce regressive behaviors in children of all ages, and negatively impact cooperation with history taking, urgent diagnostic examinations, and therapeutic procedures. As a result, both diagnostic errors and delayed treatment are more likely to occur in children than in adults. Parental presence is often necessary to counter these regressive behaviors, and although this may enhance prompt diagnosis and management of the injured child, such presence may create additional communication challenges for the healthcare team. Comprehensive summaries of these issues unique to pediatric trauma victims, as well as strategies for their clinical management are available [5].

Secondly, the interdisciplinary care of the pediatric trauma patient is even more complex than that of the adult trauma patient, and includes the pediatrician, pediatric subspecialists, pediatric psychologist, and most importantly, parents or other family members. Orchestrating the complementary skills of each team member in such a rapidly changing clinical setting requires clear communication, a mutual understanding of each individual's roles, and well-defined leadership strategies. Because the cost and time commitment associated with ATLS training may be prohibitive, a convenient online curriculum designed by pediatric trauma anesthesiologists is available at no and may be of value in training members of this expansive pediatric trauma care team [6].

Non-Clinical Roles for Anesthesiologists in Pediatric Trauma Care

The nature of the anesthesiologists' professional toolkit – including interprofessional communication, team management, clinical research, education, and clinical/procedural skills applicable to non-operating-room settings – offers us unique opportunities to improve pediatric trauma care in several novel venues. Among these are injury prevention and research programs, trauma system policy development and implementation, and education/training of prehospital trauma care providers in appropriate life-saving procedures (e.g., airway management).

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6. Acute Assessment & Management of Pediatric Trauma**:** A 7-Module Course Designed for Providers of Early Care to Injured Children <https://depts.washington.edu/pedtraum/>.

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A Mother's Broken Heart: Obstetric Anesthesia in Heart Disease

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Introduction:

In the developed world, cardiac disease is now the leading cause of maternal mortality.[1,2,3] Myocardial infarction, aortic dissection and cardiomyopathy account for a large portion of cardiac maternal death.[4] Congenital heart disease (CHD) in pregnancy is becoming increasingly common,[5] likely because advancements in medical and surgical care have allowed women with CHD to reach child-bearing age. Acquired heart disease (AHD) amongst pregnant women is also growing. This is likely because of increasing maternal age, increasing rates of obesity, and advanced reproductive technologies resulting in older and less-healthy women becoming pregnant. As a result, more women with chronic hypertension, acquired coronary artery disease, aortopathies, and cardiomyopathies are becoming pregnant and presenting to our labor and delivery units.

The anesthetic management of women with CHD and AHD in labor and delivery is complex. Each case should be individualized because each patient's cardiac, obstetric and anesthetic history is unique. For high-risk cardiac patients, multidisciplinary management is paramount and should include obstetrics, cardiology, anesthesiology and neonatology. In planning an obstetric anesthetic for a parturient with cardiac disease it is important to understand the patient's cardiovascular anatomy and hemodynamic physiology, the physiologic changes of pregnancy labor and delivery, the obstetric plan for her delivery, the hemodynamic alterations our anesthetic techniques induce, and what, if any, cardiac or obstetric complications for which she may be at particularly high risk.

Cardiovascular Changes during Pregnancy

The normal cardiovascular changes that occur during pregnancy are listed in Table 1. Systemic vascular resistance and blood pressure decrease while plasma volume and cardiac output (CO) increase during pregnancy. During labor and delivery, CO increases significantly and peaks immediately after birth from contraction of the evacuated uterus resulting in aorto-caval decompression and auto-transfusion of uterine blood into the venous system. The CO at this moment has been documented to be 80% greater than pre-labor values which are already 30-50% greater than pre-pregnancy values.[6]

Table 1. **Normal Cardiovascular Changes During Pregnancy**

Variable	Direction of Change	Average Change
Blood volume	↑	+35%
Plasma volume	↑	+45%
Red blood cell volume	↑	+20%
Cardiac output	↑	+40%
Stroke volume	↑	+30%
Heart rate	↑	+15%
Femoral venous pressure	↑	+15 mm Hg
Total peripheral resistance	↓	–15%
Mean arterial blood pressure	↓	–15 mm Hg
Systolic blood pressure	↓	–0–15 mm Hg
Diastolic blood pressure	↓	–10–20 mm Hg
Central venous pressure	↔	No change

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Planning and Risk Stratification of Parturients with Heart Disease

An anesthesiology consultation should occur in advance of delivery in patients with cardiac disease to review the patient's anesthetic, obstetric and cardiac history with particular attention to the following:

- Functional status

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- Intra-cardiac shunting and cyanosis
- Prior arrhythmias
- Pacemaker or defibrillator
- Left heart obstructive lesions
- Prior or current episodes of heart failure
- Left and right heart function.

Because severe morbidity and mortality during pregnancy, labor and delivery is more common in patients with preexisting heart disease,[7] it is important that these patients deliver at tertiary and quaternary care centers. Predicting which cardiac parturients may do poorly helps the anesthesiologist in planning the location for the delivery as well as planning monitoring and anesthetic techniques.

Although various risk stratification systems have been published,[8,9,10,11] an understanding of the normal cardiovascular adaptations to pregnancy can predict which patients may decompensate in the antepartum or in labor and delivery, and which ones are at lower risk for complications. For example, patients with stenotic aortic valvular lesions are at higher risk of pregnancy-related heart failure than those with insufficient aortic valvular lesions because as the systemic vascular resistance decreases with pregnancy, the decreased afterload deleteriously results in lesser coronary perfusion in aortic stenosis, but beneficially reduces the regurgitate volume in aortic insufficiency. The following lesions in Table 2 and 3 are considered high risk in pregnancy by the American Heart Association, the American College of Cardiology and the European Society of Cardiology.[12,13] It is imperative that these patients deliver at a tertiary/quaternary care center that can care for their cardiac as well as obstetric needs.

Table 2. **High Risk CHD in Pregnancy**
Severe Pulmonary arterial hypertension
Cyanotic CHD
Fontan circulation
Complex CHD complicated by CHF, valvular disease or the need for anticoagulation
CHD with history of malignant arrhythmias
Marfan Syndrome

Table 3. **High Risk Valvular Disease in Pregnancy**
Severe aortic stenosis with or without symptoms
Mitral stenosis with NYHA class II – IV symptoms
Aortic or mitral regurgitation with NYHA class III to IV symptoms
Aortic or mitral valve disease with severe LV dysfunction (EF < 40%)
Aortic or mitral valve disease severe pulmonary hypertension (PA pressure >75 percent of systemic pressure)
Mechanical prosthetic valve

Once the anesthesiologist determines the risk of the patient's cardiac condition in pregnancy, an anesthetic plan can be formulated by combining the predicted physiologic consequences associated with the patient's cardiac lesion, the physiologic changes associated with pregnancy, labor, and delivery, and the hemodynamic alterations induced by different analgesic and anesthetic techniques.

Obstetric Management of Parturients with Heart Disease

Typically, cardiac disease is not an indication for cesarean delivery. Exceptions may include patients with aortic dissection, aortic dilation of > 4.5cm, patients anticoagulated with warfarin at the time of delivery, patients with severe pulmonary hypertension or patients who are in distress requiring intubation or vasopressor administration. Many obstetricians perform a "cardiac delivery" for laboring parturients with significant heart disease. Such a delivery involves an early, dense epidural followed by a passive second stage (no pushing) and a forceps or vacuum delivery. With this technique, catecholamine release is limited by excellent pain control, and hemodynamic fluctuations from maternal expulsive efforts are avoided. However, the risks of a surgical vaginal

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delivery to both the parturient (e.g. trauma, bleeding) and the neonate (e.g. head injury) need to be weighed against the potential hemodynamic compromise of maternal expulsive efforts.

Labor Analgesia and Monitoring

A "cardiac delivery" with a passive second stage involves an excellent epidural and an involved anesthesia team. In this technique, after uterine contractions bring the fetus to the pelvic floor, low or outlet forceps or vacuum is used to avoid maternal Valsalva. However, even if pushing during second stage is planned, neuraxial analgesia is important in the cardiac parturient for it reduces catecholamine surges from labor pain that can result in tachycardia, hypertension, increased cardiac output, and ventricular stress. Maintaining a dense epidural not only decreases such cardiac stress but it also decreases the degree of hemodynamic alteration should an urgent cesarean delivery be required and the epidural need to be converted to a surgical block quickly.

Pulse oximetry in laboring women is often incorporated in the tocodynonometer machine and provides neither a visible waveform nor audible tones. Laboring women with heart disease should have a pulse oximeter with a waveform for assessment and audible alarms. If the patient has a history of a tachyarrhythmia, ischemic heart disease, aortic stenosis or hypertrophic cardiomyopathy, then 5-lead ECG telemetry should be utilized during labor and delivery. Specialized nursing in labor and delivery may need to be arranged to interpret telemetric monitoring. Occasionally, an arterial line could be placed for labor management. Rarely would a central line or pulmonary artery catheter be necessary during labor.

The physiologic implications of pregnancy and the anesthetic goals for some common valvular and CHD lesions are reviewed in Table 4. This is not a complete list of all possible cardiac lesions, and many with CHD have multiple different lesions that have been repaired with various techniques resulting in complex hemodynamic physiology. In contrast, patients that have had complete repairs, for example, repaired tetralogy of Fallot with little residual hemodynamic defect, can have few physiologic concerns. However, experts in CHD emphasize that a "repair" is not a "cure" or complete "correction," and therefore patients with CHD, even with good repairs, should be followed by a CHD specialist and have their labor and delivery occur at tertiary centers if possible.

Table 4. **Anesthetic Considerations for Valvular & Shunt Lesions in Pregnancy**

	Physiologic Effects of Pregnancy	**Anesthetic Goals**
Mitral Stenosis	(-) Because of relatively fixed preload to the left ventricle, the heart may not be able to generate increased cardiac output necessary for pregnancy. (-) The increase in blood volume increases left atrial pressure and may lead to atrial fibrillation or pulmonary edema.	-Avoid sinus tachycardia: this allows less time for ventricular filling during diastole. -Avoid atrial fibrillation: loss of atrial contraction can result in failure. In Afib, cardioversion should be considered if drug therapy fails to decrease ventricular rate. -Avoid increases in excess fluids: may precipitate pulmonary edema.
Aortic Stenosis	(-)The decreased SVR can result in lesser coronary perfusion pressure to the thickened LV myocardium.	-Avoid decreases in SVR (neuraxial anesthesia should be titrated carefully) -Avoid hypovolemia, bradycardia or tachycardia.
Mitral / Aortic Insufficiency	(+) The decreased SVR results in a lesser regurgitate volume.	-Avoid increases in SVR and decreases in contractility. Avoid bradycardia. -Maintain sinus rhythm. -Consider afterload reduction (neuraxial anesthesia is generally tolerated well)

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R to L Shunt (e.g. TOF, Eisenmenger's, CCHD)	(-)The decrease in SVR increases the right-to-left shunting and possible cyanosis. (+)In unrepaired TOF, the increase in blood volume is beneficial because adequate right ventricular preload is necessary to eject blood past the outflow obstruction and increase pulmonary blood flow. *CCHD, Eisenmenger's and all pulmonary vascular hypertensive diseases, carry a high mortality rate in pregnancy, labor, delivery and the postpartum. Pregnancy implications and anesthetic management is beyond this table.	-Avoid decreases in SVR, which can lead to episodes of cyanosis. Cyanotic episodes can be treated with phenylephrine. -Maintain adequate blood volume and venous return. -Avoid myocardial depressants, because any decrease in right ventricular contractility can decrease pulmonary circulation. -If pulmonary vascular disease is present, invasive pulmonary artery catheter monitoring as well as vasoactive agents may be necessary.
L to R Shunt (e.g.VSD, ASD)	(+)The decrease in SVR decreases the left-to-right shunting. (-)The increase in blood volume can precipitate failure because the patient is in a state of compensatory hypervolemia.	-Avoid excessive fluid administration, over-transfusion, and Trendelenburg position. -Avoid increases in SVR.

SVR= systemic vascular resistance, LV= left ventricular, , TOF= tetralogy of Fallot, CCHD= cyanotic congenital heart disease, VSD= ventricular septal defect, ASD= atrial septal defect.

Anesthesia for Cesarean Delivery

The anesthesiologist must provide general or regional anesthesia for surgical anesthesia for cesarean delivery. Regional anesthesia is typically preferred unless the patient is anticoagulated (risking spinal hematoma) or is critically ill and thereby unable to lie flat or maintain their natural airway. Further, with some CHDs, such as Fontan circulation, maintenance of spontaneous respirations with a neuraxial approach may result in more optimal hemodynamics. Alternatively, general anesthesia may be dictated by obstetric or anesthetic indications.

If regional anesthesia is chosen, then the anesthesiologist must decide between a single-shot spinal, an epidural, a combined spinal-epidural (CSE), or a continuous spinal technique. The rapid decrease in preload and afterload associated with a single shot spinal may carry additional risk in some cardiac lesions (eg, severe mitral stenosis, severe aortic stenosis, aortic coarctation, or patients at risk for right-to-left shunting). An arterial line placed prior to the spinal anesthetic with a carefully titrated phenylephrine infusion initiated at the time of the spinal anesthetic may provide adequate hemodynamic stability. On the other hand, an epidural dosed slowly with appropriate vigilance is likely to result in the least cardiovascular disruption. Addition of an opioid when dosing the neuraxial anesthetic will reduce the amount of local anesthetic required while improving both intraoperative and postoperative analgesia. The elimination of epinephrine from the epidural test dose or loading dose will eliminate the possible deleterious effects of systemic epinephrine.

An epidural, however, may not provide the density of block that intrathecal local anesthetics provide. An excellent alternative to a single-shot spinal or epidural technique is a low-dose CSE technique that has been reported successful in high-risk cardiac patients.[14] A low-dose CSE technique is performed with an intrathecal dose of 4 to 5 mg of heavy bupivacaine along with 15 mcg fentanyl and long-acting opioid. This is followed by slow loading of the epidural local anesthetic (eg. 2% lidocaine) to achieve a T4 surgical level. The benefits of the low-dose CSE technique include slow-onset of the neuraxial block, which allows the anesthesiologist to maintain preload and afterload during the onset, while still achieving the greater block reliability of intrathecal local anesthetic administration.

The anesthesiologist must remain vigilant during the onset of neuraxial surgical or analgesic anesthesia. Maintaining uterine blood flow is important for fetal well-being and, in patients with intravascular shunting, maintaining systemic vascular resistance is important for preventing worsening cyanosis. Cautious intravenous hydration and/or gentle titration of a phenylephrine infusion or ephedrine boluses are options to counteract the hemodynamic effects of surgical neuraxial block.

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Management of Hemorrhage

It is important for the anesthesiologist to know the hemodynamic effects of various uterotonic agents (Table 5) and avoid those that would be deleterious in particular lesions.

Table 5. **Uterotonic Use in Patients with Cardiac Disease**

Drug	Cardiopulmonary effects	Lesions to avoid Agent or Use with Caution	Notes
Oxytocin	↓ MAP Slight ↑ PAP	Aortic stenosis HOCM Ischemic disease Aortopathy with risk of dissection	-Most effective uterotonic agent -Administer cautiously and slowly (via pump) in patients intolerant of ↓ MAP -Consider counteracting ↓ MAP with phenylephrine infusion -Do not administer in bolus IV form in patients with cardiac disease
Methergine	Can cause sudden profound: ↑ SVR ↑ PVR	Hypertension, Preeclampsia Pulmonary HTN Ischemic disease Intracardiac shunts	-Generally avoided in cardiac patients
Carboprost (Prostaglandin F2 alpha)	↑↑↑PAP Bronchospasm → ventilation perfusion mismatch	Fontan circulation Intracardiac shunt Pulmonary HTN	-Do not use in patients who cannot tolerate increased PA pressure.
Misoprostol	None	None	-The least effective uterotonic agent. -Can be used prophylactically

MAP = mean arterial pressure, PAP = pulmonary artery pressure, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance, PAP = pulmonary arterial pressure, HTN = hypertension

Beta Agonist Drugs in Labor

Beta agonist drugs such as terbutaline are occasionally used in labor to urgently relax the uterus when uterine hyperstimulation or tachysystole results in fetal compromise. It is important for the obstetric team to be aware that this drug is contraindicated in some cardiac lesions. Patients with Hypertrophic Obstructive Cardiomyopathy (HOCM) could have infundibular spasm and/or worsen their outflow gradient as a result of beta agonism. Likewise, patients who would not tolerate tachycardia or patients with a history of tachyarrhythmias should not receive beta agonist drugs in labor.

Arrhythmias and Management of Cardioverter Defibrillators during Labor

Patients with a history of tachyarrhythmias are at risk of experiencing their arrhythmia during labor which can result in fetal compromise.[15] Patients with a history of arrhythmias should have 5-lead ECG monitoring during labor. Maternal cardioversion can be performed in pregnancy. If the patient has a fetal scalp electrode, this should be removed prior to the cardioversion. Automatic implantable cardioverters defibrillators should be left "on" in labor as these provide the most rapid response to a tachyarrythmia. A magnet should be immediately available to use in the event of an emergent cesarean delivery requiring unipolar cautery.

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Blood Pressure and the Brain: How Low Can You Go?

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A physiology-based answer to the title question, with its unattractive suggestion of the deliberate brinksmanship that we all seek to avoid, should begin with reference to the standard depictions of cerebral blood flow (CBF) autoregulation. One would pay particular attention to the inflection point at which CBF becomes "pressure-passive", i.e., that mean arterial pressure (MAP) below which reduction results in a *pari passu* reduction in CBF. We refer to that MAP as the "lower limit of CBF autoregulation" (LLA). While the MAP value attributed to that inflection point has traditionally been an MAP below a clinician does not want his/her patient to fall, MAP can, in fact, fall below the individual's LLA without doing immediate harm. Resting normal CBF levels actually provide luxury perfusion to the central nervous system (CNS). Mother Nature has built in a buffer (herein referred to as "the CNS blood flow reserve") that allows a considerable reduction in MAP below the LLA before CNS ischemia occurs. CBF can fall approximately 40% from resting values before symptoms of ischemia occur in awake subjects.

The Lower Limit of CBF Autoregulation. Diagrams that appear in standard texts have frequently depicted the lower limit of human cerebral blood flow autoregulation as being a mean arterial pressure of 50 mmHg. While this number may in fact be a reasonable representation of the LLA in several animal species, it is unlikely to be an accurate value in adult humans. The first rendering of a CBF autoregulation curve was probably that drawn by Lassen.[1] His diagram depicted an LLA that might be easily interpreted to be 50 mmHg. On close inspection, however, the inflection point of that hand-drawn curve is probably not less than 60 mmHg. Lassen's diagram, and the misreading of it, are probably the origin of subsequent widely reproduced diagrams that appeared in textbooks of Anesthesiology depicting the human LLA as 50 mmHg. Numerous subsequent investigations (see Drummond[2] for additional references) suggest that the average LLA in non-anesthetized adult humans is nothing less than 70 mmHg. It is noteworthy that the BP ranges or standard deviations for the LLAs in the subjects in the cited studies[2] and in more recent investigations[4] were large indicating that the variation about that average LLA among individuals is substantial.

While the data just cited argue that the average LLA in non-anesthetized adults is nothing less than a value in the low 70's mmHg, it should be acknowledged that the "rules" *might* be different during general anesthesia. There are at least two reasons. The first is the frequent inclusion of vasodilating substances in anesthetic recipes. Vasodilators might serve to shift the autoregulation curve in a leftward direction. The second resides in the observation that sympathectomy in both experimental animals and humans during hypotension increases CBF.[3] This suggests that the normal autonomic response to hypotension includes some vasoconstriction of large extracranial and perhaps intracranial vessels thereby producing effective right shifting of the autoregulation curve. If a general anesthetic were to effectively prevent that autonomic response, it is possible that some left shifting of the curve might occur. The reality, however, is that there has been exceptionally little systematic study of normal (non-injured) adult human CBF autoregulation during anesthesia. The only context in which extensive study has occurred is during cardiopulmonary bypass (involving, hypothermia, non-pulsatile flow, relative anemia, volatile agent and high-dose narcotic anesthesia). In those circumstances, which are arguably poorly representative of the physiology that prevails during the majority of general anesthetic states, the average LLA was in fact about 66 mmHg, with a very large confidence interval indicating considerable inter-individual heterogeneity.[4] However, it seems inappropriate to extrapolate that average value (obtained in the context of non-pulsatile flow, low hematocrit and well maintained cardiac output) to all other anesthetic circumstances. In fact, it further seems likely that what pertains to any one anesthetic circumstance, e.g., spontaneous ventilation during anesthesia with a volatile agent, might not be relevant in another, e.g., a TIVA anesthetic with remifentanil and propofol. We know very little about the LLA during general anesthesia in humans and it seems prudent that conservative assumptions should be made in the absence of more detailed knowledge.

The Physiologic Central Nervous System Blood Flow Reserve. Many clinicians may well respond to the preceding discussion of the LLA with their own observation that numerous patients in the span of their experience have tolerated MAPs in the 40's, 50's and 60's, i.e., well below the proposed LLA of 70 mmHg. That is inevitably

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true. Patients tolerate blood pressure (BP) below their individual LLAs because there is a substantial CNS blood flow reserve. That knowledge dates from the study of Finnerty et al.,[5] data from which were used by Lassen to anchor the low MAP end of his "first-ever" autoregulation curve. The left hand end of that hand-drawn curve, i.e.,

the region depicting the lowest CBF, is anchored by CBF data that were derived in non-anesthetized adults in whom BP was lowered using cerebral vasodilating drugs (which might have helped to sustain CBF as MAP fell). In that study, BP reduction was stopped when the subjects developed symptoms suggestive of cerebral ischemia. That occurred at an average MAP of 48 mmHg, at which point CBF had been reduced by about 40% of its baseline value. Quantitatively similar data were obtained in an investigation by Njemanze, who used a tilt table and a transcranial Doppler to study individuals with postural hypotension.[6] His observations were that symptoms suggestive of CNS ischemia occurred with a 35% reduction in CBFV (cf: 40% reduction in the study by Finnerty above) and that syncope occurred with a reduction of CBFV by 50%. There are additional data to support this concept, i.e., that CBF can be reduced by approximately 40% of baseline values before symptoms of ischemia begin to occur.[7-9]

Impairment of the CNS blood flow reserve. This reserve is, in essence, a physiologic buffer that protects patients in the event of hypotension, and that buffer means that MAPs (at head level) in the upper 40's will be tolerated by many, if not most, normotensive adults. However, it is important that clinicians recognize the situations in which that buffer may not be present, often because it has been encroached upon by some pre-existing pathologic process. Among the most common situations in which the buffer is likely to have been attenuated are circumstances in which CNS tissue is under increased local pressure.

Increased local CNS tissue pressure. This may occur in the circumstances of increased intracranial pressure (ICP), increased intra-orbital pressure or when CNS tissue is under extrinsic pressure, e.g., compressed under retractors or by a bulging disc or a stenotic spinal canal. The significance of these situations is that the principal determinant of flow to the tissue is "transmural pressure" rather than blood pressure. Transmural pressure (which is commonly but probably inaccurately referred to as "perfusion pressure") equals MAP minus local tissue pressure. Among the most commonly overlooked situations in which tissue pressure is increased (and the effective perfusion pressure is therefore less for a given value of MAP) is in the circumstances of spinal stenosis, in particular cervical spinal stenosis. In that group of patients, the normally wide latitudes for intraoperative BP that anesthesiologists commonly allow should be tightly restricted. It is our approach at UCSD to maintain MAPs during anesthesia in these patients (at least until the decompression is complete) very close to normal waking levels. With cervical spinal stenosis the prudent answer to the "How low can you go" question is . . . "Not very".

The other common situations that reduce the blood flow reserve are central nervous system injury and chronic hypertension. Variability in collateral blood supply may also be relevant.

Central nervous system injury. Autoregulation is physiologically fragile and can be assumed to be impaired in at least some portions of the nervous system in the common injury states, i.e., traumatic brain injury (TBI), subarachnoid hemorrhage (SAH) and probably spinal cord injury. Resting CBF is commonly at values approximately half of normal after TBI and SAH[10-12] and can probably be assumed to be so after spinal cord injury as well. The combination of impaired autoregulation and low resting blood flow means that BPs that would be below the LLA but would probably be well-tolerated in normal subjects will have the potential to reduce flow to precariously low levels in the common injury states.

Chronic Hypertension. Chronic hypertension is associated with a thickening of the intima and media of cerebral vessels. Teleologically speaking, this is Mother Nature's way of preventing vessel rupture and intracerebral hemorrhage in response to the increased pressure head. The "downside" is that cerebral vessels are less able to relax in the face of decreasing pressure. This results in a functional "right shifting" of the autoregulatory curve, with the potential consequence that BPs that would be tolerated in normotensive subjects might have to potential to result in ischemia in those with chronic hypertension. This phenomenon has been well demonstrated in human investigations. While it is often said that treating hypertension "resets" the autoregulatory curve resetting has not, in fact, being demonstrated in humans. It has been demonstrated in spontaneously hypertensive rats and in baboons with relatively brief reno-vascular hypertension. The only study that has looked at treated hypertensive human beings,

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revealed persistently elevated LLAs. Intuition, which should not substitute for science, might lead one to be suspicious of the resetting phenomenon. Does it seem likely that collagen deposition in intima and media of vessels that has occurred over many years would resolve over any reasonably short time course?

Variability in collateral supply. Lastly, and perhaps most insidiously, a phenomenon with the potential to

encroach upon the reserve is variation in collateral circulation. A significant part of the CNS's tolerance hypotension resides in the generous collateralization that is present in many vascular beds. An analogy may help. In most circumstances, the human nervous system is, in essence, like a very well watered lawn with numerous pop-up sprinkler heads with overlapping circles of distribution. Pressure in the system can fall substantially before "brown spots" develop between the overlapping distributions. However, congenital variation and vascular disease can result in individuals, some of whom will be impossible to anticipate, who have less generous collateralization in some vascular beds. The congenital variations include variability of the circle of Willis (see Drummond[13] for references), variability of vessel input to the anterior spinal artery[14] and probably variability in the vascular supply to the optic disc and the mid-portion of the optic nerve.[15] It is in particular variations in circle of Willis anatomy that have the potential to give rise to the seemingly idiosyncratic occurrence of cerebral ischemic injury after BP management that an individual clinician may think of as routine.[13,16]. It is very difficult to translate this concern into a firm clinical recommendation. The incidence of harm attributable to unanticipated collateral variation is probably relatively low. Nonetheless, it is one more reason for clinicians to avoid hypotension, which I will arbitrarily define has an MAP less than 60 mmHg at the level of the Circle of Willis, that is not necessary for the conduct of the surgical procedure. I must emphasize that that threshold, 60 mmHg, is entirely arbitrary and is not evidence based. It allows for some encroachment on the CNS blood flow reserve while avoiding burdensome constraints upon clinicians. That number should be adjusted upwards in patients in whom the clinician has reason to suspect that the CNS blood flow reserve is already compromised.

The Effect of Hydrostatic Gradients on Cerebral Blood Pressure. This phenomenon represents another, probably under appreciated, mechanism for the potential encroachment on the CNS blood flow of reserve. As any fluid (including blood) is pumped vertically against gravity, the pressure in the fluid column decreases as it rises above the pump. When there is a vertical height difference between the heart and the head, a pressure differential between the two that is equivalent to the weight of a column of blood of that height can be expected to occur. That gradient will be equal to approximately 2 mmHg for each one inch of height difference. Accordingly, in many vertical adults the mean pressure at the level of the circle of Willis (for which the tragus or external auditory meatus (EAM) are commonly used as landmarks) is probably about 25 mmHg less than the pressure that would be simultaneously recorded by a BP cuff on the arm. For a normotensive adult with a BP of 125/80 and an MAP of 95, MAP at the EAM is approximately 71 mmHg. (95 – [12 inches x 2 mmHg/inch = 24] = 71). The first implication of this is that with a patient in a horizontal posture and MAP of 70 mmHg at the level of a BP cuff on the arm has an MAP at the EAM that is at the baseline waking value. In horizontal patients (supine, prone, lateral), in essence, the first 20% of MAP "reduction" is physiologically absolutely free with respect to the brain! But, not so when positions are used that place the head above the level of the heart.

When there is a vertical height difference between the height of the heart and the head, a pressure differential between the two that is equivalent to the weight of a column of blood of that height can be expected to occur. The standard teaching in neuroanesthesia has long been that BP should be transduced at (or an arithmetic correction imposed using the formula in the preceding paragraph to correct to) the level of the EAM. Clinicians who are unfamiliar with the neurosurgical use of the sitting position have occasionally failed to make this correction in transducer height, or have raised it only to the level of the heart with sometimes severe adverse consequences for the perfusion of the brain and/or the cervical spinal cord.[17,18] This issue has been popularized recently in the context of injuries occurring in the so called "beach chair position". A minority have disputed this notion, arguing that siphon-like mechanism maintains CBF in spite of reductions MAP at the EAM as calculated above.[19] Unless and until there is wider proof of that concept, i.e., the siphon or closed loop model of the cerebral circulation, conventional hydrostatic gradient concepts should apply, and arterial transducers should be raised to the level of the EAM or arithmetic corrections should be applied to BP cuff pressures in order to "think" in terms of BP at the EAM.[20]

Summary and Conclusions. Once upon a time, it was considered acceptable to reduce MAP to 50 mmHg because

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50 mmHg was perceived to be the lower limit of human CBF autoregulation. However, an objective review of the literature confirms that the LLA is actually nothing less than a value in the low 70s mmHg. If we were to be consistent with the original rationale, we would now deem 70 mmHg to be an acceptable minimal intraoperative MAP. But that would be unnecessarily restrictive. I say "unnecessary" because the CNS blood flow reserve, as described above, assures that the CNS will be adequately perfused at MAPs significantly below the LLA in most individuals. Data cited above suggest that an MAP in the vicinity of 50 mmHg (at the level of the circle of Willis) is the average threshold for the onset of early ischemic symptoms in normotensive adults (and even at that level

hypotension will not be immediately injurious). Accordingly, when hypotension is absolutely necessary for the efficient conduct of a surgical procedure and the clinician has reason to anticipate that the CBF reserve is intact, MAPs as low as 50 mmHg (at the level of the circle of Willis) can be justified. However, hypotension of that degree should be undertaken with the knowledge that there will be little remaining margin for error and that there may be a small subset of physiologic outliers (outliers in terms of LLA or collateralization) who will be intolerant of even that pressure. Hypotension should therefore be as brief as is necessary. For other normotensive adult patients undergoing procedures with no necessity for hypotension who are in reasonable vascular health, with the CNS flow reserve likely to be intact (this excludes patients with increased local pressures on CNS tissue), a minimum MAP of 60 mmHg (at the level of the circle of Willis) is likely to be safe.

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Management of Anticoagulation for Cardiac Surgery: Working With Imperfect Tools When Heparin is not an Option

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Clinical situations that might call for avoidance of heparin include heparin or protamine allergy, or heparin-induced thrombocytopenia (HIT). At least three intravenous alternatives to UH are currently available, however, no drug is yet approved by the U.S Food and Drug Administration (FDA) for use in cardiac surgery in the United States.

HEPARIN-INDUCED THROMBOCYTOPENIA

Pathophysiology

The syndrome known as HIT develops in anywhere from 5% to 28% of patients receiving heparin and is commonly divided into two subtypes. Type I HIT, characterized by a mild decrease in platelet count, results from the proaggregatory effects of heparin on platelets. Type II HIT is considerably more severe, most often occurs after more than 5 days of heparin administration (average onset time of 9 days), and is most likely immune mediated. Heparin exposure results in the formation of antibodies, priamarily of the IgG type. It is now known that the Fc portion of the antibody binds to the complex formed between heparin and PF4 on the platelet surface. The Fab portion of the antibody then causes platelet activation and hyperaggregability. Therefore, the heparin–PF4 complex acts as an antigenic stimulus.(1) Antibody binding also results in generation of procoagulant, platelet derived microparticles. The end result of these processes is the generation of thrombin and subsequent arterial and venous thrombosis. Heparin–PF4 complexes can also exist on the surface of platelets or can bind to endothelial cells, which become activated when the antibody binds. Associated immune-mediated endothelial injury and complement activation may set the stage for the activated platelets to adhere, aggregate, and form platelet clots. Among the patients in whom HIT develops, the incidence of thrombotic complications (HIT type II) approximates 20%, which in turn may carry a mortality rate as high as 35%. Both of these figures may be overestimated as a result of reporting bias, although some prospective investigations support the 20% incidence of thrombosis. Although venous thrombotic events (deep vein thrombosis or pulmonary embolus) are more common in medical patients, the majority of HIT-related thrombotic events in cardiac surgical patients are arterial. Additionally, HIT II can be a subclinical syndrome masquerading as other more frequent entities until devastating thrombosis occurs. The most important step toward diagnosis is the need to consider HIT as the cause of a decrease in platelet count in patients receiving heparin.

Heparin-induced thrombocytopenia is a clinicopathologic syndrome; identification of HIT is based upon both a clinical diagnosis a nd positive laboratory testing (antigen assay or functional assay-see below). Clinicians should consider a possible diagnosis of HIT whenever thrombocytopenia develops in the postoperative period. The thrombocytopenia typically observed in a patient with HIT (90% to 95% of patients) is a reduction in platelet count to less than 150 X 10^9/L or a 30% to 50% decrease in platelet number, even if the platelet count remains greater than 150 X 10^9/L. Most commonly, the fall in platelet count occurs 5-10 days after the initial dose of heparin however, a rapid reduction in platelet count can occur within 24 hours if circulating HIT antibodies are present due to recent heparin exposure (rapid-onset HIT).(2) On occasion, the drop in platelet number can occur up to three weeks after heparin exposure was discontinued (delay-onst HIT). Clinical diagnosis of HIT is often difficult in the postoperative period. In a postoperative patient with a decrease in platelet count, the use of a clinical probability scoring system, in addition to laboratory testing, can increase the likelyhood of determining whether HIT is present. The “4T” scoring system is the most commonly used clinical prediction tool.(3) The four “Ts” assessed in this system are Thrombocytopenia, Timing (of platelet count fall or thrombosis), Thrombosis (or other clinical sequelae, and oTher causes of thrombocytopenia. A score of 0 to 2 is assigned to each category, and a total score determined. Patients with a low 4T score have a low probabilty of HIT (0%-3%), whereas up to 61% of patients with high 4T scores may not actually have HIT. Therefore, laboratory testing is essentail in the diagnosis of HIT.

Two categories of laboratory testing are available; antigen assays that detect the presence of HIT antibodies and functional assays that demonstrate platelet activation by HIT antibodies in the presence of heparin. Functional assays (demonstration of heparin-induced aggregation of platelets) are used to confirm the diagnosis of HIT type II. This can be accomplished with a heparin-induced serotonin release assay or a specific heparin-induced platelet activation assay.(4) However, these tests are difficult to perform and are avalable at only a small number of medical centers. Most hospitals perform antigen assays to help confirm a clinical diagnosis of HIT. A highly specific enzyme-linked

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immunosorbent assay (ELISA) for the heparin–PF4 complex has been developed and used to delineate the course of immunoglobulin G and immunoglobulin M antibody responses in patients exposed to UH during cardiac surgery. Many centers use the ELISA as the sole confirmatory evidence of a HIT II diagnosis. However, the antibody is present in many patients who receive heparin and who never develop thrombocytopenia or thrombosis. When unfractionated heparin is used perioperatively, 25%-50% of cardiac surgical patients will demonstrate HIT antibodies on ELISA testing, but only 1-3% of these patients will develop actual HIT.(5) Therefore, the presence of antibody as judged by the ELISA assay is very sensitive to yet nonspecific for HIT. Antibody titers may be helpful in that high titers appear to be more predictive of thrombocytopenia or thrombosis. The currently accepted threshold for HIT at many centers is an optical density (OD) of 0.40 units (optical density reflects the strength of the ELISA reaction). Specificity of the ELISA test may be increased by raising the OD threshold. However, confirmatory diagnostic testing with a functional test for platelet hyperaggregability is recommended before embarking on a treatment course with an alternative anticoagulant, since this testing remains the "gold standard" in the diagnosis of HIT. Management decisions may be made in the absence of functional testing if such testing is unavailable, or if delays in treatment may place the patient at high risk for adverse outcomes (the rate of thrombosis is 5% per day prior to treatment with alternative anticoagulants).(3)

The mere presence of heparin-PF4 antibody has been associated with adverse outcomes after cardiac surgery.(6) The presence of antibody serves as a marker of exposure to a heparin compound. It is not clear that the presence of antibody portends an adverse outcome or predicts it by signaling the potential for microembolic phenomena. It is also very likely that the presence of antibody marks a patient who has had a complex medical course and who is already known to be at risk for adverse outcomes. Diagnosis of HIT in cardiac surgical patients is further complicated by the observation that a decrease in platelet count is frequently observed in postoperative period in patients without HIT. In the majority of cardiac surgical patients, platelet count decreases by approximately 40%-50% due to hemodilution and platelet consumption during cardiopulmonary bypass. For the first 1-2 postoperative days, platelet counts will continue to decline, before increasing to (or above) preoperative levels beginning on postoperative day three. A diagnosis of HIT should be suspected when a fall in platelet count ≥ 50% from this peak postoperative value occurs within 5-10 days of surgery, or if thrombocytopenia persists for more than four postoperative days.

HIT differs from other immune-mediated, drug-induced thrombocytopenias in the following ways: (a) The antibodies associated with HIT often become undetectable several weeks after the drug is discontinued, (b) the clinical syndrome does not always recur on reexposure to the drug and sometimes resolves despite continued drug therapy, (c) the *in vitro* platelet aggregation reaction is sometimes patient-specific, and (d) intravascular thrombosis develops only in some patients.(7) Patients with cardiovascular disease frequently receive heparin, because this reduces the incidence of thrombotic complications of anterior myocardial infarction, of recurrent thrombosis after percutaneous transluminal coronary angioplasty for acute coronary thrombosis, and of myocardial infarction in patients with unstable angina pectoris. Because some of these patients may need subsequent surgical myocardial revascularization, the possibility exists that patients with unrecognized HIT could present for urgent surgery.

At the present time there are no alternative anticoagulants that are approved for use during on- or off-pump cardiac surgery. This necessitates the off-label use of these agents under exceptional circumstances. As HIT is a relatively uncommon complication of heparin treatment, it is unlikely that a definitive treatment strategy will be clearly defined by large-scale randomized trials. However, some recommendations about therapeutic options in the patient with HIT are provided in guidelines published by the American College of Chest Physicians.(3) Patients with a history of HIT whose antibody levels have dropped to undetectable concentrations and who have not received heparin for 90 or more days can receive heparin for CPB and they will probably not mount an antibody response to this dose.(8) All other heparin must be carefully avoided in the preoperative period. If postoperative anticoagulation is needed, consideration must be given to selecting a different anticoagulant such as a direct thrombin inhibitor.

MANAGEMENT OF ANTICOAGULATION

There are two possible management strategies for patients with a history of HIT in whom HIT antibodies are still present. If cardiac surgery is not urgent, it is recommended that surgery should be delayed if possible until HIT antibodies are no longer detectable. Heparin can then be administered intraoperatively (but carefully avoided pre- and postoperatively). If surgery cannot be delayed, anticoagulation should be achieved with an alternative anticoagulant for CPB or with a combination of heparin and a profound platelet-inhibiting drug such as tirofiban, eptifibatide, or prostaglandin congeners possessing these properties.(9) Success with UH plus tirofiban has been reported.(10)

Low Molecular Weight Heparins

Some types of LMWH have proved effective in HIT (not in the setting of cardiac surgery), but their use presents

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another set of problems. Nonreactivity with the patient's platelets should be confirmed *in vitro* before this option is selected. Use of these agents in CPB is not recommended due to a risk of excessive bleeding, difficulties in monitoring, and lack of an effective neutralizing agent. Treatment with heparin administration and pharmacologic platelet inhibition through prostacyclin, iloprost, tirofiban, aspirin, or aspirin and dipyridamole has been reported, all with favorable outcomes.(10, 15) The use of iloprost titrated to a documented level of platelet functional suppression permitted heparin use without undue thrombocytopenia It seems logical that prostaglandin E_1 would also serve effectively in this role, although this agent shares the vasodilator side effect of prostacyclin.(16) Plasmapheresis acutely reduced heparin-induced platelet aggregation in two cases.(17)

Unlike heparin compounds of any molecular size from any tissue source, direct thrombin inhibitors do not require cofactors such as ATIII or heparin cofactor II to inhibit thrombin. This provides them with some advantages over heparin, but there are disadvantages as well. Direct thrombin inhibitors fall into two categories, which are hirudin-like agents and argatroban.

Direct Thrombin Inhibitors

Hirudin and bivalirudin offer specific advantages in patients with HIT because, unlike heparin, these direct thrombin inhibitors do not require a cofactor, are capable of inhibiting "clot-bound" thrombin, are not susceptible to neutralization by PF4, and do not activate platelets. Because of a shorter half-life and a reduced need for normal renal function for complete elimination, bivalirudin has replaced hirudin for the treatment of patients with HIT requiring CPB. The CHOOSE and EVOLUTION clinical trials have demonstrated that this agent can be used successfully and safely in cardiac surgery and that it compares well with UH for this purpose.(11, 12) At the present time, no randomized clinical trials have directly compared outcomes between patients receiving different non-heparin anticoagulation agents in the setting of cardiac surgery. In patients with HIT antibodies requiring urgent cardiac surgery, the highest level of evidence supports the use of bivalirudin (for both on- and off-CPB procedures). When cardiac surgery cannot be delayed until HIT antibodies are negative, recent evidence-based guidelines recommend the use of bivalirudin over other alternative anticoagulant agents (including heparin plus antiplatelet agents).(13) However, the choice of agent may be impacted by other factors which include drug availability, cost, and monitoring capability at each clinical center. In the CHOOSE-ON and EVOLUTION-ON clinical trials, the ACT was used to monitor the anticoagulant effect of bivalirudin during cardiopulmonary bypass. Anticoagulation was considered adequate if if a 2.5-fold or greater prolongation of the baseline ACT value was achieved. In the CHOOSE-OFF and EVOLUTION-OFF, an ACT of 300 seconds or greater was the target for acceptable anticoagulation during off-pump cardiac surgery.(11, 12, 14)

In clinical settings other than CPB, initiating therapeutic heparin doses in patients with unrecognized HIT has been associated with life-threatening complications. It is also possible that some of the reports of total intravascular thrombosis seen as a complication of cardiac surgery are actually instances of undiagnosed HIT type II. Many of these thrombotic events have been reported in the literature. Other hypercoagulable states have also been attributed to these events. Heparin resistance commonly occurs in patients receiving heparin infusions in whom thrombocytopenia has not developed, but it has also been temporally associated with HIT. Consequently, unrecognized HIT should be considered in the differential diagnosis of intraoperative heparin resistance in patients receiving preoperative heparin therapy.

Hirudin and Congeners

Hirudin

A coagulation inhibitor isolated from the salivary glands of the medicinal leech (*Hirudo medicinalis*), hirudin is a potent inhibitor of thrombin that, unlike heparin, acts independently of AT III and inhibits clot-bound thrombin in addition to fluid-phase thrombin. Currently available through recombinant genetics, this substance is a polypeptide (molecular weight of approximately 7,000 Da) that has been used in patients with chronic disseminated intravascular coagulation. After an intravenous bolus, the aPTT is prolonged markedly but transiently, returning to normal in 15 minutes, whereas the thrombin time (TT) remains markedly prolonged for 2 to 3 hours. The aPTT prolongation correlates well with plasma hirudin concentrations but does not correlate well with chromogenic antifactor II levels. For this reason, a surrogate aPTT using the snake venom ecarin for activation has been described. This whole blood test yields excellent linear correlation with *in vitro* hirudin concentrations between 0.5 and 4 μg/mL, with coefficients of variation from 2% to 5%.

Hirudin may demonstrate benefit as an anticoagulant for CPB in that it has been shown to inhibit the platelet activation induced by nonionic contrast media. The mechanism of this has not been investigated; however, one could speculate that hirudin inhibits platelet activation induced by CPB. Hirudin does not activate platelets nearly as much

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as UH does. This property of direct thrombin inhibitors makes them more "biofriendly" than UH. Using direct thrombin inhibitors preserves platelet activity and reduces release of platelet activation markers as compared with UH.

There are some data examining the use of recombinant hirudin (r-hirudin) in humans. In a small clinical trial, 20 patients were randomized to receive either r-hirudin or heparin.(18) A bolus dose of r-hirudin was administered (0.25 mg/kg with 0.2 mg/kg added to the CPB prime) and additional drug (5 mg) administered on the basis of the ecarin clotting time. Blood loss in the first 36 hours was higher in the r-hirudin group (1,226) compared to the heparin group (869 mL), and one patient in the r-hirudin group developed a pulmonary embolus. The limitations of hirudin use during cardiopulmonary bypass include a relatively long half-life and increased risk of bleeding, particularly in the setting of renal insufficiency. This indicates that in the setting of heparin avoidance, agents with a shorter half-life and less reliance on renal elimination would be preferable.

Bivalirudin

Bivalirudin is a synthetic peptide formerly known as Hirulog and currently marketed as Angiomax (The Medicines Company, Parsippany, NJ, USA). A bivalent thrombin inhibitor, bivalirudin consists of one moiety that binds thrombin on its active-site cleft, and a second hirudin-like C-terminal region that binds thrombin at its positively charged surface groove known as the *anion-binding exosite*. Bivalirudin is a synthetic derivative of hirudin and therefore acts as a direct thrombin inhibitor. Bivalirudin offers advantages over hirudin in both safety and potential efficacy. Bivalirudin appears to have a wider therapeutic window, possibly because it only transiently inhibits the active site of thrombin. This broader safety margin for bivalirudin permits administration of higher doses, which probably gives it an efficacy advantage over hirudin as well. Bivalirudin binds to both of its thrombin binding sites in both fluid phase and clot-bound thrombin. Thrombin itself cleaves the part of the bivalirudin molecule that binds to it, so bivalirudin activity elimination is independent of specific organ metabolism. This presents another advantage over hirudin, which requires renal elimination for drug metabolism and dissipation of anticoagulant effect. Bivalirudin has been used successfully as an anticoagulant in interventional cardiology procedures as a replacement for heparin. In fact, in interventional cardiology, bivalirudin has been associated with less bleeding and equivalent ischemic outcomes when compared with heparin plus a platelet inhibitor. This may result from the capacity of bivalirudin to inhibit fluid-phase thrombin anticoagulant and platelet-bound thrombin. At lower bivalirudin plasma concentrations, the anticoagulant effects will dissipate whereas antiplatelet effects continue. Bivalirudin's half-life of aPTT prolongation is approximately 40 minutes, and reductions in FpA formation provide evidence of thrombin inhibition and fibrinogen preservation. Careful monitoring should be employed because there may be a rebound prothrombotic state after cessation of therapy, which could lead to recurrence of anginal symptoms.

Of the alternative agents to heparin for cardiac surgery, bivalirudin has been the most extensively studied in clinical trails (retrospective, observational, and randomized). On the basis of case reports describing the successful use of bivalirudin in both on- and off-pump cardiac cases, Merry et al.performed the first randomized clinical trial using this agent in 2004(19). One hundred patients undergoing off-pump (OPCAB) surgery were randomized to receive bivalirudin (0.75 mk /kg followed by a 1.75 mg /kg /hour infusion) or heparin. Blood loss 12 hours after surgery did not differ between groups. During coronary angiography three months following surgery, patients in the bivalirudin group had higher median graft flow rates, as well as more patients with full flow in at least one graft. Four randomized clinical trials were performed in patients with (CHOOSE-ON and CHOOSE-OFF) and without (EVOLUTION-ON and EVOLUTION-OFF) HIT.(11, 12, 14) The primary outcome measure in all of the investigations was in-hospital procedural success, defined as freedom from death, Q-wave myocardial infarction, stroke, or repeat vascularization. In the EVOLUTION-ON study, patients were randomized to receive bivalirudin (n=101) or heparin.(11) Dosing of bivalirudin was standardized (1.0 mg/kg bolus followed by a 2.5 mg/kg/hour infusion), with additional boluses provided to maintain the ACT 2.5 times baseline. There were no differences between groups in the primary endpoint (procedural success) up to 12 weeks following surgery. In addition, the two groups did not differ in 24-hour blood loss or transfusion requirements. Similar results were observed in the EVOLUTION-OFF study (105 patients randomized to receive bivalirudin and 52 to heparin).(12) Bivalirudin was administered as a 0.75 mg /kg bolus and a 1.75 mg/kg /hour infusion, with adjustments to the infusion to maintain the ACT greater than 300 seconds. Procedural success rates (93%) were identical in the two groups, and blood loss and transfusions did not differ between groups. In both the CHOOSE-ON and CHOOSE-OFF trials, 50 patients with confirmed or suspected HIT or positive HIT antibodies were given bivalirudin for on- or off-CPB surgery.(20) Dosing and monitoring of bivalirudin was identical to the EVOLUTION studies. In the CHOOSE-ON trial, procedural success at 7 days was achieved in 94% of patients. Mean 24-hour blood loss was 998 mL, with a mean of 5.6 units

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of red blood cells transfused by 7 days. Similarly, procedural success was achieved in 92% of patients in the CHOOSE-OFF trial. Chest tube output at 24 hours was 936 mL, and 25% of patients received a red cell transfusion. Studies suggest that bilvalirudin is a safe and effective alternative anticoagulant for cardiac surgical procedures when it is used by experienced clinicians.

When bivalirudin is administered , surgical and perfusion techniques must be altered to reduce the risk of clot formation in the CPB circuit or in saphenous vein or internal mammery artery grafts. Care should be exercised to ensure the absence of stasis in the CPB circuit, and a recirculation limb should be incorporated into the extracorporeal circuit if periods of stasis are expected. This need ensues from thombin's aforementioned capacity to metabolize bivalirudin even as it remains bound to and inhibits thrombin-induced anticoagulation, so bivalirudin will be consumed in static blood if drug is not continuously infused. Similarly, care must be taken to be sure that saphenous vein grafts that have been flushed with anticoagulated blood are perfused regularly with anticoagulant, and that there is no static blood in internal mammary artery grafts between arterial harvest and anastomosis.

The anticoagulant effects of the thrombin antagonists can be monitored using the ACT, aPTT, or the thrombin time when lower doses of inhibitor are used such as occurs in the catheterization laboratory or vascular surgical operating rooms. The safest approach is probably to continue the maintenance bivalirudin infusion rate at 2.5 mg/kg/hr or higher until the conclusion of CPB, although the duration of its residual effect and the absence of a reversal agent lend some appeal to reducing or discontinuing the infusion 15 to 30 minutes before discontinuing CPB, especially if the ACT exceeds the minimum threshold by a substantial margin. The problem with stasis in the extracorporeal circuit does not end at the discontinuation of CPB, so care must be taken to recirculate the residual CPB circuit after CPB as long as one wishes to either transfuse from the circuit or preserve the potential opportunity to resume CPB. It is also important to add bivalirudin (50 mg bolus, 50 mg/hour infusion) to the circulation of the closed circuit to prevent clotting until it is determined that CPB does not have to be re-established.

Argatroban

Argatroban (MW 527 Da) is a synthetic derivative of arginine that inhibits thrombin by binding only to its catalytic site. It is approved for use as an alternative anticoagulant to heparin for patients with HIT. Like hirudin and bivalirudin (and unlike heparin), argatroban inhibits both circulating and fibrin-bound thrombin. The plasma elimination half-life is approximately 40 minutes, and the agent is metabolized by the liver with biliary elimination. Therefore, argatroban offers appeal in patients with severe renal insufficiency or renal failure. Argatroban anticoagulation for CPB is initiated (with or without a loading dose) with a bolus of 0.1 to 0.2 mg/kg followed by an intravenous infusion at 5 to 10 µg/kg/min (less if there is hepatic insufficiency), and the dose is then adjusted to maintain the aPTT 1.5 to 3 times normal. The ACT may also be used to guide therapy, in which case the optimal ACT level appears to be 300 to 400 seconds.(21)

Although the principal indication for argatroban is for patients with HIT, its use has also been well-described in non-HIT patients undergoing interventional cardiology procedures and investigationally as an elective heparin alternative for patients with acute coronary syndromes, unstable angina, and thromboembolic stroke. In general, such investigations have found a similar efficacy as heparin, although some have reported a tendency to fewer bleeding complications. Argatroban has been used safely as a heparin substitute for CPB; however, many bleeding complications have been reported. Although argatroban's theoretic appeal as a CPB anticoagulant for chronic dialysis patients is compelling, scattered anecdotal clinical experiences to date suggest the possibility that either bivalirudin alone or UH in combination with a potent platelet inhibitor such as eptifibatide or a prostaglandin derivative may be preferred over argatroban. Problems with both bleeding and clotting (even in the same patient) have been reported, so the drug may be unsatisfactory for CPB, or alternatively the optimal dosing and monitoring may have not yet been determined.

Platelet Inhibitors

Pharmacologic platelet inhibition has been used to supplement or replace heparin for CPB anticoagulation. Iloprost (prostacyclin analogue) was used in several studies of HIT patients in order to inhibit platelet activation during cardiac surgery. In a large retrospective analysis of 1518 consecutive cardiac surgery patients, Palatianos et al. identified 10 patients with clinical symptoms of HIT with heparin-PF4 antibodies and compared them to 10 randomly selected controls(15).(15) Patients presenting with HIT received a protocol of iloprost infusion, supplemented with norepinephrine as needed, in conjunction with heparin. The postoperative reduction in platelet count was less in the iloprost group (12.5% +/-8.7%) versus the control (38.1% +/- 15.2%) and no thrombotic complications were detected. The use of heparin plus platelet antagonist therapy is recommended as a Class IIb indication for CPB in HIT patients, in patients in whom direct thrombin inhibitors may not be used.(13)

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Bivalirudin is recommended as a Class IIa anticoagulant in HIT, however its use requires experience and careful monitoring.(13)

Summary

Heparin is an imperfect anticoagulant, however it has been used with impunity for more than 60 years. It is critical that we understand the limitations of unfractionated heparin use, its monitoring, and to have alternative anticoagulants available for patients in whom heparin is not an option.

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Management of Anticoagulation for Cardiac Surgery: Working with Imperfect Tools

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Altered Heparin Responsiveness

When cardiopulmonary bypass (CPB) was in its infancy, it was assumed that a standardized weight-based bolus dose of unfractionated heparin would provide the desired level of anticoagulation; intraoperative testing was not usually performed to verify this appropriate response.[1] It was not until the mid-1970's when the activated clotting time (ACT) was introduced into the operating room, and Bull, et al. introduced the "safe zone" of 300-600 seconds that intraoperative monitoring of the heparin dose response was routinely performed.[2, 3] While there still exists some practice variability in heparin doses and ACT targets to this day.[4] an individual patient's response to heparin can be assessed by calculating a heparin sensitivity index (HSI):

$$\text{HSI} = \frac{(\text{ACT}_{\text{post-bolus}} - \text{ACT}_{\text{baseline}})}{\text{Heparin Dose}_{(\text{in units/kg})}}$$

While few clinicians routinely calculate the HSI, most practitioners have a general feel for what ACT value should be obtained following a bolus dose of heparin. When the ACT is greater than expected, which might occur if a patient is already therapeutic on another anticoagulant such as coumadin, the HSI can be significantly greater than 1.0 and the patient is said to have *increased* heparin responsiveness. When the post-bolus ACT is lower than expected, the patient has *decreased* heparin responsiveness, and the HSI is typically less than 1.0. The latter situation is commonly encountered just prior to initiating CPB and is often termed "heparin resistance."

Unfortunately, as shown in Table 1, no consensus on the definition of clinically significant heparin resistance exists. This lack of a universal definition means its incidence varies by local heparinization practices and ACT targets. It is estimated that heparin resistance occurs somewhere between 4-26% of cardiac surgical patients.[5]

Table 1: Definitions of "Heparin Resistance" Used in Various Clinical Studies on Cardiac Surgical Patients

1st Author, Year	Study Population	Definition
Williams, MR, 2000[6]	Aprotinin and EACA treated patients, mixture of procedures	450 u/kg UFH failed to achieve ACT≥480 s or ACT≥600 s if treated with aprotinin
Lemmer JH, 2002[7]	Aprotinin-treated patients, mixture of procedures	600 u/kg UFH failed to achieve ACT >600 s
Koster A, 2003[8]	No antifibrinolytics, mixture of procedures	500 u/kg UFH failed to achieve ACT≥480s
Avidan MS, 2005[9]	No antifibrinolytics, mixture of procedures	400 u/kg UFH failed to achieve ACT≥480 s
Chan T, 2006[10]	Mixture of procedures	5 mg/kg UFH failed to achieve ACT≥400 s
Knapik P, 2012[11]	CABG patients	300 u/kg UFH failed to achieve ACT≥400 s or 400 u/kg UFH failed to achieve ACT≥480 s or Heparin Sensitivity Index < 1.3 s/u

CPB=cardiopulmonary bypass; EACA=ε-aminocaproic acid; UFH=unfractionated heparin; ACT=activated clotting time; CABG=coronary artery bypass graft

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Causes of Heparin Resistance

There are several clinical factors commonly encountered in cardiac surgical patients that have been associated with heparin resistance, as shown in Table 2. Given heparin's anticoagulant actions are predominantly achieved via its interaction with antithrombin (AT),[12] investigations on hematological mechanisms for decreased heparin responsiveness have largely focused on states of AT deficiency or dysfunction. These causes of decreased heparin responsiveness are generally termed "AT-mediated heparin resistance." AT levels, however, have not been shown to be predictive of heparin responsiveness.[13] This is likely because clotting times themselves are affected by a variety of hematologic factors which can lead to a reduction in the measured heparin response. Therefore, there are also causes of heparin resistance that are "non-AT-mediated." Hematologic factors associated with heparin resistance are also listed in Table 2.

Table 2: Reported Clinical and Hematological Factors Associated with Decreased Heparin Responsiveness[5, 10, 14-16]

Clinical Factors	Hematologic Factors
• Prior heparin (UFH/LMWH) administration • Preoperative IABP use • Preoperative nitroglycerine infusion • Impaired liver synthetic function • Age ≥ 65 • Endocarditis • DIC	• Low AT levels (<60%) • Platelet counts > 300,000/ml • Elevated platelet factor 4 levels • Elevated Factor VIII levels • Increased heparin binding proteins

UFH/LMWH = unfractionated or low molecular weight, IABP = intra-aortic balloon pump, DIC = disseminated intravascular coagulation, AT = antithrombin, heparin binding proteins would include lipoproteins, albumin, extracellular matrix proteins such as collagen and fibronectin, and other various enzymes and growth factors.

Consequences of Heparin Resistance

At the very least, heparin resistance causes concerns and delays for perfusionists and the rest of the cardiac surgical team. Clinicians are hesitant to institute CPB when ACT results are suggestive of inadequate anticoagulation. Recent CPB anticoagulation guidelines from the Society of Thoracic Surgeons, Society of Cardiovascular Anesthesiologists, and American Society of Extracorporeal Technology recommend maintaining a minimum ACT of 400 s or 480 s.[17] Failure to achieve this goal after the initial bolus will usually result in higher than normal doses of heparin being administered in an effort to meet this minimum. The consequences of supra-normal heparin doses are not well-defined, but likely increase the risk of heparin rebound,[18, 19] and have potentially deleterious effects on platelet function.[20]

Since low AT levels will almost always results in reduced heparin responsiveness, it is difficult to separate the consequences of these two entities. In retrospective analyses, low levels of AT upon ICU arrival have been associated with prolonged ICU stay, thromboembolic events, neurological injury.[21] However, it is unclear if the low AT levels contribute to these poor outcomes, or if AT is simply consumed as part of a separate pathological process.[22] Clinical trials investigating the effects of AT supplementation on cardiac surgical outcomes are underway, but little work has been done on non-AT mediated forms of heparin resistance.

Treatment of Heparin Resistance

Treatment for AT-mediated heparin resistance is best accomplished by replacement of AT. From a practical standpoint, the clinician has three options to choose from: purified human antithrombin concentrate, recombinant antithrombin concentrate, or fresh frozen plasma (FFP). FFP is the oldest therapy, being first reported in 1984 as a treatment for heparin resistance.[23] Two units of FFP (500 ml) contains about 500 units of AT.[24] Concerns over volume administration, transfusion exposure, and the time needed to thaw FFP, have lead cardiac anesthesia and surgical societies to recommend administration of AT concentrates in cases of AT-mediated heparin resistance.[25]

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While several trials have shown both the purified concentrate and the recombinant concentrate to be effective at restoring heparin responsiveness,[26, 27] clinicians should be aware that there are some differences between the two agents. The purified concentrate is made from human plasma which has been pasteurized, while the recombinant form is made in goat's milk.[28] The recombinant form has a higher affinity for heparin, and a much shorter half-life, although for purposes of restoring heparin responsiveness these differences may not be important.

The treatment for non-AT-mediated heparin resistance is less clear. If the issue is high levels of heparin binding proteins, then higher doses of heparin would seem warranted, taking into account the increased risk of heparin rebound. Unfortunately, it is rarely known if this is the cause of reduced heparin sensitivity since the relevant proteins are rarely, if ever, measured as part of a pre-operative work-up for cardiac surgery. Thrombocytosis is much more readily identified and known to shorten the ACT.[29] So, on one hand it could be argued that high platelet counts create an artificial heparin resistance, since *in vivo* actions may not be affected. However, platelet factor 4 (PF4) is known to neutralize heparin,[30] so high platelet counts could result in less circulating heparin, It may be advisable to obtain a heparin level in these situations. Reduction in circulating platelet counts on CPB using acute normovolemic hemodilution (ANH) may also represent a therapeutic option.

Future Directions

Heparin resistance is likely to be encountered by all cardiac anesthesiologists. Whether it represents a symptom of a potentially hypercoagulable state or is simply a nuisance that delays institution of CPB remains poorly defined. Current research efforts have focused on the role AT and AT supplementation for treating this condition. Future directions should include research into better tools to determine adequacy of anticoagulation in the operating room, and best practices for managing non-AT-mediated decreases in heparin sensitivity.

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Management of Anticoagulation for Cardiac Surgery: Working With Imperfect Tools

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Heparin Monitoring: Do we need more data?

Introduction:

Heparin was first discovered in 1916 by Doctors Howell and McLean, but it was not widely available for distribution and use until many years later. It was in part due to heparin becoming more accessible that cardiopulmonary bypass (CPB) began to be succesfully performed in the early 1950's. (1) Since this time, there continues to be debate around how to best monitor heparin's effect and the best ways to determine the appropriate dosing. Survey data shows that most North American institutions use a weight-based dosing regimen and target an ACT somwhere between 400 and 480 seconds. (2) This target is largely based off of the work done by Dr. Bull and his colleagues in the 1970's (3) showing that the safe zone for ACT (at which clot is unlikely to form) lies somewhere between 300 and 600 seconds. Dr. Bull also demonstrated that individual heparin dose response curves could be constructed using a target ACT of 480 seconds (4). Now, almost 50 years later, perhaps it is time for us to ask if there exists a better way to monitor and manage anticoagulation for CPB?

The need for anticoagulation:

When blood comes in contact with the surfaces of the CPB circuit, the coagulation system is activated. The ultimate end result is the generation of thrombin and further activation of platelets and fibrinogen. This can lead to coagulopathy upon termination of CPB due to consumption of coagulation factors. The effects are more significant with longer bypass times and with excessive cooling. Maintaining an adequate level of coagulation helps to inhibit thrombin formation and keep the coagulation system "in check", preserving coagulation factors for the post-bypass period.

Heparin Mechanism of Action:

Although there are many anticoagulants on the market, heparin remains the preferred agent for bypass for several reasons. Heparin is quick acting, easy to titrate, easy to reverse, and currently very affordable. Unfractionated heparin works primarily by binding antithrombin and enhancing its inhibition of both thrombin and factor Xa. (5) This mechanism of action is a bit oversimplified, however, given that a single bottle of unfractionated heparin contains both low molecular and high molecular weight fractions. Although all fractions of heparin inhibit factor Xa, only those with a minimum of 18 oligosaccharide chains are able to bind antithrombin and inactivate thrombin. Heparin is also thought to work through various other endogenous proteins such as vitronectin, fibronectin, and tissue factor pathway inhibitor. The variability we see in individual patient responses to heparin boluses is thought to be due in part to varying levels of these endogenous proteins. (6) Due to the interpatient variation in heparin responsiveness and the potential for heparin resistance, monitoring of heparin therapy is clearly indicated.

Activated Clotting Time:

The Lee-White Whole Blood Clotting Time (WBCT) was the first test used to monitor heparin's effects. (7) Whole blood was placed in a glass tube and the tube manually tilted until clot formation could be detected. This test was labor intensive and impractical for use in the operating room given the amount of time necessary to achieve the result. The Activated Clotting Time (ACT) was introduced by Dr. Hattersley in 1966 and was originally described as a test to detect patients that may have prolonged bleeding after surgery (8). The ACT uses an activator (celite or kaolin) to stimulate the intrinsic pathway. It is now considered the gold standard for monitoring anticoagulation for CPB.

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There are several automated ACT systems in use today. The most popular in use are: the iSTAT celite-ACT (Abbot Point of Care, Inc., Princeton, NJ), the Medtronic kaolin-ACT Plus (Medtronic Perfusion Services, Minneapolis, MN), the Hemochron celite-ACT system (International Technidyne Corp., Edison, NJ) and the maximally activated MAX-ACT (Actalyke MAX-ACT; Array Medical, Somerville NJ). The hemochron and ACT Plus systems detect mechanical clot formation. The hemochron uses a magnet inside of a glass specimen tube. As the blood clots, the magnet is displaced signaling the clotting time. The ACT plus has a daisy shaped plunger that moves up and down. As clot forms, the speed of the plunger movement is slowed and the ACT is recorded. The iSTAT uses an electrochemical sensor to detect conversion of a thrombate substrate inside the celite containing cartridge. (9) The MAX-ACT is unique in that it uses a "cocktail" of kaolin, celite, and glass beads as activators for clot formation. While some studies do show similarity between devices when used to measure clotting time, others have shown large amounts of variability largely due to differences in the measurement techniques and concluded that results are not interchangeable (6,9-10). This disparity seems to be most noticable at higher heparin concentrations, typical of what would be needed for CPB.

Understanding factors which prolong ACT:

It is important to remember that the ACT is not a direct measure of heparin concentration and there are several factors which can prolong ACT even in the absence of heparin. If the patient is not adquately anticoagulated, he or she may deplete coagulation factors while on CPB. Hemodilution and hypothermia are both known to alter heparin metabolism and significantly prolong the ACT in patietnts who are heparinized for CPB. (11,12) This is even more pronounced in the pediatric population where heparin is metabolized at a much higher rate. Thrombocytopenia and platelet inhibiting drugs can also prolong ACT.(13) Furthermore, several studies have shown a lack of correlation between ACT values and plasma anti-Xa, considered to be the gold standard for heparin monitoring. (14)

Heparin Dose Response:

As previously stated, there is large interpatient variation seen in response to a single bolus dose of heparin. Weight-based dosing remains the most common method used in North American institutions, with most using a dose of 300-400 units/Kg to achieve an ACT of 400-480 seconds.(2) There are a certain portion of patients who will fail to reach target ACT using this method, and some who will acheieve an ACT much higher than intended, as weight based dosing does not take into account that each patient may have a different sensitivity to heparin dosing and some patients may be resistnat. Some have advocated for the use of individual heparin-dose response curves for the management of anticoagulation during CPB.(4) This can be done manually, or by using the Hemochron RxDx (International Technidyne Corp., Edison, NJ) or Hepcon HMS (Medtronic Perfusion Services, Minneapolis, MN) devices. The specifics of each test vary, but both work by determining the patient's response to heaparin and then use the patient's baseline ACT and estimated blood volume to determine the bolus dose of heparin required to reach target ACT. These machines also calculate the protamine dose necessary to reverse the circulating heparin at the end of CPB.
In a study by Garvin and colleagues, however, the hepcon HMS failed to reliably predict the heparin bolus dose/ (15) The post-heparin ACT did not reach target in 7.4% of patient when the target was 300s and in 16.9% of patients when the targe was 350s. The authors cite potential error in the HMS estimation of blood volume, extravascular sequestration of heparin, and variation in the circulating plasma proteins as possible causes of the failure to reach targe. These results were not compared to standard weight-based dosing regimens and the target ACTs were lower than used in most institutions. The authors concluded that more prospective studies are needed to guide anticoagulation for CPB.

Heparin Concentration:

Since ACT can be falsely elevated due to factors other than heparinization and this may lead to inadequate levels of anticoagulation and consumption of coagulation factors on bypass, some have advocated for following heparin concentration instead of ACT during CPB. Theoretically, using heparin-concentration based anticoagulation should maintain a stable heparin level, result in less thrombin generation, minimize hemostatic activation and lessen blood

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loss and transfusion.(15-18) Several studies have shown that heparin concentration correlates more closely with anti-factor Xa measurements, especially during periods of hypothermia. Using heparin concentration has also been shown in some studies to cause less thrombin generation and fibrinolysis, and better preservation of platelet function. (14, 16-17) The Hepcon HMS can be used to determine heparin concentration using automated protamine titration. A heparinzed sample of patient blood is placed into a cartridge containing chambers that have different concentrations of protamine. The chamber in which clot forms first is thought to contain the ideal amount of protamine to neutralize the circulating heparin and this dose of protamine is used to then calculate the heparin concentration.

Several studies have shown that when following a heparin concentration based protocol, typically more heparin is administered overall, but that lower doses of protamine are also given. One proposed benefit of the HMS is the ability to measure circulating heparin and thus determine the exact protamine dose necessary to reverse it after CPB. This may lead to less overall protamine administered and a lower protamine-to-heparin ratio when compared to weight based algorithms or algorithms based off heparin bolus dose or total dose.(18) Low-dose administration of protamine may help to better preserve platelet function. (19-20)

High-dose Thrombin Time (HiTT):

The high-dose thrombin time (HiTT; International Technidyne Coporation, Edison, NJ) measures the conversion of fibrinogen to fibrin by thrombin. The HiTT test consists of a large amount of human thrombin to which much smaller amounts of snake venom (Bothrops atrox) and protamine are added. A sample of 1.5mL of blood is added to the tube which has been prewarmed (37°C). The tube is gently tilted up and down to ensure good mixing and is inserted into the Hemochron machine. The time elapsed until the formation of fibrin is detected by the device. An advantage of using HiTT over ACT is that it is not altered by hemodilution and hypothermia and correlates better with heparin concentration than ACT. A potential advantage of this test is that it is not affected by aprotonin therapy as is ACT. (21-22)

STS/SCA/AmSect Recommendations:

In 2018, the Society of Thoracic Surgeons (STS), Society of Cardiovascular Anestheisiologists (SCA) and the American Society of Extracorporeal Technology (AmSECT) published guidelines on perioperative blood transfusion and conservation. (23) To date, these are the only guidelines that have been written regarding management of anticoagulation for CPB. The following recommendations were made:

1. *A functional whole blood test of anticoagulation, in the form of a clotting time, should be measured and should demonstrate adequate anticoagulation before initiating and at regular intervals during CPB. (Class I, Level of Evidence C)*
2. *In patients requiring longer CPB time (2 to 3 hours), maintenace of higher and/or patient-specific heparin concentrations during CPB may be considered to reduce hemostatic system activation, reduce consumption of platelets and coagulation proteins, and to reduce blood transfusion. (Class IIb, Level of evidence B)*
3. *It can be beneficial to calculate the protamine dose based on a titration to existing heparin in the blood as this technique has been associated with reduced bleeding and blood transfusion. (Class IIa, level of evidence C)*
4. *Use of either protamine tritration or empiric low dose regimens (eg. 50% of total heparin dose) to lower the total protamine/heparin ratio at the end of CPB may be considered to reduce bleeding and blood transfusion requirements. (Class IIb, Level of evidence B)*

Summary:

It has been well established that monitoring anticoagulation during CPB is necessary due to patient variation in heparin responsiveness. Doing so leads to less blood loss and decreased need for transfusion. There exist several strategies for appropriate monitoring, but each of these has pros and cons and each is subject to error. In keeping with guidelines, it may be wise to maintain a higher heparin concentration to decrease activation of the coagulation

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system, and to avoid excessive doses of protamine to better preserve platelet function; however, those looking for specific targets may be disappointed to know that 50 years later, this still does not exist. More prospective are needed in this area to determine the superior strategy.

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A Walk Through the Literature in Obstetric Anesthesia and Obstetrics Since the Last Annual Meeting

Robert Gaiser, MD **Lexington, KY**
Brenda A. Bucklin, MD **Denver, CO**

For this lecture, we have gathered the most recent evidence-based information from various sources to provide an overview of the leading articles from the obstetric and obstetric anesthesia literature.

U.S. Birth Data

National Vital Statistics reported a total of 3.9 million births in their U.S. birth data from 2016.[1] The total number of births declined by 1% and the birth rate for teenagers declined 9%. Although 77% of women began prenatal care in the 1st trimester, the preterm birth rate increased to nearly 10%. The cesarean delivery (CD) rate declined to 32%.

Antepartum Management

Surgery during pregnancy is accompanied by an FDA Warning concerning the effect of anesthetics on the developing brain of children under the age of 3 years because this time-period represents an important period of synaptogenesis for the developing brain. The warning also applies to pregnant women in the 3rd trimester who require surgery. The greatest concern occurs when the procedure lasts longer than 3 hrs. or if multiple procedures are required. The obstetric community recommends the use of opioids or alpha-2 agonists for sedation and limiting the interval between induction and surgical incision.[2]

Maternal Comorbidities

Obesity is often encountered in the obstetric population. In laboring women who receive epidural analgesia and require cesarean delivery (CD), local anesthetic is injected into the epidural catheter. Many times, injection of local anesthetic fails to achieve an adequate anesthetic level for surgery. An analysis of 100 obese women showed that the odds ratio of extension failure was 1.69 but there was no difference compared to non-obese women (20% vs. 13%; 95% CI: 0.88-3.21, P = 0.11).[3] However, risk factors for extension failure were BMI > 50 kg/m^2 and ineffective labor analgesia requiring anesthesiologist intervention.

Preeclampsia is most often seen in first-time pregnancies, in pregnant teens, and in women over 40. The impact of low-dose (50-150 mg/d) aspirin (ASA) for prevention of preeclampsia was evaluated in the literature. When low-dose ASA was initiated before 16 wks' gestation, there was a significant reduction in the risk of preeclampsia regardless of the time to delivery. This outcome was greater for preterm preeclampsia as compared to term preeclampsia. Furthermore, there was a decrease in intrauterine growth restriction and small for gestational age neonates.[4] The Aspirin for Evidence-Based Preeclampsia Prevention Trial was a multicenter study in women with singleton pregnancies at 11-13 wks' gestation who were randomized to ASA 150 mg/d or placebo. Maternal placental growth factor and uterine artery pulsatility index were followed. Preeclampsia was decreased only in the group who complied with the daily ASA. If compliance was less than 90%, there was no difference compared to placebo.[5] Aspirin administration in women at risk for preeclampsia has also been shown to reduce the length of stay in the NICU by about 70% because of prevention of early preeclampsia.[6]

Labor and Delivery

NPO status during labor and delivery remains controversial. The Practice Guidelines for Obstetric Anesthesia recommend the oral intake of moderate amounts of clear liquids during labor with clear liquids up to 2 hours before induction of anesthesia.[7] Solid foods should be avoided in laboring patients. Yet, a systematic review of 10 studies including 3,982 patients, examined less restrictive food intake during labor and found no cases of aspiration.[8] There was only one trial that allowed unrestricted food intake while the rest of the studies used some form of liquid intake. When food intake was unrestricted, the duration of labor was shorter by 16 min. While this review does not endorse the intake of solid food during labor, it addresses the fact that women and anesthesiologists continue to be troubled by the policy concerning solids. There may be some benefit of considering solids in low-risk parturients.

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Non-neuraxial Analgesia

Labor analgesia is requested by many women for pain relief during labor and delivery. Although over the last three decades, increasing numbers of women have received neuraxial analgesia, other pharmacologic and non-pharmacologic interventions are common.[9]

Remifentanil has been studied for the last two decades as an alternative to other parenteral opioids because of its rapid onset, short half-life, and potency. Although it is more often administered by PCA for labor analgesia, a 2014-15 survey of obstetric anesthesia directors (84 of 126 responded, 67% response rate) revealed ~36% (95% CI: 25.7-46.3) of U.S. academic centers used remifentanil, most less than 5 times.[10] There were 14 serious maternal and neonatal complications (e.g., desaturation, hypoventilation, and apnea). Another study evaluated respiratory variables (pulse oximetry, $ETCO_2$, respiratory rate, and integrated pulmonary index) to determine which type of monitoring is most sensitive for detecting apnea in patients who receive remifentanil PCA during labor.[11] Although pulse oximetry failed to detect most episodes of apnea, false positives occurred with $ETCO_2$, respiratory rate, and integrated pulmonary index monitoring. The authors concluded that continuous observation at the bedside is best due to the fact that 53% (10 of 19) of women experienced apnea. Taken together, remifentanil may be considered when neuraxial labor analgesia is contraindicated. However, protocols and adequacy of monitoring are necessary to ensure maternal and neonatal safety.

Nitrous oxide (N_2O) is an anesthetic gas with a rapid onset that is used as a labor analgesic around the world. Use of N_2O is increasing in the U.S. A recent review of N_2O utilization at a large teaching hospital determined that 146 (3% of total deliveries) women chose N_2O for labor analgesia.[12] The conversion rate to neuraxial analgesia was 63% in women receiving N_2O and 85% of the women only chose neuraxial analgesia. Labor induction and augmentation were associated with higher rates of conversion to neuraxial analgesia. A retrospective analysis of data from 2011-14 including 6,242 women determined that 19% chose N_2O and 81% of patients chose neuraxial analgesia.[13] More than 90% of women who received neuraxial analgesia reported high effectiveness. Women who only received N_2O reported variable analgesic effectiveness with ~50% reporting high satisfaction. The authors concluded that women who received only N_2O were "as likely to express satisfaction with anesthesia care" compared with women who received neuraxial analgesia, "even though they were less likely to report excellent analgesia." This study suggests that analgesia is not the only contributor to maternal satisfaction.

Neuraxial Labor Analgesia

Neuraxial labor analgesia and its potential effects on obstetric outcome have been an area of longstanding interest and controversy. A meta-analysis of randomized controlled trials (1,809 women in 10 studies) evaluated low concentrations of local anesthetics and obstetric outcome and determined that there were no differences in duration of 2nd stage, instrumented delivery, rate of CD, or duration of 1st stage labor.[14] Others have evaluated whether epidural infusions should be continued during the 2nd stage of labor.[15] Four hundred nulliparous women were randomized to receive a blinded infusion of placebo or local anesthetic when they were completely dilated. There were no significant differences between the groups in duration of 2nd stage, spontaneous vaginal delivery rate or pain scores during 2nd stage. Collectively, these studies in addition to already existing evidence should prompt continued work to individualize analgesic techniques in order to minimize any negative impact on the progress of labor and mode of delivery. Currently used concentrations of local anesthetic for epidural labor analgesia do not affect the duration of labor.

Aseptic technique is used prior to placement of neuraxial anesthetics. In the U.S., the anesthesiologist or anesthesia provider will wear a hat, mask, and sterile gloves. Worldwide, this practice is not universal. In a study of 151 institutions in 13 countries, 50% of providers will wear a sterile gown.[16] Although, only 96.7% wear facemasks and 88% use chlorhexidine prep, the estimated incidence of neuraxial infections was 1:41,898 catheterizations. The lack of universal aseptic technique makes determining the optimal technique difficult. Chlorhexidine-based solutions are often considered the antiseptic of choice for neuraxial anesthetic procedures. However, over 46 years, 43 cases of allergic reactions and 2 deaths from anaphylaxis have been identified with half of them occurring since 2010. These complications prompted a Safety Communication from the FDA about the use of skin antiseptic products containing chlorhexidine.[17]

Loss of resistance (LOR) to air versus saline has been an area of longstanding interest. A study in which 400 patients were randomized to one of the two techniques examined whether air versus saline provided better labor analgesia.[18]

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In the study, there were no significant differences between the groups with regard to onset, pain scores, more block, or overall efficacy at 30 min.

Dural puncture epidural (DPE) technique was first described nearly a decade ago and demonstrated improved maternal satisfaction and sacral analgesia by puncturing the dura without injecting medication into the CSF. More recently, 124 parturients were randomized to CSE vs. DPE vs. CLE.[19] Onset of analgesia was quicker in patients receiving CSE (2 min) vs. DPE (11 min) vs. CLE (18 min). Top-ups were required less often and side-effects (pruritus, hypotension, asymmetric block) were less in the DPE group. The authors concluded that DPE improved the quality of analgesia with fewer side effects compared with CSE and CLE.

Programmed intermittent epidural bolus (PIEB) technique is used to deliver a mandatory bolus of local anesthetic solution by a programmed infusion pump to maintain analgesia rather than by continuous infusion. Overall, studies have demonstrated decreased local anesthetic consumption, improved maternal satisfaction scores, reduced risk of motor blockade, decreased duration of the 2nd stage of labor and decreased number of clinician rescue boluses in PIEB groups compared to continuous infusion groups. However, optimal dosing regimens have not been established [20] and there have been questions about optimal bolus volume, rate, time interval, and drug concentrations. A study evaluated the optimal time interval (30, 40, 50, 60-min intervals) between PIEB boluses and used a double-blind sequential allocation trial to determine the ED_{90}.[21] Bolus doses were fixed at 10 mL/h of a 0.0625 bupivacaine + 3.3 mcg/mL. Forty minutes was the optimal interval.

Injection through the epidural needle was a popular technique in the 1980's and was re-evaluated in a study of injection of local anesthetic through the epidural needle compared to injection through an epidural catheter. This study used 0.125% bupivacaine 10 mL and found no difference in the onset of analgesia between groups. This practice should be discouraged as it does not improve the onset of analgesia and fails to identify an improperly placed epidural catheter.[22]

Local anesthetics are now in short supply. Please consult the Society of Obstetric Anesthesia and Perinatology advisory in response to shortages of local anesthetics in North America.[23]

Impact of ne*uraxial fentanyl on breastfeeding success* has been an area of controversy in obstetric anesthesia. Three-hundred five women who had successfully breastfed a prior infant, had planned to breast feed, and who received neuraxial labor analgesia were randomized to epidural bupivacaine 1 mg/mL, bupivacaine 0.8 mg/mL with fentanyl 1 mcg/mL, or bupivacaine 0.625 mg/mL with fentanyl 2mcg/mL for maintenance analgesia.[24] All three groups had similar high rates of breastfeeding success at 6 weeks and 3 months.

Psychology of labor has become a popular area of study. Women in Norway were studied to determine the characteristics of women who chose epidural analgesia. The use of epidural analgesia in Norway and the U.K. is less than in the U.S. The major reason women chose epidural analgesia was fear of childbirth.[25] Given this fear, education will improve understanding and the process of childbirth for the parturient.

Cesarean Delivery

In 2014, the ACOG published a document for the safe prevention of primary CD.[26] The recommendations of this group were to revisit the definition of labor dystocia because recent data show that contemporary labor progresses at a rate substantially slower than what was historically taught. Improved and standardized fetal heart rate interpretation and management will also have an effect. Increasing women's access to nonmedical interventions during labor, such as continuous labor and delivery support has been shown to reduce cesarean birth rates. External cephalic version for breech presentation and a trial of labor for women with twin gestations when the first twin is in cephalic presentation will also lower the primary CD rate. When these changes were instituted, one health care system reported a decrease in its global CD rate from 9.4% to 6.9%; CDs for arrest of 1st stage of labor decreased by 50% with no change in CD for arrest in 2nd stage of labor.[27]

Duration of CD was reviewed in 1,348 CDs to determine the influence of these various factors on the duration of CD. The mean operative time for first, second, third, and fourth or more CDs was 56, 60, 69, and 82 min, respectively. Operating with a first year resident increased the time for a CD by 14 min and the time for a tubal ligation 7 min.[28]

Left uterine displacement is fundamental to the practice of obstetric anesthesia. Venal caval compression in term pregnant women may reduce maternal cardiac output, blood pressure, and uteroplacental perfusion. In healthy pregnant women, cardiac output may decrease despite increased phenylephrine requirements when women are placed in the supine position compared to a 15° left lateral tilt after spinal anesthetic administration.[29] In a study of 105

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women undergoing elective CD during spinal anesthesia with the table tilted 15°, there was an increase in cardiac output and mean arterial pressure. Increasing to 30° did not improve from 15° tilt.[30] The goal is to maintain systolic blood pressure greater than 90% of baseline and avoid a decrease to less than 80% of baseline. Another conclusion from the study is that women with pre-eclampsia develop less hypotension after spinal anesthesia than healthy women. Left uterine displacement continues to be important during induction of neuraxial analgesia/anesthesia during the last half of pregnancy. In otherwise healthy patients, the supine position can be used safely immediately prior to skin incision and timely delivery with special attention paid to maternal blood pressure.[31]

Phenylephrine has become the preferred vasopressor for the prevention and treatment of hypotension during CD. An international consensus statement for the management of hypotension during CD was published.[32] Recommendations from this group included the use of alpha-agonists for the treatment of hypotension and left lateral uterine displacement. A comparison of a closed-loop feedback computer-controlled phenylephrine infusion versus automated boluses in 214 healthy patients who were randomized to either technique determined that the precision of BP control was greater in the bolus group. Phenylephrine consumption was also less but systolic BP was slightly lower over time. There were no differences in cardiac output, nausea or vomiting, or neonatal outcome between the two groups.

Difficult airways in patients presenting for emergency CD for non-reassuring fetal status are challenging. Using a decision tree analysis based on a systematic review of the literature, several factors were evaluated including the time taken to establish anesthesia and probability of failure for three anesthetic methods in women with no existing epidural. Time for rapid sequence induction of general anesthesia with rocuronium and videolaryngoscopy, awake fiberoptic intubation, and spinal anesthesia were quantified.[33] The authors found a shorter mean (95% CI) time to induction of 100 (87, 114) s using rapid sequence induction compared with 9 (7,11) min for awake fiberoptic intubation ($p<0.0001$) and 6.3 (5.4, 7.2) min for spinal anesthesia ($p<0.0001$). The risk of failed airway control after rapid sequence induction was 21 per 100,000 cases.

Cricoid pressure is the gold standard in delivering general anesthesia for CD, but does it prevent aspiration? A recent review discussed the most effective technique, it's effect on laryngoscopic view, complications and contraindications, as well as how to best train personnel in performing cricoid pressure.[34]

Awareness during general anesthesia for CD is a concern with a reported incidence of 1:1200, accounting for 10% of all cases of awareness during general anesthesia. Besides awareness, difficult and failed intubation may contribute to morbidity and mortality. This comprehensive review discusses the future of general anesthesia in obstetrics.[35]

Azithromycin is being used as an antibiotic adjunct in addition to cephalosporin for routine CD. Cost-effectiveness was evaluated in a model based on 700,000 CDs that occurred during labor or after rupture of membranes.[36] In the model, there were 16,000 fewer cases of endometritis, 17 fewer cases of sepsis, 8 fewer cases of VTE, and 1 less maternal death. More importantly, use of azithromycin led to decreased cost and improved quality of life. Azithromycin is likely to become routine for unscheduled CD.

Delayed Umbilical Cord Clamping is being used increasingly at the time of CD. ACOG recommends delaying cord clamping in vigorous term and preterm infants for 30-60 s after birth.[37] However, neonatal and maternal indications may dictate immediate clamping. Term infants are noted to have increased Hb levels and improved iron stores in the first months of life. In preterm infants, there is improved transitional circulation, red cell volume, decreased need for blood transfusion, and reduced risk of necrotizing enterocolitis and intraventricular hemorrhage. Risk of postpartum hemorrhage or need for blood transfusion is not increased. Active management of 3rd stage of labor and use of uterotonics after delivery are not affected by the delay.

Post-Cesarean Analgesia

Practice Guidelines for Obstetric Anesthesia suggest that practitioners "should consider selecting neuraxial opioids rather than intermittent injections of parenteral opioids."[7] In a study of patients undergoing CD, 721 women received intrathecal morphine 150 µg. Of these patients, 169 had at least one episode of desaturation, 91 experienced two or more mild desaturations, and 26 suffered a severe desaturation event. Desaturations were observed more frequently 4-8 hrs. after morphine administration and obesity was a risk factor.[38] In an evaluation of multimodal analgesia after CD, the administration of 1g acetaminophen preoperatively did not decrease the number of opioid medication doses or the amount of morphine administered.[39]

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Maternal Morbidity

Higher rates of morbidity have been noted in rural, low-volume, non-teaching hospitals.[42] In the U.S., 60% of U.S. hospitals provide obstetric care for less that 1,000 deliveries per year. Higher rates of morbidity may be related to staff competency and recruitment. The Maternal Health Compact is recommending a formal link of lower-resource hospitals with tertiary care hospitals to facilitate transports, consults, and QI activities.

Hemorrhage continues to be a leading cause of maternal morbidity and mortality. Use of the Obstetric Hemorrhage Bundle is well established. One of the recommendations is actual measurement of blood loss as compared to visual estimation. When measured blood loss was compared to visual estimation during CD, obstetricians were more likely to underestimate blood loss with urgent surgery, use of general anesthesia, and higher experience by the obstetrician. Previous CD and intra-abdominal adhesions were likely to cause the obstetrician to overestimate the blood loss.[48] When confronted with a patient with abnormal placentation, the provider must decide whether to perform the case in the main operating room or on the labor and delivery unit. In a survey of directors of obstetric anesthesia, the majority of respondents would manage women with abnormal placentation in the main operating room. In places where management occurred on the labor and delivery unit, there was better access to human and technical resources, the main operating room was in a convenient location to labor and delivery, and neuraxial rather than general anesthesia was used.[49]

Women undergoing intrapartum CD during labor are at increased risk for postpartum hemorrhage (PPH) compared to those undergoing prelabor CD. A recent case-control study evaluated women in each of these groups to determine differences in risk for PPH. Although general anesthesia and multiple pregnancies are shared risk factors in both groups, placenta previa increases risk in patients undergoing prelabor CD and a predelivery hemoglobin $\leq$ 9.9g/dL increases risk in patients undergoing intrapartum CD.[40] In a secondary analysis of data, surgical interventions, blood component use, and maternal outcomes were evaluated.[41] Prelabor CD increased the risk for morbidity, including increased rates of hysterectomy (18%) and ICU admission (16%). In addition, one third of these women received red blood cells either intraoperatively or postoperatively. In the intrapartum cohort, 18% of the women received RBCs intraoperatively vs. 44% postoperatively ($P<0.001$). In both groups, methylergonovine was the most common 2nd-line uterotonic.

Maternal Mortality

Rates of maternal mortality have decreased worldwide. However, the U.S. is an outlier in that rates of maternal mortality have increased despite the U.S. having "some of the most cutting edge medical treatments." While the increase has previously been explained by a lack of surveillance and documentation resulting in under-estimation, a retrospective study evaluating improved surveillance, including 2 new ICD-10 codes determined that a complete understanding of maternal deaths continues to be a challenge.[43] To further evaluate causes of maternal mortality, population data was used from the Pregnancy Mortality Surveillance System to estimate pregnancy-related maternal mortality and its causes.[44] Compared to 2006-2010, 2011-2013 rates were comparable with estimates of 17 maternal deaths per 100,000 live births. Maternal mortality increased with increasing maternal age and although hemorrhage, hypertension, and anesthesia complications declined, cardiovascular, CVA, and other medical conditions increased. Racial disparities persisted with African-American women's death rates being 3.4 times higher than other groups. Although there is much interest in determining actual causes of maternal death in the U.S., a focused review is needed to determine the types of disease, cause of death, and how death can be prevented.[45] In the U.K., the 4th report of the Confidential Enquiry into Maternal Deaths and Morbidity was published in 2017. In this time period, two women died directly from anesthesia with the rate decreasing from 1.2:100,00 in 1976-78 to 0.9:100,000 in 2013-15.[46] One woman died from hypoxic brain injury following resuscitation for anaphylactic reaction following induction of anesthesia while the other maternal death occurred from aspiration during surgery in a woman with small bowel obstruction.

Cardiovascular disease has emerged as a leading cause of maternal mortality in both the U.S. and U.K. A recent retrospective analysis evaluated maternal deaths due to cardiovascular disease in Illinois from 2002-11.[47]

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Of 636 deaths of pregnant women, 140 (22.2%) died of cardiovascular causes: cardiomyopathy (28%); stroke (23%); hypertensive disorders (13%); arrhythmias (11%) and coronary disease (9%). Acquired cardiovascular disease accounted for most of the deaths and 28% were potentially preventable.

Trauma and violence are underappreciated causes of maternal mortality. A retrospective study evaluated the Pennsylvania Trauma Outcome Study database from 2005-15 to learn more about the impact of trauma on maternal mortality.[50] In the report, there were 1,148 trauma events in pregnant women and 43,608 events among women of reproductive age (14-49 years). Compared to non-pregnant women, pregnant women had a lower injury severity score, were significantly more likely to experience violent trauma, and had a 1.6-fold higher rate of mortality. In the state of Illinois, a statewide maternal mortality committee reviewed maternal deaths associated with violence.[51] Nearly 25% of pregnancy-associated deaths were complicated by homicide, suicide, and substance abuse. Authors suggested a greater focus on opportunities to intervene and identify appropriate resources, including social services.

Sepsis is an important cause of obstetric morbidity and mortality. Several studies using mortality prediction scores have overpredicted mortality from sepsis in the obstetric population. A study of 797 women with either an admission diagnosis or suspicion of sepsis were included in a study evaluating the Sepsis in Obstetrics Score compared to the Acute Physiology and Chronic Health Evaluation II, Simplified Acute Physiology Score II, Sequential Organ Failure Assessment, and Multiple Organ Dysfunction Scores.[52] The Sepsis in Obstetrics Score did not demonstrate increased specificity for sepsis in the obstetric population compared to the other scores with the exception of the Multiple Organ Dysfunction Scores which was significantly better.

Cardiac arrest during pregnancy is rare in the obstetric population. Current ACLS guidelines recommend that the guidelines for cardiopulmonary resuscitation be followed. During cardiac compressions, the patient should be supine with manual left uterine displacement. Perimortem CD should be considered if maternal circulation has not returned by four min.[53] A recent retrospective population-based cohort study in Canada evaluated maternal cardiac arrest among 3,568,597 hospitalizations for delivery over a 13-year period from 2002-15.[54] Two hundred eighty-six cases of cardiac arrest were identified over the study period. The overall incidence was 1:12,500 deliveries. The risk of cardiac arrest was increased in women older than 35 years of age, higher order pregnancies, and <37 wks' gestational age. Seventy-one percent of patients survived. Etiologies included postpartum hemorrhage, heart failure, amniotic fluid embolism, and anesthetic complications. The U.K. reported their experience with maternal cardiac arrest. From 2011 to 2014, there were 66 cases of maternal cardiac arrest resulting in an incidence of 2.78 per 100,000 deliveries. Of these 66 cases, 16 arrested solely as a consequence of obstetric anesthesia (12 of whom were obese). Perimortem CD was performed in 49 women resulting in a maternal survival rate of 58% and an infant survival rate of 66%. [55]

Complications

Complications in Obstetric Anesthesia have been a major focus this year. Maronge and Bogod [56] provided a review of complications in obstetric anesthesia. While postdural puncture headache (PDPHA) is the most common complication (estimated to be 1:100 labor epidurals), nerve injury is the second most common; the risk of permanent injury from an obstetric neuraxial anesthetic is 0.2-1.2 per 100,000. For CD, the U.K. has set an audit standard that fewer than 1% of patients undergoing an elective CD should experience pain and fewer than 1% should require conversion to general anesthesia. All malpractice claims from the Controlled Risk Insurance Company related to obstetric anesthesia from 2005-15 were reviewed.[57] Of the 106 claims, 55% were for maternal nerve injury; of these cases, 77.6% did not receive payment. Maternal death was most likely to receive payment with the most common causes of maternal death being high neuraxial blocks, embolic events, and failed intubation. Pain and discomfort during the procedure were the least likely to receive payment. Nerve injuries continue to represent a significant cause of malpractice cases against the anesthesiologist. Of 19,840 patients who received neuraxial anesthesia, 19 had a peripheral nerve injury. The majority of injuries resolved within 40 d. Gestational age greater than 41 weeks, forceps delivery, and macrosomia were associated with nerve injury. Four injuries were judged to be anesthesia related. Repeated Tuohy needle puncture and cervical dilation greater than 5 cm increased the risk of anesthesia-related nerve injury. All patients had difficult epidural placement with pain at injection or several attempts at catheter insertion.[57]

Postdural puncture headache continues to be a complication following accidental dural puncture with an epidural needle. Previous research suggests that the accidental dural puncture may be a result of atypical anatomy as identified by ultrasound. However, 10 women with unintentional dural puncture who underwent magnetic resonance imaging showed no abnormalities.[58]

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Neonate

Antenatal Corticosteroids have beneficial effects when delivery is imminent in gestations 24-34 wks. Both betamethasone and dexamethasone are used. The greatest benefit occurs 24 h after administration and lasts for at least 7 d. A recent study investigated the use of corticosteroids for pregnancies in which delivery was imminent with gestational ages 34-37 wks. There was less severe respiratory morbidity and less surfactant use in the steroid group. Therefore, a single course of steroids is recommended for patients in this group to reduce the short-term respiratory morbidity of prematurity.[59]

The Neonatal Gut Microbiome is a focus of recent research. The early-life gut microbiota release metabolites and degradation products contributing to immune programming.[60] Consequently, there may be a benefit to the exposure of bacteria that occurs during vaginal delivery. This exposure may prevent asthma, allergies, and autoimmune disorders. This has led to the practice of vaginal seeding, the iatrogenic transfer of vaginal microbiota to the neonate. In women with chorioamnionitis, there is no increased risk of early-onset sepsis in exposed infants.[61]

Conclusion: The obstetric population is becoming older and pregnancies are often complicated by comorbidities. As a result, maternal morbidity and mortality have increased. More sophisticated levels of maternal care and systems will become increasingly important in order to facilitate rapid diagnosis and treatment as the prevalence of severe illness increases in obstetric patients. Care of parturients and pregnant patients requires profound knowledge about both obstetric and anesthetic concerns. The great news is that it is extremely rewarding and appreciated by patients and their families.

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Understanding Medical Accidents

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History

In the nearly two decades since the IOM published "To Err is Human", there has been little progress on patient safety in medicine. How did this happen? This refresher course will present the well-established models for how accidents happen, demonstrate their application to accidents within and outside medicine, and the explore the countervailing forces to the production of safety in medicine. It will also review (briefly) the low-hanging fruit of the first 15 years after the IOM report, none of which had the effects/benefits that their proponents believed they promised. The lecture will also review the countervailing forces: forces in health care and society that frustrate progress on patient safety.

Lexicon of Accidents

The Sharp End – In human factors and accident investigation, the "sharp end" is where the actual work of an organization happens. In aviation, the sharp end practitioners are the flight crew and air traffic controllers, in space flight, it is the astronauts and mission control, and in health care, it is the nurses, physicians and any other providers who work close in time and space to patients. The "human error" that is invoked as the cause of most accidents is almost always attributed to sharp end practitioners, who are regarded as important sources of variability and non-compliance, which are the most commonly invoked "causes" of accidents. (Cook 1994)

Human Error – The notion that faulty decision making by sharp end human operators is the principle cause of or a major cause of accidents and failures. The notion that human error is a major cause of accidents had been discredited by the time "To Err is Human" was published, but it remains the most commonly invoked explanation for failures in health care. The pivotal role that these same operators play in producing safety has only recently been recognized within health care (Reason 1990). More recent approaches even embrace these actions as the source of success, resilience, and safety in complex systems. The use of the word "error" has been abandoned by many experts in accident analysis (or has come to mean something completely different than it does in health care). (Berg, Hollnagel)

Latent Failure Model (Swiss Cheese) – Accidents in complex domains have multiple causes. In any well designed (and even in most poorly designed) systems, multiple failures, many of which my not have been recognized prior to the event, are necessary to create the circumstances necessary for catastrophe to happen. These failures need not occur close in time and space to the event in question, and many do not. (Reason)

Hindsight Bias – The sequence of events that lead-up to an accident are incredibly obvious in hindsight, and often completely inapparent to the operators involved. This makes it easy to judge the performance of these operators as incompetent, negligent, distracted, or uninterested. Competent accident investigation, as conducted by the National Transportation Safety Board, can mitigate the effect of hindsight bias in shaping the understanding of and learn from an accident. Hindsight bias remains a significant problem in the analysis of accidents and failures in healthcare. (Card, Cook 2010, Caplan, Fischoff)

Root Cause – An idea that persists in health care and its analysis of accidents. This notion originated in manufacturing, where it is commonly believed that there is one "root cause" of an accident or failure, and that the goal of an analysis is to identify and remedy this cause. In many health care organizations, those who analyze accidents state that accidents are the product of systems-failures, but can still often be seduced by the attractiveness of a single cause. The most commonly used tools to diagram how accidents happen are oriented toward identifying a single cause. (Card)

Near Miss – An event that contains all of the elements of an accident except the final bad outcome. These are believed to be useful in understanding how accidents within a system happen, and identifying persistent latent failures that might be remedied and thus reduce the risk of a bad outcome.

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The Low Hanging Fruit of the Early Days

The patient safety movement inspired by the IOM report embraced Incident Reporting, the Electronic Medical Record (EMR), Computer Provider Order Entry (CPOE), Bar Code Medication Administration (BCMA), and Simulation as approaches that could dramatically improve patient safety and reduce harm. To date, none of these produced the dramatic benefits promised. Their proponents argue that this is because of flawed/imperfect implementation, and that each will provide increasing benefit over time. While this argument is necessarily correct, safety experts from outside of medicine argued that health care did not invest resources into understanding how safety is made and broken in medicine, and absent the understanding from such research, had no chance of implementing effective changes.

Incident Reporting – The assumption behind incident reporting is that sharp end operators would report events and near misses, which would then prompt those who receive these reports to investigate them. Legal considerations have precluded many incident reporting systems from accepting reports of events; these systems are thus limited to near-misses. Most health care incident reporting systems were modeled after the Aviation Safety Reporting System (ASRS), a near-miss analysis system. A large number of incident reporting systems were established (in addition to those that were already in existence), many with overlapping "urisdictions. A practitioner could in theory report a near- miss to a half-dozen reporting systems. This redundancy has created a situation where many systems collect reports about a very small minority of relevant events. Sadly, the vast majority of incident reporting systems simply collect reports, and have little or no resources to analyze reports or disseminate lessons learned to practitioners. The Anesthesia Incident Reporting System (AIRS) at the Anesthesia Quality Institute is by far the best incident reporting system in health care today. At present, no health care incident reporting system commands analytic resources even close to those employed by the ASRS.

EMR/CPOE – There was great confidence that the EMR and CPOE would produce dramatic improvements in patient safety. Most practitioners have direct experience that this has not been the case. EMR and CPOE introduced new safety hazards to approximately the same extent that they mitigated the hazards associated with the paper-based world. This outcome was predicted by experts with experience outside of medicine. The high frequency of first generation CPOE medication "alerts" and their incredibly low clinical value has now been amply described in the literature. These alerts are disabled at some institutions, or clicked through as a necessary obstacle to doing work at others. (Kane-Gill, Winters)

BCMA – Bar Code Medication Administration is intended to ensure patients get the correct medication in a timely manner. In many or most instances, it has ensured that the correct bar codes are scanned in a timely manner. Ultimately, the effect of this technology on medication administration has not been determined. (Patterson)

Simulation – Simulation affords health care the opportunity to take providers into a safe, high-fidelity learning environment and practice generating care in a variety of stressful and hazardous situations. In most instances, providers do not train as a team, nor do they deploy as a team. This limits the benefit from the simulation experience. Taking teams off-line to train on a simulator is expensive, and difficult to do under the cost pressures of modern medicine.

Countervailing Forces

Production Pressure – The pressure to produce better outcomes utilizing less time and resources is palpable everywhere in modern medicine. Progress on safety, if any has been made, has likely been consumed by production pressure.

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Risk Homeostasis – Is a phenomenon first described by economists, but also observed by safety researchers. The idea is that operators have an acceptable level of safety with which they are comfortable, and will gravitate toward. If operations are becoming more hazardous, operators will seek ways to make them safer. If operations are becoming safer, operators or systems will generally increase production or expand the envelope of operations in a way that consumes the improved margin of safety. (Peltzman)

Policy Fantasy –When analyses of accidents/failures in health care have been completed, the result is often new or updated policy and procedures. The fantasy is that practitioners, working in uncertainty or faced with conflicting demands/priorities, will seek guidance about how to proceed in a policy manual. In reality, this almost never happens. The policy fantasy is ubiquitous in medicine.

Cycle of Error – One of the consequences of the policy fantasy is that the response to an accident is minimally effective or completely ineffectual. Thankfully, because accidents are rare, this failure is of little practical consequence. Sadly, the presence of a detailed policy manual increases the chances that the actions of sharp end practitioners will be judged deviant (non-compliant) and therefore the cause of a subsequent failure. Most organizations fail to recognize that the presence of detailed policies and procedures is a boon to plaintiff's attorneys, who only need show that work as it was being done deviated from work as imagined in the policy manual (thus, a plaintiff's attorney is often the the greatest beneficiary of the policy fantasy).

Quality/Safety Confusion – Accidents are truly rare events, whose incidence/frequency can only be estimated, not calculated with precision. Bad outcomes that occur with measurable frequency are simply that: bad outcomes. They are undesirable, but can be better conceptualized as a 'cost of doing business' that can be controlled rather than an accident, and should be approached as such. Central line bloodstream infections, bed sores, and wound infections are all bad outcomes, but none of them is an accident. By analogy, flat tire is not a car 'accident'. Bad outcomes in medicine, such as those noted above, are anticipated in the care of complex, ill patients. These can and should be managed with conventional quality techniques and approaches. More rare outcomes, such as chemotherapy overdoses, unintentional transfusion of ABO mismatched blood, or wrong side surgery, are the kinds of events that human factors experts and accident investigators would classify as 'accidents'.

Accident Exploitation – "Never let a good crisis go to waste" – Rahm Emmanuel. Spectacular accidents are opportunities for actors outside an organization to advance their agendas. Politicians, regulators (government and non-government), competing health care organizations, equipment manufacturers, advocacy groups, and the media will all exploit an accident to advance their agendas. As long as health care has accidents, this phenomenon will persist.

Forgetting – Learning about safety, like learning about clinical medicine, is largely experience driven. If an organization is not having accidents, it will not be learning about accidents and safety. Because accidents are inherently rare, it is easy for organizations to forget what they have learned from the accidents they have had. In the rapidly changing world of modern health care, many of the detailed "lessons-learned" are obsolesced by advances in practice or changes in organizational structure. (Leveson)

Modern Approaches

Thinking about safety outside of medicine continues to advance. The modern view is best represented in the Safety II approach (Hollnagel 2015), and in research into Resilience (Hollnagel 2013).

Within the world of medicine, there has been little critical appraisal of the outcome of implementation of the low-hanging fruit interventions of the first decade, but what has been published has generally been unfavorable (Wears). The blizzard of alerts generated by CPOE has spawned an entire literature surrounding alert fatigue (Kane-Gill, Winters). Similarly, the threats to safety created by the EMR are now being studied; it is not clear if there will be any research or regulatory mandate to remedy them (Holden 2011, IOM/Cook 2012, Lowry 2012, Zahabi 2015).

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Checklists are used with increasing frequency within medicine. Checklists, like other cognitive artifacts, can dramatically improve performance under stressful conditions. This outcome is not inevitable. In other domains, human factors experts are often engaged in the iterative development and maintenance of checklists. In health care, many checklists are simply created and imposed by fiat, without testing that demonstrates efficacy, or any improvement in a measurable outcome (Bosk, Catchpole, Stahel).

Accident analysis itself has moved beyond Root Cause Analysis. STAMP and SCAD are two of the newer, promising approaches to accident analysis (Leveson, Walker).

Medicine continues to invest resources into "solutions" without having first invested resources in understanding safety in healthcare, causation of accidents in healthcare, or sources of resilience in health care.

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Perioperative Management of Patients With Coronary Stents

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Introduction:

Coronary artery disease (CAD) is among the leading causes of morbidity and mortality worldwide.[1] It has been estimated that there occurs about one death each minute from a coronary event. Percutaneous coronary intervention (PCI) is a minimally invasive technique which is increasingly being utilized to treat CAD. It includes balloon angioplasties which may be combined with the placement of coronary stents. Approximately 600, 000 PCI procedures annually are currently being performed in the United States, and coronary stents are being placed in over 80% of these procedures. It has been estimated that 15-25% of patients with coronary stents present for non-cardiac surgeries within 1-5 years of stenting.[2,3] For a variety of reasons, these patients present with a unique set of challenges in the perioperative period. Observational studies have shown that they are predisposed to a higher risk of perioperative events.[4-6] Anesthesiologists can play a pivotal role in preventing major adverse cardiovascular events (MACE) in these patients. It is therefore imperative for the anesthesia provider to be familiar with the pathophysiology, pharmacology and management strategies of patients with coronary stents. They must have a clear understanding of the perioperative dynamics at play that predispose these patients to a greater risk. They should understand the importance and duration of dual antiplatelet therapy (DAPT) and be able to counterbalance the risk of surgical bleeding against the risk of stent thrombosis. At the present time, there is an insufficient evidence base to guide decisions about timing of surgery and management of DAPT.[7] However, based on consensus statements and expert opinion, the American College of Cardiology and American Heart Association (ACC/AHA) 2016 guidelines recommend delaying non-cardiac surgery (NCS) for a month after a bare metal stent (BMS), and for 6 months (3 months if urgent) after a drug eluting stent (DES).[8] This is based on contemporary evidence suggesting reduced risk of stent thrombosis (ST) with newer generation DES.[4] The guidelines also recommend that for elective surgery, patients should continue aspirin (ASA) throughout the perioperative period and restart the P2Y12 inhibitor as soon as possible after surgery.

History:

The word “stent” originates from the work of an English dentist named Stent (1807-1885) who pioneered a dental impression compound which evolved into a surgical tool. Stent technology has undergone explosive evolution since the pioneering success of Andreas Gruntzig in 1977 with the balloon angioplasty.[9] Plain old balloon angioplasty (POBA) alone, without stenting is associated with a high risk of elastic recoil resulting in early vessel closure as well as late restenosis due to inflammation. The reintervention rate may be as high as 30-40%. As a result, the performance of POBA alone without stenting is uncommon.

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BMS, introduced in the 1980's helped prevent the shortcomings of POBA. Designed to serve as vascular scaffolds they prevent the elastic recoil and collapse of the vessel. They were FDA approved in 1993. This was a major advance in stent technology and helped reduce the restenosis and dissection rates of coronary arteries. However, trauma to the vessel wall as a result of stent implantation initiates a complex interplay between the vessel wall, stent surface and blood components leading to activation of platelets and neointimal hyperplasia, much like scar tissue formation. As a result, 10-30% of patients over the course of a few months after BMS implantation get affected by in-stent restenosis. This can significantly reduce the lumen of the coronary artery resulting in stent occlusion and a gradual return of ischemic symptoms. Currently, only about 25% of all stents implanted during PCI are BMS.[10]

First generation DES were introduced in the early 2000's and FDA approved in 2003 as a potential solution to the shortcomings of the BMS. The metallic scaffold was coated with a drug delivery polymer embedded with an antiproliferative agent to prevent in-stent restenosis and scar tissue formation. The pharmacologic agents used to coat the stents belonged to the taxus and limus families. This resulted in a significant reduction in the rates of in-stent restenosis to 5-8%. However, it was soon realized that this new advance in stent technology also came with a price. After the implantation of BMS, the damaged vascular endothelium regenerates within the first 6-7 months. However, with DES regeneration and healing of the protective vascular endothelium is delayed or inhibited by the antiproliferative drug coating. First generation DES may not be fully endothelialized even after 3 years of stent placement.[11] This leaves the subendothelial connective tissue exposed to the circulating platelets and inflammatory mediators. The subendothelial collagen when in contact with platelets is a potent stimulus for thrombogenesis. As a result, patients with DES remain at risk for ST for prolonged periods. According to the Academic Research Consortium, in-stent thrombosis is considered acute when it occurs within 24 hours of stent placement; early when it occurs within 30 days; late when it occurs within a year of stent placement, and very late when it occurs beyond a year after stent placement.[12] Whereas in-stent restenosis is a pathology which gradually evolves over several months, typically in patients with BMS, ST is an abrupt, life threatening process that can lead to an acute myocardial infarction with a mortality of 10-30%. In 2005 85-90% of stents in United States were DES. After several adverse reports related to stent thrombosis, this rate dropped to 66% in 2007. Enthusiasm has since balanced out and DES use has again increased. In 2010, about 75% of stents implanted during PCI's were DES.[10]

It is believed that stent architecture, flexibility, apposition to the coronary vessel wall, the polymer coating, and choice of the pharmacologic agent may play a significant role in the safety profile of DES. Several generations of DES are currently available commercially:

First Generation DES:

These consist of a stainless steel metallic stent platform coated with a durable polymer that elutes the antiproliferative and immunosuppressive agent. Sirolimus elution is complete in about 6 weeks (Cypher). On the other hand, 10% of Paclitaxel elution occurs in the first 10 days, and the remainder is released indefinitely (Taxus).

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Second Generation DES:

These struts are constructed of more radiopaque cobalt-chromium (Xience/Promus, Resolute, Resolute Integrity) or platinum-chromium alloys (Taxus element, Pomus element, Promus premier) which are thinner, more flexible and easier to navigate. They are coated with a biocompatible durable polymer with superior re-endothelialization kineics. Zotarolimus completely disappears after full elution and everolimus is more lipophilic allowing rapid absorption into the arterial wall.

Next Generation DES:

Stent technology is continuing to evolve at a rapid pace. The newest generation stents include the bio absorbable polymer and polymer free devices (BioFreedom, Cre8). The use of durable polymers in DES is thought to contribute to a local inflammatory response responsible for stent complications. Novel manufacturing technology has eliminated the need for a durable polymer coating.[13] The first bioresorbable polymer DES (synergy) was FDA approved in 2015.

Totally bioresorbable stent (Absorb) was FDA approved in 2016. It was originally hailed as a major breakthrough in stent technology, however, trial data revealed that it had several limitations like thicker struts, stent recoil and poorer outcomes in smaller coronaries.[14] Abbot Vascular announced in September 2017 that it would end commercial sales of Absorb, however would continue to follow patients already enrolled in ongoing trials. The FDA issued a warning letter to healthcare providers in Oct 2017 stating increased rates of MACE in patients receiving the Absorb compared to Xience stents.[15] Regarding DAPT, the FDA advised that patients follow the recommendations prescribed by their providers.

Early reports of stent thrombosis and evolution of guidelines:

No official guidelines existed regarding antiplatelet therapy after the initial approval of BMS in 1993. In the early 2000's, early reports of perioperative morbidity began to appear in patients undergoing surgery within 6 weeks of BMS placement. As a result, in 2002, ACC/AHA guidelines were modified to specify that surgery should be postponed for 6 weeks after BMS implantation. Similarly, after the approval of DES in 2003, 290 reports of thrombosis in patients with DES were reported to FDA. An emergency meeting was ultimately convened, and the guidelines were revised in 2007 to recommend postponing non-cardiac surgery for a year after drug eluting stent placement. As the stent technology evolved, so did the safety profile. Data on second generation drug eluting stents was encouraging and the guidelines were liberalized in 2014 to recommend postponing surgery for 6 months to a year. As stent technology continued to rapidly advance, data on newer generation drug eluting stents prompted further liberalization of guidelines in 2016, which is current as of now.[16] The current guidelines recommend postponing non-cardiac surgery for 3 to 6 months after DES. Since the publication of these guidelines, recent data on the newest generation stents (bioresorbable stents) has also emerged.[15]

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Antiplatelet Therapy:

The cornerstone for antithrombotic prophylaxis in patients with coronary stents is antiplatelet therapy. Various pharmacologic agents are available to block different receptor sites on the platelets. There is, however, significant cross-talk between these receptor sites, hence blocking just one receptor is usually not sufficient during the high-risk period. In order to reliably block platelets, it becomes important to block more than one receptor. DAPT is therefore commonly utilized in most patients with fresh coronary stents. Clopidogrel (Plavix) and aspirin (ASA) are the commonly utilized pharmacologic agents for the prevention of stent thrombosis. ASA is a thromboxane inhibitor and clopidogrel is a P2Y12 receptor inhibitor. Of note, up to 30% of patients may be resistant to one of both of these drugs due to pharmacogenetic factors. Several newer potent drugs (Prasugrel, Ticagrelor, Cangrelor) are now available in the P2Y12 inhibitor class. Patients are less likely to be resistant to these newer agents. Currently available antiplatelet drugs fall into one of several categories:

Thromboxane inhibitors (ASA): ASA is an irreversible platelet inhibitors Guidelines recommend lifelong ASA therapy after PCI unless the risk from bleeding exceeds the risk of stent thrombosis.

GpIIb/IIIa inhibitors (tirofiban, eptifibatide, abciximab): These agents are commonly used by interventional cardiologists during stent deployment to avoid thrombus generation. Tirofiban and eptifibatide have a half-life of 2 hours. They have been utilized in high risk patients as bridging agents in the perioperative period, and bleeding time returns to normal about 4 hours of stopping infusion. However bleeding risk is higher with these than with oral drugs and platelet transfusions are not efficacious to reverse their effects.

P2Y12 or ADP receptor blockers (clopidogrel, prasugrel, ticlopidine, ticagrelor, cangrelor): Clopidogrel is an irreversible platelet inhibitor that requires metabolic activation for clinical effect. Prasugrel (Effient, Daiichi Sankyo/Lily), a third generation thienopyridine was approved by the FDA in 2009. It is orally active, more potent than clopidogrel, has a more predictable response and less drug resistance, with a higher bleeding risk. Ticagrelor (Brilinta, Astra Zeneca) is an orally active reversible agent FDA approved in 2011, that does not require metabolic activation for effect. Cangrelor, FDA approved in 2015 is an intravenous agent with an ultrashort half-life and has been utilized as a bridging agent in high risk patients.[3]

Heparins have been attempted in various combinations as bridging agents, however they possess insignificant antiplatelet effects, hence, unsuitable as a bridging therapy for antiplatelet effects in the perioperative period. Additionally, heparin causes a paradoxical platelet aggregation.[17]

Perioperative Considerations:

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Perioperative management of antiplatelet and anticoagulant agents raises some unique challenges. Maintaining antithrombotic therapy may increase the surgical bleeding and transfusion risk. On the other hand, withholding therapy may predispose patients to ischemic risks, including the risk of life-threatening stent thrombosis leading to MACE. Observational data regarding this dilemma is conflicting, and large randomized clinical trials to guide clinical decisions are lacking. Guidelines are therefore based on consensus statements and expert opinion, however, each clinical scenario may warrant an individual risk-benefit assessment and clinical judgment.[19]

The perioperative period is particularly risky, because the stress response of surgery activates the sympathetic system resulting in the release of inflammatory mediators. Stress hormones in turn, cause platelet activation, vasospasm and impaired fibrinolysis leading to a hypercoagulable state. Patients with recently placed coronary stents may already have a disrupted endothelial lining at a high risk of thrombosis. Well-meaning medical providers, may inappropriately advise patients to prematurely withhold DAPT to avoid surgical bleeding. An abrupt cessation of DAPT, beyond reversing the antiplatelet effect, may also contribute to a rebound prothrombotic state. This, together with the pain and anxiety related hyperdynamic state can lead to a demand-supply mismatch and add additional shear stress to the coronary plaques.

Discontinuation of DAPT after coronary stenting is a strong predictor of MACE, and the magnitude of risk is related to timing of surgery after PCI.[20] Recent data suggests that perioperative ST risk falls predominantly into the 6 month post stenting window.[4] Second generation DES exhibit a better safety profile, however acute coronary syndrome (ACS) is an independent predictor of perioperative ischemic events.[4] Angiographic features such as complex PCI's also predispose to high thrombotic risk.[21] Complex PCI includes one or more of the following characteristics: 3 or more lesions treated or 3 stents implanted, 2 or more bifurcating stents implanted, total stent length > 60mm, stenting for acute MI or history of prior ST.

An improved safety profile with newer generation stents have led to liberalization of guidelines with a 3-6 month DAPT duration (in non-ACS patients). However, the risk of ischemic complications must be individualized with a careful risk-benefit assessment of bleeding risk, ischemic complications and consequences of delayed surgery. The subset of patients who fall in the high bleeding risk and high thrombotic risk category deserve extra caution. Procedures with a high bleeding risk include intracranial, intramedullary spinal, prostate, middle ear, ophthalmologic and aortic surgery. Since DAPT must be stopped in these patients, a pharmacologic bridging therapy may be warranted within the high-risk period.[19] Although high quality evidence to support this strategy is lacking, there are reports of post PCI patients successfully receiving intravenous antiplatelet bridging therapy in the perioperative period within 6 months of coronary stenting.[22] Despite limited evidence, in a national survey of

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interventional cardiologists regarding urgent surgeries, respondents favored continuing DAPT or bridging with intravenous antiplatelet therapy.[23]

Adequate preparation with intravenous access and availability of blood products must be planned for patients who remain on APT in the perioperative period. Platelet transfusions may be performed approximately 4 hours after the discontinuation of clopidogrel due to its short half-life. Tight hemodynamic control to optimize the oxygen demand-supply balance and to minimize shear stress on coronaries is especially important in this patient population. Vigilance for signs of cardiac ischemia and ST must be maintained, with a plan for quick access to an interventional cardiology suite, should the need arise. Decision to perform regional/neuraxial anesthesia must be carefully analyzed, keeping in mind that should the patient require an additional urgent PCI procedure, additional antiplatelet/anticoagulant therapy may be administered.

Conclusion:

1. 15-25% of patients with coronary stents present for non-cardiac surgeries within 1-5 years of stenting
2. These patients present with a unique set of challenges in the perioperative period and are predisposed to a higher risk of perioperative MACE.
3. Anesthesiologists can play a pivotal role in preventing MACE in these patients.
4. As stent technology is evolving, so is the safety profile. Data on second generation drug eluting stents was encouraging and the guidelines have been evolving.
5. At the present time, there is an insufficient evidence base to guide decisions about timing of surgery and management of DAPT. However, based on consensus statements and expert opinion, the American College of Cardiology and American Heart Association (ACC/AHA) 2016 guidelines recommend delaying NCS for a month after a BMS, and for 6 months (3 months if urgent) after a DES. Based on angiographic and clinical risk factors, the DAPT duration may need to be extended in some cases.
6. Guidelines are helpful but cannot be followed blindly. Each decision must be individualized with a careful risk-benefit assessment of bleeding risk, ischemic complications and consequences of delayed surgery.

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Fluids, Osmolality and the Neurosurgical Patient

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History

The routine administration of iv fluids other than blood, and, starting in WWII, plasma, to surgical patients was uncommon prior to the 1950s – and when it was given, the most common fluid was dextrose in water. This probably stemmed from observations suggesting that since urine sodium concentrations in surgical patients were high, the patients must be "retaining sodium" so water was the thing to give. Somewhere around this time, the "mythology" of fluid restriction in neurosurgery arose – perhaps due the adverse consequences of large volumes of free water contained in D5W, or due to the observed facial/body swelling associated with the administration of large volumes of salt-containing crystalloids which first began to be practiced in the 1960's ("if the face is swollen, the brain must be swollen too"). No one knows. Fortunately, modern neurosurgeons are not as dogmatic as their predecessors although you can still encounter it from time to time. But a better understanding of the impact of fluids on the brain – and various fluid-related disorders that you will encounter in neurosurgical patients – can aid in the care of these patients.

Classic Science

In 1896 E.H. Starling basically told us about 90% of what we need to know about fluid movement into and out of brain with a very simple equation.

$$\mathbf{FM = K\,[(P_c - P_t) - \sigma(\pi_c - \pi_t)]}$$

We can simplify this even more

$$\mathbf{FM = K\,[Driving\ Forces]}$$

Where FM = Fluid Movement into (or, if a negative value, out of) an organ, and K is the "Filtration Coefficient" which represents the RATE of water movement across any given boundary (e.g. the blood brain barrier) for any given driving force (units are "ml per min per cm^2 of membrane surface per mmHg driving pressure). So if a boundary is "leaky" it will have a high K and water will move easily even if driving forces are low; if the boundary is "tight", it will have a low K and water moves only with difficulty (higher forces are required).

<u>K (Filtration Coefficient)</u>

Different organs have different K values – and this plays a huge role in understanding what happens in brain vs other tissues. For bowel/mesentery, K ≈ 1000 x 10^{-6} ml/min/cm2/mmHg). Skeletal muscle is much "tighter", with a K ≈ 40 x 10^{-6}. But BRAIN is perhaps the "tightest" of all with K ≈ 1 x 10^{-6} So for any given driving force, water will move into bowel/mesentery 1000 times faster than it will into brain.

And there is another factor that makes it hard to move water into brain (beyond K). Unlike many other organ, the brain is a tightly interwoven tangle of neurons, axons and glia. It has been nicely shown in animal studies (involving direct fluid infusion into brain tissue) that this matrix has a very low "elastance" or "elastic resistance" (mmHg change in pressure for each ml of fluid injected) [We always talk about brain or intracranial "compliance" – strictly speaking the term is wrong – it should be elastance which is the inverse of compliance.]. By contrast, most other tissues are much "looser" (witness how much fluid you can infuse simply by gravity via an infiltrated iv). Bottom line:

IT IS MUCH HARDER TO MOVE FLUID INTO THE BRAIN THAN INTO ANY OTHER ORGAN!

Teleologically, this makes sense – if you live inside a rigid box, you want to do everything possible to avoid unwanted increases in volume (or ICP will rise rapidly, ala Monroe Kellie).

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Driving Forces: What about the material inside the brackets of the simplified equation above, i.e.

$$[(P_c - P_t) - \sigma(\pi_c - \pi_t)]$$

P stands for hydrostatic pressure (like we measure with a transducer) while π stands for osmotic pressure. c means "in the capillary bed", t means "in the tissue". σ (the Greek lower-case sigma) is the osmotic reflection coefficient which basically tells you how good a "semipermeable membrane" the osmotic forces are working across.

If, for example, Pc =10mmHg, Pt = 5mmHg, $\sigma = 1$ (a perfect semipermeable membrane – which is very close to the actual σ value for brain), π_c = 285mOsm/kg and π_t = 288 mOsm/kg (in normal conditions, the interstitium of brain is a tiny bit hyperosmolar relative to blood), we get

$$[(10 - 5) - 1\ (285 - 288) = 5 - (-3) = 8.$$

BIG OOPS! We have to translate the osmotic gradient into a PRESSURE gradient so we're working with common units. Easy – a 1mOsm gradient across a perfect semipermeable membrane will generate about 19mmHg driving force (osmotic forces are really strong). So our -3 mOsm gradient translates into 57mmHg, and the solution to our equation becomes 5 – (-57) or 62mmHg. Multiply this by K (1×10^{-6}) and you can calculate that water is moving into brain at the rate of about 62uL/min/cm^2 of membrane. This isn't too far off – there is normally a continuous influx of fluid from blood to brain – which is then cleared via CSF circulation.

Now flip the osmotic gradient (make blood higher than tissue). Make the -3 into a + 3. Now we have 5 – (57) = -52mmHg or a 52 mmHg force moving water OUT of the tissue.

Since the hydrostatic pressures in our capillary beds are generally very low, you quickly see how important OSMOTIC forces become in moving water. In fact, the brain is a near-perfect "osmometer". In the laboratory, it is possible to measure a change in brain water content with as little as a 5mOsm/kg increase or decrease in serum osmolality.

How do you increase hydrostatic pressures? One way is to increase blood pressure – but since there is a huge gradient between arterial pressure and capillary pressure, it takes really large BP increases to meaningfully increase capillary pressures. But this is what happens with sustained "malignant hypertension" – patients develop cerebral edema (if they don't hemorrhage first). [It's unlikely that TRANSIENT increases in BP, such as commonly occurs intraoperatively, will have much effect.]. Another way is to increase VENOUS pressure – and this has been directly measured in HUMANS by looking at the efflux of dye from blood into the CSF (drained via a ventriculostomy) in the head-up vs head-down position. More dye moves from blood into brain in the head-down posture.

Oncotic pressure – and the Effects of Crystalloid Solutions

Oncotic pressure is that fraction of the total osmolality that is due to LARGE molecules (e.g. albumin). It is typically measured using a membrane oncometer and expressed directly as mmHg – not in molar terms. One of the arguments against giving large volumes of crystalloids is that it will reduce oncotic pressure (and hence total osmolality) and drive water into brain. Theoretically true – and possible to show under some extreme situations in the laboratory. But almost certainly NOT in the real world. Why not? Because TOTAL oncotic pressure under normal conditions is only about 20mmHg – meaning it's equivalent to what happens with only a 1mOsm gradient. And in clinical settings, the lowest oncotic pressure we can get, even with bucket loads of crystalloids – is about 10mmHg (equal to about 0.5mOsm/kg change. So one would predict that changes in oncotic pressure alone would have no meaningful effect on brain water – and that is exactly what is seen in the animal laboratory. Giving large amounts of crystalloids – as long as you make an effort to avoid major changes in total serum osmolality – has no measurable effect.

BUT, then why, when I give lots of crystalloids to my patient, do I see edema – edema of the face, swelling of the bowel etc? Because of our old friend K (the filtration coefficient). As noted, the vasculature of other tissues is much "leakier" than brain, and, as also noted, it is more "compliant" (easier to move water). But there is another factor –σ, the osmotic reflection coefficient. As a given membrane gets leakier, σ decreases. It becomes progressively more permeable to SMALL molecules (Na, K etc.) which make up the bulk of our total osmotic forces

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– but may remain impermeable to larger molecules (the oncotically active ones). Now the effect of changes in small molecules begins to disappear – leaving only oncotic forces active. These forces are still small – but in the face of a low K and compliant tissue, they are enough to produce swelling. Hence the explanation for why you can see peripheral edema – and yet have no cerebral edema.

Albumin and Other Colloids

Based on some of the aforementioned fears re.crystalloids, some have advocated the more aggressive use of colloidal solution. Given the concerns with hetastarch and renal injury, I will comment only on albumin use. Most of the arguments in favor of albumin have been on a theoretical basis, until the completion of the SAFE trial, which showed in its overall population that there were no differences in outcomes among trauma patients treated with saline or albumin. However, a subsequent sub-group analysis showed an excess mortality in HEAD TRAUMA patients who received albumin. This difference may have stemmed from the fact that the albumin solution used in the trial was relatively hypotonic (compared with the solutions used in the USA). There have been no studies of the use of crystalloids vs colloids in elective neurosurgery.

Osmotic Agents (Mannitol and Hypertonic Saline - HtSal)

As mentioned, changes in serum osmolality are a potent driver of fluid into and out of brain. Give too much free water, decrease serum osmolality, and the brain will swell. INCREASE serum osmolality and the brain shrinks. This phenomenon was recognized by neurosurgeons almost 100 years ago – and since then, a wide variety of hyperosmolar fluids have been used to reduce brain swelling: hypertonic saline, glucose, sorbitol, glycerol, urea etc. But currently only mannitol and hypertonic saline are used.

Mannitol: Mannitol is a 6-carbon alcohol with a molecular weight very close to glucose. It is derived from plants and is totally unmetabolized (cleared intact via the kidneys). We typically use a 20% solution with an osmolarity of 1100 mOsm/L. 500ml of 20% mannitol (i.e. 1gm/kg for a 100kg patient) is an osmotic dose of about 550 mOsm. This will TRANSIENTLY increase total serum osmolality by about 20mOsm/kg if given over 15minutes (e.g. from 290 to 310mOsm/kg) – but serum osmolality falls rapidly, reaching a value of about 300mOsm/kg after 60minutes.

But for some reason, mannitol confuses people. A hundred times I've heard it referred to as an "osmotic diuretic". It is, but somehow people connect the diuresis with its effect on brain water. NO. Mannitol works just fine *vis a vis* brain in anephric animals – its effect on brain is due almost entirely due to increasing serum osmolality, with some – and of doubtful relevance - component of vasoconstriction probably due to a decrease in blood viscosity. Don't use it in patients with severe renal failure – since they can't clear the mannitol. You also see some funny things. For example, measured serum Na will DECREASE after the infusion of mannitol. This is simply dilutional – water is moving from tissue into blood in response to an increased concentration of mannitol molecules. As mannitol is filtered via the kidneys it will take free water with it – and serum Na will progressively increase back towards baseline – or even above if enough free water is lost.

Hypertonic Saline: HtSal is simpler than mannitol in terms of its action. Like mannitol, a 500ml bag of 3% saline represents a 550mOsm dose of salt (3% saline is equi-osmolar with 20% mannitol). But instead of raising serum osmolality with a "foreign" molecule, it just raises Na+ and Cl- concentrations. Even though the Na ion is much smaller than a mannitol molecule, the σ value for the blood brain barrier for Na is still close to 1.0 – and so water moves in a fashion indistinguishable from mannitol. But unlike mannitol, there is no diuresis (although urine output may increase from hypervolemia). The kinetics of HtSal are remarkable similar to that for mannitol (in terms of serum osmolality).

More concentrated saline solutions have also attracted attention both as agents to shrink the brain and as resuscitation fluids. This has stemmed largely from military interest – 7.5% saline has the volume-expanding ability equivalent to several liters of normal saline and weighs much less (and hence easier to carry in combat). The disadvantage is that, if extravasated, it can cause tissue injury and in a civilian setting, is usually given via a central vascular catheter. While some have argued that 7.5% saline has greater effects on ICP than 3% saline, this is not convincing; most studies that show differences have failed to carefully match resultant osmolalities between treatment groups. And the delay (and risks) in establishing central access raise questions (in my mind) about its true clinical value (as opposed to 3% saline).

Adverse Effects

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Neither mannitol nor HtSal are risk free – although these are a largely trivial following a single operative dose except in the face of severe left ventricular failure (where the resultant volume expansion can precipitate pulmonary edema). Also, if either agent is given very rapidly (over a few minutes), profound transient hypotension may result due to vasodilation – any hypertonic drug will do the same. If given "by gravity" (just let it drip) or infused over 15minutes, this problem does not occur.

The greater risks come following repeated doses over longer periods of time, where both medications can result in hypernatremia (and kidney injury), and mannitol can result in striking degrees of dehydration/hypovolemia. There is also a potential (with both drugs) of "rebound swelling". This has been attributed by some to mannitol (or sodium) "leaking" into the brain interstitium and drawing water back into the tissue. However, a better explanation is the excessively rapid normalization of serum osmolality after a long period of hyperosmolality. With chronically elevated serum osmolality, the TISSUE osmolality is increased (our old friend π_t). If serum osmolality is then rapidly reduced, water will now move INTO brain, causing swelling. This phenomenon is seen nicely when patients with chronic, severe hyperglycemia are overly-aggressively treated with insulin. Serum osmolality (due to glucose) falls rapidly – but brain osmolality does not (insulin does not enter brain) – and cerebral edema results.
[Note: Glucose is a poor therapeutic osmotic agent because it is actively transported across the blood brain barrier. In effect, the effective σ value is low and, except under rapidly changing conditions (as above), little water is moved. Giving D5W or D10W is not much different from an osmotic perspective from giving distilled water.]

IV Fluids and Osmolality: We typically think of our mainstay crystalloids (lactated Ringers, normal saline, Plasmalyte) as "isotonic". If you read the labels on the bags, they list "osmolarity" values that appear to be normal. But osmolarity (mOsm/L) and osmolality (mOsm/kg) are NOT the same. I won't get into the physical differences – but you can think of the difference as "theoretical vs actual"; osmolarity is a theoretical value based on the mM concentration of ions in the solution (e.g. 150uM Na^+ and 150mM Cl^- add up to 300mM = 300 mOsm/L). In reality, some of the Na+ and Cl- ions "stick together, to the EFFECTIVE number of independent particles is less than this (and osmotic forces are just a measure of the number of particles). What we measure in our patient's blood is the EFFECTIVE osmotic concentration – or osmolality (mOsm/kg) – and if you measure osmolality in some of our IV fluids, you will see that they are uniformly LESS than the calculated osmolarity. For example, lactated Ringers has a listed osmolarity of 273mOsm/kg – but its measured osmolality is 250 mOsm/kg – notably hypotonic relative to blood. Normal saline has a listed osmolarity of 308 mOsm/L – but a measured osmolality of 282 mOsm/kg (much closer to true isotonicity).

Does this matter? If you are giving 1-2 liters of fluid in the OR, probably not. But if you get into a high-volume replacement situation (e.g. with lots of blood loss), it can. 5 liters of lactated Ringers is roughly equivalent to giving 4+ liters of normal saline – and just shy of a liter of free water. What do you do? The simplest approach is just to measure serum osmolality repeatedly – and adjust your fluids (mix LR with NS). You could use just normal saline – but now the hypercholemic acidosis may become problematic and there is some data suggesting that excessive amounts of normal saline are associated with acute kidney injury.

Furosemide: Furosemide in very large doses (e.g. 1mg/kg) has been shown to reduce ICP. However, multiple studies have shown that it DOES NOT reduce the water content of edematous brain. Combining furosemide with hypertonic agents DOES NOT result in a greater reduction in brain water content than achieved with the hypertonic agent alone. General consensus is that it acts by reducing CSF production.

The Open Blood Brain Barrier

Everything said so far has been about what happens in NORMAL brain with an intact blood-brain barrier(BBB). But what happens when the BBB is open (vasogenic edema) – something we encounter in head trauma and with some brain tumors? Much of the effects of fluids and osmolality can be deduced by understanding the changes to the Starling equation. When the BBB opens, K (the permeability coefficient) decreases – making it easier to move water – meaning that lower driving forces are needed to produce edema. In addition, σ also begins to fall (the BBB becomes a less effective "semipermeable membrane) – reducing the impact of osmotic forces (since now both ions and protein can pass through the "holes". In the laboratory, BBB disruption essentially eliminates the impact of changing osmolality; changing serum osmolality (by giving water or by giving HtSal) has no effect on water content. This can be seen in human imaging studies where mannitol administration effectively reduces water content – but ONLY in areas of brain where the BBB is intact. Under such situations, hydrostatic forces become the predominant driving forces.

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Other Factors - Aquaporins

So far, I've talked about water movement as a purely physical phenomenon. But in the last few decades, research has shown that other factors play an important role. Perhaps the most important of these are the so-called aquaporins. These are a family of protein transmembrane pores (channels) that can actively regulate the movement of water; the AQP4 channels are plentiful in brain and are located on astrocyte membranes adjacent to capillaries (as well as the ventricles and subarachnoid space). As these channels open and close, water (and other molecules) can move faster or slower. One can think of these channels as actively modulating the K and σ factors in the Starling equation. Studies have shown that the channels play an important role in peritumoral edema and blocking these channels can reduce swelling (in animals). Similar work has shown that either blocking these channels – or eliminating them entirely (knockout mice) can influence edema formation in many other situations. Most disorders associated with cerebral edema formation are also associated with upregulation of AQP channels. Nevertheless, no clinical methods for influencing AQP channels are available – and osmotic agents still remain the mainstay of cerebral edema management.

Other Neurosurgical "Fluid Disorders"

The two "fluid disorders" seen most commonly in neurosurgical patients are diabetes insipidus and SIADH (Syndrome of Inappropriate ADH). Both involve abnormalities in vasopressin release and actions.

Diabetes Insipidus: Vasopressin (AVP) release is tightly linked to serum osmolality; small increase in osmolality result in large increases in circulating AVP – which acts on the kidney to enhance water reabsorption (intended to restore osmolality to normal). DI can either be central (due to a reduction in circulating AVP and a loss of the normal response to increasing osmolality) or it can be nephrogenic (due to renal tubules failing to respond to vasopressin). In neurosurgery, central DI is by far the most common, due to damage to either the posterior pituitary, the pituitary stalk, or the periventricular nucleus (where vasopressin is formed). It can be seen in pituitary surgery, surgery around the base on the brain (e.g. craniopharyngioma surgery) or after trauma. What we see is an often-sudden increase in urine output unexplained by the administration of mannitol or other diuretics. The diagnosis is straightforward – but please don't just assume that all diuresis is DI. First, you need to back off on your IV fluids (hypervolemia will suppress ADH production, hypovolemia will increase it). Then you need to measure both serum and urine osmolality. If serum osmolality is high and urine osmolality is low, then DI is likely. Fortunately, treatment is easy – a small dose of desmopressin iv will usually result in a decrease in urine output. This is seen as so safe (unlike in old days when all we had was aqueous and old-based pitressin) that it can be used as a diagnostic challenge – although DDAVP will, in some patients, reduce urine output even in the absence of DI.

SIADH: You can think of SIADH as the inverse of DI – too much vasopressin is being produced. The stimulus to ADH release is usually unknown. The result is water retention and otherwise unexplained hyponatremia. Unfortunately, unlike DI, definitive diagnosis is difficult. Look for "euvolemic hyponatremia" combined with concentrated urine (high sodium, high specific gravity). The treatment is with saline-containing fluids.

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Coagulation factor concentrates:

When are they indicated to treat coagulopathy?

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Perioperative coagulopathy occurs in about 10-15% of cardiac surgeries and is associated with excessive blood loss, greater red blood cell and blood component transfusion, and chest re-exploration for surgical hemostasis. Preoperative use of anticoagulants and antiplatelet agents as well as hereditary bleeding disorders increase risk for perioperative coagulopathy. Intraoperative factors which increase risk for coagulopathy include greater procedural complexity, prolonged duration of cardiopulmonary bypass, and reoperative surgery.[1] Factors associated with cardiopulmonary bypass, including hemodilution, activation and consumption of coagulation factors and platelets, heparin administration, hypothermia, and excessive fibrinolysis, further contribute to perioperative coagulopathy.

Treatment of perioperative coagulopathy with platelets, fresh frozen plasma, and cryoprecipitate is usually effective. At times, however, coagulopathy may be refractory to usual therapy. When this occurs, new formulations of activated factors, prothrombin complex concentrations, and fibrinogen replacements may be considered as alternative options to treat life-threatening perioperative coagulopathy. Indications, risks, and benefits for these new products are discussed below.

Assessment of perioperative coagulopathy

When coagulopathy occurs, standard coagulation tests, including International Normalized Ratio [INR], activated partial thromboplastin time [aPTT], fibrinogen concentration, and platelet count, are recommended to identify coagulation defects and guide therapy. Additional monitoring for coagulopathy may include tests for platelet function and viscoelastic assays, including thromboelastography (TEG) and rotational thromboelastometry (ROTEM). Most algorithms suggest transfusion when excessive nonsurgical bleeding is accompanied by a prothrombin time/International Normalized Ratio (INR)/activated partial thromboplastin time more than 1.5 times normal, a platelet count less than 50 to 100,000, or fibrinogen concentration less than 100 mg/dL.[2] D-dimers or fibrin degradation products may suggest that fibrinolysis is occurring. Thromboelastography and rotational thromboelastometry are also useful to detect fibrinolysis. Platelet function testing has been reported but has limited availability and correlation between abnormal platelet function and perioperative bleeding is not consistent.[3]

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Conventional treatment for perioperative coagulopathy includes platelet transfusion, transfusion of fresh-frozen plasma (FFP), and transfusion of cryoprecipitate. Transfusion algorithms are helpful and preset triggers usually reduce the need for blood component transfusion.[2] When these therapies fail, however, pharmacologic treatment of excessive bleeding with prothrombin complex concentrates, coagulation factors, or fibrinogen may be considered. Please note that most of these therapies are not FDA-approved for perioperative coagulopathy and are considered off-label use; thus serious evaluation of the risk versus benefit of these alternative therapies is recommended.

Prothrombin complex concentrates (PCCs)

PCCs are coagulation factor replacement products that are usually described as "3 factor" products that contain vitamin K-dependent coagulation factors II, IX, and X, versus "4 factor" products containing factors II, VII, IX, and X. Anti-thrombin, proteins C and S, and/or heparin may also be included in several formulations of PCCs. Activated PCC (aPCC) products contain four coagulation factors in inactive and activated forms.

PCCs are FDA-approved for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (e.g., warfarin) therapy in adult patients with acute major bleeding.

PCCs have important advantages over alternative therapies such as vitamin K administration or fresh-frozen plasma (FFP) for reversal of anticoagulant effects of warfarin and other vitamin K antagonists. Certainly, PCCs correct the INR more rapidly than vitamin K administration for warfarin reversal. Further, vitamin K lacks an ability to reverse the anticoagulant effects of newer agents, such as the oral direct thrombin inhibitors or factor Xa inhibitors. PCCs also provide more rapid reversal than FFP, because ABO-matching is not required and additional time for thawing is not needed before PCC administration. Another important advantage of PCCs for reversal of vitamin K antagonism is a reduction of intravascular volume transfusion compared with FFP, thus reducing risk of transfusion-associated cardiopulmonary overload and other transfusion reactions, including acute lung injury.

One aPCC product is a freeze-dried sterile human plasma fraction with **f**actor **e**ight (VIII) **i**nhibitor **b**ypassing **a**ctivity (FEIBA). This aPCC product contains activated factor VII and X and non-activated factors II, IX, and X, thrombin, and protein C. Factor VIIa, prothrombin, and Factor Xa serve as the main active factors. FEIBA products are FDA-approved to control spontaneous bleeding episodes or to prevent bleeding with surgical interventions in hemophilia A and hemophilia B patients <u>with inhibitors</u>. FEIBA products have been used in an off-label fashion as an anticoagulant-reversal agent.[4,5]

The ASA issued updated guidelines for perioperative blood management in 2015, which reviewed alternative therapies for coagulopathy, including use of PCCs.[6] These guidelines

recommend administration of PCCs for urgent reversal of warfarin in consultation with an appropriate specialist. With severe perioperative bleeding, patients on vitamin K antagonists should be given PCC and intravenous vitamin K before other coagulation management steps. In patients with excessive bleeding and increased INR, the use of PCCs may be considered. These guidelines are supported by evidence that intraoperative administration of four factor PCCs were followed by a reduction in blood loss and normalization of INR values in several observational studies and case reports.[7,8]

The EACTS/EACTA issued guidelines in 2017[9] which recommend that in patients in whom bleeding is related to coagulation factor deficiency, PCC or FFP administration should be used to reduce bleeding and transfusions. These guidelines state that PCC may be preferred over FFP when rapid normalization of coagulation factors is needed. Please note that this recommendation is stronger than the guidelines released by the ASA. In support of this recommendation, a recent propensity matched comparison of patients receiving PCC compared with FFP as a first-line therapy for coagulopathy found that patients who received PCC demonstrated reduced 24 hr postoperative blood loss and less red blood cell transfusions.[10] Although mortality was not different between groups, risk of acute kidney injury and renal replacement therapy were increased with PCCs.

FEIBA has also been reported for rescue of postoperative coagulopathy after complex heart surgery. FEIBA was effective in decreasing need for FFP and platelet transfusion and correcting an elevated INR.[11] No mortality occurred though one patient developed an upper extremity deep vein thrombosis. The FDA indications, however, clearly state that FEIBA is not indicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to factor VIII or factor IX.

Recombinant factor VIIa (rVIIa)

rVIIa is a recombinant genetically engineered clotting factor that is structurally similar to human plasma-derived factor VIIa. The FDA indications for rVIIa include the following: 1) the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX or in patients with acquired hemophilia, 2) the prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B in patients with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia, 3) treatment of bleeding episodes in patients with congenital FVII deficiency, and 4) prevention of bleeding in surgical interventions or invasive procedures in patients with congenital FVII deficiency.

rVIIa effectively promotes hemostasis by activating the coagulation cascade. rVIIa complexes with tissue factor at the site of vascular injury and cleaves factor X to the enzyme-activated factor X, thus promoting the conversion of prothrombin to thrombin and fibrinogen to fibrin, facilitating

the formation of a hemostatic plug. rFVIIa enhances site-specific thrombin generation and tissue factor mediated activation of coagulation.[12]

The observed hemostatic properties of rFVIIa have led to its off-label use in life-threatening bleeding, though concerns for thromboembolic events suggest that rFVIIa use should be considered only as a last resort. A recent Cochrane review examined the results of 29 clinical trials (N=4290) which assessed the therapeutic and prophylactic use of rFVIIa in patients without hemophilia.[13] When rFVII given for therapeutic benefit (after the onset of coagulopathy), there was a small trend in favor of rFVIIa for reducing mortality (RR 0.91; 95% CI 0.78 to 1.06). However, there was a trend against rFVIIa for increased thromboembolic adverse events (RR 1.14; 95% CI 0.89 to 1.47). When trials that examined the therapeutic and prophylactic use of rFVII were pooled together, an increase in arterial thromboembolic events was observed (RR 1.45; 95% CI 1.02 to 2.05). These data provided evidence that prophylactic use of rFVIIa is not recommended in cardiac surgery. Therapeutic use of rVII may be considered in patients with uncontrollable bleeding that cannot be managed by other procoagulant interventions.

The ASA recently published recommendations regarding the use of rFVIIa.[6] Because meta-analysis of placebo-controlled RCTs of rFVIIa report equivocal findings regarding the volume of blood loss, the volume of blood transfused, and the number of patients transfused, the ASA recommends that administration of rVII may be considered when traditional options for treating excessive bleeding due to coagulopathy have been exhausted. Prophylactic use of rFVIIa is not recommended due to increased risk of fatal thrombosis. Off-label administration of rFVIIa can be considered for life-threatening bleeding which cannot be stopped by conventional, surgical or interventional radiological means and/or when comprehensive coagulation therapy fails.

The 2017 EACTS/EACTA guidelines[9] state that prophylactic use of rFVIIa cannot be recommended in cardiac surgery; therapeutic use should only be considered in patients with uncontrollable bleeding that cannot be managed by other procoagulant interventions.

Fibrinogen concentrate

Fibrinogen Concentrate (Human) is FDA-approved for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. Fibrinogen concentrate has some advantages over other sources of fibrinogen, including cryoprecipitate, which is a pooled product that does not undergo pathogen inactivation, and its administration has been associated with a number of adverse events, particularly transmission of blood-borne pathogens and transfusion-related acute lung injury. However, some benefits of cryoprecipitate compared with fibrinogen concentration include the presence of additional coagulation factors that may improve hemostasis, such as von Willebrand factor, factor VIII, factor XIII, and fibronectin.

Fibrinogen loss during surgery results from acute bleeding, dilution of the circulatory volume due to administration of fluids and priming of the CPB circuit, and consumption due to activation of the coagulation cascade during CPB. Acquired hypofibrinogenemia, defined as a decrease in plasma fibrinogen levels below 150-200 mg/dL, increases risk for coagulopathy and blood loss after CPB.[14,15] Fibrin formation is more impaired than both thrombin generation and the platelet component of the whole blood clot immediately after cardiopulmonary bypass,[16] and fibrinogen is the first coagulation factor to reach critically low concentrations in major bleeding.[17] Hypofibrinogenemia has been associated with adverse outcomes in patients having cardiovascular surgery and trauma.

Despite development of acquired fibrinogenemia in patients having cardiac surgery, evidence to support prophylactic administration of fibrinogen concentrate is mixed. Early small clinical trials (n=61) showed a benefit of reduced blood transfusion when fibrinogen concentrate was given for clinical bleeding after cardiopulmonary bypass.[18] In contrast, a large multi-center clinical trial unexpectedly found no benefit to fibrinogen transfusion: the Randomized Evaluation of fibrinogen vs PLACEbo in complex cardiovascular surgery (REPLACE) randomized 519 patients to human fibrinogen concentrate vs. placebo and reported an increase in blood product transfusion in patients that received fibrinogen.[19] The authors speculated that low bleeding rates and normal-range plasma fibrinogen concentrations before study medication as well as variability in adherence to the complex transfusion algorithm may have contributed to these results. Another trial of 120 patients having high-risk cardiac surgery were randomized to receive fibrinogen or placebo and blood loss was not different between groups.[20] A multi-center, randomized trial called the FIBrinogen REplenishment in Surgery (FIBRES) is currently underway. FIBRES is a single-blinded, phase III trial of adult cardiac surgical patients who are experiencing clinically significant bleeding related to acquired hypofibrinogenemia. Noninferiority of 4 gm of fibrinogen concentrate will be compared to 10u of cryoprecipitate and total red cell, platelet and plasma transfusions administered within 24 hours of bypass will be examined.[21] The results of this trial will help guide future use of fibrinogen concentrations.

ASA 2015 guidelines currently state that insufficient evidence is available in the literature to evaluate intraoperative or postoperative transfusion of cryoprecipitate to manage hypofibrinogenemia.[6] The ASA guidelines regarding fibrinogen concentrate are based on small early investigations which compare fibrinogen concentrate with placebo and report a lower volume of RBC transfusion and a reduced frequency of patients transfused when fibrinogen concentrate is administered intraoperatively. (The ASA guidelines were published before the results of the REPLACE trial[19] were reported.) Thus the ASA recommends that, in patients with excessive bleeding, the use of fibrinogen concentrate may be considered with an initial fibrinogen concentrate dose of 25 to 50 mg/kg.[6] In cases where fibrinogen concentrate is not available,

cryoprecipitate at an initial dose of 4 to 6 ml/kg is suggested. Plasma transfusion alone is not sufficient to correct hypofibrinogenemia.

The 2017 EACTS/EACTA Guidelines include data from a Cochrane review of 6 clinical trials suggesting a beneficial effect of fibrinogen concentrate in reducing the incidence of allogenic transfusions[22] and a propensity score analysis in 380 patients undergoing cardiac surgery which suggested no increased risk of thromboembolic events or death after fibrinogen substitution.[23] However, the conflicting results from the REPLACE trial[19] were noted and the guidelines comment that additional safety data from larger RCTs, which also addressed different fibrinogen target concentrations, are necessary. The EACTS/EACTA guidelines thus state that prophylactic fibrinogen administration is not recommended for reducing postoperative bleeding and transfusion risks. However, in patients with a low-fibrinogen level and signs of persistent microvascular bleeding, fibrinogen substitution may be considered to reduce the requirement for transfusions.

Factor XIII

FXIII is the terminal enzyme in the coagulation cascade and is necessary for cross-linking fibrin monomers to form a stable, strong fibrin clot. Low FXIII levels have been reported after cardiac surgery and are associated with increased blood loss after coronary artery bypass grafting.[24] A recombinant form of FXIII is now available and has been administered to patients having cardiac surgery. A recent double-blind, placebo-controlled, multi-center trial in 409 patients at moderate risk for transfusion (*n* = 409) reported that replenishing factor XIII levels did not reduce postoperative transfusion or surgical re-exploration in patients requiring cardiopulmonary bypass.[25] Adverse events were comparable between groups.[24]

Recommendations for use of factor XIII include cases of bleeding and low factor XIII activity (e.g. <30%). The EACTS/EACTA 2017 guidelines[9] state that there is no evidence that administration of FXIII is beneficial regarding the reduction of postoperative bleeding volumes and transfusion rates in patients with normal concentrations of FXIII.

Complications associated with administration of PCCs, coagulation factors, and fibrinogen

Emergent reversal of the antithrombotic effects of anticoagulant drugs is necessary when life-threatening hemorrhage occurs; however, no pharmacological agent has been developed that specifically reverses the anticoagulant effects of these medications without some procoagulant activity. Especially in patients taking oral anticoagulant medications who have underlying risk factors for thrombosis, reversing the action of these agents may increase risk for thromboembolic adverse events. Thromboembolic complications may include venous

thromboembolism, disseminated intravascular coagulation, myocardial infarction, and pulmonary embolism.[26,27] Observational studies and case reports indicate that four-factor PCCs administered preoperatively are followed by a reduction in International Normalized Ratio (INR) values, with low risk of thromboembolic events. A recent retrospective study of four-factor PCC Beriplex P/N (CSL Behring, Marburg, Germany) reported a low risk of thromboembolic events (approximately one in 31,000).[28] Reports estimate that four to nine thrombotic events occur for every 100,000 infusions with aPCC therapy used for its FDA-approved indication.[29]

A history of liver disease and high doses of a given PCC product have been associated with the greatest risk of thromboembolic adverse events.[30] Please note that aPCC and other PCC products are not intended to be used off-label as reversal agents for dabigatran or other anticoagulant therapies, nor have they been adequately assessed for appropriate dosing, efficacy, and safety in off-label situations. Although coagulation factor products, such as recombinant factor VIIa, can reverse the effects of anticoagulant therapy, thromboembolic complications are increased.[31]

When PCC products are administered for excessive bleeding and an acquired coagulopathy, rather than reversal of anticoagulant medications, PCC products carry an inherent risk of thrombosis. The prothrombin content of a given PCC product is a major determinant of its potential to generate excessive thrombin generation.[32] Repeated dosing may increase the risks of bleeding because of accumulation of prothrombin and thrombin resulting from their prolonged half-life, compared with other coagulation factors. aPCC has a high content of both prothrombin and thrombin compared with other PCC products, and may therefore pose a higher risk of thrombosis.[33]

The balance between procoagulant and anticoagulant activity plays a large part in the potential for thrombosis with PCC products. Proteins C and S are found in some three-factor and four-factor PCC products, but not in most aPCC products, which may affect the risk for procoagulant activity and thrombosis.

The risk of thromboembolic complications with fibrinogen concentrates requires further investigation. A recent propensity analysis reported that fibrinogen concentrates was not associated with an increased risk for mortality and thromboembolic or cardiac events within 1 yr after cardiac surgery.[23]

Conclusion

More formulations of activated and nonactivated factors, prothrombin complex concentrates, and fibrinogen replacement therapy are becoming available; however, their use to treat serious perioperative coagulopathy refractory to conventional therapy is considered off-label in the US and careful consideration of the effectiveness, risks, and benefits of these therapies is needed.

Ongoing research will provide more knowledge about the appropriate use of these agents aimed at the ultimate goal of improving outcomes in patients who require cardiac surgery.

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Blood Sparing Methods in Cardiac Surgery

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Introduction

Despite the known risks and costs associated with allogeneic transfusions, transfusion rates continue to vary widely among centers that perform cardiac surgery.[1] In the past decade, not only have landmark studies been published supporting the principle that "less is more" for transfusion in cardiac surgery, but multiple blood-sparing techniques have been described and incorporated into clinical practice. The aim of this refresher course is to review evidence-based best practices concerning patient blood management and the various methods of blood conservation used for cardiac surgery patients (Table 1). These methods will be discussed in sections titled preoperative, intraoperative, and postoperative blood conservation, as well as those related to cardiopulmonary bypass (CPB) and hemoglobin (Hb) transfusion triggers.

Table 1. Methods of Patient Blood Management for Cardiac Surgery

1. Education (with emphasis on the RCTs supporting restrictive transfusion)
2. Creation of transfusion guidelines for all blood components
3. Decision support for computerized provider order entry (with best practice advisories)
4. Transfusion guideline compliance audits w/ feedback (reports) to providers
5. Methods to achieve perioperative blood conservation
   - Preoperative anemia management
   - Discontinuation of anticoagulants and anti-platelet medications before surgery
   - Antifibrinolytics (e.g., aminocaproic acid, tranexamic acid)
   - Anesthetic management
     (autologous normovolemic hemodilution, controlled hypotension, normothermia)
   - Point-of-care coagulation testing (e.g., viscoelastic testing – TEG or ROTEM)
   - Surgical methods (newer cautery methods, topical hemostatics and sealants)
   - Hemoconcentrators for pump reservoir blood (MUF, ZBUF)
   - Autologous cell salvage
   - Evidence-based transfusion triggers
   - "Why give 2 when 1 will do" Choosing Wisely® single unit transfusion campaign for RBCs
   - Reducing phlebotomy blood loss (use smaller tubes, eliminate unnecessary testing)

MUF, modified ultrafiltration; RBC, red blood cell; RCT, randomized controlled trial;
ROTEM, rotational thromboelastometry; TEG, thromboelastography; ZBUF, zero-balance ultrafiltration.

Preoperative Blood Conservation

Preoperatively, if time allows, it is important to wait for anticoagulant medication effects to abate before the day of surgery. The advent of direct oral anticoagulant medications and the widespread use of the thienopyridines (e.g., clopidogrel) have challenged cardiac surgeons, as these are widely prescribed by cardiologists for acute coronary events as well as newly inserted coronary stents. The typical patient needs to be off of direct oral anticoagulants for 2 to 5 days, depending on the medication and the patient's renal function. Patients need between 3 and 5 days for thienopyridines, although both the response to these drugs and the time required for drug-effect resolution are highly variable.[2] Although not yet widespread, ideal practice should include P2Y12 testing when assessing recovery of normal platelet function to determine a patient's readiness for surgery after discontinuation of these drugs.

Preoperative anemia diagnosis and treatment represents an opportunity to reduce unnecessary transfusions. Iron deficiency anemia is common, and recent studies have shown that patients with heart failure are particularly

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susceptible.[3] Anemia of chronic disease—recently renamed anemia of inflammation—is also common in elderly patients with chronic conditions. Both these conditions are treatable, given enough time before surgery and assuming that the surgery is not urgent or emergent. Intravenous iron and/or erythropoietin have been used to increase the Hb at a rate of about 1 gram per week.[4] Ensuring that patients are diagnosed and treated early enough before scheduled surgery can be challenging even when surgery is non-emergent.

Intraoperative Blood Conservation

Multiple methods of intraoperative blood conservation are available. Autologous blood salvage (cell salvage or autotransfusion) has been an important method of blood conservation for cardiac surgery since the late 1970s when the technology was first introduced. In this procedure, shed blood is collected and washed in a conical-shaped centrifuge bowl to remove debris and concentrate the cells. The final product returned to the patient consists of red blood cells (RBCs) and saline, devoid of any plasma, clotting factors, and platelets. The efficacy of cell salvage for reducing transfusion requirements in cardiac surgery was shown in a meta-analysis by Carless et al.,[5] who reported the relative risk of allogeneic RBC exposure to be 0.77 and the RBC savings to be 0.68 units per patient. A longstanding belief that cell salvage promotes coagulopathy is based on two premises: residual heparin and dilutional coagulopathy. However, little evidence supports these assertions. First, the amount of residual heparin in salvaged, washed blood is negligible, especially in relation to the amount of heparin administered during CPB. In addition, protamine reversal should neutralize any leftover heparin. Second, the dilutional coagulopathy after salvaged blood should be no different than that which occurs with banked RBCs. The need for plasma and platelets should be considered when approximately 50% or more of the total blood volume has been replaced. Ideally, coagulation testing with a point-of-care, rapid-turnaround result will guide the decision to transfuse plasma and/or platelets, as well as the need for fibrinogen replacement with cryoprecipitate.

Acute normovolemic hemodilution (ANH) has been used despite ongoing debate regarding its effectiveness.[6] This method involves phlebotomy at the beginning of surgery, storage of the fresh whole blood in citrated anticoagulant, and then dilution of the patient's blood so that when bleeding occurs, fewer red blood cells are lost from the circulation. Based on a recent meta-analysis, ANH does appear to be effective at reducing exposure to allogeneic blood, providing that (1) patients have a high enough starting Hb level, (2) enough blood is removed to allow substantial hemodilution, and (3) enough blood is shed during surgery to make ANH worthwhile. Given the use of cell salvage and hemoconcentration of pump blood, the main benefit of ANH may be the fresh clotting factors and platelets that are given back to the patient at the end of surgery, as the ANH blood is fresh whole blood.

One common cause of excess bleeding during and after cardiac surgery is hypothermia, which impairs coagulation at the level of the clotting cascade and decreases platelet function. Furthermore, coagulation tests such as the INR and the thromboelastogram are routinely run at 37°C and will come back normal in hypothermic patients, giving a false picture of normal clotting function. Prevention of hypothermia-related bleeding includes use of milder hypothermia during surgery with local (topical) cardiac cooling rather than systemic cooling, and also more complete rewarming before separation from bypass. However, rewarming at too high a temperature can adversely impact neurologic outcomes by overheating the brain at a time when it is most susceptible to ischemic insults. The completeness of rewarming is typically assessed using a peripheral (bladder or rectal) temperature rather than a true core (blood, esophageal, or nasopharyngeal) temperature. Slower rewarming at a lower blood temperature can result in more complete warming and prevent overheating of the vital organs.

Antifibrinolytics such as epsilon aminocaproic acid and tranexamic acid (the lysine analogs) have become almost universally administered during cardiac surgery. Until 2008, aprotinin was the antifibrinolytic of choice, but it was removed from the US market after a randomized trial (the BART trial)[7] reported increased mortality. A longstanding question over effectiveness of antifibrinolytics was addressed in the recent large randomized trial by Myles et al.,[8] which showed that tranexamic acid was effective compared to placebo at reducing transfusion requirements (46% reduction) and reoperation for bleeding (1.4% vs. 2.8%); however the incidence of postoperative seizures was increased (0.7% vs. 0.1%). Because seizures appeared to be a dose-related side effect, the dose was reduced by 50% partway through the study. Importantly, tranexamic acid did not increase the incidence of thrombotic events. Aminocaproic acid is sometimes used to avoid the risk of seizures with tranexamic acid.

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Topical hemostatic agents and sealants are efficacious for reducing bleeding during cardiac surgery. Achneck et al.[9] comprehensively reviewed the numerous products that are available, including those most often used in cardiac surgery. Thrombin and gelatin are often mixed together and are also sold as a combination product. Fibrin sealants, also used in cardiac surgery, have shown effectiveness in reoperative cases. Because patients undergoing revision cardiac surgery can require 2- to 3-fold the amount of transfused blood products, every method of blood conservation becomes critically important.[10]

The delicate balance between clotting and bleeding is sometimes a challenge, especially during cardiac surgery. Adding to this challenge is the turnaround time for lab tests, which ideally is short enough to make important clinical decisions on therapy. Typically, the activated clotting time (ACT) is used to determine dosing of heparin and its reversal for patients who require CPB. Since the test result is measured in seconds, and the typical target during extracorporeal support is 400-480, the meaningful results take 7-8 minutes.

Residual coagulation abnormalities occur commonly after reversal of heparin. In such patients, viscoelastic testing can be helpful for diagnosing and treating the bleeding. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are the two primary tests available. These are whole blood clotting tests that yield useful information within 5-10 minutes (for initiation of clot) or 10-30 minutes (for clot strength and stability). These tests can help the clinician determine if the coagulopathy is due to clotting factor or fibrinogen deficiency, and they offer quantitative and qualitative information about platelet dysfunction. New variations of these tests that include addition of tissue factor yield more rapid results (1-2 minutes), especially for clot initiation, which is used to diagnose clotting factor deficiencies.

Clinical studies showing utility for viscoelastic testing in cardiac surgery are limited in number, but in general they support the use of this testing to reduce transfusion requirements, and perhaps even to improve outcomes. A 1999 study by Shore-Lesserson et al.[11] in patients undergoing complex cardiac surgery (e.g., combined coronary artery bypass graft (CABG) valve, multiple valve, reoperation, or thoracic aortic procedure) used a TEG-based algorithm to determine treatment for microvascular bleeding. The decision to give protamine, plasma, platelets, cryoprecipitate, or antifibrinolytics was determined by TEG results and an algorithm. Use of this algorithm led to decreases in the percentage of patients who required plasma (7.5% vs. 30.8%) and platelets (13.2% vs. 28.8%). The conclusion was that earlier diagnosis and treatment of coagulation abnormalities resulted in earlier hemostasis and a decreased transfusion requirement. In a recent meta-analysis[12] of 15 trials, viscoelastic testing (TEG or ROTEM) reduced overall mortality (RR, 0.52; 95% CI, 0.28 to 0.95), but only 8 trials provided data on mortality, and the studies included had a high risk of bias. The viscoelastic testing group had a reduced chance of receiving RBCs (RR, 0.86), plasma (RR, 0.57), and platelets (RR, 0.73), but the risk of reoperation did not decrease. In summary, viscoelastic testing seems to play a valuable role in cardiac surgery and may be useful for more accurately targeting blood component therapy. A TEG-based algorithm is being used at Johns Hopkins Hospital to manage post-CPB microvascular bleeding with success in reducing unnecessary transfusions.

Blood Conservation Related to Cardiopulmonary Bypass

Membrane oxygenators activate the coagulation cascade, dilute platelets and clotting factors, and induce fibrinolysis and systemic inflammatory response syndrome. Various studies have attempted to mitigate these risks with a technique known as modified ultrafiltration (MUF), which has been shown to reduce postoperative blood loss and blood product utilization. MUF involves use of a hydrostatic pressure gradient to remove water and some low-molecular-weight substances from plasma, producing protein-rich whole blood to be returned to the patient after the cessation of CPB. When this technique is used during CPB, it is considered conventional ultrafiltration, or zero-balance ultrafiltration. The ultrafiltration occurs on the arterial side of the pump after blood has been pressurized by the roller pump and gone through the oxygenator membrane. The outlet is connected to the patient's venous line as blood reenters the patient's right atrium after passing through the hemofilter. MUF was created by pediatric cardiac surgeons who were attempting to reduce the hemodilutional effects of CPB, which are particularly pronounced in children but also occur in adults. In a meta-analysis that compared MUF to no ultrafiltration, Boodhwani et al.[13] showed that MUF significantly reduced transfusion requirements. In a prospective randomized trial of 573 patients,

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Luciani et al.[14] found not only that the mean volume of RBCs transfused for each patient was lower when MUF was used, but also that the proportion of patients who did not receive any blood products was higher (51.8% vs. 38.1%, P=0.001). MUF is a blood conservation strategy that is likely underutilized in adults but has become the standard of care for pediatric cardiac surgical patients.

For zero-balance or conventional ultrafiltration during CPB, and the ultrafiltrate is replaced with an equal volume of balanced electrolyte solution. The zero-balance ultrafiltration filter unit is connected to the CPB pump, takes blood from a pre-membrane port, and runs in parallel to the main cardiopulmonary circuit. To prevent patient blood flow from dropping, the arterial pump rate is increased to compensate for the blood flow through the hemofilter. The main theoretical advantage is that zero-balance ultrafiltration can be used to reduce the inflammatory mediators that are activated when blood contacts a foreign surface. Thus, this technique might decrease lung injury, neurologic inflammation, bleeding, and acute kidney injury, as well as other indicators of morbidity. A recent meta-analysis showed no significant difference in intensive care unit length of stay, duration of ventilation, chest tube output, or other parameters between patients who received zero-balance ultrafiltration and those who received no hemofiltration.[15]

Smaller diameter tubing, shorter tubing length, and low-volume oxygenators can reduce the hemodilution that occurs when patients are placed on CPB. Such low-volume circuits conserve blood and can reduce transfusion requirements. One result, however, is that the pump is moved closer to the surgical field, resulting in less physical space between the operating surgeons and the bypass pump.

Another commonly used perfusion-driven method of blood conservation is retrograde autologous prime (RAP). By using the patient's own venous blood to prime the cardiopulmonary bypass circuit by retrograde flow, hemodilution can be reduced, thereby reducing anemia and transfusion requirements. Typically, the crystalloid used to prime the circuit is pushed out and discarded during the RAP. RAP has been shown to reduce hemodilution and transfusion requirements in both adult and pediatric patients. In one study of adults, RAP reduced hemodilution by 10% (by nadir hematocrit), decreased the percentage of patients who required intraoperative transfusion (from 23% to 3%), and decreased the percentage that required transfusion during the entire hospitalization (from 53% to 27%).[16]

Postoperative Blood Conservation

Some patients who undergo cardiac surgery require as much transfusion in the postoperative period as they do during surgery. The primary goal postoperatively is to reduce bleeding, which is typically measured by the chest tube output. Excessive or massive bleeding is defined as blood loss of 100–200 mL per hour, on average, for the first 4 hours, or more than 2 L in 24 hours after surgery. Return to the operating room should be considered when this level of bleeding occurs. Viscoelastic testing often can be used to accurately diagnose the cause of postoperative bleeding; however it will not detect bleeding that results from residual hypothermia as the test is run at 37°C. Patients are more at risk for bleeding at core temperatures ≤ 35°C.

Some centers collect the shed blood from chest and mediastinal drains, which can be transfused with or without cell washing. The transfusion of unwashed blood, however, may incur risk, because such blood is laden with various inflammatory mediators.[17] Furthermore this practice has not been clearly shown to reduce transfusion requirements and has been shown to induce fever, perhaps from an inflammatory reaction.

A particularly concerning problem is the large amount of blood removed from patients for lab testing. Such blood loss from phlebotomy can be substantial, especially for patients in intensive care units, where it can account for more than 60 mL/day. The blood lost includes not only that sent to the laboratory, but also the blood discarded when saline is cleared from the indwelling catheter tubing through which the blood is drawn. In a recent study, Koch, et al,[18] demonstrated that the average cardiac surgery patient loses 500 mL of blood for lab testing after 10 days in the hospital, and 1,000 mL of blood after 20 days. These investigators "were astonished by the extent of bloodletting," with some patients losing a volume of blood equivalent to 1 to 2 RBC units. At least three methods can be offered as potential solutions to this problem. First, reduce lab test ordering to those tests that are truly essential, rather than ordering daily blood draws just because the patient is in the hospital. Second, use an in-line blood return device so

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that the blood drawn to clear the saline from the lines can be returned in a sterile fashion back to the patient. And third, use smaller phlebotomy tubes. Tube volumes vary from 0.5 to 10 mL, or a 20-fold difference. We have switched to pediatric-size tubes throughout most of our hospital (2-4 mL size), rather than adult-size tubes (6-10 mL). The neonatal tubes (0.5 mL) are challenging to use because they do not run through the automated lab machines and must be manually run. Also, because their caps cannot be punctured by a needle, they must be uncapped, which poses a small risk of splash.

The concept of postoperative Hb drift is well recognized. Hb levels nearly always decrease while patients are hospitalized. This phenomenon is especially true in the acute postoperative period for four reasons: (1) bleeding continues at varied rates after a patient leaves the operating room; (2) blood is lost through phlebotomy, as described above; (3) hemodilution occurs as a result of intravenous fluid given or fluids that are redistributed into the vascular compartment; and (4) erythropoiesis becomes impaired as a result of surgical stress, which elevates the hepcidin level, a substance critical for mobilizing iron stores for erythropoiesis. Since the body routinely creates and destroys 1% of the red cell mass daily, impaired erythropoiesis predisposes patients to hospital-acquired anemia. After cardiac surgery, Hb levels typically decrease by an average of 1.8 g/dL. The nadir is usually seen on postoperative day 3-4, followed by an average increase of 0.7 g/dL over postoperative days 4-10, likely due to hemoconcentration from diuresis.[19] This small but significant upward trend should be considered when using the Hb level to determine need for transfusion.

Transfusion Triggers

One caveat with any transfusion trigger trial is that when patients are actively bleeding, they will need to be transfused more liberally because whatever Hb threshold is chosen, transfusion must at least keep pace with the rate of bleeding. Another consideration is that the Hb "trigger" refers to the level at which RBC transfusion is initiated, whereas the Hb "target" indicates when RBC transfusion is stopped.[20] The difference is often determined by the dose of blood, which, in virtually all recent studies, has been a single unit, followed by reassessment, unless the patient is actively bleeding. In fact, a single unit transfusion policy, which at Johns Hopkins we call "Why Give 2 When 1 Will Do?",[21] is supported by the Choosing Wisely campaign[22] and can be more effective at reducing overall blood utilization than a Hb trigger policy alone.[23]

Intraoperative transfusion triggers

In contrast to the postoperative setting, the ideal intraoperative Hb transfusion trigger for cardiac surgical patients has not been rigorously studied. The Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines[24] suggest a lower limit of 6 g/dL for patients on CPB with moderate hypothermia, although they recognize that high-risk patients may need higher Hb levels. This recommendation is supported by relatively weak evidence in the guideline. Some centers have begun monitoring cerebral tissue oxygen content with near-infrared spectroscopy technology; however no conclusive evidence shows that this type of monitoring can reliably guide transfusion therapy. By lowering metabolic rate, hypothermic bypass reduces oxygen demands for all vital organs, meaning that lower Hb levels will be tolerated. However, some groups now use either very mild or no systemic hypothermia. Instead they use selective regional cooling of the chest cavity, leaving the brain and kidneys at normal temperature. Additional studies are needed to determine the ideal Hb levels during CPB.

Postoperative transfusion triggers

In the past decade, practice has moved toward transfusing less blood to patients, including those undergoing cardiac surgery. This change in practice is supported by one small[25] and three large randomized trials, all of which showed non-inferiority when a restrictive transfusion strategy was compared to a liberal strategy. The three large studies carried out in cardiac surgical patients were the Transfusion Requirements after Cardiac Surgery (TRACS) Trial in 2010,[26] the Transfusion Indication Threshold Reduction (TITRe2) in 2015,[27] and the TRICS III study in 2017,[28] which are summarized below.

TRACS trial[26] - The TRACS trial enrolled 502 patients and compared restrictive and liberal transfusion triggers after cardiac surgery (hematocrit 24% vs. 30%, respectively). The primary outcome was a composite of morbidity

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and mortality, which occurred with similar frequency in the liberal (10%) and restrictive (11%) groups ($P = 0.85$).

TITRe2 trial[27] - The TITRe2 trial compared Hb triggers of 7.5 g/dL (restrictive) and 9.0 g/dL (liberal) in 2,007 postoperative cardiac surgery patients. The primary outcome was a serious infection or ischemic event, which occurred with similar frequency in the liberal (33.0%) and restrictive (35.1%) groups ($P = 0.30$). The fact that outcome event rates were similar in the two transfusion groups strongly supports use of a restrictive approach, as administering more blood than necessary only adds risk and cost without benefit. Although the restrictive group in the TITRe2 trial had higher postoperative mortality at 90 days (4.2 vs. 2.6%, P = 0.045), this was a secondary outcome with no statistical adjustment for multiple comparisons, making the significance questionable.

TRICS III trial[28] - The TRICS III trial, with 5,243 patients enrolled, is the largest study ever to compare restrictive and liberal transfusion strategies in any patient population. These cardiac surgery patients were assigned to intraoperative and ICU Hb triggers of 7.5 or 9.5 g/dL and post-ICU ward triggers of 7.5 or 8.5 g/dL. Unlike the two above-mentioned studies, these investigators included not just the postoperative period, but also the intraoperative period. Overall, there were no significant differences between the restrictive and liberal groups in the primary composite outcome for adverse events (11.4% vs. 12.5%) or mortality (3.0% vs. 3.6%). The percentage of patients transfused was lower [52.3% vs. 72.6%; OR 95% CI 0.41 (0.37-0.47)], and the median (IQR) number of RBC units was lower [2 (1-4) vs. 3 (2-5); OR 95% CI 0.85 (0.82-0.88)] in the restrictive group. Interestingly, the subgroup of older patients (≥75 years) had a lower occurrence of the composite adverse outcome when assigned to the restrictive group [OR 95% CI 0.70 (0.54-0.89)]. Although only a subgroup of the trial, it included a large number (n = 2,431) of elderly patients and offers evidence that counters the long-held belief that older patients need a higher Hb trigger, just because of their age.

In summary, recent advances in patient blood management have resulted in a better understanding of how to do "more with less" for blood transfusion in cardiac surgery. Opportunities exist to reduce unnecessary transfusions before, during, and after surgery, including special techniques for CPB. The three landmark trials supporting lower Hb triggers (and targets) have also resulted in decreased overall blood utilization. By fully implementing these blood-sparing methods, we can reduce risk and costs, while maintaining good outcomes, thereby increasing the value of care we deliver to our cardiac surgery patients.

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Tranfusion Reactions and Other Unfortunate Events

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Introduction

Blood transfusion is a life-saving intervention in actively bleeding patients, but is not without a risk. It is considered one of the most overused procedures in medicine. In the last decade, the transfusion practice has slowly changed to a more restrictive approach for several reasons – shortage of donor blood, improved understanding of the deleterious effects of the allogenic blood, and high health care costs associated with it.

I. Risks/adverse effects associated with blood transfusions

Transfusion of allogenic blood products has become safer today than at any other time in history, due to improved testing, reduced clerk errors and changes in transfusion practices. The complications from blood transfusion range from pathogen transmission, acute lung injury, abrupt increase in the intravascular volume, creation of antibodies, delayed hemolytic reactions, etc. The Food and Drug Administration (FDA) Annual Report on Fatalities Following Blood Collection and Transfusion for fiscal year 2016 (last published report), identified a total of 67 fatalities related to allogenic transfusion of blood products. Leading causes of transfusion related deaths according to this report were transfusion associated circulatory overload (TACO) (44%), followed by transfusion related acute lung injury (TRALI) (19%), bacterial contamination (12%), hemolytic transfusion reactions 9% and others.[1] Transfusion related adverse effects are defined as infectious or non-infectious. (Table 1) The risk of infectious complications such as blood transmitted viral and bacterial infections in the modern transfusion medicine are extremely rare. Procedural/clerk errors, along with transfusion related volume overload and acute lung injury, represent the greatest hazards related to transfusion of blood products.

Hemolytic Transfusion Reactions

Immune mediated hemolytic reaction may occur as a result of transfusion of blood product in a patient with preexisting antibodies, most often immunoglobulin M (IgM) or IgG. Acute hemolytic reaction presents with a spectrum of non-specific symptoms such as fever, chills, rigors, back pain, dyspnea, nausea, vomiting, hypotension, oliguria, hemoglobinuria and coagulopathy. In rare occasions, hemolysis may occur with transfusion of plasma containing products, such as red blood cell concentrates, fresh frozen plasma and platelet concentrates due to high titer of antibodies. The most common scenario is if plasma containing product of group O, which has anti-A and anti-B antibodies is transfused in a patient with blood type other than O. Therefore, different practices have been implemented to limit the potential for hemolytic reactions, such as limitation of incompatible plasma transfusion to a blood type specific, measurement of the antibody titer and predominantly transfusing plasma containing products from group AB patients.

Delayed hemolytic transfusion reaction manifests between 24 hours and 28 days after transfusion in patients, previously alloimmunized either during pregnancy or previous transfusions, which led to development of antibodies against RBC with very low titers. The signs and symptoms are similar to the acute hemolytic reactions, however, less severe. These reactions can be minimized by obtaining transfusion history, antibody screening, and selecting RBC without the offending antigen for transfusion.

Transfusion Associated Circulatory Overload (TACO)

According to the revised criteria released by the TACO definition revision group in 2017, TACO is defined as acute and severe respiratory and cardiovascular compromise following administration of blood products within 12 hours of transfusion.[2] Because of the nonspecific signs, TACO is largely underrecognised. The clinical presentation of TACO is similar to other causes of hydrostatic edema. Patients classified as TACO experience at least two of the following criteria along with temporal association with blood transfusions. These are: pulmonary edema, evidence of fluid overload, increase in type B natriuretic peptide and cardiovascular changes, such as hypertension, jugular venous

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distention and peripheral edema. Post-transfusion elevation in natriuretic peptide > 1.5 the baseline value is supportive of TACO. Although signs of volume overload might be present before, transfusion may precipitate acute pulmonary edema. The volume of transfused blood products may constitute only a percentage of the total volume of administered fluid.

Transfusion Associated Acute Lung Injury (TRALI)

TRALI is the second most common cause of mortality related to blood transfusions according to the 2016 annual FDA report. It is defined by the National Heart, Lung and Blood Institute as an acute noncardiogenic pulmonary edema that develops within 6 hours of completed transfusion of blood products, in patients without other risk factors for acute lung injury.[3] If acute lung injury occurred temporary related to the allogenic blood transfusion, however, in the presence of alternate risk factor for acute lung injury, it is defined as possible TRALI. The latter is considered of nonimmune origin due to recipient's risk factors, rather than donor blood antibodies.[4]

Antineutrophil antigen antibodies and anti-HLA antibodies are considered responsible for development of TRALI. It has been reported from all types of blood products that contain more than 50ml of plasma, however, the blood product which carries the highest risk of incidence and fatality from TRALI is fresh frozen plasma. Several studies have documented decreased incidence of TRALI with elimination of female donors of plasma or reducing the plasma content in the blood product.[5] In a case-control study at two major institutions (Mayo clinic and University of SanFrancisco), after implemntation of risk reduction measures such as male-only or female never pregnant donors of plasma, the TRALI incidence decreased by almost 70%. [6] By 2010, most US blood collection facilities had adopted the TRALI risk mitigation strategy proposed by the American Association of Blood Banks TRALI Task Force.[7] The policy was published in 2013 in the Standards for Blood Banks and Transfusion Services and it states that plasma and whole blood for allogenic transfusion should be obtained from males, females who have never been pregnant, or females who tested negative for HLA antibodies after their last pregnancy.[8] Although the risk of HLA antibody detection is greater in multiparous women, approximately 11% of all female donors with only one pregnancy tested HLA positive. Only pregnancies carried to term can increase the risk of HLA antibody formation, but not abortions and miscarriages. For those institutions that prefer to not obtain pregnancy history, HLA testing is mandatory in all female donors of plasma and whole blood.

Bacterial contamination and sepsis

Between 2012 and 2016, septic transfusion reactions constituted 10% of all FDA reported deaths from blood transfusion in the United States. The most common offenders of blood product contamination are skin bacteria from the venipuncture site, Gram positive flora, such as S. aureus, coagulase negative staph, streptococcus, etc. Platelet concentrates are especially susceptible to bacterial growth due to room temperature storage. Bacterial contamination of platelet concentrates remains the leading infectious risk of transfusion therapy, because of their storage at room temperature. Bacterial contamination is suspected when symptoms and signs of septic shock are present during or within 24 hours of transfusion. These are fever > 38.0C, tachycardia (> 40 beats per minute difference with pretransfusion heart rate), hypotension, rigors, shock.[9] The source of infection is confirmed when the blood culture species from the patient match the platelet culture from the donor unit. Platelet collection via apheresis have lower infectious risk than pooled platelets, because it is collected from a single donor. Changes that have been implemented to decrease the risk of bacterial contamination from platelet transfusion include one-arm puncture, adding a diversion pouch in the collection system, bacterial screening at the collection facility and subsequently second screening at the transfusion center (mandatory since 2004), limitation of platelet shelf life to 5 days.[10]

Allergic transfusion reactions

Allergic transfusion reactions include a wide spectrum of clinical symptoms of isolated hives to anaphylactic shock during or within 4 hours of transfusion. The mechanism is the presence of antigens in the donor plasma, to which the patient has been previously sensitized. Anaphylactic reactions have been associated with IgA deficiewncy (in < 20% of the cases)[11], anti-human leukocyte antigen (HLA), anti-complement antigen. Leukoreduction does not decrease the incidence of allergic reactions. In the presence of IgA antibodies in the recipient, anaphylaxis can be prevented by avoidance of future transfusions of plasma containing IgA. This can be achieved by blood collection from IgA

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deficient donors or by washing the product to remove IgA from the plasma. A rise in mast cell triptase can support the diagnosis of allergic reaction.

II. Transfusion Related ImmunoModulation (TRIM)

There are multiple reports confirming that administration of allogenic blood has a profound effect on the human immune response, a condition known as transfusion related immunomodulation (TRIM). Blood transfusions have been found to improve allograft function and survival after renal and liver transplantation. However, significant adverse events have been linked to blood transfusions, such as cancer recurrence, nosocomial infections and increased mortality. The mechanism for TRIM include suppression of monocyte activity and IL-2 production, release of immunosuppressive prostaglandins and increase in suppressor T-cell activity.

Nosocomial infection

Several multicenter observational studies have examined the effect of blood transfusion on hospital and ICU mortality across Europe and United States.[12] Propensity match analysis of patients who received transfusions compared with their matched controls showed an increased mortality in patients who received blood during their ICU stay. A meta-analysis of 17 randomized trials examined the effect of restrictive versus liberal blood transfusion strategy om the incidence of health care-related infections.[13] The restrictive transfusion strategy was associated with decreased rate of serious infections in patients undergoing hip or knee replacement, but not in patients after cardiac surgery, critically ill or with gastrointestinal bleeding. In contrast, a study examining patients after cardiac surgery, showed 5.8% rate of major postoperative infections. There was 29% increase in the risk of major infection with each unit of RBC transfused.[14] There are data showing that pre-storage leukocyte reduction helps to reduce the release of some bioactive substances from the white blood cells, implicated in transfusion related immunosuppression, and to decrease the incidence of post-transfusion infections, febrile transfusion reactions, HLA alloimmunization. By 2014, 85% of the RBC were leukoreduced prior to storage.

Cancer recurrence

Multiple animal and human studies have demonstrated the effect of stored red cells on tumor progression. Currently, there is no conclusive evidence except for some small retrospective trials, that transfusion of platelets and fresh frozen plasma accelerates cancer recurrence in patients undergoing oncologic surgery. In one report, both autologous and allogenic blood when stored for more than > 9 days increased tumor retention, as oppose to fresh blood, whether autologous or allogenic, had no deleterious effects[15], while other studies show that autologous blood is not associated with increase in cancer recurrence. A large meta-analysis including randomized trials, along with prospective and retrospective observational studies, demonstrated a link of perioperative blood transfusions to colon cancer recurrence with OR 1.42 (95% CI 1.2-1.7).[16] Although it was supposed that leukocyte depletion would induce less immunosuppression, clinical studies have not demonstrated beneficial effect on survival and cancer recurrence. Some authors suggest a dose dependent effect of blood transfusions on cancer recurrence, while others explain these results by the more complex surgery and advanced disease in patients requiring higher rate of transfusions.[17]

III. Storage lesion

The blood undergoes various biochemical and structural alterations during shelf storage, which result in decreased ability to release oxygen from the hemoglobin molecule at tissue level once transfused. Thus, increasing the hemoglobin level with blood transfusion does not effectively augment the oxygen delivery to the organs. These biochemical processes include depletion of 2,3-diphosphoglycerate, depletion of adenosine triphosphate, intracellular stores and elevated lactate. In addition, the cells undergo significant structural changes, namely loss of deformability, osmotic cell damage and loss of integrity of the cellular phospholipid membrane. Equally important are the changes that take place in the storage medium over time, with decreased pH, increased potassium release of hemoglobin and iron as a result of cell disruption. In a landmark study examining the effect of transfusing blood less than 14 days

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versus blood older than 14 days of shelf time, the authors found significant increase in the in-hospital mortality, incidence of sepsis, renal failure and prolonged intubation in patients who received "old" blood.[18] In contrast with this study, is a recently published randomized controlled trial of > 20,000 patients from 6 hospitals, randomized to receive short term storage blood versus long term storage blood in a ratio of 1:2. The primary outcome was in-hospital mortality, which was similar in both groups (fresh blood 9.1% vs old blood 8.7%, OR 1.05; CI 0.95-1.16; p = 0.34). The mean storage duration was 13 days in the short term storage group and 23 days in the long term storage group. [19]

IV. The use of uncrossmatched blood in emergencies

The process of determining the patient's ABO type takes about 15 minutes, and the process of determining the presence of other erythrocyte antibodies ("screen") takes about 45 minutes. Cross-match refers to the process of identifying a RBC unit compatible with the patient's plasma. When the patient's antibody screen is negative, the RBC can be released using quick electronic crossmatch. In the presence of "positive antibody screen", the antibody specificity is identified, and a process of crossmatch is initiated in order to locate erythrocyte concentrates compatible with the patient's antibodies (antigen negative erythrocytes). There are clinical situations though, in which emergent transfusion of blood is indicated. In this case, uncrossmatched erythrocytes may be allocated and transfused. Typically, uncrossmatched RBC units are group O, unless the type of blood is already known, in which case ABO group-specific uncrossmatched erythrocytes could be issued. Since these erythrocytes do not carry antigens A and B, there is no risk of intravascular life-threatening hemolysis. However, there is a potential risk for less severe extravascular hemolysis due to presence of other erythrocyte antigens, such as D, E, Kell, Duffy. Extravascular hemolysis is primarily due to immunoglobulin G antibodies (preformed), and occurs in the liver and spleen. Although rarely fatal, it leads to decreased life span of the transfused erythrocytes and decreased efficacy of the blood transfusion. The patient presents with increased bilirubin and lactate dehydrogenase levels, decreased haptoglobin several days after blood transfusion. The literature indicates that the overall risk of hemolysis after transfusion of uncross-matched RBC is 0.1%, which indicates that this procedure is relatively safe.[20] This has been studied only in emergent indication for blood transfusion and this practice should not be expanded to patients requiring elective transfusion for correction of low hemoglobin, who are otherwise stable.

Uncross-matched RBC units should be Rh negative (-) if transfused in children or female patients in child baring age (defined as < 50 years) to prevent formation of antibodies in Rh (-) patients from Rh (+) donor blood. In male patients, type specific or group O, Rh (+) RBC is acceptable to spare the Rh (-) units.[21] The rate of seroconversion of Rh (-) patient from transfusion of Rh (+) RBC is about 20%. This rate is much lower in transfusion of Rh (+) platelet concentrates in Rh (-) patients (1.4%), because of extremely low content of RBC in this product. In order to prevent alloimmunization of Rh (-) patient who has received Rh (+) RBC, a product containing Rh immunoglobulin can be administered in the first 72 hours after the transfusion (RhIg). Group AB is the universal donor of plasma because of lack of antibodies (anti-A and anti-B), however, only a small percentage of the population is group AB. Because AB plasma is rare, most centers release group A plasma when ABO status is unknown.

Table 1

Transfusion reactions and rate of complications[22,23]

Transfusion reaction	Events per number of transfusions
Noninfectious	
TRALI	1:500 – 1:17,000
TACO	1:350
Hemolysis	1:10,000 – 1:50,000
Delayed hemolytic transfusion reaction	1:1,500
Anaphylaxis	1:20,000 – 1:50,000

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Mistransfusion ("wrong unit" or "wrong patient")	1:14,000 – 1:38,000
Infectious	
Human immunodeficiency virus	1:1,000,000 - 5,000,000
Hepatitis B	1:400,000 – 1,200,000
Hepatitis C	1:1,000,000 – 10,000,000
Bacterial contamination leading to sepsis	1:250,000 (1:100,000 in platelets)
Rare events	
Graft versus host disease	
Posttransfusion purpura	

TRALI – transfusion related acute lung injury; TACO – Transfusion associated circulatory overload

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Blood transfusion and recent controversies: Old or new? 28 or 22?

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Introduction: The perioperative management of patients undergoing cardiac surgery is an important clinical challenge. Cardiopulmonary bypass (CPB) predisposes to perioperative bleeding and transfusion because of thrombocytopenia, functional platelet defects, activation of fibrinolysis, hemodilution and depletion of coagulation factors.[1-3] As a result, up to 3% of patients develop major bleeding requiring reoperation after cardiac surgery,[4] and perioperative transfusions account for 7% of all red cell transfusions.[5] Although there is much variability in transfusion practice, the following factors have been independently associated with increased risk of transfusion: age, anemia, female gender, body size, preoperative use of antithrombotic therapy, significant systemic disease, CPB time, and type and urgency of procedure.[6] This refresher course will review 2 recent controversies related to RBC transfusion in cardiac surgery: Age of blood and liberal vs restrictive transfusion strategies.

Age of Blood – Old vs New

The shelf life of red blood cells (RBCs) is determined by a minimum 24-hour post-transfusion survival of 75% of the transfused red cells. Other criteria relate to free hemoglobin (<1.0%) and white blood cell levels (<1 million/unit in leuko-reduced blood). Advancements in additives and storage techniques have increased the shelf-life of blood from 21 to the current 42 days.[7] RBCs undergo numerous biochemical, physiological and mechanical changes during storage. Within minutes of collection, the RBCs are subjected to a lower pH and higher glucose concentration within the storage solution and within hours to days of storage there are progressive changes in 2,3 DPG, potassium, lactate, free hemoglobin, RBC ATP, pO_2, Hb O_2 saturation, antioxidant status and RBC deformability and stiffness.[7] Within 2-3 weeks the 2,3 DPG levels approach zero and there is a marked fall in 2 bioactive forms of RBC nitric oxide (Hb-bound NO, and S-nitrosohemoglobin), as well as their effector response, RBC mediated hypoxic vasodilation.[7] By the end of 6 weeks, although the pO_2 is well over 100 mmHg and the Hb O_2 saturation near 100%, the potassium concentration is over 20 mmol/L, and the lactate is greater than 15 mmol/L, and extravascular hemolysis is increased.[7-10] The shape of the red cell is transformed from a normal biconcave disc to a spiculated and crenated echinocyte, then to a swollen sphereocyte.[11] Cytokines and lipids similar to platelet activating factor may prime neutrophils, activate endothelial cells and could produce a systemic inflammatory syndrome and/or affect acute lung injury.[2,3] Whether or not such time-related changes in stored RBCs adversely affects clinical outcome has been the subject of considerable debate.

Prolonged RBC storage time has been associated with increased morbidity and mortality in a wide variety of clinical settings, including patients with trauma, sepsis, and critical illness.[12-14] For cardiac surgery, length of RBC storage has been correlated with death, renal dysfunction, delirium, and ICU length of stay.[15-18] It has been estimated that each additional day of RBC storage could increase the risk of pneumonia by 1-6%.[19] The largest observational study examining the effect of RBC storage assessed over 6000 patients undergoing cardiac surgery who received either new (<14 day storage) vs old (>14 day) RBC transfusions.[20] Using regression analysis and propensity scoring to balance some pre-existing population imbalances, they found that patients given older blood had significantly worse clinical outcomes of renal failure (2.7% vs 1.6%), prolonged intubation (9.7% vs 5.6%), and sepsis (4.0% vs 2.8%). In addition, in-hospital and 1-year mortality were significantly higher in the old-blood group.

On the other hand, randomized controlled trials have not found that longer duration of red cell storage leads to worse outcome. Weiskopf et al reported that fresh blood and aged stored blood were equally effective in reversing anemia-induced brain oxygenation deficits in human volunteers.[21] The RECESS study of short vs longer duration of transfused RBCs in 1098 patients undergoing cardiac surgery found no difference in the change in Multiple Organ Dysfunction Score (primary outcome), or in a variety of secondary outcomes such as mortality or length of stay.[22] A large pragmatic trial of >20,000 hospitalized patients randomized to receive RBCs of either longest or shortest storage duration found no difference in overall mortality, or in prespecified subgroups (CV surgery, ICU or cancer).[23] Similarly, two recent RCTs of old vs new RBC transfusion in critically ill/ICU patients reported no difference between groups in the primary outcome of 90 day mortality or any of the secondary outcomes (major illness/infection, short term mortality, organ dysfunction, duration of supportive care or length of stay).[24,25] Finally,

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several meta-analyses and trial sequential analysis have concluded that use of fresher compared to standard issue RBCs does not significantly influence mortality or major adverse events.[26-29]

Summary of Selected Randomized Controlled Trials of RBC Storage Duration

Author	RBC Storage time target and (observed mean); days		Sample size	P value for primary clinical outcome
	Control	Experimental		
Heddle[30]	Oldest available (26.6)	Freshest available (12.0)	1,075	0.56
Steiner[22]	>20 days (28.3)	<10 days (7.8)	1,098	0.44
Lacroix[25]	Standard issue (22.0)	<8 days (6.1)	2,413	0.38
Heddle[23]	Longest storage duration (23.6)	Shortest duration (13.0)	20,858	0.34
Cooper[24]	Standard issue (22.4)	Freshest available (11.8)	4,919	0.57

In summary, the literature regarding age of RBC transfusion is complicated by differences in design, definitions and outcome variables, but the present evidence to date (including several large RCTs and meta-analyses) does not demonstrate a causal link between age of blood and meaningful clinical outcomes in surgical or ICU patients, nor is there a benefit from transfusion of younger blood compared to standard issue blood. However, no randomized trials have directly compared old blood (>35 days) with standard issue blood so the question of whether RBCs that are nearing expiry may be associated with adverse outcome remains unanswered.

Restrictive vs Liberal Transfusion Threshold in Cardiac Surgery- 28 or 22

Several observational studies have identified an association of both anemia and RBC transfusion with adverse clinical outcome, including mortality, length of stay, infection, and major organ dysfunction.[31-36] Varying degrees of multivariable analysis and propensity matching have been used in an attempt to reduce possible confounding, but the possibility remains that both anemia and transfusion are markers of patients with more severe illness.

Given the competing risks of both anemia and transfusion, the decision about when to transfuse a patient should be based on assessment of when the risks of anemia outweigh the risks of transfusion.[37] Such evaluations are generally based on hemoglobin levels or clinical/physiological parameters such as hemodynamics, chest pain, ischemia, lactate or venous oxygen saturation. While this may be intuitively attractive in the age of personalized medicine, the superiority of such an approach or any of these parameters has not been demonstrated in well conducted trials.[38] In addition, clinical transfusion guidelines are often based on expert opinion or results of RCTs in which patients are randomized to either a restrictive or liberal hemoglobin based transfusion trigger. In these trials, the trigger for restrictive transfusion is generally between 7-8 g/dL and between 9-10g/dL for liberal transfusion.[39-47] For example, the ASA, AABB and STS/SCA guidelines for transfusion suggest that transfusion may be indicated for hemoglobin < 7-8 g/dL, and recommend that transfusion is not indicated for a hemoglobin > 10 g/dL.[48-50]

Randomized controlled trials of transfusion triggers in cardiac surgical patients have readily demonstrated that restrictive transfusion results in less allogeneic blood exposure; however, an important clinical question has been whether such practices are safe and do not result in increased adverse clinical outcomes. One such single center RCT of 502 patients in Brazil found significantly reduced transfusion rates in the restrictive group (47% vs 78%), but no difference compared to liberal transfusion in a variety of clinical outcomes including mortality and severe morbidity (cardiogenic shock, acute respiratory distress syndrome, or acute renal injury requiring dialysis).[41] The more recently published TITRe2 trial, randomized 2007 postoperative cardiac surgery patients in the ICU to a liberal or restrictive hemoglobin based transfusion strategy and assessed the impact on serious infectious or ischemic events.[44] There was no difference between the liberal and restrictive arm in either this primary (35.1% vs 33.0%) or most of the secondary outcomes. However, a significant difference in mortality at 90 days postoperatively favoring liberal transfusion was observed (4.2% vs. 2.6%; hazard ratio, 1.64; 95% CI, 1.00 to 2.67; p = 0.045). Although the study was limited by lack of intraoperative randomization and a fragility index of 1, the data provided uncertainty

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about the safety of restrictive transfusion in this setting. This question was directly addressed in TRICS III (Transfusion Requirements in Cardiac Surgery III) study.[47] TRICS III was a global study of >5000 moderate-high risk patients undergoing cardiac surgery who were randomized to either restrictive (transfuse if Hb <7.5 g/dL) or liberal (<9.5 g/dL in OR and ICU; <8.5 on ward) transfusion from start of index surgery until hospital discharge or day 28, whichever came first. The primary outcome was a composite of death, MI, stroke or dialysis, and secondary outcomes included transfusion amounts and other important clinical outcomes. Restrictive transfusion resulted in significantly reduced transfusion and was non-inferior to the liberal strategy for the primary outcome which occurred in 11.4% of the restrictive group and 12.5% of the liberal group (absolute risk difference -1.11%; 95% CI -2.93 to 0.72%), or for 28 day mortality (3.0% vs 3.6% in the liberal group). Consistent results were obtained for other secondary outcomes and sensitivity analyses. In subgroup analyses, a significant interaction with age was observed with restrictive transfusion strategy being associated with a lower risk of the composite outcome than the liberal strategy among patients 75 years of age or older, an observation that challenges current beliefs about age and transfusion thresholds. Longer term (6 month) outcome data for TRICS III to compare with TITRe2 should be available soon

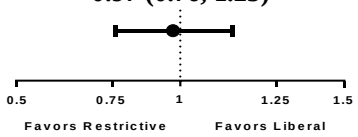
Comparison of TITRe2[44] and TRICS III[47]

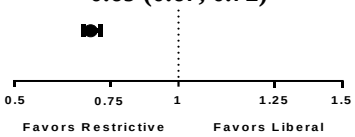
Inclusion	Cardiac surgery with postoperative hemoglobin < 90 g/L (Initially excluded age ≥ 80)	Cardiac surgery with CPB Euroscore (I) ≥ 6
Primary outcome	Composite of serious Infectious (sepsis, wound infection) or Ischemic events (stroke, MI, AKI, gut infarction)	Composite of Death, MI, stroke, dialysis dependent renal failure
Hypothesis	Superiority of restrictive transfusion	Non-inferiority of restrictive transfusion
Intraoperative trigger	No (randomization post-op)	<75 vs. <95 g/L
Pre-randomization transfusion in OR	Yes (~25%)	No
Postoperative trigger	<7.5 g/dL vs. <9.0 g/dL	<7.5 g/dL vs. <9.5 (8.5) g/dL
Sample size	~2000	~5000
P value for primary outcome	0.30	<0.0001
Location	UK	Global

Recent meta-analyses of RCTs of restrictive vs liberal transfusion in cardiac surgery have concluded that restrictive red blood cell transfusion is not inferior to a liberal strategy in terms of 30-day mortality, pulmonary morbidity, postoperative infection, stroke, acute kidney injury, or acute MI, with fewer RBCs being transfused.[51, 52]

Summary of Randomized Controlled Trials of Transfusion Thresholds in Cardiac Surgery

Author	Patients Randomized	Hospital or 30 Day Mortality Risk Ratio (95% Confidence Interval)	Red Blood Cell Transfusion Risk Ratio (95% Confidence Interval)
Mazer[47]	5243	0.85 (0.63, 1.15)	0.72 (0.69, 0.75)
Koch[45]	722	--	0.72 (0.64, 0.80)
Murphy[44]	2007	1.37 (0.76, 2.46)	0.67 (0.64, 0.70)
Shehata[42]	50	4.00 (0.48, 33.33)	0.59 (0.39, 0.88)
Hajjar[41]	502	1.27 (0.61, 2.66)	0.60 (0.52, 0.70)
Bracey[39]	428	0.52 (0.13, 2.04)	0.72 (0.58, 0.91)
Total	**8952**	**0.97 (0.76, 1.25)**	**0.69 (0.67, 0.72)**





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Total risk ratio was calculated utilizing an inverse variance fixed effects model with Review Manager 5.3 software

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Changing the brain for better and worse with anesthesia & surgery (310-NA)

A. Davidson, D. Culley, L. Vutskits

Anesthesia-surgery and the Developing Brain

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Animal data

There is substantial preclinical evidence that many general anesthetics have the capacity to cause morphological and functional changes to the developing brain. This has been demonstrated in a wide variety of species, ranging from the nematode to the non-human primate. A variety of different morphological changes have been seen. Accelerated neuronal apoptosis is the most widely recognised. Several mechanisms have been identified; however it is unclear if these mechanisms are linked. The effects are greatest with grater doses and longer exposure; however it is difficult to identify the upper limit of duration of exposure which has no effect. The effect also varies with age of exposure. Generally the effects are greater in the more immature brain – which may translate to the late trimester of infant period but some effects are seen in older animals. The area of the brain affected may also vary with age of exposure. Effects are greatest with GABA agonists and NMDA antagonists and hence have been seen with propofol, benzodiazepines, volatile anesthetics and ketamine. There is contradictory evidence for an effect with alpha 2 agonists. Functional experiments have demonstrated that animals exposed to anesthesia in early life may have deficits in learning and altered behavior; however not all experiments have demonstrated functional deficits and it is unclear if the functional deficits are a function of the morphological changes seen.

There are considerable problems translating the animal data to humans. Translating doses is problematic as is understanding exactly how a particular age of animal correlates to the age of a human. In small animals homeostasis may be deranged during anesthesia and few models examine the impact of concurrent surgery. Human brains are complex and develop over a longer period. The impact of an injury in humans will depend on the type of injury and timing of the injury. Human brains can be extraordinarily vulnerable to injuries of a particular type at particular times, or demonstrate considerable plasticity and recovery. Importantly genetic and environmental factors have a huge impact on resilience and recovery or vulnerability.

What outcomes do human studies examine?

The human studies can be broadly grouped according to their design and the outcomes they look at. So far there is only one prospective trial with published results. All other studies are observational. This is a crucial point which will be explained later.

The ***design*** of observational studies broadly consist of:

- *Data linkage population based studies.* These use existing datasets which can be linked. They are inherently retrospective and limited by the outcomes and exposure variables that have already been collected. They can however be very large, examining whole of country or whole of state populations. The outcomes commonly used are some form of preschool test for school readiness, or school grades.

- *Use of existing birth cohorts or longitudinal studies.* These studies use existing data in longitudinal cohorts that have usually been set up for other purposes. They often include access to more detailed outcome measures including some psychometric outcomes; they may also include diagnoses of disability and school grades. While often large, they are not as big as the population linkage studies. The details of exposure may be limited but there are usually good data about other factors that may contribute to outcome.

- *Purpose built cohort studies.* These studies recruit children that have been exposed to anaesthesia and match them to those that have not, and then test the children for range of psychometric outcomes. These studies enable researchers to focus on neurodevelopmental areas of greatest interest but logistically it is difficult to recruit large numbers of children. Children may be recruited various ways including from existing longitudinal studies.

The ***outcome measures*** used are to some extend limited by the study design discussed above but can be broadly classified as:

- *School grades or school readiness tests.* These are of great interest and importance to families but they are course measures of neurodevelopment. A deficit may exist in one aspect of neurodevelopment which is not reflected in school grades; conversely many other factors influence school grades, diluting any possible “injury” effect. Their advantage is not only their importance to families, but also that they are easy to obtain in very large numbers.

- *Diagnosis of a learning disorder or specific neurodevelopmental disorder.* These are also of great importance to the families and the community. A major problem is that the diagnosis may not always be clear and indeed definitions of

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disorders vary between jurisdictions and over time. Another potential disadvantage is that these disorders are still not common enough to be able to produce precise results except in very large studies.

- *Psychometric testing.* Many tests are available to test a wide range of neurodevelopmental domains. Apical tests, such as IQ, are composite scores which pool results from several domains. Apical tests have the best value as far as predicting future function, but using apical tests may miss deficits in some sub domains. Looking at multiple domains raises the problem of type 1 error (finding a "significant" association due to multiple testing). The psychology literature abounds with studies that are not replicable – partly because of this issue. If a "deficit" is found in only one or two of many sub domains tested then the results must be interpreted very cautiously until they are replicated in following studies. Performing psychometric testing is labour intensive and must be done to a high standard to be useful.

- *Imaging.* MRI may provide some insight however these studies are usually small due to logistic problems and, like psychometric testing, there are usually many outcomes measured increasing the risk of type 1 error. While our understanding of MRI is rapidly increasing there is still a degree of disconnect between what is seen on MRI and functional relevance.

In all these studies it is important to consider the ***age of testing***. Some aspects of neurodevelopment such as higher executive function cannot be tested until the child is older. Also, after an injury children will usually "grow into their deficit". An injury in a particular aspect of brain function will become more apparent as the child develops and lacks that function. This is contrary to the idea that the brain will always have plasticity and recovery.

Confounding

Confounding occurs when an observed association between A and B is not direct or causal but due to another factor C, which increases the likelihood of both A and B. There are huge issues with confounding in all the observational studies looking at anaesthesia and developmental outcome. Children have anesthesia because they are having surgery or an investigational procedure. The surgery or procedure may itself cause injury – for example the stress response of surgery or poorly managed pain. Also the condition that warrants surgery may be associated with increased risk of poor neurodevelopmental outcome. This may be obvious in the case of genetic abnormalities or major illnesses, but it can also be more subtle. Children having ear tube insertion may have the tubes because they are already showing signs of delay and the pediatrician wants to optimise their hearing. Or a child needing dental extractions may come from an environment where dental care is suboptimal or have subtle behavioural problems that make non GA dental care more problematic.

Confounding can be reduced by careful sample selection, matching, or statistical adjustments in the analysis, but these measures are never mathematically perfect and thus cannot completely remove the influence of confounding. Importantly they can only reduce the influence of known confounding factors. The problem of confounding means that, by itself, any association seen in an observational study cannot ever be regarded as anything better than weak evidence for causation. Randomized trials are by far the best way to reduce confounding however it is near impossible to randomise children to anaesthesia or no anaesthesia.

Results from population based clinical studies

Most, but not all, large population based studies looking at school grades or readiness for school found evidence for a small difference in school grade or readiness in children that have had anesthesia in early childhood. The increase in risk is small. Indeed much smaller than the risk associated with gender or month of birth. Interestingly the studies do not indicate that exposure at 0-2 years is worse than 2-4 years, and some find the opposite. As far as frequency of exposure, some show weak evidence for a greater risk with multiple exposure but most have insufficient power to determine if having multiple exposures poses any greater risk than single exposure. Several found that surgery increased the risk of not getting to school or not being able to sit the test. This may be consistent with an increased risk of developing a specific developmental disorder.

Results from studies that look at specific developmental disorders

Again, most but all studies, that have diagnosis of a learning or developmental disorder as their outcome found evidence for an association between anesthesia in early childhood and an increased risk of a diagnosis of a behavioral disorder or learning disability. Most of these studies do find good evidence that the association is greater with multiple exposures.

Results from studies that use psychometric testing for outcomes

There is no clear pattern that links the results of these studies. Many find evidence for an association between anesthesia in early childhood and one or two particular domains of psychometric testing. These domains include: language, reading, abstract reasoning, executive function, some aspects of memory, processing speed, fine motor abilities, and some aspects of behavior. Some but not all find an association with a small reduction in IQ. At least one study finds the associations only in children that had multiple exposures.
Some robust studies such as PANDA found no evidence for an association with any deficit. The only trial to report an outcome

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(the GAS trial) found no evidence for a difference in children tested at age 2 after being randomised to either general or awake regional anesthesia for hernia repair. Note however that testing at age 2 has limited sensitivity and the results of the 5 year testing won't be available until later this year.

Conclusion

In spite of strong animal evidence, there is inconsistent human evidence for an association between anesthesia in early childhood and a range of later neurodevelopmental outcomes but, to date, no coherent pattern of deficit is emerging. A causal relationship cannot be ruled out; however the human evidence that these associations could be casual is very weak. These associations could be simply explained by confounding. Clinical decisions need to be made in the context of the preclinical and clinical data. Currently this is an imprecise task; however as further data emerge the task will become clearer.

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Preoperative Cognitive Screening in Elderly Surgical Patients: Feasibility and Utility for Predicting Adverse Outcomes

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Approximately 1 in 3 surgical procedures performed nationally involve patients that are 65 years of age or older.[1] These older surgical patients have a high rate of perioperative complications and often do poorly postoperatively such that there is intense interest in identifying predictors of adverse outcomes in these older patients.[2,3] Although preoperative assessment of major vital organs has been a routine part of preparation for surgery for decades, brain function is typically not evaluated. A number of studies have demonstrated that preexisting cognitive impairment is a strong predictor of poor medical-surgical and functional outcomes after surgery and anesthesia and that preoperative cognitive screening could identify those at risk.[4] Approximately, 20-40% of older patients living in the community and those having elective surgical procedures have been shown to have probably cognitive impairment based upon a preoperative cognitive screen.[4,5,6] We have demonstrated that preoperative cognitive screening can be performed in a busy preadmission testing center without increasing the time of the preoperative appointment and that it is predictive of postoperative medical- surgical complications and poor functional outcomes. To this end, a number of studies have been conducted demonstrating that cognitive screening using items such as the Mini-Cog, animal fluency, and MOCA can be used to identify patients at risk for baseline cognitive impairment and adverse postoperative outcomes.[4,5,6,7] Accordingly, we would advocate that preoperative cognitive screening should be performed in all older surgical patients to aid in identifying those patients at high risk of adverse postoperative outcomes.

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Anesthesia-surgery and the depressed brain

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Major depressive disorder (MDD) is a seriously debilitating condition characterized by a combination of abnormal thoughts, perceptions, emotions, behaviour and relationships with others [1]. The burden of MDDs continues to grow and the estimated global lifetime prevalence of this pathological state is estimated to reach over one third of the population worldwide with important regional differences [2]. The clinical effectiveness of currently approved pharmacological approaches to treat MDD is hampered by the fact that these drugs may need several weeks to provide therapeutic effects, and that they operate with a relatively low rate of clinical effectiveness along with a high incidence of relapse [3]. New therapeutic modalities with shorter onset of action and sustained efficacy are therefore strongly warranted. In this context, an increasing number of observations suggest that general anesthetics, or at least some of them, can rapidly improve mood in patients with MDD. The present lecture is aimed to review these datasets and provide some mechanistic insights into the underlying mechanisms.

The concept that general anesthetics and/or general anesthesia could exert therapeutic anti-depressant effects in patients with MDD dates back to the implementation of electroconvulsive therapy (ECT) in the midst of the last century. Indeed, in most cases, ECT is performed under general anesthesia. Since general anesthetics are robust modulators of brain states, an obviously important question was to know whether the therapeutic improvement following the ECT procedure is linked to the effects of the delivery of electrical impulses to the brain or to the impact of general anesthetics on neural networks. Indeed, ECT-induced seizure activity is followed by a transient post-ictal burst suppression, a brain state that can also be achieved by general anesthetics. Therefore, an intriguing possibility is that anesthetics-induced decrease in neural activity might be an important component of the antidepressant effects. Following initial observational studies with important methodological biases and conflicting results, the Northwick Park Electroconvulsive Therapy randomized control trial, involving a 6-months-long follow-

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up of 70 patients with severe depression, revealed equivalent therapeutic value of 8 successive ECT sessions over a period of 4 weeks under thiopentone anesthesia when compared with a similar simulated ECT protocol where only thiopentone was administered [4]. These observations were corroborated with subsequent trials where 6 sessions of isoflurane anesthesia-induced brief burst suppression over 2 weeks had comparable effects with the delivery of 6 bitemporal ECT under general anesthesia in terms of both objective and subjective mood scales for up to 5 weeks [5, 6]. Importantly, the capacity for sustained concentration was significantly better in patients having received isoflurane compared to the ECT group [6]. The antidepressant and neurocognitive effects of isoflurane anesthesia were then reconfirmed in a group of 20 patients with medication-refractory depression [7]. In this study, ECT had modestly better effect at follow-up in severity-matched patients, while the isoflurane group showed better neurocognitive score improvement [7]. More recently, a prospective pilot study demonstrated anti-depressant properties of 50% nitrous oxide inhalation in patients with treatment resistant MDD [8].

Over the past 15 years, the NMDA receptor antagonist ketamine emerged as an attractive therapeutic option to treat MDD. The rational for focusing on ketamine was independent from the anesthesia-induced burst suppression hypothesis and was motivated by the facts that (i) NMDA receptor antagonists have shown antidepressant effects in animal models of depression; (ii) glutamate levels are elevated in patients with unipolar depression; and that (iii) glutamate release inhibitors show antidepressant properties in clinical trials. In seminal randomized cross-over trials, it has been demonstrated that a single dose of intravenously administered ketamine (0.5 mg/kg) can rapidly (in within 2 hours) induce a clinically relevant amelioration in depressive scores in patients with MDD, an effect that is maintained at least up to one week following ketamine administration [9] [10]. These pioneering observations have since been confirmed by other trials and recent meta-analyses unanimously support the antidepressant therapeutic potential of ketamine [11].

Identifying the molecular mechanisms and the neural substrates involved in the antidepressant effects of ketamine will provide us with important new information about the neurobiology of depression and, ultimately, regarding mood disorder therapeutics. At the molecular level, both NMDA and AMPA/kainate receptors have been shown to mediate the antidepressant effects of ketamine through the modulation of the mTOR pathway and neurotrophin signaling (reviewed in [12]). At the cellular level, ketamine has been shown to induce the formation of excitatory synapses in the prefrontal cortex of rodents [13]. Recent investigations in patients with MDD revealed no change in whole brain metabolism two hours following ketamine injection while *a priori* region of interest (ROI) analysis showed acute ketamine-induced alterations in the activity levels of several brain structures specifically involved in emotional and reward processing. [14–19].

There are several important remaining questions related to ketamine administration in MDD. For example, neither the most efficient dosing regimen nor the best route of administration in terms of therapeutic efficacy have so far been determined. In a recent placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in MDD, all three routes of administration were comparable and most patient responded favorable to ketamine at concentration as low as 0.1 mg/kg [20]. In contrast, a systematic review on the effects of low- versus very low-dose ketamine in MDD concluded that 0.5 mg/kg is more effective than lower dosing regimens [21]. Little is known about the therapeutic efficacy of repeated long-term administration of ketamine in MDD, although pilot studies and case reports suggest that it may be an interesting option [22] [23]. Further studies are needed on the safety profile of ketamine administration. Indeed, while single bolus ketamine administration appeared safe in most clinical trials with no life-threatening events, mild psychotomimetic symptoms, including unpleasant dissociative effects along with transient hypertension and tachycardia were frequently reported. Repeated administration of ketamine, although not in the context of MDD, have been reported to induce adverse effects on the urinary system as well as decline in cognitive performance along with abuse/dependence [24].

In light of the increasing data on the antidepressant effects of ketamine, one of the most interesting question in terms of perioperative care is whether administration of this drug at “antidepressant concentration” may improve depression states in the postoperative period. In a group of 70 patients with MDD undergoing orthopedic surgery, co-administration of a single bolus ketamine (1 mg/kg) on top of a propofol/fentanyl anesthesia regiment improved the Hamilton depression rating score in the postoperative period [25]. In contrast, single bolus low dose ketamine (0.25 mg/kg) did not prevent postpartum depression in a randomized placebo-controlled trial of 330 parturients scheduled for C-section [26]. Further prospective trial need to be designed to better elucidate this possibility.

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Obesity in the Operating Room: How Big a Problem?

Stephanie B Jones, MD **Boston, MA**

Obesity is commonly defined as a body mass index (BMI) > 30 kg/m2. It is commonly perceived that the higher the BMI, the higher the risk of perioperative complications. But how big a problem is obesity, really?

The Obesity Paradox and Metabolic Syndrome

Several studies over the past decade have demonstrated what is commonly referred to as the obesity paradox – that mild to moderate obesity is relatively protective against mortality after events ranging from non-cardiac surgery to myocardial infarction, percutaneous coronary intervention (PCI), and ICU admission. For example, Mullen et al [1] in 2009 examined the NSQIP databased and found an odds ratio of 0.73 for death in patients with Class II obesity (BMI 35-40) relative to normal weight patients, despite an increase in morbidity (primarily wound infection) as BMI increased. In multivariate analysis, obesity was an independent predictor of lower major adverse cardiac events at 12 months after PCI in an Australian study [2].

Ideas abound as to the possible reasons behind this apparent paradox. One is reverse causality, in this case that weight loss in induced by illness, so obese patients are healthier. A population based study from 2014 supports this concept [3]. All-cause mortality over time was tracked for BMI at time of the survey compared to maximum BMI. When maximum values were used, 33% of mortality was attributed to obesity, compared to just 5%. A second possibility is that the data simply isn't reliable because BMI does not accurately reflect obesity [4]. Body composition changes as we age, with a relative increase in body fat and decrease in muscle mass. It does not reflect the amount of visceral (versus subcutaneous) fat, and in many studies weight is self-reported or retrospectively documented. Waist circumference has been proposed as a better reflection of obesity and metabolic health, but is rarely included in typical databases, often the favorite mining ground for obesity outcome studies. Finally, it is clear that patients with obesity are a heterogeneous population. Some, even in the super obese BMI range, are metabolically "healthy". Metabolic syndrome impacts perioperative outcomes in general. Those studies that demonstrate no difference between non-obese and obese patient outcomes may have a disproportionate number of patients in the obese group without metabolic syndrome due to patient selection criteria.

Metabolic syndrome (MetS) is distinct from simple obesity, with an increased risk of type 2 diabetes mellitus and cardiovascular disease. Definitions vary by specialty group and guideline, but in general include:

- Increased waist circumference
- Hypertension
- Increased serum triglycerides
- Decreased serum HDL
- Impaired fasting glucose

MetS has been shown to effect perioperative outcomes. Glance et al [5] used a modified definition of MetS (obesity, hypertension, diabetes) to retrospectively examine non-cardiac surgical outcomes in >300,000 patients in the NSQIP database. Patients who met their criteria had a 2-3 fold increase in cardiac adverse events, 1.5-3 x pulmonary events, 3-7 x acute kidney injury, and 2 x CNS events. Schumann et al [6] looked specifically at pulmonary outcomes in the BOLD database. 12.7% of over 20,000 patients met criteria for MetS and had increased odds of pneumonia, respiratory failure, ARDS, pleural effusion and atelectasis. The composite pulmonary adverse events odds ratio was 1.87 (1.65-2.13).

Adipose tissue is an endocrine organ and, at least in some indivduals, creates a state of chronic, low grade inflammation. Fat secretes adipokines, including tumor necrosis factor alpha, C-reactive protein, and interleukin-6, all of which contribute to the inflammatory milieu [7]. Visceral fat is felt to be more pro-inflammatory, with greater

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macrophage infiltration. An increased proportion of visceral fat is often cited as one reason why cardiovascular disease occurs at lower BMIs in Asian populations relative to Caucasian [8].

The question remains as to how best use this information in the perioperative period. With appropriate preparation the vast majority of patients with obesity will suffer no adverse outcomes. But how can we preemptively identify those at higher risk due to MetS or other factors, and how should our anesthetic plan be altered to prevent adverse outcomes? BMI is convenient, but insufficient. Future research that will help clinicians discern which obese patients need higher levels of perioperative care should be made a priority as the number of patients with obesity continues to rise in the US and elsewhere.

The Airway

While the patient with obesity is traditionally regarded as at high risk of difficult intubation, the evidence in the literature does not necessary bear this out. Weight alone is not predictive of difficult intubation, as variously defined in the literature, and BMI is weakly predictive at best. The traditional risk factors still hold when applied to the patient with obesity: presence of obstructive sleep apnea (OSA), large neck circumference, and Mallampati classification 3 or 4. These items should be included as part of the airway history and physical in all patients, and certainly in the patient with obesity. In fact, one of the contributing factors in the 4th National Audit Project (NAP4) of the Royal College of Anaesthetists and the Difficult Airway Society, "Major complications of airway management in the UK", was failure to document an airway exam in an obese patient [9]. This implies failure to perform the exam; 17 of the 53 patients with obesity included in the audit did not even have a Mallampati class recorded. In the 2013 update of the ASA Practice Guidelines for Management of the Difficult Airway, obesity is similarly mentioned in the context of the airway history and physical, i.e. that there is observational correlation with difficulty [10].

Despite the perhaps lower than expected rate of difficult endotracheal intubation, the bariatric airway must still be respected. Obesity is a risk factor for difficult mask ventilation (MV). A 4 year observational study at the University of Michigan examined > 53,000 attempts at MV [11]. Of these, 2.2% were "difficult", defined as "inadequate to maintain oxygenation, unstable MV, or MV requiring two providers" and 0.15% were "impossible", "absence of end-tidal carbon dioxide measurement and lack of perceptible chest wall movement during positive pressure ventilation attempts despite airway adjuvants and additional personnel". BMI > 30 kg/m2 was predictive of difficult MV. Independent predictors of difficult MV overlap with difficult intubation criteria – OSA, Mallampati 3 or 4, neck irradiation changes and add male sex and beard.

Therefore, in the rare instance that intubation becomes difficult, our fundamental rescue technique of MV may also fail. One is then confronted with the realities of cardiopulmonary physiology of the patient with severe obesity. Increasing body mass requires an increase in cardiac output to supply oxygen to tissues. Recall that an increase in total body mass is accompanied not only by increasing adipose tissue, which is relatively poorly perfused, but also by increased well perfused lean body mass. While the body needs an increased oxygen supply, a decreased functional residual capacity (FRC) works in opposition to that goal, creating less reserve for apneic oxygenation during induction and intubation. Various maneuvers have been utilized to improve FRC during induction including application of continuous positive airway pressure or positive end expiratory pressure, 25-30 degree reverse Trendelenburg positioning and, more recently, high flow nasal oxygen. Studies are still ongoing as to the benefits of high flow nasal oxygen, delivered either via standard nasal cannula (5-15 L/min) or commercially available devices (humidified, up to 70 L/min), for the obese population in the perioperative context [12]. At least one study was able to demonstrate an increase in time before O2 saturation dropped below 95% after induction in a population of male patients with BMIs between 30 and 35 wearing 5L/min nasal O2 [13].

Another interesting and somewhat regional controversy is the use of succinylcholine versus nondepolarizing neuromuscular blockade when securing the airway in a patient with severe obesity. Obesity has been cited in older literature as a risk factor for aspiration; more recent work has shown this is likely due to prolonged airway manipulation rather than obesity per se. Thus the rationale for choosing succinylcholine is more rapid access to the airway, avoiding the need for potentially difficult MV, not necessarily as part of a rapid sequence induction.

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Opponents of succinylcholine cite the well-known side effects (postoperative myalgias, arrhythmia) as well as increased oxygen utilization caused by fasciculations, creating a situation where more rapid desaturation could occur. This has been demonstrated in a study from China in overweight patients where the time from administration of neuromuscular blockade to a SpO2 of 92% decreased from 329 seconds for rocuronium (0.9 mg/kg) to 283 seconds for succinylcholine (1.5 mg/kg) [14]. Recovery upon initiation of ventilation to SpO2 97% was also prolonged (36 vs 43 seconds). The dose of succinylcholine is higher than commonly used; it is unclear whether this may have affected the results.

While a great deal of attention is paid to induction and intubation, with optimal positioning, preoxygenation and availability of airway adjuncts, the risks of emergence and extubation for the patient with obesity remain, in my opinion, underappreciated. An ASA Closed Claims Project study published back in 2005 found that 37% of brain damage and death claims related to induction of anesthesia involved obesity as a contributing factor, compared to 67% of extubation claims [15]. Similar data emerged from the later NAP 4 audit, with 46% of airway events during emergence or recovery occurring in obese patients. Ensuring full reversal of neuromuscular blockade, utilization of multimodal, opioid-sparing analgesic regimens, and appropriate screening for and treatment of OSA may improve our performance in this area.

Obesity and Pharmacology

The physiologic changes associated with obesity may have a significant effect on the pharmacokinetics and dynamics of anesthetics and perioperative medications [16]. Adipose tissue mass increases, along with lean body mass to a greater or lesser extent (less as BMI increases). Cardiac output is increased to supply blood to the larger tissue mass, although the adipose component is relatively poorly perfused. Splanchnic blood flow is also elevated. Serum albumin levels are not different in patients with obesity, but alpha-1 acid glycoprotein concentrations my altered, affecting plasma binding of basic drugs. All of the above can potentially affect the volume of distribution of medications, although not in an entirely predictable manner. Metabolism may be altered as well, albeit to a lesser degree. Approximately 20-30% of patients with obesity will have elevated liver function tests, but this appears to have little effect on hepatic metabolism until severe stages of nonalcoholic steatohepatitis. An interesting exception is glucuronidation and sulfation, which are the main elimination pathways for acetaminophen. An older study [17] demonstrated increased clearance of intravenous acetaminophen in obese versus non-obese volunteers. Renal clearance of medications may be increased as well, secondary to increased renal blood flow and glomerular filtration rate. Of course, obesity related co-morbidities (e.g. diabetes mellitus, hypertension) as well as compression of the kidney by visceral adipose tissue may eventually impair renal function and drug clearance.

Despite the multiple variables that may impact medication dosing and clearance in the patient with obesity, there remains a relative dearth of pharmacologic studies specific to this patient group. The FDA encourages, but does not require, the inclusion of patients with obesity in drug dosing studies. Even when included, the numbers are typically insufficient to inform specific dosing recommendations. A recent systematic review of the literature on perioperative medication dosing yielded only 33 studies meeting the authors' inclusion criteria [18]. A variety of dosing scalars are tested in these studies including total (actual) body weight (TBW); ideal body weight (IBW), based upon gender, weight and height); lean body weight (LBW), weight minus fat mass; and BMI.

The majority of anesthetic-related studies specific to obesity involve neuromuscular blocking agents. Lemmens and Brodsky [19] found optimal intubating conditions when succinylcholine was dosed at TBW. The increased dose requirement is likely due to expanded extracellular volume and possibly increased pseudocholinesterase activity. In contrast, Leykin recommends IBW dosing of the non-depolarizing agents cisatracurium and rocuronium [20,21], as the TBW dose increased duration of action without improving intubating conditions. Peak concentrations and duration of propofol is significantly affected by cardiac output. Ingrande et al [22] found LBW to be an effective induction dose without worsening post-induction hypotension when compared with non-obese patients. Dosing of other important perioperative medications, such as prophylactic antibiotics and anticoagulants is less clear. Four studies examining higher doses of cefazolin found no significant differences in rates of surgical site infection [18]. And despite the clearly increased risk of venous thromboembolism in patients with obesity during the perioperative period, there is little consensus on agent, dosing, timing, or duration [23]. Dosing by TBW is likely excessive and

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may increase bleeding risk. The use of anti-factor Xa levels to determine adequacy of anticoagulation is of uncertain predictive value.

In the absence of available well-designed trials, common sense is best applied. With the notable exception of succinylcholine (TBW), perioperative medications should be titrated to effect, when possible. Otherwise, the use of LBW appears to be the most prudent dosing scalar.

The Obese Outpatient

The anesthesiologist practicing in an ambulatory surgery center (ASC) will increasingly face the question of whether a body mass index (BMI) or weight cut-off exists (or should exist) for patients in that setting. According to data derived from the Behavioral Risk Factor Surveillance System (BRFSS), an estimated 15.5 million adults in the United States (6.6% of the population) had a BMI $\geq$ 40 kg/m^2 in 2010 [24]. Regression modeling from the BRFSS data predicts a severe obesity prevalence of 11% by 2030, and a 42% prevalence of obesity (BMI $\geq$ 30 kg/m^2) [25]. If obese and severely obese patients are deemed ineligible for ambulatory anesthesia in significant numbers, timely access to surgical care could be compromised. Thus is it important to understand when and which patients with obesity may safely be cared for in the ambulatory setting.

The answer can be quite simple when total body weight is the limiting factor. Critical equipment such as stretchers, operating tables, and radiology imaging tables must be able to bear the weight load of the patient. Tables and stretchers should be clearly labeled with weight limits, which frequently differ depending on table position. Additional facility items must accommodate the larger patient's weight and breadth: CT and MRI gantry apertures, bathroom commodes, cardiac chairs, and waiting room seating, for example. [26]

The BMI limit, however, requires a more complex response. Although attempts have been made, the literature is currently of insufficient quality and quantity to provide a definitive BMI above which alternate surgical arrangements should be made in every case, or below which perioperative complications could be avoided with near certainty. Obesity has been identified as a risk factor for perioperative complications after outpatient surgery in several, often retrospective, studies. Sieffert et al [27] used discharge data from four states (California, Florida, Nebraska, and New York) to examine complications following outpatient liposuction, abdominoplasty, blepharoplasty, and reduction mammoplasty. Of 47741 patients cared for in 978 ASC or outpatient surgery departments, 2052 (4.3%) were overweight or obese. 7.3% had at least one hospital-based encounter within 30 days of discharge, compared to 3.6% in the non-obese/overweight group. The highest risk group was those undergoing abdominoplasty with three or more comorbid medical conditions. 32% presented for an acute care encounter compared with 14% for those with 2 or less comorbidities. Similarly, Ranum [28] et al studied closed ambulatory surgery claims from a single insurer between 2007 and 2012. The most frequent injuries attributed to anesthesia providers, aside from dental injury, were death and nerve damage. Obesity was identified as the most frequently contributing patient factor, impacting outcome in 15% of cases. The presence of obesity influenced surgical difficulty, obscured anatomy during the placement of neuraxial and peripheral regional blocks, and affected airway management complications at the time of initial or rescue intubation, as well as following extubation. The larger American College of Surgeons National Surgical Quality Improvement Program (NSQIP) supports these findings. [29] Nearly 250,000 patients were identified as having undergone day case surgery between 2005 and 2010. Of these, 232 (0.1%) were found to have early perioperative morbidity or mortality. When controlled for surgical complexity, seven independent risk factors for this early morbidity and mortality emerged. Two were overweight BMI (BMI $\geq$ 25 kg/m^2), with an adjusted odds ratio (AOR) of 1.58 (CI 1.07-2.35), and obese BMI (AOR 2.02, CI 1.37-2.98).

Contrast the above examples with a number of published case series touting successful outpatient performance of procedures not thought to typically fall into the ambulatory category. Laparoscopic sleeve gastrectomy (LSG) has quickly become the most common weight loss surgery in the United States, constituting 54% of the 196,000 bariatric procedures performed in 2015 [30]. A French group prospectively studied 100 patients meeting criteria for day case LSG [31]. Patients were ineligible for day case surgery if their BMI exceeded 60 kg/m^2, if they had obstructive sleep apnea (OSA), cardiac disease, or poorly controlled diabetes, or lived over an hour from the hospital. 416 patients were screened during the study period; 24% met inclusion criteria and all consented to the day

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case procedure. Unplanned overnight admission was the primary endpoint. Eight patients were admitted for a variety of reasons including pain, nausea, somnolence in the day surgery unit, difficult intubation, and discomfort following the mandatory postoperative upper GI exam. Although this study lacked a true control group, there were no significant differences in major complications or hospital readmissions between the day case group and standard care group. Billing et al [32] published a series of 250 patients undergoing LSG at a single ASC. The BMI range was wide, between 29 and 71, but patients were excluded if weight was greater than 450 pounds. Other exclusion criteria included anticipated surgical time of over 2 hours, significant medical comorbidities that would require monitoring greater than 23 hours, and impaired mobility. Only 2 patients (0.8%) required admission, both related to untreated OSA. Nine (3.6%) were readmitted within 30 days. Interestingly, patients were discharged from the ASC with a saline-locked IV in place, and received 1-2 liters of intravenous fluids during their visit on postoperative day 1. The authors, two of whom own the ASC, describe strengthening the patient selection criteria following this series. They now observe all OSA patients overnight, and enforce an upper BMI limit of 50 kg/m^2 "for purposes of reducing airway concerns". Common to both of these reports is multimodal analgesic regimens, aggressive prophylactic antiemetic therapy, and an emphasis on appropriate patient selection.

Indirect evidence of the importance of patient selection can be found in a study by Rosero and Joshi [33]. They derived a propensity-matched cohort of morbidly obese and non-obese patients from the 2006 National Survey of Ambulatory Surgery. Only 0.32% of procedures in the database were performed on morbidly obese patients, despite a prevalence of morbid obesity of approximately 4% in the overall population that year. Most of the procedures were performed in a hospital outpatient department, as opposed to an ASC. The low number of obese patients in the database and choice of setting implies conservative patient selection. Given the apparent caution, it is not surprising that no difference was found between the groups in postoperative adverse outcomes or delayed discharge.

Few studies have attempted to probe whether the degree of obesity makes a difference. Kakarla et al compared bariatric surgical patients with BMI < 50 kg/m^2 versus ≥ 50 kg/m^2 (super obese) [34]. These were laparoscopic but not necessarily ambulatory procedures. The super obese patients had a significantly higher incidence of a variety of postoperative complications including wound infections, myocardial infarction, pulmonary embolus, sepsis and 30 day mortality. A study by Morton et al [35] from the Bariatric Outcomes Longitudinal Database (BOLD) investigating the impact of length of stay on 30 day outcomes after laparoscopic Roux-en-Y gastric bypass was able to demonstrate a significant increase in 30 day serious complications when patients with BMIs between 50 and 70 kg/m^2 were compared to those with BMIs under 50 kg/m^2. The odds ratio after adjusting for covariates was 1.42, CI 1.15-1.74.

The key for deciding on appropriateness for ambulatory surgery does not depend solely on BMI. Joshi et al, on behalf of the Society for Ambulatory Anesthesia (SAMBA) Committee on Clinical Practice Guidelines, make several general recommendations after stating that the evidence is too weak to support creation of a specific practice guideline [36]. They suggest, based on a review of 23 studies, that the super obese may be at higher risk and caution must be used when considering ambulatory surgery; that patients with BMI ≤ 40 kg/m^2 may be appropriate candidates for outpatient surgery so long as comorbid conditions are optimized; and that those with BMIs between 40 and 50 kg/m^2 are in a relative gray zone. These patients should be considered for ambulatory surgery on a case-by-case basis, after careful assessment and optimization of comorbidities, taking surgical site and acuity into account and designing an anesthetic plan that minimizes potential complications.

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HELLP! How to Keep Moms with Preeclampsia Safe

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Introduction

Hypertensive disorders are the most common medical disorder of pregnancy and are a major source of fetal and maternal morbidity and mortality.[1,2,3,4] The prevalence of hypertensive disorders in the United States have increased markedly over the past two decades,[5] attributable, at least in part, to rising rates of maternal obesity and an increase in the proportion of pregnancies to women of advanced maternal age.

Hypertensive disorders, particularly preeclampsia and eclampsia, present a number of important management challenges for anesthesiologists.[6] Often anesthesiologists are the physicians on the labor and delivery unit with the most experience in the critical care skills necessary to care for these patients, and thus they play in ensuring a good outcomes. In the Refresher Course Lecture (RCL), we will provide an evidenced-based, up-to-date overview of the approach to the management of these high-risk patients.

Classification of Hypertensive Disorders

The classification of hypertensive disorders in pregnancy currently employed is based on the report from the 2013 American College of Obstetricians and Gynecologists (ACOG) Taskforce on Hypertension in Pregnancy.[7] The types of hypertensive disorders in pregnancy include gestational hypertension, preeclampsia without severe features, preeclampsia with severe features, and chronic hypertension.

Gestational hypertension is the most common type of hypertension during pregnancy. When severe, adverse outcomes have a frequency similar to that seen with preeclampsia.[8] A substantial fraction of women with gestational hypertension will progress to preeclampsia. Gestation hypertension is generally an indication for delivery after 37 weeks' gestation.

Preeclampsia is characterized by the new onset of hypertension and proteinuria after 20 weeks' gestation. Preeclampsia without severe features is defined on the basis of a blood pressure (BP) > 140/90 mmHg after 20 weeks' gestation and proteinuria (> 300 mg/24 hr, protein-creatinine ratio > 0.3, or 1+ on urine dipstick specimen).[7] Preeclampsia without severe features is also generally an indication for delivery after 37 weeks' gestation.

Preeclampsia is classified as with severe features based on one or more of the following criteria: BP > 160/110 mm Hg, thrombocytopenia (platelet count < 100,000/mm^3), serum creatinine > 1.1 mg/dL or > 2x the baseline serum, pulmonary edema, new-onset cerebral or visual disturbances, or impaired liver function (indicated by elevated blood concentrations of liver enzymes (> 2x normal) and severe persistent right upper quadrant, or epigastric pain).[7] Preeclampsia with severe features is usually an indication for delivery irrespective of gestational age.

HELLP syndrome is characterized by hemolysis, elevated liver enzymes, and low platelet count. Some consider this a variant of severe preeclampsia, but this is controversial because it thought to have a distinct pathophysiology.

Management of hypertensive emergency

Hypertensive disorders of pregnancy, particularly preeclampsia, confer a markedly elevated risk of hemorrhagic stroke[9,10] as preeclampsia not only causes hypertension, but also a loss of cerebral autoregulation leading to cerebral hyperperfusion. This risk can be exacerbated by the thrombocytopenia and coagulopathy that can accompany preeclampsia.[9,11] Systolic blood pressures of ≥160 mmHg or diastolic blood pressures of ≥110 mmHg in pregnant or postpartum woman, if persistent over 15 minutes, should be treated as a hypertensive emergency and blood pressure should be treated immediately to reduce the risk of stroke.[12-14]

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Intravenous labetalol or hydralazine are first-line therapies for the management of hypertension in this setting, with oral nifedipine a reasonable alternative if the patient does not have intravenous access or has contraindications to the first-line therapies.[13] If the hypertension cannot be brought into good control with these agents, consideration should be given to administering a second-line agent as an infusion. Alternative for this include nicardipine, esmolol, or nitroprusside; there is no data to support the choice of any of these agents over the others, and the decision as to which agent to use should be based on clinician familiarity with the drug and the known side-effect profile.[15] Nitroglycerine should generally be avoided in this setting due to its effect on uterine tone (causes relaxation). If an infusion is needed, placement of an arterial catheter should be considered. Normotension is not the goal, but rather to decrease the blood pressure by 15-20% below baseline (provided this is a SBP<150 mmHg). Drops in blood pressure that are greater than this can result in reduced uterine perfusion which can compromise fetal well-being.

Note, because it causes vasoconstriction and increases the blood pressure, the second-line uterotonic methylergonovine maleate is relatively contraindicated in patients with hypertensive disorders of pregnancy and an alternative second-line uterotonic should be administered (e.g., carboprost) if one is needed.

Regional anesthesia

Regional anesthesia should be used whenever possible for preeclamptics, as preeclampsia may increase the risks associated with general anesthesia. Preeclampsia can cause airway edema, which may make intubation more difficult, and the hypertensive response associated with laryngoscopy may increase the risk for hemorrhagic stroke.[6,16,17]

Spinal anesthesia was traditionally considered relatively contraindicated in severe preeclampsia because of concern about marked hypotension given the intravascular volume depletion that can accompany preeclampsia. However, robust data from studies performed over the past two decades suggest this is not the case and that spinals can be safely used in this population provided no other contraindications exist.[18]

In general, women with preeclampsia are hypercoagulable. However, thrombocytopenia is common and disseminated intravascular coagulation can occur, particularly in the setting of co-occurring placental abruption. Epidural hematomas are exceptionally rare in obstetric patients,[19,20] but cases associated with preeclampsia/HELLP have been reported.[21] Therefore, a determination of platelet count is indicated prior to the placement of a neuraxial anesthetic in women with preeclampsia with severe features. Historically, a platelet count of 100,000/mm^3 was considered the safe cutoff for neuraxial analgesia/anesthesia. While data are limited,[20] most practioners consider around 80,000/mm^3 safe for neuraxial technique (provide there are no other abnormal coagulation parameters) and 50,000 a level that precludes its safe use—with counts between 50,000/mm^3 and 80,000/mm^3 requiring careful weighing of the potential risks and benefits for the patient (e.g., whether the patient has indicators suggesting a potentially difficult airway).

Patients with severe preeclampsia should have their platelet count checked at routine intervals once in labor, so that that there is a recent measurement when epidural analgesia is requested. For patients with falling platelet counts, it is sometimes prudent to place an epidural early before the count falls below a level that precludes safe placement.

If the platelet count is >100,000/mm^3, neuraxial techniques can generally be safely performed without checking PT/PTT (assuming the patient does not have an abruption or other risk factors for coagulopathy). However, counts below this level are sometimes associated derangements in other coagulation parameters[22] and PT/PTT should be checked in this instance.

General anesthesia

When general anesthesia is needed, either because of coagulopathy or due to the need for emergent delivery, attempts should be made to stabilize maternal blood pressure prior to induction (targeting ~140/90 or less)[6] and then a medication (e.g., remifentanil, esmolol) should be administered to blunt the hypertensive response associated with laryngoscopy.[23] Placement of an arterial line prior to induction should be considered. Preparations should be made for the potential for difficult intubation given the upper airway edema that can accompany preeclampsia. Note,

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magnesium interacts with non-depolarizing neuromuscular blockers which can increase both the potency and duration of their action. Emergence can also result acute increases in blood pressure that need to be blunted.

Systems-based improvements

The National Partnership for Maternal Safety recently released a "hypertension bundle" which includes recommendations for practices that should be implemented on all labor and delivery units for the management of hypertensive disorders.[13] Anesthesiologists should work with their nursing and obstetric colleagues to implement the practices described in this bundle on their unit. An editorial accompanied the publication of the bundle in *Anesthesia and Analgesia* that emphasizes the elements of the bundle that are of particular relevance to anesthesiologists.[6]

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Impact of Regional Anesthesia Use on Perioperative Outcomes in Orthopedics

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Total joint arthroplasty for the hip and knee are among the most common surgical procedures in the United States. There is growing evidence that the use of regional anesthesia and analgesia contributes to equivalent if not superior outcomes in orthopedic surgery. Neuraxial blocks (e.g., spinal and epidural anesthesia) are well established anesthesia alternatives or adjuvants to general anesthesia for total hip arthroplasty (THA) and total knee arthroplasty (TKA). Moreover, inclusion of peripheral nerve blocks into multimodal analgesia clinical pathways for THA and TKA has been shown to reduce the need for opioid analgesia and enhances early rehabilitation. Important short-term benefits to regional anesthesia use include reduced hospitalization time and fewer adverse events, when multimodal analgesia with regional analgesia is used.[1] However, the effects of central and peripheral nerve blocks on long-term outcomes such as mortality, function, and quality of recovery beyond the duration of analgesia is less clear. With epic rates of THA and TKA projected in the next 15 years[2], discussion on how regional anesthesia may influence perioperative short and long term outcomes has profound significance. This Refresher Course focusing on the existing evidence, inclusive of limitations, and will provide such an update.

Learning Objectives:
At the conclusion of this activity, participants should be able to:

- Detail associations of regional anesthesia and analgesia use on perioperative outcomes
- Discuss the limitations of existing outcomes research
- Highlight sociocultural factors and public health level issue influences on perioperative outcomes research

Why is Outcomes Research in Orthopedic Surgery Patients Important?

There is little doubt that the population presenting for THA and TKA has inherently higher measures of comorbidity burden shown over the last decade.[3] In this same epoch of time, research has reported increases in several major in-hospital complications (e.g., pulmonary embolism, sepsis, myocardial infarction, pneumonia) among patients presenting for total joint arthroplasty. Most of the time THA and TKA are considered elective procedures; yet risky, with more than 100,000 postoperative complications per year[4] and 50,000 THA and TKA patients require ICU admission and escalated critical care services.[5] However, despite this Kirksey and colleagues have reported a simultaneous trend in reduction in mortality in this same patient population.[3] It is natural to question what role type of primary anesthesia and postoperative analgesia may have had in these outcome trends. If the type of anesthetic affects major morbidity and mortality, it might therefore be reasonable to expect it to be most able to demonstrate such effects in those of advanced age or with multi-morbidity.

It is important to place the influence of anesthesia alone in perspective of the entire perioperative exposure. Our professional "reality check" should consider whether a short anesthesia exposure can really impact outcomes. The past decade has seen a general shift in thinking about the entire total joint arthroplasty experience. Recent innovations including minimally invasive techniques, computer-assisted surgery/robotic joint replacement, advanced rehabilitation protocols, as well as, multimodal perioperative pain management strategies that include regional anesthesia and analgesia. We are all looking to "fast track" our patients in such a manner to minimize hospital intervention and shepherd the patient through all phases of surgical preparation, intraoperative management and postoperative recovery in such a manner as to facilitate an efficient discharge, whether that be on the same day or until the patient is able. In the end it is very difficult to provide an informed, evidenced-based answer on whether regional anesthesia improves outcomes most likely because of the lack of experimental study.

Neuraxial versus General Anesthesia for Orthopedic Surgery: A Brief Summary of the Findings

Advocates for spinal anesthesia, often cite benefits such as avoidance of endotracheal intubation, mechanical ventilation, and reduced exposures to neuromuscular blockade medication as support to use spinal over general anesthesia. Arguably, this may be based more on conjecture as improved cardiovascular, pulmonary, and other

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systems effects are based on limited evidence. Neuraxial anesthesia, with its often fixed time of action, can at times (e.g., ambulatory surgery, early mobilization) be less desirable. Few clinical trials in the 20th century focused specifically on rare, fatal or life threatening outcomes of which small samples lead mostly to conflicting results across studies (e.g., underpowered). In the beginning of the 21st century, Rodgers et al.[6] in a landmark systematic review attempted to form a consensus on the best form of anesthesia to impact outcomes. One of the biggest criticisms of the Rodger's review was even though it synthesized the prior work, this broad review was too inclusive (composed of multiple surgical types from abdominal to orthopedic surgery) which resulted in wide confidence intervals for limited outcomes and lower confidence in precision of the findings.

This last decade has seen a surge of "Big Data" research. These large sample studies based on available secondary data repositories allow for all the advantages of population-level analyses with very large sample sizes able to inform on low frequency outcomes (e.g., thromboembolism). Although not truly reflective of a longitudinal cohort, the term population-based has been adapted by "Big Data" researchers to emphasize the generalizability that these large cohorts may have on reflecting everyday practice with less constraints (e.g., time and resources) required of randomized clinical trial (RCT) designs. However, unlike RCTs these observational studies are still restricted to the clinical information available, are subject to residual bias/confounding, are limited by follow-up capture, and are unable to establish causality. Furthermore, it wasn't until recently that anesthesia-related outcomes were even collected with regularity or credibly in most administrative databases.

Memtsoudis and colleagues published the first of many investigations designed to answer important clinical questions surrounding what influence anesthesia technique can impart on postoperative outcomes. Using the Premier Perspectives, Inc. (a validated, administrative database containing information on discharges from approximately 400 acute care hospitals located throughout the United States), Memtsoudis was able to review nearly 400,000 patients undergoing total hip or knee arthroplasty.[7] The intervention groups were broken into three subgroups: general, neuraxial and combined neuraxial/general anesthesia types. Among those undergoing TKA and THA, neuraxial use was associated with significant differences in pulmonary and cardiac compromise postoperatively. Also, those receiving neuraxial had fewer infections and acute renal failure. Overall, neuraxial use was associated with significantly decreased 30-day mortality among patients undergoing TKA; but without such association for THA. Notably, the patients receiving a combination of neuraxial and general anesthesia showed intermediate risk results (neuraxial only >combined neuraxial/general > general only) suggesting that beneficial effects of are not explainable simply by the avoidance of general anesthesia. Next, Memtsoudis provided evidence that certain populations may benefit even more from selection of regional anesthesia. In a study stratified by age and presence of cardiopulmonary disease, we catch a glimpse of the possibility that although the incidence of major complications was found to be significantly higher among older and sicker patients (26.1%) compared to the younger group without cardiopulmonary disease (4.5%), the use of neuraxial anesthesia was independently associated with better outcomes across all age and comorbidity cohorts.[8] Similar positive results were shown in a cohort of patients with sleep apnea that received neuraxial anesthesia.[9] Once again, neuraxial anesthesia use was associated with lower major complications than any other anesthesia group type.

During this time, other independent and equally prominent researchers were studying associations with regional anesthesia use and outcomes with alternative study designs, Perlas and colleagues[10] were among the first to use propensity score analysis matching in her large single-center cohort. Propensity matching allowed this research team to minimize baseline differences between groups thus limiting the extent of treatment selection bias that is inherent of other retrospective observational study designs. Spinal anesthesia was associated with lower 30-day mortality with an absolute risk reduction from spinal anesthesia use reported (0.61%). With that being said these methods are not without limitations, it is important to mention that propensity scoring can only balance confounding factors that are known and recorded. Using different retrospective methods, Guay's overview of Cochrane systematic reviews of neuraxial blockade for the prevention of postoperative mortality and major morbidity found evidence, albeit weak, for reduced mortality and pneumonia in high-risk patients who received neuraxial anesthesia.[11]

Without a doubt as the demands for total joint replacement grow into and perhaps surpass the 4 million mark in the United States in the next 15 years[2], it is certainly important to know what long-term consequences selection for anesthesia type could have on optimizing medical and resource allocation outcomes. A tour of the literature to date

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provides convincing arguments on selection of neuraxial anesthesia impacting short-term mortality and major morbidity, yet long-term survival is less clear. Limited evidence exists beyond what can be acquired through nationwide longitudinal studies in countries with single health care delivery where loss of follow-up is of lesser concern. Chen and colleagues[12] in a propensity-score matched observation study looked into whether general or regional anesthesia influenced survival over the first five years after surgery. The short-term survival rates were similar in the two groups; however, the long-term survival was better for the sample given neuraxial rather than given general anesthesia. The neuraxial group also experienced shorter lengths of stay and lower hospital treatment costs than those undergoing general anesthesia. The page limit constraints of this Refresher Course summary keeps me from highlighting all of the literature over the last 20 years; however, it may be safe to conclude that the evidence to date shows neuraxial appears equally effective (or clearly better for some short-term outcomes) with no more adverse events compared with general anesthesia.[13] Yet, there is small, if any, applicable benefits to regional anesthesia in regards to long-term outcomes. Most likely the interactions between patient factors, the surgical procedure, and the entire perioperative management (including different types of anesthesia) remain to be elucidated.

Peripheral Nerve Blockade for Orthopedic Surgery:

Although many neuraxial vs general anesthesia questions have been addressed, evidence on the added impact of peripheral nerve blockade (PNB) continues to be lacking. Hebl and colleagues[1] showed better pain control, shortened hospital LOS, and fewer adverse events when multimodals plus peripheral nerve catheters (THA and TKA) and in the case of TKA single-injection sciatic nerve techniques were used (compared to those patients on traditional IV opioids alone). However, the major concerns with PNB use again may be linked to conjecture with opponents citing quadriceps weakness and delays in rehabilitation in opposition to widespread PNB use. In a large systematic review and meta-analysis, we were able to show continuous lumbar plexus blockade *was* associated with an increase in risk for falls; however, the attributable risk (0.7-1.7%) was not outside the expected probability for postoperative falls after orthopedic surgery.[14] Similar to our systematic review, Memtsoudis and colleagues, once again using Premier Perspectives data, found a fall incidence of 1.6% with PNB use not linked to increases in falling.[15]

Without a doubt, even outside anesthesia circles, the role of anesthesia techniques on perioperative outcomes has gained international attention. Using the Premier Perspectives, Memtsoudis and team examined one million cases of THA and TKA from 2006-2013 measuring associations between PNB use and outcomes.[16] Of note, the group identified substantial interhospital variation in the use of PNB (range 0-100%). Notably, PNBs were more frequently performed in large (≥500 beds) and teaching hospitals. PNB use was less common in patients receiving general anesthesia compared with those receiving neuraxial anesthesia. Moreover, PNB use increased over time, more so for TKA than THA. Differences in the overall comorbidity burden were small between those receiving and not receiving a PNB. Also, McIsaac and colleagues[17] using population-based administrative data from Canada used propensity-scoring to show those receiving nerve blocks in TKA (as opposed to no blocks) was associated with statistically significant reductions in length of stay and readmission without impacting emergency department visits or falls. Similar to neuraxial, for PNB, there has yet to be a study to show longer-term benefits. Recently, Sun and colleagues[18] examined health care utilization billing data constructing a sample of >120,000 patients undergoing TKA between 2002 and 2012 using billing data to identify those receiving peripheral or neuraxial blockade. Logistic regression was used to investigate whether there was an association between nerve blockade and chronic opioid use (defined as having filled >10 prescriptions or ≥ 120 days supply for an opioid within the first postsurgical year). Sun et al.[18] concluded no association between nerve blockade and a reduction in chronic opioid use after TKA. This same investigative team conceded similar results in a cohort of patients undergoing total shoulder arthroplasty.[19]

The value of using "Big Data" to help answer these important anesthesia delivery questions cannot be overstated. Administrative claims researchers have been successfully leveraging the numbers that previously had been difficult to obtain from even large-sample single-center and even multicenter prospective studies. In our editorial[20], Brian Williams and I celebrated the generalizability of the results and applauded the attempts by Sun and colleagues[18] to answer longer-term impact questions from PNB use. Yet, we were not surprised that an observational study was unable to show any associations with long-term opioid sparing. The methods were necessarily limited by a myriad

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of sociocultural factors and limited demographic subsets available for inclusion. Such studies are crucially reliant on the quality of data contained within them.

Determinants of Anesthesia and Analgesia Selection

The choice of anesthesia is actually quite complex with intertwining patient, provider, and systems preferences at play. Total joint replacement is associated with higher levels of pain compared to other intermediate risk surgeries. Pain is a sensory and emotional experience that is influenced by physiologic, sensory, affective, cognitive, socio-cultural, and behavioral factors. There are significant clinical and psychological consequences to unmanaged postoperative acute pain including thromboembolic and pulmonary complications, poor postoperative wound healing, insomnia, and demoralization.[21] However, patients receiving central and peripheral nerve analgesia have lower risks for reporting moderate to intense postoperative pain.[22] Furthermore, there are medical and economic implications to managing not only complications related to pain; but also side effects from the alternatives to regional anesthesia which would require providing more opioid medications to patients.

Starting in 2001 The Joint Commission declared pain as the 5th vital sign. This resulted in a time period where pain management drove a significant part of all patient care activities. Further, patients were encouraged and even "armed" to advocate for reaching aggressive pain control goals. Apfelbaum and colleagues sampled a random group of adults undergoing surgical procedures asking about severity of pain, treatment, satisfaction with pain medications, and perceptions about postoperative pain and medications.[23] Interestingly, about 86% had moderate to extreme pain ratings postoperatively despite treatment. Almost 25% of patients experienced adverse effects of pain medications; however, almost all of them (90%) reported being "satisfied" with their pain medications. In other words, despite patient education on the dangers of opioid medications and overtreatment of pain, patients still preferred the "security blanket" of opioids being within immediate reach. Opioid-related complications result in extended length-of-stays, delayed rehabilitation, increased readmissions following dismissal and reduced patient satisfaction with the surgical experience.[24] Despite our best efforts at routine regional anesthesia utilization, we have not implemented universal regional anesthesia use and also have failed to move the needle toward opioid independence. Effective pain management should not only improve clinical outcomes and avoid complications (e.g., prevention of chronic pain states); but in doing so remain mindful of heath care resource utilization and national mandates to reduce opioid pain medication use.

Key Components?

Multimodal analgesia is commonly used in total joint arthroplasty. This strategy of using multiple classes of medications to target sites along the nociceptive pathway has mounting evidence of clinical effectiveness. Common examples of multimodal analgesia agents include: nonsteroidal anti-inflammatories, acetaminophen, ketamine, gabapentanoids, steroids and germane to our discussion--local anesthetics (e.g., intravenous, central and peripheral local nerve blocks). The main premise to using 1, 2, or more additional non-opioid modalities is the hope that patients will experience less opioid-related side effects. Recently, multimodal pain therapy has been shown to be used in 86% of THA and TKA cases.[25] Further, there may be a stepwise decrease in parenteral opioid use, opioid prescriptions, and some opioid-related side effects, but without change in costs of hospitalizations, when multimodal pain management strategies are employed.

Geographic variation in anesthesia practice deserves mention as a potential missing link in our important discussion of regional anesthesia use as part of a multimodal pain management strategy. Fleishcut and colleagues, using anesthesia quality institute's national anesthesia clinical outcomes registry data (NACOR), have shown different regions tend to favor the use of different anesthesia techniques.[26] A majority of patients undergoing THA and TKA receive general anesthesia with few east coast pattern exceptions. Moreover, national PNB frequency is also shockingly low.[27] In a NACOR study of over 3 million outpatient surgeries amendable to PNB, the overall frequency of use of PNB was just over 3% of the possible cases.[28]

Like it or not performance measures are here, and although they are not clinical guidelines per se, they provide targets for regulatory agencies such as the Centers for Medicare & Medicaid Services (CMS) to evaluate care across providers. Fortunately, the American Society of Anesthesiologists has interjected and provided NACOR data to

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update CMS on an ongoing basis. As a result in 2018, measures (AQI56 & AQI59) applicable to our discussion have been added. You may now be evaluated on the percentages of patients you provide regional anesthesia techniques, as well as, inclusion of multimodal strategies to combat postoperative pain.

Conclusions:

Multimodal analgesia including regional anesthesia may confer improvements for both medical and economic perioperative outcomes. While not all data shows benefits, virtually no literature to date relates regional anesthesia use to worse outcomes compared to general anesthesia. Regional anesthesia use is not associated with increased risk for falling beyond the attributable risks from undergoing orthopedic surgery. Nationally, use of regional anesthesia and analgesia techniques remain underutilized. The impact of neuraxial and peripheral nerve blockade use on long term outcomes beyond the duration of analgesia and whether use expedites resumption of activities of daily living is unclear. Future prospective investigations accounting for patient and sociocultural factors and perioperative, opioid-sparing, management strategies including regional anesthesia and analgesia techniques are warranted.

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Central Line Insertion: Current controversies and best practices in 2018

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Introduction:

Few procedures in medicine have benefitted from improvements in technology and training as much as central line insertion. Driven by a decreasing number of central lines inserted by anesthesiologists, radiologists, and surgeons, aawareness of the role of medical error in patient outcomes, and a desire to minimize preventable complications, clinicians of all specialties have revolutionized the avoidance, detection, and treatment of central line complications including failed insertion, pneumothorax, air embolism, arterial cannulation, catheter related bloodstream infections, and retained guide wire. As an example, the Pubmed search term "central venous catheter" returned 70 entries in 1990 vs 970 in 2017. As a result of new technology, systematic optimization, safety culture, and a belief that lower complication rates are possible, central line insertion has become markedly safer even as the number of central lines inserted by anesthesiologist decreases.

The development and widespread use of high fidelity 2 dimensional ultrasound stands out as a major advance in central line insertion. These devices have not only enabled clinicians to define central vein anatomy with greater accuracy than by landmark methods, but allowed inserters to visualize vein cannulation in real time, verify wire tip position, and troubleshoot potential complications such as pneumothorax (2). Existing literature is nearly unanimous that ultrasound reduces line insertion complications (3), and a 2015 Cochrane review (4) lists advantages of ultrasound including increased first stick success, fewer arterial puncture and hematomas, and shorter time to successful line insertion. The ready availability of ultrasound has also led to new central line approaches including axillary and supraclavicular insertion locations. (5,6)

The second advance in line insertion safety has been an evolution in training processes. In many large teaching hospitals, historic "see one do one" approaches have been supplanted by multidimensional training programs including video, computer based training programs, low and high fidelity hands on simulation, and "live" insertions. With these advanced educational approaches, novices can become familiar with insertion hardware, patient anatomy, ultrasound visualization, sterile technique, and rescue or troubleshooting strategies with far less risk to actual patients. Existing evidence suggests that such simulation approaches can increase learner confidence (7) and reduce complications (8).

Finally, improvements in organizational aspects of line insertion have reduced central line complications. Operationally, the use of checklists, supply carts and EMR pathways has focused attention on the availability of needed equipment and transformed line placement from "just another clinical chore" into a technical, complex task. In addition, newer strategies for identifying central line insertions and complications via computer text string searches have improved our ability to feedback line complication events to providers. Considerable evidence suggests that such pragmatic, operational approaches are working. In addition to the seminal 2006 report of reduced central line infections with checklist use (10), large national databases also suggest dramatic reductions in central line infections (11) when specific processes are used. Of the checklist items commonly used, avoiding the femoral site and removing unnecessary lines have the greatest impact on line infection rates (12).

Partly as a consequence of these interventions, numerous medical specialty societies have recommended guidelines. The American Society of Anesthesiologists (ASA) (13), American College of Surgeons (14), British National Institute of Clinical Excellence (15), Australian Clinical Excellence Commission (CEC) (16), Swedish Society of Anaesthesiology and Intensive Care (17), Asia Pacific Society for Infection Control (18), and the Centers for Disease Control (19) have all issued recommendations regarding best practice for some aspect of central line insertion. This talk will review existing literature (including these guidelines where relevant) with respect to central line insertion, identify best practice where applicable, and briefly address specific complications of line insertion.

Pre-insertion

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a. Indications

A full discussion of indications (and contraindications) for central line placement are beyond the scope of this talk. Two trends in clinical practice are worth noting. The first is a decreasing emphasis on central venous access for hemodynamic monitoring purposes. Neither central venous pressure measurement nor Swan Ganz catheterization, for example, clearly improve outcomes when used for hemodynamic monitoring (20,21). PA catheter use is declining (22) in all areas except for heart failure, where an explosion of assist device technology is driving an increase (23). The second is the increasing use of peripherally inserted central access (PICC) lines and tunneled lines for intravenous infusions. In fact, radiologists now place most of the central lines in the United States (24)

b. Location and resource preparation:

If time permits, surveying the anticipated site of central line insertion with ultrasound can identify anatomical issues that may complicate placement. "Pre-scanning" can be particularly useful in complex patients with other venous hardware, previous central lines, prior neck surgery and/or venous thrombosis. Unanticipated abnormalities in the size/location of the target vein, hematomas or clot, and/or foreign bodies are all identifiable with ultrasound. In one study of ultrasound surveillance, the internal jugular vein could not be visualized in up to 2.5% of patients (25). For the internal jugular site, prescanning may permit positioning the head to maximize lateral separation of the carotid and internal jugular vein. Increased head rotation frequently increases carotid/internal jugular overlap (26), raising the risk of inadvertent carotid puncture.

Although not evidence-based, Both ASA and CEC guidelines recommend basic levels of ancillary support for central line insertion. An environment with adequate space and lighting that permits use of aseptic techniques, a trained assistant, monitoring equipment for ECG, BP, and pulse oximetry, and immediate access to resuscitation equipment and drugs are considered basic support requirements for line insertion.

c. Site Selection:

Historically, femoral insertion sites have been considered at higher risk for infection than either IJ or subclavian sites, and one element of the original insertion bundle was avoidance of the femoral site (10). However, more recent data suggest little difference in infectious risk between sites (27). A 2012 Cochrane review (28) likewise found no site specific difference in catheter-related blood stream infections or colonization and also observed "no overall differences in catheter-related complications between the subclavian and internal jugular sites". Declining infection rates with femoral catheters due to improved management and more prompt removal may partly explain this narrowing in infection risk among central cannulation sites (29).

The Cochrane review also found more thrombotic and mechanical complications with the femoral (vs subclavian) site but fewer mechanical complications than the internal jugular site and no difference between subclavian and internal jugular insertion sites with respect to mechanical or thrombotic complications.

The largest *randomized* analysis of line sites and complications is the 2015 "3Sites" study, published in the New England Journal (30). This multicenter trial randomized 3,471 insertions to the subclavian, femoral, or internal jugular sites and found a higher incidence of their prespecified composite outcome (vein thrombosis & CLABSI) in the femoral and IJ sites when compared to subclavian. The 3site authors also found a higher incidence of mechanical complications in the subclavian group…primarily pneumothorax. Variation in line insertion techniques among sites (twice as many IJ lines were inserted under ultrasound than subclavian or femoral, an overall low rate of ultrasound use,…a failure rate for subclavian use twice that for IJ), and an unusually high CLABSI rate (>1:1000 catheter days) make the study difficult to generalize.

With respect to other aspects of line site selection, anatomy favors the right vs the left internal jugular insertion site, due to the larger diameter and straighter course of the right IJ, the lower right pleural dome, absence of the thoracic duct, and ease of access for the right handed operator (31, 32). Although existing evidence does not clearly favor internal jugular over subclavian approaches, multiple case reports describe aortic injury, hemothorax, and tamponade with subclavian central venous catheterization. In addition, literature reviews suggest slightly higher risk for arterial puncture with the right subclavian approach, possibly due to kinking of the guidewire during vessel dilation (29). One 2002 (pre-ultrasound) meta-analysis assessed 6 comparative trials with >2000 internal jugular and subclavian catheters and found more arterial punctures with the jugular approach, more malpositions with the

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subclavian approach, and no difference in hemo or pneumothoraces (33). Post-ultrasound era data largely confirm these risk factors (34)

Changes in clinical practice may also affect line site selection. Most prominent among these is the use of ultrasound. Because of anatomical considerations, ultrasound imaging is better for internal jugular than for subclavian insertion. This slight advantage to internal jugular line placement may affect clinical decision making, particularly when patients are anticoagulated or have a history of difficult line insertion. In addition, the tendency for large bore subclavian lines to result in subclavian vein stenosis (35) has caused current CDC guidelines and the National Kidney Foundation to recommend against subclavian dialysis access (35). The use of small -footprint phased array probes with nonzero elevation may change this preference, as they increase the likelihood of visualizing the tip of the needle and thus decrease the chance of pneumothorax.

Taken together, these data and guidelines suggest the following "best practice" approach to line site selection:

1. Identify available sites. If possible, avoid sites with prior surgery, known thrombotic complications, broken/infected skin, or existing hardware (such as transvenous pacemakers). Be aware that case reports identify the left IJ site as more complication prone than the right IJ, suggest a higher likelihood of aortic injury/tamponade with subclavian vs internal jugular approaches, and imply that the more tortuous path of the right subclavian approach may predispose to aortic injury due to guidewire kinking.
2. Prioritize the femoral site LAST for thrombosis and infectious control reasons, particularly if the duration of the line is expected to be long. Although existing data find no clear evidence of increased infectious risk in the femoral position, these results may be due to shorter line durations or better dressing technology. If access requirements are emergent, however, femoral access followed by relocation to a less infection prone site after stabilization is reasonable
3. Scan available sites to identify potential barriers to site insertion
4. If placing a large-bore introducer, consider the smaller size and more variable location of the left IJ, and risk of subclavian stenosis with large bore indwelling catheters as potential decision factors.
5. Recognize The risk of pneumothorax during ultrasound guided subclavian insertion due to an inability to visualize the entire needle tip.

e. Aseptic technique

Although the mechanism by which "bundles" of activities performed together reduce central line infections is unclear (10), the effect is robust. Elements of such bundles include cap, mask, sterile gown and gloves, and handwashing prior to performing the procedure (36). The drop in central line infections triggered by revamping organizational aspects of line insertion was sufficiently dramatic that it was highlighted in a US Morbidity.Mortality Weekly Report in March of 2011. (37)

Among bundle components, avoiding the femoral site and removing unneeded lines have the greatest impact (12). But even partial bundle compliance reduces infection rates, and compliance is worst for avoiding the femoral site (38, 39). These data suggest that specific elements of a line insertion "bundle" may not be as important as whether a bundle is used at all.

With respect to skin preparation, chlorhexidine and alcohol has largely supplanted Povidine-Iodine due to controversial guideline pressure (40). The largest trial to date comparing the two strategies finds Chlorhexidine superior for CLABSI prevention, but that it also caused more skin reactions (41). A 2016 Cochrane review found weak evidence for the superiority of Chlorhexidine when compared to Povidine Iodine (42). Note that the package insert for chlorhexidine/alcohol recommends a, "back and forth" scrubbing application pattern for 30 seconds rather than the "inside to outside' circular pattern used for Povidine Iodine to adequately penetrate skin layers (43).

One emerging concern is chlorhexidine allergy. Because chlorhexidine may be present in shampoo, rectal and gynecological gel, shampoo and toothpaste, exposure to chlorhexidine in the healthcare setting is common. In 2017 An FDA warning noted that of the 43 cases reported since June 2015, more than half occurred after 2010 (44). A classical pattern is severe, persistent hypotension on exposure to topical skin preparation, and in one 2016 study the most common mechanism of repeat allergic reaction is central line insertion (45).

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With respect to antibiotic-impregnated central lines, a 2013 Cochrane review (46) found a reduction in catheter colonization and related bloodstream infections only in the ICU and no effect on mortality. A 2016 trial of chlorhexidine impregnated lines also found no reduction in CLABSI with chlorhexidine impregnated lines (47) CDC guidelines recommend use of impregnated catheters only for prolonged use, or if a comprehensive strategy to reduce infection rates does not work.

Insertion

a. Patient position

Existing evidence suggests that abdominal compression, increased intrathoracic pressure, and Trendelenburg position increase internal jugular vein size (48). Effects of similar maneuvers on subclavian vein size are unclear (49). Nevertheless, using the Trendelenburg position where clinically feasible for both access sites reduces the risk of air embolism. When targeting the internal jugular site, current evidence suggests that head rotation should be limited as increasing head rotation increases overlap between the internal jugular vein and carotid artery (31). Evidence suggests modest improvements in subclavian vein size with the head in the neutral position (49).

Observational studies from the pre-ultrasound era find that central venous access complication rates increase with the number of needle passes (50), and that more experienced operators have higher success rates (51). Based on these data, practitioners should consider changing operators or techniques if multiple passes by a single operator are unsuccessful.

All guidelines listed on page 1 of this handout recommend the use of ultrasound to facilitate central line insertion. Arguments against routine use of ultrasound include time, availability of equipment during emergencies, and adverse effects of improper use. One important caveat to ultrasound use is verifying visualization of the needle tip. In short axis scanning, the tip and shaft of the needle will appear identical and inexperienced operators failing to scan distally to locate the tip may increase the risk of carotid puncture and pneumothorax. Long axis visualization may lower (but not eliminate) that risk, Current literature finds arguments for long and short axis views (52, 53) Focusing on the ultrasound image instead of the patient during insertion may also lead to overadvancing the needle (54). CDC guidelines for prevention of central line infections consider training a category 1B recommendation and CEC guidelines explicitly state that “previous training or experience is required to use this technology effectively”. Two “clinical pearls” that may help with needle and wire visualization is maintaining a 90° angle between ultrasound beam and needle and aiming the beam into the chest to follow the wire below the clavicle.

Although no direct evidence exists to specify how deep the wire should be inserted into the vein, reported complications from deep insertion of the wire include dislodgement and ensnarement of vena caval filters (55), entanglement in the tricuspid valve (56), and complete heart block (57). This literature suggests that best practice should avoid inserting the wire too deeply. Once the wire is inserted, a verification step is strongly recommended to verify wire location in the target vein. However, few verification strategies are validated by high quality current evidence and no comparative trials exist. Strategies to distinguish venous from arterial location with equivocal (and thus not recommended) evidence include pressure waveform analysis, color of blood, blood gas analysis, or absence of pulsatile flow. Other strategies such as fluoroscopy, continuous electrocardiography, transesophageal echo, or chest XRay have little comparative evidence, but considerable face validity. The “bicaval” TEE view of the right atrium is widely considered the most reliable guide to verifying wire location in the right atrium. Transthoracic ultrasound may also be helpful for wire visualization. (58)

The strongest published evidence for verifying catheterization of the vein is manometry. With this technique, a length of IV tubing is attached to an IV catheter or needle located inside the vessel in question. The pressure in the vessel is then measured either by holding the tubing vertically and visualizing the height of the column, or by connecting the tubing to a pressure transducer. In a 2009 retrospective review, 9,348 central venous catheters placed during a 15 year period using manometry to verify venous location of the wire (59). No cases of dilator placement into adjacent arteries were noted, and the authors calculated that use of manometry prevented up to 56 possible arterial dilations.

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The choice of verification technique depends in part on cannulation technique. With the Seldinger technique, use of manometry to verify wire placement must be performed with the needle tip manually stabilized while in the vein or by inserting the wire and switching over to a plastic catheter. It is easy to see that this approach requires a high degree of manual dexterity, and may result in loss of access or air embolism, particularly when access is difficult or the patient is breathing spontaneously or moving. In contrast, with the modified Seldinger technique the inserter threads a plastic catheter over the hollow needle into the vein. Manometry can then be performed via this catheter.

Overall, existing evidence is insufficient to dictate a 'best practice". Nevertheless, case reports, observational trials, clinical experience, and expert opinion can be integrated to recommend a reasonable practice with respect to the insertion process:
1. Because the consequences of arterial puncture are significant, verification that the target vein has been cannulated (vs the artery) is strongly recommended by ASA and CEC guidelines
2. Blood color, waveform analysis, and/or pulsatility are NOT recommended due to the high likelihood of error
3. Case reports and observational trials support the use of fluoroscopy, catheter tip electrocardiography, or TEE/TEE
4. The two verification strategies with the greatest degree of overall support are pressure transduction of the target vessel (manometry) and ultrasound imaging of the catheter inside the target vessel.
5. Choice of verification technique should depend on operator experience and technical issues. Because use of manometry with the Seldinger "wire through needle' technique is technically more difficult than with the modified "catheter over needle" Seldinger approach, consider using ultrasound verification with the Seldinger technique.

Some controversy exists with respect to tip position. While tip location in the right atrium predisposes to perforation and tamponade (60), cadaver studies suggest that the pericardial reflection can reach as high as the middle third of the superior vena cava (61). In addition, a "high" catheter tip from the left subclavian or IJ site is prone to thrombosis/malfunction (62) and may form an acute angle to the SVC and predispose to perforation (63). Verifying that the tip of the line does not protrude below the bottom border of the right mainstem bronchus is helpful in preventing atrial location (64). CEC guidelines provide a table to specify insertion depth as a function of patient height and insertion site.

Complications and aftercare

The list of complications referable to central line insertion is large. These include arterial puncture, hematoma, hemothorax, pneumothorax, aortic injury, vena caval or atrial perforation, tamponade, intrathecal insertion, guide wire loss, thoracic duct damage, arrhythmia, and catheter-related infection. A 2003 New England Journal review estimated the incidence of arterial puncture as 6-9% for the IJ site and 3-5% for the subclavian site, and the incidence of pneumothorax as 0.1-0.2% for IJ and 6 to 11% for subclavian sites (65). With ultrasound, the incidence of arterial puncture is now ~1% for the IJ site.

A 1970- 2004 closed claims analysis of central line complications found 110 claims for injuries related to central lines (66). The most common were wire/catheter embolus (N=20), followed by tamponade, carotid artery puncture/cannulation, and hemothorax/pneumothorax. Post-insertion best practice should thus include maintaining a high degree of suspicion for the possibility of injury.

Other elements of central line aftercare includes attention to infection prevention. Daily attention to the ongoing need for central access, and prompt removal if the line is no longer necessary can clearly shorten line duration and reduce infectious complications. Existing literature recommends against routine replacement of central venous catheters (67), against routine use of antibiotic ointments (62), and against routine wire guided line exchange (67).

Summary

Advances in central line insertion techniques, increased attention to central line complications, and improved training strategies have dramatically improved the safety of central line insertion. Best practices likely include an organized, systematic approach to inserter training, line insertion, use of static and dynamic ultrasound when feasible, evidence based site selection, verification of wire position, localization of the catheter tip, and post-insertion maintenance.

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Management of the Patient With Pulmonary Hypertension and Right Ventricular Failure

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Introduction

Pulmonary hypertension (PH) is associated with significant morbidity and mortality. While disease-modifying therapies in the treatment of PH have dramatically increased the life expectancy of these patients, they still remain at high risk for perioperative complications after either non-cardiac or cardiac surgery [1-4]. Furthermore, PH may lead to right ventricular (RV) failure, which is a predictor of poor outcome. Managing the patient with PH and RV failure requires understanding of pulmonary physiology and how to avoid increases in pulmonary vascular resistance (PVR). Therapy primarily consists of intravenous and inhaled vasodilators to decrease PVR and inotropic agents to support underlying RV failure.

Definition of PH, classification and epidemiology

The pulmonary circulation is normally a low pressure and resistance circuit. The normal systolic, diastolic, and mean pulmonary artery pressures (PAP) are 22 mmHg, 10 mmHg, and 15 mmHg, respectively. The PVR is normally 90 to 120 dynes.sec.cm^{-5}. PH is defined as a mean PAP of greater than 25 mmHg at rest or a PVR greater than 250 dynes.sec.cm^{-5} [5]. A mean PAP greater than 50 mmHg or a PVR greater than 600 dynes.sec.cm^{-5} is considered severe PH. An updated World Health Organization (WHO) clinical classification of PH has been published in 2013[6]. This classification has 5 major groups: 1) **pulmonary arterial hypertension** (idiopathic, heritable, drug/toxin induced, associated with other pathologies such as connective tissue disorders or hepatopulmonary syndrome); 2) **pulmonary veno-occlusive disease** (PH associated with congenital or acquired left heart disease, persistent PH of the newborn); 3) **PH due to lung disease and/or chronic hypoxia** (chronic lung disease, sleep-disordered breathing, alveolar hypoventilation); 4) **chronic thromboembolic PH**; 5) **PH with unclear/multifactorial mechanisms** (glycogen storage diseases, malignancy etc.).

A distinction between pre-capillary and post-capillary PH is fundamental to understanding the vascular and hemodynamic changes present in patients with PH. The characterization of the different hemodynamic profiles of pre or post-capillary disease is summarized in table 1.

Table 1: hemodynamic characterization of PH:

Definition	Hemodynamics	WHO clinical groups
	mPAP > 25mmHg	All groups
1) Pre-capillary PH	mPAP > 25mmHg PAWP < 15mmHg PVR > 250 dynes.sec.cm^{-5} CO normal/reduced/high	Pulmonary arterial hypertension PH due to lung disease CTEPH PH with unclear and/or multifactorial mechanisms
2) Post-capillary PH	mPAP > 25mmHg PAWP > 15mmHg CO normal/reduced/high*	PH due to left heart disease

CO - cardiac output; CTEPH - chronic thromboembolic pulmonary hypertension; mPAP - mean pulmonary arterial pressure; PAWP - pulmonary artery wedge pressure; PVR - pulmonary vascular resistance;
*High cardiac output could be present in cases of hyperkinetic conditions such as systemic to pulmonary shunts, anemia, hyperthyroidism, portal hypertension, sepsis etc.

PH most commonly observed in the perioperative period is caused by cardiac (post-capillary) or pulmonary (pre-capillary) disease. Left ventricular systolic dysfunction, diastolic dysfunction and mitral valve disease result in elevations in left atrial pressure (LAP). This increase in LAP passively increases PAP and pulmonary venous pressure, eventually leading to increased PVR. Congenital heart diseases that cause left to right shunting result in chronic increased pulmonary blood flow that causes hypertrophy and fibrosis of the smooth muscle surrounding the pulmonary vessels - eventually leading to an elevated PVR. Respiratory disorders such as chronic obstructive airway disease lead to PH, at least in part, via hypoxia-induced vasoconstriction. PH may initially consist of vasoconstriction only, which is easily reversible with vasodilator therapy. However, as the underlying pathology progresses, vasoconstriction may

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result in smooth muscle hypertrophy and narrowing of the vascular lumen. Reversal of smooth muscle hypertrophy is possible over weeks to months with vasodilator therapy. Further progression of the disease involves fibrosis and more fixed disease. Therapy at this point becomes difficult, and attempts to decrease PVR with vasodilators may only result in a decrease in systemic vascular resistance and low blood pressure. Endothelial dysfunction may also lead to decreased pulmonary prostacyclin to thromboxane A_2 ratio, as well as decreased production of nitric oxide (NO)[7,8]. Prostacyclin is a potent vasodilator that inhibits platelet aggregation and smooth muscle cell proliferation[9]. Thromboxane A_2 stimulates vasoconstriction and platelet aggregation. Nitric oxide (NO) acts via cyclic guanosine mono phosphate (cGMP), causes vasodilatation and has antiproliferative properties [8]. All forms of PH are believed to result in a state of reduced NO bioavailability [10]. Phosphodiesterase-5 (PDE-5) is the enzyme that breaks down cGMP into inactive metabolites. In PH patients there is increased expression of PDE-5 both in the endothelial smooth muscle cells and in the right ventricle [11]. There is also an association between PAH and increased expression of endothelin-1 (ET-1), which is a potent vasoconstrictor and stimulates smooth muscle cell proliferation [8,11,12]. Therefore, the main focus of treatment in PH is the reversal of vasoconstriction using endothelin-1 receptor antagonists (Bosentan, Ambrisentan, Macitentan), prostanoids (Epoprostenol, Iloprost, Treprostinil), PDE-3 or 5 inhibitors (Milrinone or Sildenafil, Tadalafil, respectively) and inhaled NO.

Pulmonary vascular resistance (PVR)

In contrast to the systemic circulation, the pulmonary vessels have relatively thin walls and the vascular smooth muscle is sparsely distributed in the smaller arterioles. As such, increases in cardiac output (CO) distend open vessels and recruit previously closed vessels, resulting in a decrease in PVR. Clinically, this means that increasing CO with inotropic agents or increasing blood volume will passively decrease PVR. This relationship becomes less pronounced in disease states of the pulmonary circulation. The endothelium plays an important role in maintaining low resting pulmonary vascular tone. Endothelial dysfunction and alterations of endogenous vasodilators is associated with the development of PH [13].

An important aspect of treating PH is understanding how certain factors alter PVR. Oxygen has a large influence on PVR, with alveolar hypoxia being a potent vasoconstrictor. In this context, hypoxic pulmonary vasoconstriction (HPV) is a protective mechanism that improves ventilation/perfusion matching. This becomes important when treating PH because all intravenous vasodilators inhibit HPV and may decrease PaO_2. Acidosis is another potent vasoconstrictor, whereas alkalosis vasodilates the pulmonary circulation. Hypercapnia and hypocapnia most likely alter PVR via their effects on pH. Atelectasis can increase PVR via stimulation of HPV and mechanical compression; therefore, the lungs should be adequately expanded in patients with PH, yet it is important to remember that PEEP can result in over-inflation, which by itself can result in increase in PAP. Providing adequate oxygenation and treating acidosis (respiratory or metabolic) represents one of the most important and first line treatments of PH. Sympathetic stimulation, hypothermia, and catecholamines are also important factors that increase PVR. Alpha-1 adrenoreceptors and beta-2 adrenoreceptors are the most clinically relevant receptors in the pulmonary vasculature. Beta-2 agonists decrease PVR, whereas alpha-1 agonists increase PVR. These receptors are less densely distributed compared to the systemic circulation, so one would expect the effects of agonists to be decreased. Furthermore, the tone of the pulmonary circulation is normally low, therefore beta-2 stimulation normally has little effect; however, in the presence of PH, beta-2 agonists decrease PVR. Alpha-1 agonists increase PVR but not to same extent as the systemic vascular resistance (SVR)[14]. Beta-2 receptors responsible for vasodilation are located on the endothelium; therefore, their effect may be decreased in the presence of endothelial dysfunction.

The Right Ventricle (RV)

The right ventricle is a thin walled, crescent shaped structure that is suited for volume work, in contrast to the thick walled LV that is suited for pressure work. While the LV maintains a constant output over a wide range of afterloads, RV function is more sensitive to changes in PAP. An acute increase in mean PAP above 40 mmHg results in a decrease in RV ejection fraction, even in the presence of normal RV contractility. In the presence of decreased RV contractility the RV is even more sensitive to acute increases in afterload. On the other hand, more gradual changes in PAP may allow time for the RV to hypertrophy and sustain a relatively normal output. Coronary blood flow to the RV normally occurs throughout both systole and diastole because of the continuous pressure gradient (coronary perfusion pressure, CPP) between the aorta and the RV. The RV blood/oxygen supply is proportional to the systemic blood pressure and inversely proportional to the RV pressure. Systemic hypotension or increased RV pressure may result in decreased RV CPP. RV oxygen demand is proportional to the RV pressure, RV volume and heart rate. Hence, increased RV pressure not only decreases RV oxygen supply but also increases oxygen demand. Therefore, decreasing PAP with the use of vasodilators to decrease RV pressure is critically important in treating PH and RV failure. Yet, at the same time it is important to avoid decreasing systemic blood pressure and CPP.

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Right Ventricular Failure

RV failure is most commonly caused by acute or chronic pressure overload. While acute increases in RV afterload are poorly tolerated, more gradual increases in pressure overload of the RV is sometimes tolerated for years before symptoms and signs of RV failure become evident. In the presence of a chronic buildup of PH the RV may hypertrophy and be able to generate systemic pressures. Nevertheless, PH eventually leads to RV dilation, decreased RV stroke volume, and decreased global cardiac function. Ischemia and infarction may also contribute to RV failure. Although angina generally occurs because of LV ischemia, ischemia may also arise from a decrease in RV coronary blood flow or increased RV oxygen demand. RV ischemia may also result from inadequate myocardial protection during cardiopulmonary bypass (CPB). Volume overload from tricuspid regurgitation (TR) or atrial septal defects may also contribute to RV failure.

Common symptoms of PH and RV failure are dyspnea, fatigue, reduced exercise tolerance, syncope and chest pain. Signs of PH and RV failure include peripheral edema, tachypnea, tachycardia, neck veins distension and hepatomegaly. RV lifts may be palpated and tricuspid regurgitation auscultated. The CVP, which is normally less than 5 mmHg, may increase to above 20 mmHg in the presence of RV failure.

PH and RV failure can also alter LV function. Interdependence between the ventricles occurs in the presence of increased PVR and RV end-diastolic volume and pressure, such that the intraventricular septum shifts towards the LV cavity[15]. PH increases RV afterload, which may increase RV pressure and volume, while decreasing RV stroke volume. This may cause a decrease in LV preload and thus a decrease in systemic cardiac output (CO). Increased RV volume and pressure may also decrease coronary blood flow and worsen RV ischemia, which will further deteriorate CO. A decrease in CO may cause metabolic acidosis and worsen PH. Treatment of PH may include vasodilators to decrease PVR, inotropic agents to improve RV function, optimizing ventricular volume, and correction of acid base and oxygenation status. In order to treat PH and RV failure continuous assessment of hemodynamics may be required.

Patients may be best monitored with an arterial line and PA catheter. Transesophageal echocardiography (TEE) is an important tool that can guide the clinician in diagnosis and patient management. It is important to understand whether the patient has RV failure, PH, or both. Treatment of patients with PH without RV failure consists primarily of the use of pulmonary vasodilators. In contrast, patients with RV failure without PH may be treated primarily with inotropic agents and possibly diuretics or vasoconstrictors. Patients with PH and RV failure usually require both pulmonary vasodilators and inotropic agents.

Diagnosis and treatment

Echocardiography remains the method of choice for screening and assessing the likelihood of PH and for evaluation of RV function. Right heart catheterization is the gold standard to confirm the diagnosis and establish the severity of PH. Assessment of the RV by echocardiography is not as straightforward as evaluation of the LV; however RV function can still be evaluated. Signs of RV dysfunction include hypokinesis of the RV free wall, RV dilation or hypertrophy, a change in the normal crescent RV shape to round, and flattening or bulging of the interventricular septum from right to left. RV hypertrophy is characterized by RV free wall thickness greater than 5 mm at end-diastole. RV dilation is also defined by an end-diastolic cross-sectional area of greater than 60% of the LV. Right ventricular systolic impairment also decreases tricuspid annular plane systolic excursion (TAPSE). In addition, tricuspid regurgitation is common in patients with PH and RV failure and the velocity of the TR jet is used to estimate the PAP (using the Bernoulli equation).

The treatment of patients with PH is divided into general supportive measures and specific drug therapy. General measures include treating underlying conditions that may cause PH, as well as advice on physical activity and supervised rehabilitation, infection control, birth control and pregnancy management. Supportive measures include advice on anticoagulation, diuretics and oxygen therapy.

Drug therapy includes calcium channel blockers that have traditionally been used in the treatment of idiopathic PH although this therapy is effective only in a small fraction of the patients[16]. Synthetic prostacyclin analogues, such as epoprostenol, iloprost and treprostinil, have shown efficacy in patients with idiopathic PH. Epoprostenol has a short half-life and is stable at room temperature for only 8 h, hence, it needs to be administered via continuous intravenous infusion or by inhalation. Iloprost is available for intravenous, oral, and aerosol administration. Inhaled iloprost in patients with idiopathic PH and CTEPH showed an improvement in symptoms and clinical events[17,18]. Another group of drugs, the endothelin receptor antagonists (Bosentan, Ambrisentan and Macitentan), are effective in the treatment of PH. Studies have demonstrated improved exercise capacity[19], hemodynamics and time to exacerbations[20], as well as, decreased mortality[21]. Phosphodiesterase-5 inhibitors, such as sildenafil and tadalafil, are orally active, potent pulmonary vasodilators. The use of these drugs results in improved exercise capacity, symptoms and hemodynamics in PH patients[22,23]. Riociguat is a novel medication that stimulates

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soluble guanylate cyclase, leading to an increase in cyclic GMP, and has proven to be effective in idiopathic PH and CTEPH patients[24]. In selective patients heart–lung transplantation or double-lung transplantation may be indicated[25].

Anesthetic Management

Preoperative evaluation

Patients need to be explicitly informed of the possibility of serious complications that can lead to prolonged hospitalization or even death. The mortality associated with surgery is influenced by the severity of PH and type of surgery. Most studies that investigated perioperative outcomes in patients with PH are small retrospective case series[2,26,27]. A much larger investigation by Memtsoudis et al. matched 3302 PH patients who underwent total hip or knee arthroplasty with non-PH controls. The PH group showed a 4 to 4.5-fold increase in the adjusted risk of mortality after hip or knee arthroplasty. The highest mortality was reported in patients with idiopathic pulmonary arterial hypertension[4].

The pre-operative evaluation of a patient with PH should be based on a risk assessment that takes into account their functional state, severity of the disease and type of surgery. A detailed history and physical examination should be complemented with relevant additional studies. New York heart association (NYHA) functional class at diagnosis is an important predictor of survival and improvement from functional class 3/4 to 1/2 with treatment is associated with a better prognosis. The six-minute walking distance (6MWD) is used to assess exercise capacity in patients with PH and a reduced total distance to less than 400m is associated with higher mortality[28]. Pre-operative tests include laboratory studies, ECG, echocardiography, chest radiography and a recent right heart catheterization. Echocardiography is non invasive and readily available to assess ventricular function and the severity of PH. Echocardiographic predictors of poor outcome include right atrial enlargement, reduced tricuspid annular plane excursion and pericardial effusion[29]. Right heart catheterization confirms the diagnosis of PH, evaluates RV function and provides differentiation between pre-capillary and post-capillary PH. Prior to surgery the patients' medications need to be reviewed and therapies optimized. Anti PH medications should be continued and when oral formulations cannot be taken, temporary administration of inhaled (inhaled NO, Flolan) or intravenous (prostacyclin, milrinone) formulations should be considered.

Monitoring

Invasive arterial blood pressure monitoring before induction can facilitate early recognition of hemodynamic instability and allows intermittent arterial blood gas sampling to evaluate ventilation adequacy. Intraoperative monitoring with TEE and/or a pulmonary artery catheter should be considered in all patients with severe PH or mild-to-moderate PH with existing right-sided heart failure[30]. Use of TEE allows assessment of systolic pulmonary artery pressure, provides information on right ventricular performance and helps guiding fluid management. Studies have shown that the use of TEE triggered a change in the overall therapeutic management in as much as 50% of high-risk patients undergoing non-cardiac surgery[31,32]. The intra-operative use of a pulmonary artery catheter (PAC) is controversial. Most studies failed to demonstrate any benefit in its use for intra-operative monitoring[33]. However, these studies did not focus on patients with pulmonary hypertension, and the use of a PAC in the perioperative setting provides continuous measurement of pulmonary artery pressure, pulmonary vascular resistance and dynamic changes that occur in response to fluid administration or drug therapy. Furthermore, although there was no reduction in mortality[34], the use of a PAC can provide critical measurements postoperatively in the intensive care unit. It is important to remember though, that PAC placement is associated with certain risks, which must be considered before insertion is attempted.

Anesthetic induction and maintenance

Anesthetic induction in patients with PH and RV failure may be challenging. Prevention of PH crisis and RV failure relies on the optimal mechanical matching of the right ventricle and pulmonary circulation. These patients often have high baseline sympathetic tone and may be catecholamine deprived. As such, these patients may be prone to severe hypotension upon anesthetic induction[35]. Titrated doses of narcotics, etomidate, or ketamine may be appropriate, with maintenance of systemic pressure the primary goal. Nitrous oxide and ketamine increase PVR in patients with PH, although neither increases PVR in pediatric patients. Volatile anesthetics are unlikely to have significant effects on PVR, but they depress myocardial contractility and should be used very cautiously in patients with severe RV failure. Table 2 summarizes the effects of various anesthetics on RV contractility and afterload. In patients undergoing peripheral procedures, regional or peripheral blocks may be ideal if preload and afterload can be maintained.

Table 2: Effect of anesthetic agents on right ventricular (RV) contractility and pulmonary vascular resistance[36-41]

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Anesthetic Agent	Isoflurane/ Desflurane	Sevoflurane	N_2O	Thiopental	Etomidate	Ketamine	Propofol	Opioids
RV contractility	↓↓	↓↓	↓	↓	↔	↓	↓↓	↔
PVR	↓	↓	↑↑	↔	↔	↑ adult ↔child	↓	↔

↓↓-marked decrease; ↑↑-marked increase; ↑-increase; ↓-decrease; ↔ no change

The transition from spontaneous breathing to positive pressure ventilation may significantly increase PVR and RV afterload. While this has minimal effect in patients with normal RV function, in patients with PH and RV failure lung hyperinflation or excessive positive end-expiratory pressure (PEEP) can drastically decrease CO. Thus, optimal ventilation strategies may include a low tidal volume and low PEEP, while avoiding hypercapnia and atelectasis. Other factors such as patient positioning, pneumoperitoneum or diaphragmatic compression can also increase right ventricular afterload and precipitate a pulmonary hypertensive crisis. Every effort should be made to avoid hypoxia, hypercarbia and acidosis since they may significantly increase PVR. An adequate depth of anesthesia should be ensured before attempting laryngoscopy and tracheal intubation, as sympathetic stimulation has deleterious effects on right ventricular afterload. In general, patients with PH have low systemic arterial pressures, rendering them susceptible to decompensation. The goal is to maintain the pre-anesthetic hemodynamic condition. Therefore, invasive monitoring before induction is often required. The use of a low dose of vasoconstrictor, such as norepinephrine or vasopressin, to compensate for the reduction in systemic vascular resistance caused by anesthetic drugs is a safe and effective approach. Volume loading will increase RV output in the absence of PH if RV contractility is normal. However, if decreased contractility and PH accompany RV failure then volume loading may be detrimental. In this situation, volume loading may cause RV dilation and result in a decrease in LV volume and CO. The most appropriate action is to assess the effects of volume loading by measuring the CO and following RV and LV function by TEE. In the presence of RV volume overload, venous vasodilation with nitroglycerin or diuretic therapy may improve RV function.

Maintaining the gradient between the aorta and right ventricle is achieved by using sympathomimetic and non-sympathomimetic vasopressors. Norepinephrine and vasopressin improve right ventricular coronary perfusion, reduce the pulmonary/systemic vascular resistance ratio, enhance right ventricular performance and marginally improve cardiac output[42,43]. However, there is limited evidence regarding their impact on mortality related to right heart failure[44]. Inotropes that enhance right ventricular performance, such as epinephrine, dobutamine and levosimendan are effective in treating right-sided heart failure. The use of inotropes has a modest impact in reducing the overall mortality related to PH, and their wide availability and ease of administration make this group of drugs very attractive for use in the perioperative setting. Inodilators, such as the phosphodiesterase-3 inhibitors (milrinone) have been shown to be beneficial when compared with conventional inotropic support only[44]. It appears that the influence of phosphodiesterase-3 inhibitors on reducing pulmonary vascular resistance is more pronounced than the reduction in systemic vascular resistance. Nonetheless, reduction in systemic vascular resistance can compromise right coronary artery blood flow in patients with severe PH and therefore they should be administered cautiously. In 2010, the phosphodiesterase-5 inhibitor, sildenafil, was approved for intravenous therapy of PH and it may be an attractive option for the perioperative management of patients that are already on this medication.

Selective inhaled pulmonary vasodilators (inhaled NO, prostacyclin, and milrinone) have essentially no effect on the systemic blood pressure. These drugs improve oxygenation by decreasing pulmonary shunt, which is important in patients with ARDS-associated PH. Inhaled NO acts by diffusing from the alveoli into the pulmonary vascular smooth muscle to stimulate the production of cGMP which results in vasodilation. Inhaled NO which diffuses into the bloodstream rapidly binds to hemoglobin and becomes inactive, and therefore has no effects on the systemic blood pressure. Inhaled prostacyclin (epoprostenol) increases smooth muscle cAMP to cause pulmonary arterial vasodilation but is hydrolyzed before producing systemic effects. Inhaled vasodilators also have the potential to increase PaO_2 in patients with ventilation/perfusion abnormalities. Since these drugs are inhaled, vasodilation is primarily limited to areas that are ventilated, and hence, ventilation/perfusion matching is improved and shunt is decreased. It has been reported that the use of inhaled NO over a prolonged period is associated with rebound phenomena and direct toxicity to the lungs[45]. Prostacyclin and its analogues offer a good alternative to NO and there are several reports of the use of inhaled prostanoids in the perioperative setting[46-48]. In theory, both inhaled NO and prostacyclin can increase bleeding due to platelet inhibition, but this is usually not clinically significant. While inhaled NO is delivered as a gas via a specialized delivery system, PGI2 and the other agents are delivered as nebulized drugs.

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Postoperative management

Most patients with PH should be recovered postoperatively in the intensive care unit. There should be a robust plan for pain management, including regional blocks and non-opioid medications. Respiratory failure (60%) and right ventricular failure (50%) are the most frequent contributing causes to morbidity or mortality[1]. Atrial tachyarrhythmias are associated with right ventricular failure and death. Beta-blockers should be avoided as they are poorly tolerated in these patients[49], hence amiodarone would be the drug of choice for arrhythmias. Post-surgical complications such as bleeding and infection must be promptly controlled and treated. Right ventricular function in PH is 'preload-dependent', but at the same time, fluid overloading is detrimental. Maintenance of systemic pressures with vasopressors and inotropes, along with replacement of blood volume when necessary, is of paramount importance. Vasodilator therapies that were started intraoperatively must be continued and slowly transitioned back to the patient's pre-operative regimen.

PH and pregnancy

Historically, it is well known that pregnancy poses a very high risk to women with PH. Avoidance of pregnancy is still advocated and early termination is recommended for PH patients. Endothelin receptor antagonists are contraindicated during pregnancy due to their teratogenic effect, but prostaglandins, PDE inhibitors and inhaled nitric oxide can be used[50]. Calcium channel blockers may also be indicated.

While earlier studies reported a mortality rate as high as 50% in pregnant women with PH[51], more recent data show a lower but still significant mortality rate[52]. While vaginal delivery is associated with reduced risk for maternal bleeding and infection, elective caesarean section allows for better planning, a multidisciplinary team approach and optimal pain control. The optimal anesthetic technique (GA vs. neuraxial blockade) is still under debate[53,54]. The majority of deaths in pregnant patients with PH occur in the peripartum period, mainly due to right heart failure and pulmonary thromboembolism, thus thromboprophylaxis in pregnant patients with PH while not universally indicated is of importance[50].

Conclusions

Recent advances in the management of patients with PH and RV failure and new treatments have improved patient outcomes, but these remain extremely high-risk patients that require a multidisciplinary team approach. There is an increasing number of such patients presenting for either cardiac or non-cardiac surgery. Their successful management requires a thorough pre-operative risk assessment. Correct diagnosis, optimization of the patient's functional status and hemodynamics and management of co-morbidities are vital. Anesthetic management is dependent on an understanding of pathophysiology and avoidance of a pulmonary hypertensive crisis. Postoperative care should generally be in an intensive care unit with the understanding that the majority of complications occur in the postoperative period.

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Sepsis: Current Concepts and Perioperative Management

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Introduction

Sepsis is a high mortality syndrome and substantial health burden. In the U.S., about 270,000 people die of sepsis annually, killing more people than breast cancer, prostate cancer and AIDS combined (1). It is a comorbidity complicating many major surgeries, and is often responsible for an "emergency" designation. The increased morbidity and mortality of emergency status patients can be partially attributed to sepsis physiology. In one study, 40% of perioperative cardiac arrests were associated with sepsis, and these had a 77% mortality (2).

Sepsis also entails a re-tuning of the body's metabolic, inflammatory, neurologic and endocrine systems to coordinate a systemic response in every organ system. A new consensus definition of sepsis defines it as a dysregulated response to infection." (3) A maladaptive response causes perturbations in physiology. Some adaptations, such as a loss of systemic vascular tone, can be detrimental. Conversion to a more stable but maladaptive chronic critical illness state is more ominous, and is a risk when control of sepsis is delayed.

In an era of powerful antibiotics and a better understanding of how to use them, the primacy of sepsis should confuse us as clinicians. Our patients are dying of the same illness (infection) that other patients did 100 years ago. The details are different, but sepsis still persists and perseveres. In recognition of this intractable problem, basic science research, translational clinical trials and guidelines production continue at a fast pace.

Mastering the care of sepsis involves understanding several important concepts. Sepsis is a disease requiring aggressive and timely management. Effective management is based on controlling the source of infection and managing the body's common responses to severe illness. It entails taking corrective actions before the patient's physiology transitions from an acute to a chronic critical illness state. Finally, sepsis is ideal for examining the way clinical care is delivered and directed at institutional, societal and governmental levels.

Sepsis: common themes

Sepsis has been defined by a loose set of criteria (4), among which are signs of inflammation linked to infection. Another system for describing the syndrome is the PIRO model (predisposition, infection, response, and organ dysfunction) (5). The criteria for defining and characterizing sepsis are nonspecific. Further, the prognosis can vary substantially based on organism or site of infection. For example, urosepsis is clinically different from sepsis with influenza, even though many factors are common to both.

The traditional definition of sepsis combined the systemic inflammatory response syndrome criteria with a suspected or known infection (6). *Severe sepsis* was defined as sepsis plus evidence of organ dysfunction. *Septic shock* was sepsis with hypotension unresponsive to fluid loading. These definitions lack accuracy. The SIRS criteria are nonspecific. Worse, they miss a significant number of patients that go on to manifest sepsis (7). The definitions of sepsis have now been changed to reflect a dysregulated response to infection, manifest by organ dysfunction measured as a 2 point or greater increase in the Sequential [sepsis-related] Organ Failure Assessment (SOFA) score (Table) (3). Efforts to distinguish types of sepsis (e.g., by anatomic site or organism) in ways that impact prognosis and therapies are ongoing.

Table: Broad diagnostic criteria for sepsis (Modified from references 3 and 4):

Infection:	documented or suspected
General variables:	T > 38.3 or < 36°C, HR > 90/min, ↑ RR, encephalopathy, edema or positive fluid balance, hyperglycemia

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Inflammatory variables:	WBC > 12,000 or < 4000/mcL, > 10% immature forms, ↑ C-reactive protein, procalcitonin
Hemodynamic variables:	SBP < 90, MAP < 70 mmHg or a decrease > 40 mmHg, SvO_2 > 70%, Cardiac Index > 3.5 L/min
Organ dysfunction variables:	hypoxemia, oliguria, ↑ creatinine, coagulopathy, ileus, ↓ platelet count, ↑ bilirubin
Tissue perfusion variables:	↑ lactate, ↓ capillary refill, mottling
Sepsis-related Organ Failure Assessment (SOFA) score:	PaO_2/FiO_2, Glasgow coma score, mean arterial pressure or administration of vasopressors required, bilirubin, platelet count, creatinine or urine output as markers of end-organ dysfunction
[Sepsis-related] SOFA (qSOFA)	Respiratory rate ≥22/min, altered mentation, systolic blood pressure ≤100 mmHg

Central to sepsis is inflammation. Systemic responses to infection range from elevated white blood cell counts to fever, hyperglycemia, and changes in cellular mediators. Inflammation has been the main focus of sepsis research for over 40 years. Patients don't usually die from inflammation, however; they die from organ dysfunction.

Organ dysfunction in sepsis takes many forms and affects every organ system. Renal (e.g., acute kidney injury), vascular (vasoplegic shock) and respiratory failure (acute lung injury/acute respiratory distress syndrome) are well recognized sequelae of severe sepsis, but endocrine (hyperglycemia), neurologic (encephalopathy), and gastrointestinal (ileus) dysfunctions often presage severe sepsis and are signals to intervene before the syndrome worsens.

The cardiovascular effects of sepsis most directly affect anesthetic management, but clinicians should be aware of other risks, including electrolyte abnormalities, aspiration risk, gas exchange abnormalities, and increased sensitivity to anesthetic agents. Cardiovascular changes include a loss of arterial tone (vasoplegia), capillary leak syndrome, venous pooling of blood, and ventricular dysfunction. Typically, a patient presenting with sepsis and hypotension will respond favorably to fluid resuscitation, and guidelines recommend volume challenges on the order of 30 mL/kg crystalloid (8). However, the detrimental effects of tissue edema, especially on oxygenation, may limit resuscitation. A subset of septic patients demonstrates right heart dysfunction, and aggressive volume resuscitation in these patients might worsen their shock rather than improve it. For these reasons, a rational approach to volume resuscitation combines early volume resuscitation with enhanced monitoring to define endpoints of volume administration. Such monitoring ideally includes dynamic measures of fluid responsiveness (e.g., pulse pressure variation, hemodynamic response to straight leg raise). Many patients in septic shock will require vasopressors. Data such as lactate clearance, pulse pressure variation while on positive pressure ventilation, and central or serial mixed venous oxygen saturation measurement can help determine response to volume and define clinical criteria for vasoconstrictor administration to improve an insufficient circulation. Inotropic support is only recommended in situations where impaired contractility is a suspected contributor to shock, and echocardiographic evidence is the most helpful approach to making this distinction. Recommended vasopressors include norepinephrine (first line), epinephrine (secondary) and vasopressin (adjunct). In any special circumstance (e.g., high suspicion of right ventricular failure, nonresponse to therapy), additional monitoring, such as a pulmonary artery catheter or echocardiogram, may be helpful. Finally, in the setting of shock refractory to even vasopressors, empiric steroid administration (e.g., hydrocortisone, 50 mg IV every 6 hours) is indicated. In this circumstance, clinicians may elect to sample plasma for cortisol levels. Data do not support steroids for patients in sepsis without shock (9).

Another characteristic of the pathogenesis of sepsis is energy failure. Defects at the level of the mitochondria alter cells' ability to generate energy. These failures can predict mortality (10). Patients with ineffective aerobic respiration tend to be the ones who die. Conversely, the early sepsis response is associated with hypermetabolism.

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Although mixed venous or central venous oxygen saturation monitoring may help determine patients for whom metabolism outstrips oxygen supply, energy failure may raise central venous oxygen saturations through decreased consumption. Historically, evidence supported an "oxygen debt" of early sepsis, corrected with red cells and inotropes (11). A curve of supply-dependent oxygen consumption suggested many patients required enhanced oxygen delivery. This finding has not been replicated, and many now believe it to be an artifact of invasive hemodynamic measurements. Repeat studies using calorimetry do not replicate the supply dependency (12). Providing "supra-normal" levels of oxygen delivery above those needed to raise central venous saturation and indices of organ perfusion is no longer recommended (8).

Histologically, a characteristic of the septic response is apoptosis, or programmed cell death. Most commonly, this is expressed in lymphocytes (13). Why immune cells would selectively die off in the throes of systemic infection is a mystery. Immune dysfunction is a classic finding in sepsis, and many septic patients suffer secondary infections. Organisms like vancomycin-resistant *Enterococcus* species, *Acinetobacter baumannii*, and *Cytomegalovirus* (14, 15) afflict septic patients more than healthy ones, likely because of immune dysfunction. This, combined with coagulation abnormalities (inflammation and coagulation are linked) and elevated risk of thromboembolic disease, mean that septic patients are at heightened risk of complications.

Over time, and with worsening injury, patient physiology changes. Endocrine exhaustion manifests as a loss of hormonal pulsatility and decreased levels of secretagogues and end hormones (16). Vital signs and physiologic rhythms stabilize (an unhealthy response), the results of defective autonomic signaling. Delirium may transition to functional cognitive deficits. Survivors of this syndrome have poor functional outcomes, and many do not survive.

Why do patients become septic?

Infection drives the septic response, yet many systemic changes during sepsis are common to noninfectious causes of inflammatory responses. Components of SIRS are conserved across animal species, and in multiple animal models these components protect an organism from ongoing damage and allow it to heal. A complicated network of signals and activities that correct derangements and repair damage results in changes to the inflammation, coagulation, metabolism, immunologic function, neurologic function, and tissue growth systems. The response is fundamentally adaptive. In a case of sepsis, these responses are appropriate, but are dysregulated, and may be detrimental. Historically, many patients would not survive the initial insults of the sepsis syndrome. With intensive care, patients survive these previously fatal insults, but suffer the natural history of prolonged sepsis physiology. Modern critically ill patients are unique and their illness has progressed to physiology that would never be seen in "the wild." In later phases (i.e., chronic critical illness) dysfunction becomes prominent. It is in these later phases when many patients die.

Sepsis management: key interventions

The Surviving Sepsis Campaign, first launched in 2002, details the evidence in support of sepsis therapy, translating the large body of sepsis literature into guidelines (8). Timely diagnosis, antibiotic therapy and goal-directed fluid resuscitation are key components of sepsis management. Several of the recommendations directly influence management in the operating room. The anesthesia care team contributes to care by managing shock resuscitation. This is facilitated with physiologic goals such as mixed-venous oxygen saturation and lactate clearance. They confirm diagnoses by drawing blood, urine and sputum cultures. Finally, by facilitating the timely administration of antibiotics (ideally after cultures are drawn, but as quickly as possible), the team can have a positive impact on patient mortality. Anesthesiology-based expertise in monitoring and procedures can facilitate timely and effective care. Central venous and arterial access helps with resuscitation and management. Support of failing organs is ideally suited to anesthesiologists and should be viewed as akin to management in the intensive care unit. With surgical sepsis, the locale of the intervention (intensive care unit versus operating room) should make no difference in the goals of resuscitation and antibiotic therapy. Facilitating source control through timely surgical intervention, however, can make a major difference in outcomes.

What sort of a difference can these interventions have? Absolute mortality from sepsis decreased more than 6% as compliance with Surviving Sepsis Campaign recommendation bundles increased (17). Curiously, compliance in this

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study increased from 18.4 to 36.1%, suggesting that the recommendations are neither easily nor frequently adopted. Both evidence and rationale support timely intervention. Anesthesiologists can and should strive to facilitate cultures, antibiotics and resuscitation for septic and suspected septic patients in their care.

An evolving understanding

Any improvements have to be viewed in light of limited progress and continuing mortality. What has been accomplished in sepsis research in the last 40 years? Resuscitation and antibiotics reduce morbidity and mortality. Indirect evidence suggests that exposure to a septic source over time increases the collateral physiologic damage and overall organ dysfunction burden. However, the "goals" of resuscitation and timing of antibiotic therapy remain controversial. Adequate resuscitation underlies early sepsis care, but clinicians have crude and uncertain tools to guarantee that resuscitation is adequate. A fixed goal such as a mixed venous saturation greater than 60% may not be as important as attention to other clinical signs in an unstable patient. Recent, well-designed randomized-controlled trials (18, 19, 20) suggest that goal-directed resuscitation algorithms may not be as critical to sepsis care as previously thought. Aggressive early antibiotic administration can lead to improper use of antibiotics when a diagnosis of sepsis is unclear, as might occur with an exacerbation of congestive heart failure that is confused with pneumonia.

Previous investigations document multiple failed therapies. Many of these studies involved inflammatory mediators following the theory that the inflammatory response to infection leads to organ dysfunction in sepsis. A long list of failed therapies, including anti-TNF alpha, ibuprofen, anti-IL-2, branch-chain amino acids and, most famously, drotrecogin alfa (activated protein C), suggests that not only is a single magic bullet for sepsis unlikely, but that the model for therapeutic intervention may be wrong. Although inflammation is a key component of sepsis, immune suppression, altered endocrine activity and decreased autonomic signaling appear to influence disease progression. Since the septic patient who dies often does so in a state of chronic critical illness with multiorgan failure, a new model of disease and therapy is necessary. Sepsis patients manifest neuroendocrine exhaustion, immune dysfunction and energy failure. These findings may provide an opportunity for intervention. In the future, therapies targeting the central nervous system, hormones, or inflammatory cell apoptosis may improve outcomes more than therapies targeting inflammation.

An administrative issue

Given the substantial impact that sepsis has on morbidity and mortality, efforts should continue in the fields of aggressive management and research. The successes of the *Surviving Sepsis Campaign* argue that recommendation bundles directed at evidence-based and standardized care make a substantial difference. There is, however, a caveat. The failures in sepsis management, documented by the long list of failed anti-inflammatory therapies, suggest that simple, single solutions will not be enough to change the course of disease for many patients. Controversy continues around resuscitation and antibiotic therapy. Many adjunctive therapies, such as glucocorticoids, tight glycemic control and pulmonary artery catheter-directed resuscitation have not fulfilled the promise they had 10 years ago. Are we too easily tempted to throw ineffective therapies at a largely insoluble problem? Clinicians may be willing to embrace an uncertain therapy just to be able to do something. They want to be optimistic.

At an administrative level, problems like sepsis are an opportunity for regulation, standardization and general control. Pundits argue eloquently that care variability is the problem and that standardization lets more patients get better care. Guidelines that are useful tools to help clinicians manage complex problems also restrict their ability to respond uniquely to special circumstances. The more recent studies of protocol-driven sepsis care cast doubt on the effectiveness of this approach (18, 19, 20). In the case of sepsis, standardized care can improve outcomes, but should not be taken for granted. The failures in sepsis tell a story about a quest for an easy solution that sometimes misses the important elements altogether. Re-thinking the problem might reveal elusive opportunities.

Conclusions

Sepsis has multiple etiologies and manifestations. Although commonly described in terms of its inflammatory characteristics, effects of sepsis are broad reaching, involving immune, neurologic, endocrine and metabolic

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changes. Moreover, sepsis is a critical moment in a patient's overall hospital trajectory. Unchecked sepsis, inadequate source control and severe secondary injuries put a patient at risk for transition to a chronic critical illness state and a worsening of morbidity and mortality. As anesthesia providers, we must be prepared to deliver the best care to patients with sepsis, participate in the discussions about its causes and treatments, investigate new ideas, and generate and promote measures that can improve outcomes. Our unique skills in critical care and resuscitation make us ideally suited to these tasks. We understand as well as any physician the complex nature of medical therapies, the assets and liabilities of guidelines, and the need to think critically about them during care and consultation. We can continue to care for septic patients with fluids, vasopressors, inotropes, cultures, advanced monitoring and antibiotic therapy while supporting organ function. As clinical experts in neurosciences, anesthesiologists have an opportunity to investigate new means of treating sepsis. Finally, as experts in safety and guidelines management, anesthesiologists should offer valuable expertise to future guidelines efforts.

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Pediatric sedation: methods to enhance safety

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Introduction

Pediatric sedation has grown exponentially in response to the demand for safe, efficient and effective sedation for a range of medical and surgical procedures outside of the operating room. This growth has involved a broad range of sedatives that were administered in both traditional and non-traditional settings such as hospitals as well as dental offices, gastrointestinal clinics and radiation units, by anesthesiologists as well as non-anesthesiologists including intensive care and emergency physicians to children who presented with a host of medical conditions and who were monitored to varying degrees. To assess the risk of serious adverse outcomes in these units, data from several extensive databases and case reports together with data from randomized studies have painted a clear impression of the very limited risk for sedation provided by skilled sedationists.[38,39]1,2 When qualified and trained providers delivered sedation, the frequency of serious adverse events was small and non-life-threatening.[8]3 However, serious events have occurred during sedation (as in the well-known cases of Michael Jackson and Joan Rivers) that for the individual has been irreversibly devastating. Eighty percent of serious adverse events during sedation are respiratory in origin.[4] Respiratory events in closed claim reports of sedation in patients of all ages occurred twice as frequently outside the operating room (O.R.) as in the O.R. with inadequate oxygenation/ventilation occurring 7 times more frequently outside the O.R. than inside and twice as frequent in children <16 years outside the O.R. (11%) versus inside (6%).[5] In the gastroenterology unit, data from the pediatric sedation research consortium revealed an overall frequency of 4.8% adverse events, with no deaths or cardiac arrests but persistent desaturation (1.5%), airway obstruction (1%) and laryngospasm (0.6%) in >12,000 procedures.[6] Serious adverse events occurred in 15% of infants, 8% of children and 4% of older children.[6] In the emergency department, a meta-analysis of studies with ketamine sedation highlighted age (<2 yr or > 13yr), large doses of ketamine and co-administration of anticholinergics or benzodiazepines as factors that increased the risk of acute airway/respiratory events.[7] In the dental office, sedation in children 2-5 years was associated with the greatest risk of death, with spotty monitoring a contributing factor.[8,9] Such events should not occur to these extents and I hope you hear in this lecture will help you avoid experiencing similar adverse events in your practices.

In an effort to standardize the quality of sedation delivered and optimize outcomes, protocols and guidelines have been developed under the aegis of several national organizations. This lecture addresses a number of controversial issues that relate to pediatric sedation including:

1. What level of sedation is required?
2. Who can provide sedation?
3. Which skills are required to safely deliver sedation?
4. Infrastructure
5. Preoperative assessment of the children
6. Monitoring
7. Which sedatives?

What level of sedation is required?

Sedation is a continuum from wakefulness to general anesthesia. Although discrete levels of sedation have been carefully defined, children who are sedated may drift from one level of sedation to another and back, depending on the doses of sedatives administered, age of the subject, pre-existing medical conditions and over time. As a result, the provider must be prepared to manage a level of sedation deeper than the target level including intervening for cardiopulmonary resuscitation and potential serious adverse events that may ensue. The varied terminology for these levels of sedation has been revised recently with the following result:[10]

Minimal sedation: anxiolytics permit the child to respond to verbal commands; cardiorespiratory responses are maintained.

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Moderate sedation: sedatives permit the child to respond to verbal commands or to light, tactile stimulation; cardiorespiratory responses are maintained.
Deep sedation: consciousness is not maintained; responds to painful or repeated verbal stimuli; spontaneous respiration may be inadequate and require support, the airway may become obstructed and reflexes attenuated; cardiovascular responses may be maintained or require minimal support.
General anesthesia: an unconscious state in which painful stimuli fail to arouse the child; respiration may be spontaneous but diminished in frequency or depth, although apnea is common; cardiovascular responses may require support.

In general children require deep sedation or general anesthesia because of their inability to co-operate, lack of understanding of the nature of the investigation/procedure and fear. The term monitored anesthetic care or MAC is differentiated from "moderate sedation" as the former connotes a full preanesthetic assessment including a full assessment of the patients medical problems, our immediate availability to intervene to support and/or manage a failing airway and the possibility of administering a general anesthetic should the need arise.* The level of sedation required depends on the requirements for the intended procedure and the level of pain associated with it (eg., an MRI requires sedation to prevent movement but does not require pain control whereas a bone marrow biopsy requires sedation and pain control but movement is tolerated), age of the child, level of cooperation and co-existing diseases.

Who can provide sedation?

Sedation has been administered by anesthesiologists, intensivists, emergency medicine doctors and pediatricians. Evidence suggests that the frequency of serious adverse events with sedation by all of these providers is similar.[3] Healthcare providers (both physicians and nurses) who may provide sedation to children should maintain pediatric advanced life support credentials with skills in recognizing compromised respiration and circulation; in intervening to re-establish a patent airway and stable circulation using facemask/positive pressure ventilation as well as advanced airway skills as needed for greater depths of sedation. In the latter case, having providers with the skills to insert an LMA or intubate the trachea is preferred, although an airway expert (anesthesiologist) in the immediate vicinity may suffice. Maintaining skills for sedation providers may be challenging as rare events (eg., laryngospasm) do not permit ongoing exposure to maintain those skills, resulting in loss of skills. Sedation providers may rotate through the operating room to maintain their skill levels in airway management; in addition, simulated scenarios may be helpful.[11] In general, the minimal level of training to establish a skill set for a particular maneuver (eg., laryngoscopy) ranges from 50-100 successful attempts depending on the study design. [12,13] However, there are a number of tricks to extricating the obstructed airway that are not widely appreciated (since most instrument the airway with some device in pediatric anesthesia today) and these will be reviewed and emphasized in this lecture).

Which skills are required to safely deliver sedation?

Delivery of a specific level of sedation requires the skills to manage a deeper level of sedation than anticipated since patients commonly drift from lighter to deeper levels of sedation than the targeted level. The primary concerns that may lead to serious adverse events from sedation relate to airway issues: apnea, partial airway obstruction, laryngospasm and hypoxia. These occur with greater frequency with deeper levels of sedation (deep sedation) and ASA P/S 2 and 4 children.[14] The spectrum of skills required to identify abnormalities in respiration include basic observation of chest wall movement (is the child breathing? Is the chest wall moving? Is there evidence of upper airway obstruction-supraclavicular, suprasternal retractions?), vigilance of monitors (what is the oxygen saturation and capnogram?) and auditory cues of airway obstruction and that an alarm has sounded (desaturation pitch from the oximeter).

Adequate oxygenation in the child with normal cardiorespiratory function can usually be maintained by administering an exogenous source of oxygen (via nasal prongs or a facemask) providing the child is breathing.

Adequate ventilation on the other hand, may be more challenging to diagnose as no exogenous source of gas can maintain ventilation: for the most part, at all depths of sedation short of general

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***** http://www.asahq.org/quality-and-practice-management/standards-guidelines-and-related-resources/distinguishing-monitored-anesthesia-care-from-moderate-sedation-analgesia

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anesthesia, spontaneous respiration with or without airway support, is required.

Partial airway obstruction may be manifested by a degree of oxygen desaturation, a blunted capnogram and/or paradoxical chest wall movement. If the oxygen saturation is maintained >92% (depending on the severity of existing pulmonary disease), it is unlikely that oxygenation is a serious concern. However, when the oxygen saturation decreases to <90%, an intervention is required as the rate of desaturation may accelerate rapidly particularly if the airway has become completely obstructed. Several maneuvers may be applied to relieve the airway obstruction including insertion of an oropharyngeal airway, a nasal pharyngeal airway, repositioning the head/neck, extension of the neck and a jaw thrust maneuver. This practitioner first focuses primarily on repositioning the head/neck and the application of the jaw thrust maneuver to relieve airway obstruction. Proper application of the jaw thrust maneuver is poorly taught because most apply the jaw thrust at the angle of the jaw rather than the top of the condyle or at the condylar process of the ascending ramus of the mandible.[15] The latter maneuver not only relieves supraglottic airway obstruction by rotating the temporomandibular joint, but is also a painful stimulus that causes the child to open their vocal cords and vocalize (ie., fright and flight maneuver) thereby breaking incipient laryngospasm).

Infrastructure

Sedation requires the presence of a source of oxygen, suction and scavenging for nitrous oxide or other inhaled agents if present. In addition to these minimum requirements, an acronym known as SOAPME highlights the equipment that should be immediately available for all sedation cases: [16]
S is for size of appropriate suction catheters and equipment (including a Yankauer)
O is for oxygen source including flowmeter and control valve
A is for appropriate airway (oral or nasal) including facemask, oral and nasopharyngeal airways, LMA, laryngoscope blades and tracheal tubes.
P is for pharmacy to ensure an adequate supply of sedative/analgesic drugs and resuscitation drugs.
M is for monitors including age appropriate oximeter and blood pressure cuff, electrocardiogram, end-tidal pCO_2 and precordial stethoscope. Temperature monitoring should be available.
E is for special equipment/drugs (eg., defibrillator)

A proper preoperative record, sedation chart (paper or electronic) and postoperative recovery form should be available. Discharge criteria should be identical to standard recovery room discharge criteria.

Often overlooked, is access to a resuscitation room in the vicinity of the sedation site. This is of particular importance in the MRI radiology suite, where a child who arrests must be extricated from the vicinity of the magnet and resuscitated in a room in which full resuscitation equipment including defibrillator is immediately available. Most areas of the hospital including most sedation locations have resuscitation equipment immediately available, and it is prudent to familiarize yourself with their locations.

Preoperative assessment of the children

Children should be prepared for sedation/anesthesia in the usual manner as per ASA guidelines. Most children being ASA P/S 1 or 2 do not require specific preoperative testing (other than pregnancy testing in females who are menstruating). Children who are ASA P/S 3 or 4 may require preoperative testing depending on pre-existing diseases (eg., ECHO for a child with congenital heart disease). Children with severe OSA and ex-premature infants <60 weeks post-conception age may require careful choice of medications (such as the dose of opioids if nocturnal desaturation was reported in the child with OSA) or a period of prolonged observation or elective admission postoperatively until they are no longer at risk for postoperative adverse events. Children with obesity, Down syndrome and myopathies (including MH) must be carefully evaluated for their suitability to undergo sedation in a remote site and the need for admission as the frequency of severe adverse events, particularly airway events, in these children is substantive.[17,18]

Managing children with malformations of the airway in remote sites is discouraged. Most difficult intubation equipment is not MRI compatible and therefore should not be brought into the MRI unit or other locations that have limited space as it may pose a challenge for providers/sedationists, particularly in an emergent situation. When faced with a child with a difficult airway for sedation, it seems imminently sensible to secure the airway where assistance and equipment are both available. This is usually the operating room. Once the airway is

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secured, the child may be transported to the site where the sedation/procedure is performed and then returned for tracheal extubation. Each case should be evaluated on an individual basis, in concert with the team of care providers and family to ensure a satisfactory outcome is achieved.

All children who present for elective sedation should be fasted based on standard fasting guidelines. In the case of emergent cases (eg., sedation in the ED) there is no known time interval between eating and the accident that would reduce the risk of regurgitation and aspiration to elective levels. Such children may best be managed by tracheal intubation to reduce the risk of pulmonary aspiration. Interestingly, fasting data from two large sedation databases demonstrated that the fasting interval was not a major determinant of the risk of regurgitation and aspiration.[19,20] This may be attributed to many reasons but for now, we abide by standard fasting intervals whenever possible.

A complete history and physical examination must be documented, including ongoing medical conditions, past anesthetic difficulties, documented allergies to medications (and latex), and a family history of untoward anesthetic complications must be assessed and documented. Physical examination should focus on the key elements for anesthesia including the airway, respiratory and cardiovascular systems. Since most airways remain non-instrumented for the sedation, care must be taken to ensure that with proper positioning a patent airway is possible. Informed consent (written or verbal according to local practice) that outlines the risks, benefits and alternatives to the parents, emancipated minor or consenting teenager should be obtained before commencing the sedation the sedation.

Monitoring

Essential monitors for all level of sedation/anesthesia include electrocardiogram, blood pressure, pulse oximeter, capnometer and temperature. Supplemental monitors may include a depth of anesthesia monitor and a nerve stimulator, the latter if muscle relaxants are administered.

Each monitor contributes a discrete piece of information that may help to appreciate the overall state of the subject. An electrocardiogram is essential to not only document the heart rate, but to also identify arrhythmias should they occur. Failure to apply an electrocardiogram could delay the diagnosis and treatment of a serious arrhythmia. Pulse oximeters display the oxygen saturation and the heart rate, but cannot identify rhythm disturbances. Some also use pulse oximetry as a surrogate for ventilation, although the presence of supplemental oxygen maintains the saturation even in the presence of hypoventilation and apnea,[21] rendering the oximeter a second-line monitor of ventilation. Capnography, a display of the pCO_2 waveform, is a true monitor of ventilation. Indeed, evidence indicates that capnography detects the early onset of apnea (4.4 min before hypoxia)[22] and reduces the frequency of desaturation by almost 50%.[23,24] Ideally, we would prefer to monitor decreases in tidal volume during over sedation as an early warning sign of impending apnea and possibly hypoxemia, although few monitors currently provide such metrics. Two new monitors are under development that may provide early warning signs of such problems.[25,26]

Which sedatives?

New sedatives and anesthetics have completely written the prescription for sedation in children over the past three decades.[27] Early sedatives primarily used by nursing and non-anesthesiologists included midazolam, fentanyl, pentobarbital and chloral hydrate. In children 0.1 mg/kg midazolam has an onset of 1 minute and a maximum effect by 3-5 minutes. It is metabolized by CPY3A4 with a duration of action of 30-60 minutes. It may be infused for prolonged sedation but its context sensitive half-life increases with the duration of the infusion. One important advantage of midazolam is that it may be antagonized using flumazenil, 20 mcg/kg IV. Fentanyl is a short-acting opioid that provides mild sedation and analgesia, but is a powerful respiratory depressant. Like midazolam, it too can be antagonized with naloxone (20 mcg/kg). Pentobarbital and chloral hydrate as infrequently administered by anesthesiologists, but they have provided adequate sedation in infants and young children. We provide dental sedation in our dental clinic for single tooth and molar extractions in cognitively impaired children. We compared oral and intranasal midazolam, intranasal midazolam combined with oral transmucosal fentanyl citrate and intranasal midazolam combined with intranasal sufentanil.[28] All four sedatives were equally effective, yielding a 73% success rate. Ketamine is widely used for sedation in the emergency department. It is an effective anesthetic/sedative/analgesic with a small frequency of serious adverse events,[29] but is associated with increased postoperative nausea and vomiting. A very different profile of drugs has been used to sedate children in dental

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offices for molar extractions and other minor dental surgery including intranasal dexmedetomidine, sufentanil or midazolam, as well as oral transmucosal fentanyl citrate.[30,31]

Serious adverse events have been associated with the administration of multiple sedative concurrently, nitrous oxide and younger children.[32] Ketamine has been used extensively for sedation in the emergency department, although it has been associated with laryngospasm.[33]

The newer agents propofol and dexmedetomidine have supplanted many of these older medications for sedation. In the case of propofol, it has a rapid onset of action, rapid offset and large clearance, greater than liver blood flow. It has a long terminal elimination (3-9 hours) which may lead to a slower emergence after a prolonged infusion (increased context-sensitive half-life with decreasing age).[34] Propofol doses (1-4 mg/kg) IV induce anesthesia and may be followed with an infusion. The rate of the infusion in children is 150-300 mcg/kg/min (9-18 mg/kg/h) for most procedures. For MRIs, children 1-8 years of age usually require 250-300 mcg/kg/min (after a mask sevoflurane induction) to remain still; smaller doses will result in movement. The infusion requirements are greater in younger infants and those who are cognitively impaired; in some cases, the rate may have to be increased temporarily to 400 mcg/kg/min to prevent movement. To ensure success in these scans, a shoulder roll to extend the neck is mandatory lest upper airway obstruction occurs.

When propofol is injected into a small vein, it often causes intense pain. This can be ameliorated by administration of either 70% nitrous oxide by mask or lidocaine 1 mg/kg IV with a Bier block.[35,36] Propofol may cause transient apnea after a bolus dose particular if co-administered with other sedatives and reduces the dimensions of the upper airway similar to dexmedetomidine in children with OSA.[37] Propofol infusion syndrome is a rare complication that has not been reported in children undergoing procedural sedation so it is not a substantive risk. The sedative effects of propofol cannot be antagonized.

Dexmedetomidine, an alpha$_2$ agonist agent with much greater affinity for receptors than clonidine, is infrequently used for sedation in children because it is quite costly compared with other drugs and has a prolonged half-life. A loading doses of 1 mcg/kg IV dexmedetomidine following by an infusion of 0.7 mcg/kg/h may be used to sedate children, although it is infrequently used as the sole agent as children do not remain still with this dose. Unlike propofol, dexmedetomidine does not cause pain when administered intravenously. Either larger doses of dexmedetomidine such as 2-3 mcg/kg/h followed by an infusion of 1-2 mcg/kg/h[38] or the addition of an adjunct agent such as midazolam 0.1 mg/kg to the usual dose of dexmedetomidine must be given to prevent movement during sedation for MRI.[39] A distinguishing feature of dexmedetomidine is that it neither depresses respiration nor reduces the dimensions of the upper airway. Dexmedetomidine may cause hypotension and bradycardia (frequency 3%), which are more pronounced in infants and younger children.[40] It is important to avoid anticholinergic agents in the presence of dexmedetomidine-associated bradycardia as paroxysmal and severe hypertension may occur. Ephedrine is the most appropriate agent to treat bradycardia and hypotension. Early recovery after dexmedetomidine is predictably slower than that after a comparable dose of propofol for MRI by virtue of the former drug's context-sensitive half-time, although hospital discharge is often the same due to institutional barriers.[39,41]

Novel sedatives continue to evolve. Each offers novel characteristics that may be useful in specific situations but the most exciting breakthrough in my opinion is in opioid drug development with the synthesis of compounds capable of activating G-protein-coupled receptors (nociceptive control) while sparing activating β-arrestin2 receptors (which mediate opioid side effects including respiratory depression).[42-44] These new analgesics may enormously improvement in opioid safety especially during sedation.

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Ambulatory Anesthesia and Cancer Surgery

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Introduction

The world of ambulatory anesthesiology is rapidly evolving and expanding to incorporate more non-traditional ambulatory surgical procedures. This Refresher Course will provide information on the myriad of emerging oncologic outpatient surgery procedures. It will address special considerations and offer strategies for anesthesiologists to provide safe care focusing on improving short- and long-term patient outcomes. It will also provide information to help develop clinical pathways and enhanced recovery after surgery (ERAS) protocols that were successfully implemented at the Josie Robertson Cancer Center, a free-standing ambulatory cancer surgery center. We will discuss specific pain management strategies and ERAS protocols aimed at shortening length-of-stay (LOS) and improving other important patient outcomes. Finally, it will review clinical evidence on the effects of anesthesia on tumor progression and oncology outcomes and its application to ambulatory anesthesia.

Cancer and Ambulatory Surgery

In 2018, it is estimated that approximately 1,735,350 new cases of cancer will be diagnosed and there will be about 609,640 cancer-related deaths in the U.S.[1]. Although in recent years the overall cancer death rate has dropped worldwide due to major global advances in prevention, diagnosis, and treatment, cancer continues to rank high among causes of major morbidity and mortality. The American Cancer Society reports cancer as the second leading cause of death around the globe, accounting for nearly 22% of all deaths[1]. The prevalence increases with age, with 87% of all cancers in the U.S. diagnosed in people 50+ years of age and with the aging population, it is projected that by 2030 there will be 21.7 million new cancer cases globally and 13 million cancer-related deaths[2]. Since surgery is one of the primary treatments for cancer, clinicians practicing in ambulatory surgery will likely increasingly encounter patients for cancer procedures. A cancer diagnosis will compound on the already established challenges of patient selection and geriatric management. Nevertheless, the clear advances in ambulatory surgery over the past four decades resulting in physical, psychological, and economic benefits without compromising the quality of care are incentivizing the growth of ambulatory surgery oncology procedures.

Most recent U.S. national statistics reported that in 2010 there were 28.6 million ambulatory surgery visits, where 48.3 million surgical and non-surgical procedures were performed. Of these, 53% were in-hospital ambulatory surgeries and 47% done in an ambulatory surgery center (ASC) with the most common procedures performed on the digestive system, eye, and musculoskeletal system[3, 4]. As evidenced by the growing market of ASCs (currently numbered at 5460), ambulatory surgery has increased rapidly. This is mainly due to medical and technological advancements in anesthesia and analgesia for pain relief, and a preference for minimally invasive and non-invasive procedures. With this new landscape surgeons will perform more cancer-related ambulatory surgery procedures in these outpatient settings. The expected increase in these procedures parallels the increase in diagnosis of various cancers and the surge of minimally invasive options for oncology surgery. Breast, thyroid, and genital cancers are some of the most prevalent cancers that are currently treated with minimally invasive surgery.

In 2018, it is estimated that there will be approximately 268,670 new cases of invasive breast cancer diagnosed in the U.S[1]. From 2005 to 2013 the overall mastectomy rate increased by 21%[5]. Increasing rates of mastectomy, breast reconstruction, and bilateral mastectomies in women with early stage breast cancer were recently reported in a review of trends in breast surgery of over 1.2 million patients from a 14-year period[6]. This report found that 57% of women with early stage disease who underwent bilateral mastectomies also underwent reconstructive procedures in 2011, compared to only 37% in 1998. Additionally, there was an increase from 5% to 20% incidence in women with non-metastatic disease who undergo contralateral prophylactic mastectomy (CPM). Moreover, in 1986 all mastectomies were done as inpatient procedures, but by 1995 89% were done in as inpatient, and by 2012, only 50% were done as inpatient procedures[5].

Gynecological cancer is the second most prevalent cancer among women: in 2018, approximately 110,070 new uterine, cervix, corpus, ovary and other genital cancers are expected to be diagnosed[1]. Surgery, consisting of hysterectomy (often including bilateral salpingo-oophorectomy) without chemotherapy or radiation is used to treat at least 69% of patients with stage I and II disease[7]. Moore et. al., reported on the increase in ambulatory surgeries for hysterectomy and oophorectomy (alone or in combination) from 2005 to 2013[8]. During this 9-year period,

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hysterectomy alone had a 414% increase while oophorectomy had a 35% increase, corresponding to a 22.7% and 3.8% annual increase respectively. Several clinical studies have reported on the feasibility and safety of same-day discharge for such procedures with low re-admission rates. Older age, preop lung disease, and later surgical end-time are risk factors for prolonged stay. Identifying these factors preoperatively could facilitate early discharge[9-12].

Thyroid cancer has been continually increasing worldwide in the past few decades and in the U.S., it is the most rapidly increasing cancer. It is expected that about 56,430 new cases of endocrine cancer, including thyroid, will be diagnosed in 2018[1]. Most thyroid cancers are highly curable and the first choice of treatment is surgery[13]. Unlike other cancers the trend toward outpatient surgery has been slower, primarily because of the possibility of an expanding hematoma or potentially life-threatening hypocalcemia. A recent study illustrated the postoperative outcomes of total thyroidectomy performed in the inpatient vs. outpatient setting in 40,025 patients[14]. The total 30-day postoperative complication rate was lower for outpatients (2.72%) compared to inpatients (5.02%). Reintubation, readmission, reoperation, and overall complication rates were significantly higher in patients who underwent inpatient total thyroidectomy as compared to outpatients. Patients who underwent outpatient procedures had significantly lower odds of complications.

In 2014, 71% of male genital invasive surgical visits (testicular, prostate, and penile procedures) were completed on an ambulatory basis compared to 64% in 2012[3, 15]. This increase did not include non-traditional minimally invasive prostatectomy procedures, which are now more common. Robotically-assisted radical prostatectomy (RALP) is currently the predominant approach for prostate cancer surgery and lends itself to being managed on a short stay pathway[16]. Musser et al. illustrated an ambulatory extended recovery program with an analysis of 1,571 patients undergoing minimally invasive prostatectomy that can successfully transition most patients to a 1-night hospital stay without resulting in an increased rate of readmission[17]. Similarly, Berger et al. found that outpatient RALP resulted in higher patient satisfaction and functional outcomes when compared to inpatient procedures, and highlighted the importance of preoperative counseling for success[18].

These non-traditional outpatient oncology procedures along with the standard outpatient diagnostic biopsies have greatly increased the need for ambulatory anesthesiologists to better understand onco-anesthesia and identify optimum anesthesia clinical pathways and protocols.

Clinical Pathways and Enhanced Recovery Protocols for Ambulatory Surgery

Enhanced Recovery After Surgery (ERAS) or Enhanced Recovery Pathways (ERP) is a surgical program aimed to increase quality of patient care and satisfaction by integrating evidence-based protocols to help standardize care, decrease health care expenditures, hospital LOS, and morbidity associated with surgical stress[19, 20]. The physiological chain reaction brought on by direct surgical injury results in systemic release of cytokines and hormones as well as the local release of inflammatory mediators that contribute to the 'stress response to surgery'[21]. If left untreated the patient is catabolic, immobile, weak, and has gut dysfunction which compounds the injury, delays healing, and may lead to complications[22-24]. The overall goal of the ERAS pathways is accelerating recovery by decreasing the body's physical, physiological, and psychological response to surgical stress.

To achieve this goal, surgeons strive to minimize the primary surgical injury and reduce blood loss by using minimally invasive techniques. Anesthesiologists optimize analgesia and individualize fluid therapy to maintain physiological homeostasis. Proper fluid therapy helps maintain cellular perfusion, reduce extracellular fluid flux, and avoid salt and water overload which leads to gut ileus. Early gut function and enteral feedings help reduce insulin resistance and restore homeostasis. Postoperatively early mobilization will reduce complications, such as atelectasis, chest infection, DVT, and stimulate muscle function to maintain strength[25]. There are several important perioperative components of ERAS. Preoperatively: preadmission patient counseling and education, fluid and carbohydrate loading, unprolonged fasting, no/selective bowel prep, antibiotic prophylaxis, and thromboprophylaxis should be included. Intraoperatively: ERAS components should comprise short-acting anesthetic agents, appropriate regional anesthesia/analgesia, and maintenance of normothermia (body warmer/warm intravenous fluids). Postoperatively: appropriate regional anesthesia/analgesia, non-opioid oral analgesia/NSAIDs, no nasogastric tubes, PONV, and early oral nutrition and mobilization should be included[20, 23].

Most of the ERAS programs in the literature relate to colorectal surgery. These studies suggest that the implementation of the ERAS programs for colorectal surgery reduces LOS by more than 1 day and total complication rates in patients undergoing major surgery by 12%[26]. In mastectomy patients at a single 23-h stay surgery center, a recent retrospective study found that patients treated under an ERAS pathway had a 32% reduction in total opioid use and a 23% decrease in the incidence of PONV[27]. Furthermore, in microvascular breast

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reconstruction implementation of an ERAS protocol resulted in a 11% reduction in the total predicted cost compared to historical controls[28]. Although this study was done on an inpatient surgery population, about 50% of the reduction in costs were not associated with room and board, suggesting that significant costs reduction could also be achieved in outpatient procedures. Similarly, gynecologic surgery ERAS programs have been shown to significantly reduce LOS, narcotic use (45% decrease) and have economic benefits (8% decrease in costs) without increasing readmission and complication rates[29, 30]. ERAS pathways are being embraced in a variety of different surgical procedures (thoracic, head and neck, breast reconstruction, gastrointestinal, bariatric, urology, and orthopedics) and applied more frequently in a new era of value-based care[31-40]. Overall, results illustrate that ERAS programs are associated with shorter LOS, a reduction in overall healthcare costs, and improvements in patient satisfaction. Gan et. al., in conjunction with the American Society of Enhanced Recovery (ASER) recently noted that the impact of a successful ERAS program is not just a short-term reduction in complications but a downstream improvement in health-related quality of life and life expectancy[41].

Each ERAS program requires a multidisciplinary team to plan and develop the most optimal protocol. This team should involve patients, anesthesiologists, surgeons, administrators, nurses, physiotherapists, dieticians, and research personnel. Implementation of an ERAS program has challenges that relate to assembly of the multidisciplinary team and lack of consistency in staffing. In addition, it requires high rates of protocol compliance, staff education, significant financial support, and the variability in components based on the different surgical procedures must be considered. It is also very important to include an audit of compliance and outcomes.

How is ERAS relevant to the ambulatory setting?

Specific ERAS pathways for ambulatory surgery are limited in the literature, although many of the main principles for inpatients are relevant to patients undergoing ambulatory and short-stay surgery. As ambulatory surgery facilities expand their scope to involve more complex procedures ERAS pathways are key to ensure the success of expansion. While shorter LOS are characteristic of successful inpatient ERP, the other important benefit relevant to ambulatory surgery is a reduced variance in other patient outcomes[41]. For this reason, the focus of ambulatory surgery ERAS should be less on reducing an already short length of stay and more on implementing multimodal pathways for opioid minimization, reduced PONV, early ambulation, and improved quality of recovery. Among the most common reasons for prolonged stay after ambulatory surgery are pain and/or PONV[42, 43]. The incidence of chronic postsurgical pain varies by surgery and was reported to be as high as 20-50% following mastectomies, 20-30% in other breast surgery, and 5-35% after herniorrhaphy[44]. Several risk factors have been identified, but the degree of postoperative pain the patient endures is one that is amenable to clinical control. The goal of pain management should be to minimize pain through patient education and procedure-specific evidence-based analgesic techniques incorporated into the ERAS pathway[45, 46].

The use of opioids for postoperative analgesia results in adverse effects, such as sedation, PONV, urinary retention, ileus, and respiratory depression, which can delay discharge. Multimodal analgesia can be used to achieve effective pain control in ambulatory surgery while limiting the dose of any one agent, particularly opioids thus resulting in a reduction of opioid-related side effects[47]. A recent comprehensive literature review highlighted the importance of multimodal anesthesia (MMA) in ERAS protocols, concluding that 'in the era of ERAS, MMA has now established itself as the gold standard of standard perioperative analgesic care'[48]. Successful ERAS pain management must consider perioperative combinations of non-opioid methods, including acetaminophen, NSAIDs, intraoperative dexmedetomidine, lidocaine, and gabapentin or pregabalin[43-45, 49-53]. In addition, regional anesthesia techniques, such as epidural blocks, transversus abdominis plane (TAP) block, paravertebral blocks, and other specific regional nerve blocks can be incorporated into ERAS pathways[54-59].

The general postoperative nausea and vomiting incidence is approximately 50% and 30% respectively[60]. Prophylactic multimodal antiemetic therapy should be considered on all ambulatory surgical patients. The Apfel risk score is an excellent tool for identifying patients at risk for PONV. For most patients, a combination of IV dexamethasone after induction of anesthesia and IV ondansetron at the end of surgical procedure should be used. Patients with high Apfel scores may do well with an additional antiemetic therapy such as a preoperative transdermal scopolamine or oral aprepitant[60, 61]. Despite best attempts, however, patients could still experience PONV due to genetic factors outside clinician control. A recent systematic review suggests an association between genetic polymorphisms, such as the 5-HT3B receptor, ABCB1 transporter, and CYP2D6 allele, and PONV[62, 63]. Consequently, more research is needed on these potential genetic factors that could influence risk reduction. There is potential to develop preoperative genetic and blood profile tests in the future. Until that time, PONV algorithms include multimodal drug treatment, opioid minimization, and avoiding dehydration and prolonged fasting[64].

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Perioperative fluid management as a component of ambulatory ERAS starts preoperatively by encouraging patients to drink clear liquids up to 2 hours before surgery, remain hydrated, and avoid routine mechanical bowel preparation[65, 66]. Intraoperatively, the goal is to achieve a 'zero' fluid balance, with fluid therapy recommended for more complex cases. Postoperatively, ERAS fluid management is meant to encourage patients to eat and drink without IV fluid infusions. IV fluid can maintain and/or restore altered physiological parameters to normal[23, 65].

At JRSC, which first opened its doors in 2016, development of ERAS pathways for ambulatory surgery has been a critical component for the success of the surgery center. We accomplished this with a combination of extensive literature review, multidisciplinary collaborative efforts, and creation of ERAS surgery specific pathways. Creating a standardized clinical care pathway enables the anesthesia team to systematically approach the patients care while minimizing variability and maximizing predictable outcomes. Specifically, four surgical procedures were identified as short-stay non-traditional ambulatory procedures for cancer surgery: mastectomy with and without reconstruction, robotic prostatectomy, minimally invasive robotic and laparoscopic hysterectomy, and thyroidectomy.

We identified the following important elements in our ERAS ambulatory programs: i) administration of standardized anti-emetic protocol, which includes administration of dexamethasone, ondansetron for all patients, and aprepitant to high-risk patients; ii) minimization of opioid administration and supplementation with preoperative gabapentin, IV acetaminophen, and ketorolac if appropriate; iii) minimal use of nasogastric tubes; iv) appropriate fluid administration; and v) standardized interventions related to the specific surgical procedure. Ambulatory surgical ERAS programs should measure outcomes including LOS, pain management, need for transfer/admission to acute care hospital, return visits to ED/UCC, or readmission within 30 days. In addition to early and intermediate outcomes, Feldman et al. include later outcomes such as patient reported outcomes and health related quality of life assessment post discharge[67]. Additionally, measuring compliance is an essential assessment of postoperative LOS increases. However, recommitment through auditing compliance of elements can return to improved outcome in postoperative LOS[68].

Overall implementation of ERAS pathways for ambulatory surgery provides improved outcomes with shortened postoperative LOS, but it is only sustainable through close cooperative interdisciplinary efforts, continuous education and evaluation. Outcome data from JRSC will be presented.

Does choice of anesthesia affect patients' immediate and long-term outcomes?

The actively developing field of onco-anesthesiology is specifically geared toward addressing how anesthesia affects short- and long-term outcomes related to cancer recurrence. The perioperative period is a critical point in the biology of many cancers due to the complex interplay between inflammation, immunosuppression, angiogenesis, hypothermia, and increased catecholamine release[69, 70]. These factors may facilitate the growth of minimal residual disease (MRD) and promote the seeding of circulating tumor cells (CTCs) thus contributing to recurrence[70, 71]. Preclinical and retrospective clinical trials suggest that anesthesia interventions may be key to modulating these factors and could majorly impact cancer progression and formation of metastasis. However, it is unclear whether the same anesthetics or analgesic techniques would affect all cancers similarly. Most recently, two studies extensively reviewed the existing evidence of volatile anesthetics, opioids, NSAIDs, propofol, non-selective beta-blockers for different oncological procedures[69, 72]. Currently, there is a lack of convincing clinical evidence to select one particular anesthesia technique to reduce cancer recurrence or improve cancer-related outcomes[70, 73].

The principal line of defense against cancer-cell invasion and metastasis is thought to be a patient's own immune response. This immunopathogenic response includes an 'elimination phase' where a cancer-free state is achieved due to the interplay of various factors such as Natural Killer (NK) cells, CD4+TH1, CD8+CTL, cytokines and tumor necrosis factors. Perioperatively this response may be disrupted due to a surgical stress response in which NK-cell function needed for the clearance of tumor cells is impaired[70, 74, 75]. This inhibition could affect the process of limiting MRD and CTCs thus increasing the risk of metastasis and tumor recurrence. In this state, the immunopathogenic response enters an 'equilibrium state' where cancer cells are in a state of dormancy followed by a final 'escape phase' where the tumor cells escape immunity control. Anesthesia may attenuate this stress response and modify immune activity primarily at the elimination phase, but perhaps residual effects throughout, thereby opening the door for other theoretical proposals of preferred anesthesia choices and their impact on these phases[76, 77].

Theoretical benefits of regional anesthesia on tumor inhibition were first described in the early 1970's. Local anesthetics have anti-inflammatory, as well as opioid and volatile sparing effect and the analgesic effects of regional anesthesia provide theoretical basis for its positive effect on patient outcome[78]. Although to date in active clinical

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practice the benefits have not been definitely shown,[79] a retrospective study by Exadakyltos et al. in 2006 was the first to associate the use of regional anesthesia and propofol to a decrease of breast cancer recurrence[80]. However, these findings need to be prospectively confirmed and active NCT clinical trials comparing regional anesthesia techniques with GA and systemic opioids in breast cancer are ongoing[81]. While opioids are a mainstay of the perioperative period there is ongoing controversy as to the immunomodulating effects of such agents. Fentanyl and morphine appear to be more immunosuppressive compared to oxycodone, hydromorphone, buprenorphine, or tramadol[82]. Despite these findings, human clinical data have not yet provided conclusive evidence that opioids increase the risk and incidence of metastasis. The largest study to date is a population-based cohort study that included 30,000 patients and found no association between opioids and breast cancer recurrence[83]. Recent systematic reviews on retrospective human clinical studies for colon, gastrointestinal, breast, and other ambulatory cancer procedures concluded that though suggestive, there is not enough evidence to associate perioperative NSAIDs use and reduced cancer recurrence[84-88]. A 2018 retrospective study correlated the intraoperative use of ketorolac and lower recurrence rates in patients with increased BMI who underwent primary breast cancer surgery[89]. All these equivocal findings highlight the need for prospective randomized clinical trials to resolve inconsistencies in the literature.

Propofol has been shown to have antitumor effects in animal studies and limited clinical studies measuring serum concentrations of angiogenesis markers and metastasis suggest possible protective effects. Prospective RCTs measuring NK cell cytotoxicity *in vitro* in preop and 24 hr postop blood samples from breast cancer surgery patients found greater cytotoxicity in patients receiving propofol PVB vs. sevoflurane/opioids[90, 91]. These findings are supported by a recent retrospective study of 325 radical mastectomy patients which associated propofol/TIVA with lower incidence in 5 year recurrence compared to sevoflurane anesthesia[92].This is important evidence to advocate for propofol/TIVA supplemented with regional anesthesia as an alternative to volatile/opioid anesthesia. Whether the findings are attributable to propofol, local anesthesia, improved pain control, or opioid and volatile sparing remains unresolved. Therefore, it should not be suggested that volatile anesthetics are contraindicated in cancer surgery, especially in ambulatory surgery where sevoflurane is widely used[93, 94]. High levels of stress in this population, resulting in a physiological stress response with levels of cortisol and catecholamines, can modulate cellular immunity[95]. Shaashua et. al., investigated this possibility in a prospective trial using beta-adrenergic and COX-2 inhibitors and successfully used these agents to safely modulate cellular and molecular pathways involved in metastasis and recurrence in early stage-breast cancer patients[96]. Other strategies under investigation include immune-enhancing nutrition and perioperative immune stimulation[70, 97].

Current limitations: The majority of published clinical studies are either retrospective or unplanned analysis of controlled trials, and therefore subject to bias. These studies were not specifically designed to test the impact of one drug or anesthetic technique over another. Additionally, the lack of standardized definitions of survival outcomes adds to the inability to interpret the results. How was recurrent or progression described? Some studies included different cancer stages and histology and did not include genomic data. Ongoing and future research needs to be large enough to enroll patients with similar tumor-related variables, exposure to neoadjuvant or adjuvant therapy, and demographics. The goal is to minimize multiple confounding variables so that the impact of anesthesia or analgesia technique can be more clearly analyzed. With such current limitations, clinicians should focus on providing perioperative onco-anesthesia care that maintains homeostasis, implements ERAS pathways were appropriate, utilizes multimodal analgesia and prophylactic antiemetics coupled with providing a stable perioperative course.

Ambulatory surgery must join the global mission of cancer surgery to 'deliver safe, affordable, and timely cancer care'[98]. With the developing field of onco-anesthesia anesthesiologists practicing in ambulatory surgery facilities can contribute significantly to patient outcomes by expanding their surgical procedures, implementing ERAS protocols, and selecting an evidenced based anesthesia technique for improving cancer outcomes.

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The Anesthesiologist's Role in Disaster Medicine

Charles E. Cowles, MD, MBA, FASA **Houston, TX**

The Anesthesiologist's Role in Disaster Medicine

Introduction

Man-made and natural disasters can affect the operations of any size or type healthcare facility. The ASA has recently put forth a campaign that "when seconds count, physician anesthesiologists save lives". In the daily role of caring for the perioperative patient we plan and prepare for the worst case scenarios. When events occur, we are trained to remain calm and rely on checklists, guidelines, and standards for consistent practice. Physician anesthesiologists are also in a unique position compared to other anesthesia providers, our medical school and internship training allows us to function performing the skills required of all physicians including assessments or illnesses and injuries, medication management, use of basic diagnostic instruments along with other modalities such as ultrasound, all are extremely valuable skills in times of disaster. The nature of our work allows us to reach out to our network of consultants both in the realm of surgical specialties and medical specialties. All of these attributes make the physician anesthesiologist the ideal candidate for a disaster specialist. For preparation, we will review previous incidents and their unique signature on medical systems. We will also assess vulnerabilities of facilities to a variety of disasters. The session will illustrate how disaster preparedness can be carried out on personal, departmental, and system level and how to coordinate with local, state, and federal resources. Finally we will review examples of regional intelligence data of current threats within the United States.

Review of past incidents which resulted in straining, stressing, or overwhelming current systems

Let's examine the incidents of the Boston Marathon bombing, the Philadelphia commuter train derailment, the Garland Texas terror attack, the Pulse nightclub shooting, and Hurricane Harvey. We can look to these events to examine common factors, differences, and how timing and preparedness can make responses very different. Of these events one was a predictable landfall of a massive hurricane, three were terror attacks with a large diversity of presentation and timing, and one was a transportation accident. Each presents a unique set of challenges, we can examine their responses to learn and improve on our own situations. Also we can examine the scale of the event in relation to the amount of resources available and also whether or not the incident primarily involved the area healthcare facilities. Timing is everything, the events surrounding the Boston Marathon bombing were timed with optimal resource availability and planning. If the terror event had occurred 24 hours later, the manner in which the situation was handled would have been drastically different. The best plans made for a hurricane could not reasonably predict the intensity of flooding that occurred during hurricane Harvey's landfall to the Texas Gulf Coast area. Although the large Texas Medical Center in Houston was minimally impacted, the staff for those large hospitals became stuck either at home or at the hospital. The entire Houston metroplex was paralyzed with respect to getting people to and from hospitals, regardless of their roles. Several employees had heeded the call to evacuate from officials and could not be dispatched to relive fatigued providers. The proximity of a large hospital to the scene of the Pulse nightclub shooting created a large problem whereby a well-rehearsed EMS service was bypassed and patients were brought to only one close-by trauma center by private vehicles, police cars, and the walking wounded. This completely inundated one of Orlando's large trauma centers while other hospitals were relatively slow with minimal work performed.

Assess a facility's vulnerabilities to natural and manmade disasters

Natural disasters can offer some prediction in their occurrence, realizing that their can always be outlier events, the geographical location of a hospital or other healthcare center can suggest what disaster are most likely. Earthquakes, hurricanes, floods, and wildlife fires are usually limited to a fairly predictable area. Other disaster scenarios can be related to the area infrastructures. Infrastructure sector classification as presented by the US Department of Homeland Security (DHS) can offer some insight in the potential for threats to regional infrastructure and the impact if those resources are compromised. Facility design can offer some insight as to how a particular response will occur. In flood prone areas, how many patient care areas are in the basement or lower floor? Are back-up generators and other essential equipment located in areas likely to be impacted?

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In the XXXX earthquake in Christchurch, New Zealand, for the afternoon quake, like in many hospitals, a roster of call team members was in place. However, no one knew exactly who was on premise and who was off-site. This created a big issue as streets were impassible throughout the large city, and phone lines were jammed. Patients arrived to hospitals and no one really knew if surgical services were in the hospital or away.

Anticipate potential hazards during a disaster

Implement a program of preparedness

"Don't just train, ingrain" Many facilities undergo training sessions and create a false sense of security because they do not work in conjunction with other sectors. A good sequence to follow is to undergo basic education, then drill, and then debrief for areas of improvement. For preparedness, most support services can easily be over looked. During hurricane Harvey, one hospital had about 500 patients and family members in the facility but only fewer than 20 food service workers and no blood bank personnel. What is your current relationship with police, fire, rescue and EMS? Have individual cross-trained in other roles? Even though pathologists and hematologists was well versed in blood banking techniques, can they operate the EMR and label making machines that are typically operated by technicians. Closer to home, are anesthesiologist familiar with supply locations to turnover and re-supply operating rooms in the event that anesthesia technicians are not available?

Coordinate and integrate with regional organizations and facilities

At the local level, cities and counties typically have jurisdiction after disaster declaration. In cases of a regional disasters, usually a regional coordination system coordinates resources or supplants those which are depleted. If the incident involves an entire regional then state government disaster teams may be deployed. If the resources needed exceed the capacity of state resources, then the national guard, Department of Defense, or the Federal Emergency Management Agency (FEMA). Many of these agencies are staff by volunteer medical providers who participate in routine drills and training. It is very important for healthcare providers to not just simply self dispatch, but rather go through the vetting process prior to the occurrence, the reasons are multiple, but important considerations are the prevention of imposter medical personnel and also logistical planning for food, bathrooms, and sleeping arrangements. Also by going through a unified command, resources are allocated to the areas expressing the greatest need.

Assign responsibility for specific elements of disaster management and utilize the Incident Command System (ICS)

The FEMA has a universal system to be used in times of crisis and is potentially useful for management of both routine and unusual events. ICS is based upon the National Incident Management System (NIMS) design and curriculum that is taught to many disciplines such as fire, police, EMS, and healthcare. By using common language and hierarchy, needs are easily communicated from one facility to another and the flow of incident management is optimized by utilization of a hierarchy with commonly applied names and tiers. Communication is based on "plain English" rather than institutional or departmental jargon or codes, this eliminates the confusion of operations when a "Code pink" or "Code 11" is declared and few know what is the signification. Within ICS, responsibilities are clearly assigned, systems are defined, and communication lines are established. These attributes facilitate integration and sharing of resources and also aides in the identification of hazards and vulnerabilities. A special segment of ICS has been developed for hospitals, which includes 7 categories and 17 elements and includes the necessary terminology and responsibilities. ICS helps to coordinate the involvement of physicians, administrators, and nurses. Disaster plans are necessary for accreditation as well as the coordination with local law enforcement and fire departments and the development of mutual aid agreements. The basic structure of ICS involves a commander who coordinates all activities relative to the given situation. The Incident Commander (IC) utilizes 3 officers, the liaison officer, the public information officer and the safety officer. The IC has a minimum of 4 sections that report to him/her, these sections are 1. Operations, 2. Logistics, 3.Planning, and 4. Finance and Administration. Reporting to each of the section are branches and then unit report to the branches. This structure eliminates duplicity and also divides up responsibilities in a manageable fashion.

Anticipate future events which are likely to occur and also examine intelligence information to refine your position of readiness

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How well versed are you with respect to the types of vulnerabilities to your area? Where can you obtain more information? Within the United States, the Department of Homeland Security operates a series of Fusion Centers. These centers, serve as primary focal points within the state and local environment for the receipt, analysis, gathering, and sharing of threat-related information among federal, state, local, tribal, and territorial (SLTT) partners. Most every area in the US has an Office of Emergency Management (OEM), these serve the purpose of anticipating the potential for disasters and events as well as vulnerability assessment and resource availability. A designated representative from an anesthesia group should establish a communication line with the OEM prior to an event occurring. This simple step can eliminate miscommunications about reality and expectations.

Summary

Although no one wishes a disaster or mass casualty situation to occur, emergency preparedness should be a regular part of any practice setting. Training and disaster plans are already been created, and thanks to standardization among several fronts, these works can easily be adopted to your facility. Most of these resources are free of charge and often the your local OEM will be happy to assist. Even simple drills can be a fun experience that can be rather revealing about the level of preparedness within a hospital or surgery center. The ASA and many state societies can offer assistance in these matters. Finally, be prepared on a personal level on how to respond to a disaster situations, family drills whereby communication via cell phone is blocked can be rather telling about how truly prepared your household will be in response to a major crisis.

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Physics for Anesthesiologists

Jeffrey B. Gross, M.D. **Farmington, CT**

Why Physics?

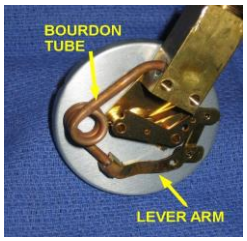
a) Understand how our equipment is SUPPOSED to work
b) Understand what might happen if things go WRONG
c) Function as a CONSULTANT in the medical specialty of Anesthesiology
d) Do well on Content Outline Section 1B of the In-Training and Part I American Board of Anesthesiology Examinations

Pressure

a) Pressure= Force per unit of area
b) Units
- Pounds / in^2 (PSI)
  - Atmospheric Pressure PATM=14.7 PSI)
- Pascals (nt / m^2) (PATM□100 KPa)
- mmHg (7.5 mmHg = 1 KPa)
- cmH_2O (1 mmHg = 1.36 cmH_2O)

c) Implications
- Even a small pressure exerts a large force if area is large
- A small force can exert a lot of pressure if the area is small

d) Absolute vs. Gauge Pressures
- Gauge pressures: relative to ambient pressure
  - Tire pressure, pressure in compressed gas cylinder, blood pressure
- Absolute pressures
  - Vapor pressure of anesthetics, H_2O
  - Blood gases
  - Other cases where you need to use gas laws



e) Pressure Gauges
- Bourdon tube (for high pressure gases such as compressed gas cylinders)
  - Deformable tube changes shape when filled with pressurized gas causing pointer to move
- Diaphragm (for low pressures such as aneroid blood pressure cuffs--the kind with a pointer)
  - Diaphragm at top of a "pancake" shaped cylinder moves outward causing pointer to move

f) Pressure Regulators
- Reduces high pressure in compressed gas cylinder to approximately 50 PSIG

Gas Cylinders

a) E Cylinder (back of machine)
- For ideal gases (air, nitrogen, oxygen)
  - Full cylinder pressure = 2000 PSI
  - Full cylinder volume = 660 liters
  - Volume remaining is proportional to pressure
  - 1000 PSI --> 330 L 500 PSI-->165 L
- For pressurized liquids (N_2O, CO_2, C_3H_8 [propane--barbecue grill], C_3H_6 [cyclopropane])
  - Pressure depends on vapor pressure of liquid at tank temperature until liquid is "gone" (740 PSI) for N_2O at room temperature
  - Full cylinder of N_2O – 1590 L
  - Remaining quantity of gas best determined by weight
    - The N_2O in a full E cylinder weighs about 3 Kg
  - Critical temperature (T_c): gas cannot be liquefied above this temperature regardless of pressure

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- For N_2O TC = 36.5° C

b) Some Simple Calculations
- What is the weight of N_2O in an E-cylinder?

$$1590L \times \frac{\text{mole}}{24L} \times \frac{44g}{\text{mole}} = 2900\text{g}=2.9\text{kg}$$

- What is the internal volume of an "E" Cylinder?
  - $2000 \cdot V_{TANK} = 14.7 \cdot 660$
  - $V_{TANK} = \frac{14.7 \cdot 660}{2000} = 4.85L$ Use Boyle's Law: $P_1V_1=P_2V_2$

c) More Simple Calculations
- How many ml of sevoflurane vapor come from 1 ml of sevoflurane liquid?

$$1\text{mlliquid} \times \frac{1.5g}{\text{ml}} \times \frac{1\text{mole}}{200g} \times \frac{24\text{Lgas}}{\text{mole}} = 0.18\text{Lgas}=180\text{mL}$$

- If the fresh-gas flow is 2 l/min, how many minutes of 2% sevoflurane anesthesia will 5 ml of liquid provide?

$$5\text{mlliquid} \times \frac{180\text{mlgas}}{\text{mlliquid}} \times \frac{1\text{minute}}{0.02 \times 2000\text{mLgas}} = 22.5\text{min}$$

Adiabatic Compression

a) Rapid compression of gas without giving heat a chance to escape
- Principle of diesel engine (no spark plugs)

b) If there is oil / grease in valve or regulator and tank opened quickly, explosion can occur :-(

Flows of Liquids and Gases

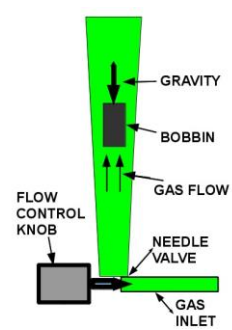
a) Laminar (streamlined)
- Pressure=Flow x Resistance

η=viscosity of liquid
R=radius of tube
L=length of tube

b) TResistance= $\frac{8 \times L \times \eta}{\pi \times R^4}$urbulent
- Pressure α Density x Flow^2
- Transition from laminar to turbulent flow when Reynold's number > 2300R= $\frac{\rho \times V \times D}{\eta}$

Flowmeters

ρ=density of liquid
V=velocity of flow
D=diameter of tube
η=viscosity of liquid



a) Tapered tube with diameter increasing toward the top

b) Bobbin position determined by equilibrium
- Upward force from flowing gas = downward force from gravity
  - At low flow rates (laminar flow) upward force depends on viscosity of gas
  - At high flow rates (turbulent flow) upward force depends on density of gas

c) Always want O_2 flow tube nearest to the common gas outlet
  - Minimizes risk of hypoxia if a flow tube is cracked

Fail Safe Valve

a) Cuts off N_2O if O_2 supply fails
- Does NOT prevent accidental or intentional "dialing in" of a hypoxic gas mixture

b) Testing
- Turn on O_2 and N_2O flows
- Disconnect wall O_2 supply (be sure O_2 tank is "off")
- Press O_2 flush valve
- Verify that N_2O flow ceases when O_2 pressure drops to zero

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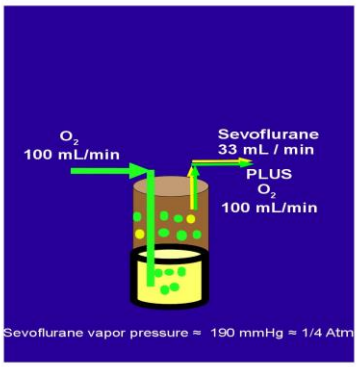
Proportioning Systems

a) Limit N_2O flow to 3 times O_2 flow

b) Link vs. pressure operated systems
- Link system: mechanically turns down N_2O needle valve if O_2 flow reduced
  - N_2O flow will NOT return to initial value if O_2 flow increased
- Pressure system: pneumatically decreases N_2O flow if O_2 flow reduced
  - N_2O flow will return to initial value if O_2 flow increased

Anesthetic Vaporizers

a) Ye Olde Copper Kettle
- Vapor output depends on O_2 inflow and vapor pressure of anesthetic
- For sevoflurane, Pv=190 mmHg = 1/4 ATM
  - 1/4 of output molecules will be Sevoflurane; 3/4 of output molecules will be O_2
  - For every 100 ml O_2 input, will get 133 ml of total output
    - 100 ml O_2 (3/4 of total)
    - 33 ml sevoflurane (1/4 of total)
  - If you use a total gas flow of 3.3 l/min (magic number :-), each 100 ml of O_2 through the vaporizer gives you 1% of sevoflurane concentration



b) Desflurane "Vaporizer"
- Boiling point of desflurane 23.5° C (vapor pressure at room temp nearly atmospheric
- Variable bypass vaporizer not controllable
  - Each 100 ml of O_2 through vaporizing chamber would give about 900 ml of desflurane output
  - Large output swings with changes in temperature
- Alternative: Use a "boiler" and deliver as a gas
  - Desflurane output determined by a "needle" valve, just like O_2 and N_2O
  - Uses electronics to make desflurane flow proportional to total gas flow, so a constant percentage is given regardless of fresh gas flow settings

c) Vaporizers at Altitude
- Recall that MAC is really a partial pressure
  - Sevoflurane MAC = 2% x 760 mmHg =15.2 mmHg
    - In Tibet P_{ATM} = 380 mmHg
    - 15.2 / 380 = 4% (MAC of sevoflurane in Tibet)
  - Vapor pressure of sevoflurane in Tibet (depends on temperature only) = 190 mmHg (same as at sea level)
    - Since vapor pressure = 1/2 barometric pressure, for every 100 ml of O_2 flowing into vaporizer the output will be 100 ml of sevoflurane plus 100 ml of O_2
    - This is 3 times as much as at sea level--vaporizer output triples
    - Since MAC is only twice as great as at sea level, actually need to turn vaporizer DOWN to 1.33% in order to get 1 MAC of anesthetic effect
- Desflurane "vaporizer"
  - Percentage output unaffected by altitude
  - MAC of desflurane in Tibet is 12%
  - Need to "dial in" 12% desflurane to get 1 MAC of anesthetic effect

Low pressure leak test

a) Checks for leaks in flowmeters, vaporizers, common gas manifold

b) Check valve just before common gas outlet on many machines
- Allows patient to be ventilated with O_2 from flush valve even if there is a leak in low pressure system--therefore, the fact that the breathing circuit "holds pressure" does not guarantee that there are no low-pressure leaks
- To check for leaks
  - Turn machine fully off (otherwise minimum mandatory O_2 flow will look like a leak
  - Apply suction bulb to common gas outlet and verify that it remains deflated for at least 5 sec

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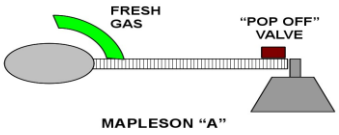
Breathing Circuits

a) Open (non-rebreathing)
- Simple face mask or nasal cannula (CO_2 diffuses away from the face)
- Bag-Valve-Mask system (Ambu®): uses 3 valves to allow either spontaneous or controlled ventilation while preventing rebreathing

b) Semi-Open (Mapleson / Bain)
- Most efficient removal of CO_2 for a given gas flow when the "pop off" valve is nearest the source of the ventilatory power
  - Spontaneous ventilation: Mapleson A
  - Controlled ventilation: Mapleson D
- However, the "A" system is very inefficient (requires high gas flows) to prevent rebreathing during controlled ventilation, while the "D" system is reasonably efficient for both controlled and spontaneous ventilation, so the "D" is preferred for most applications.
  - Bain circuit is a coaxial Mapleson D



c) Semi Closed Circle System
- Patient gas uptake < fresh gas flow < minute ventilation
- Some rebreathing of exhaled gas (following removal of CO_2 by absorber)

d) Closed System
- Gas inflow = Patient Uptake
- If using sidestream agent / CO_2 analyzer, must route exhaust back into circuit
- Starting values
  - O_2: 3-4 ml/kg/min
  - Anesthetics: First minute uptake / √time (minutes)
    - N_2O (80% concentration, 80 kg patient): First minute uptake 1600 ml
    - Sevoflurane (2%, 80 kg patient): First minute uptake 50 ml
    - Desflurane (6%, 80 kg patient): First minute uptake 100 ml
- Closed System-Adjustments
  - Total flow: Adjust N_2O and O_2 in proportion to keep volume of bag or bellows constant
  - FIO_2 : Adjust ratio of N_2O and O_2 to maintain desired F_IO_2 keeping total flow constant
  - Depth of anesthesia: Adjust vaporizer setting to maintain desired depth or inspired concentration

CO_2 Absorption

a) Granules
- Small enough to have large surface area but large enough to avoid "channeling"
- Typically 4-8 mesh

b) Composition
- Old Standbys
  - Sodalime: NaOH, $Ca(OH)_2$
  - Baralyme: KOH, $Ca(OH)_2$, $Ba(OH)_2$
    - More likely to react with anesthetics to form CO (desflurane) or compound A (sevoflurane)
- New substitutes (minimal reaction with anesthetics--safe at low flows)
  - Amsorb: $Ca(OH)_2$, $CaCl_2$
  - Litholyme: $Ca(OH)_2$, LiCl

c) Moisture
- Necessary for CO_2 absorption
- Reduces likelihood of anesthetic breakdown

d) Absorption Chemistry
- $CO_2 + H_2O \rightarrow H_2CO_3$
- $H_2CO_3 + 2\ NaOH \rightarrow Na_2CO_3 + 2H_2O$ + heat
- $Na_2CO_3 + Ca(OH)_2 \rightarrow CaCO_3 + 2NaOH$
- When the NaOH is gone, acidification causes indicator (ethyl violet) to turn "violet"

e) Zone of maximum absorption feels warm to touch (may be "hot" if malignant hyperthermia)

Pressure Transducer Systems

a) Accuracy with which transducer system reproduces actual intravascular pressure depends on

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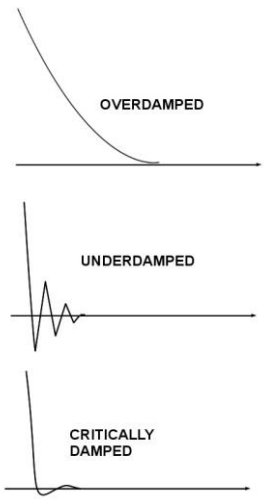
- Resonant frequency (higher is better)
- Degree of damping (most important if resonant frequency similar to 1/rise-time of waveform)

b) Zeroing Pressure Transducers
- Height of patient relative to transducer must remain constant after zeroing
- At time of zeroing
  - Transducer may be at any height relative to patient (need not be at heart level)
  - System should be "opened to air" by a stopcock at heart level before zeroing is performed

c) Site of Arterial Pressure Measurement
- Wave reflection causes systolic pressure to be higher and diastolic pressure to be lower when there is an acute change in vessel diameter (radial / dorsalis pedis)
- This does NOT affect the mean pressure
- Resistance to flow causes a (very slight) decrease in mean pressure as pressure measurement progresses from aorta to more distal vessels

d) Damping
- Oscillations within the transducer system may exaggerate or attenuate certain frequency components of the pressure waveform
- Underdamped: Systolic overshoot and diastolic undershoot
- Overdamped: Looks like a "sine wave" with underestimation of systolic and overestimation of diastolic pressure
- Regardless of damping, electronically determined **mean** pressures should be accurate
- "Squeeze and release" flush valve to assess damping



Non-Invasive Blood Pressure Measurement

a) Most "standard cuff" systems use oscillometry
- Pulsations in the cuff pressure monitored as cuff deflates
- Initial pulsations--just above systolic pressure
- Maximal pulsations--mean arterial pressure
- Diastolic pressure by mathematical algorithm

b) Continuous non-invasive monitoring
- Most systems require intermittent calibration with a cuff

Cardiac Output Measurement

a) Fick Principle
- Conservation of mass
- $Q=VO_2/[C_aO_2-C_vO_2]$
- Required measurements
  - VO_2 (Oxygen uptake--difficult to measure during anesthesia)
  - C_vO_2 (requires PA catheter)
- NICO
  - Fick formula applied to CO_2 elimination
  - Partial rebreathing to estimate mixed venous CO_2
  - Requires constant ventilatory pattern (controlled ventilation only)

b) Esophageal Doppler Monitor
- Doppler: Change in frequency of sound / ultrasound / light waves when reflected from a moving object (e.g., RBC)
- $v=f_d \cdot \frac{c}{2f_i\cos\theta}$
  - v=RBC velocity f_d= Doppler shift f_i=frequency of ultrasound
  - θ=angle between ultrasound beam and direction of blood flow
- CO = HR x CSA x VTI
  - CO=Cardiac Output CSA=Cross Sectional Area VTI=Velocity-Time Integral

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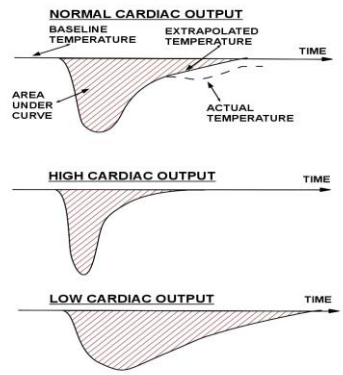
c) Thermodilution

$$C.O. = \frac{\text{QuantityofIndicator}}{\int_{t=0}^{A} \Delta \text{Tempdt}}$$



- Quantity of indicator = Volume x ($T_{PATIENT}$-$T_{INDICATOR}$)
- Sources of error
  - Quantity of indicator is "dialed in" to the C.O. computer based on the intended volume and temperature of injectate
  - If volume injected is lower than intended, then $\int_{t=0}^{A} \Delta$ Tempdtwill be too low and the Cardiac Output reading will be falsely high
  - **If the temperature of the indicator is colder than intended (e.g. using iced rather than room temperature saline) then $\int_{t=0}^{A} \Delta$ Tempdtwill be too high, and the Cardiac Output reading will be falsely low**

Disclosures: No relevant financial relationships

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Carotid Endarterectomy: Past, Present and Future!

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Carotid Endarterectomy (CEA) was first reported in 1954 (1), and it is performed in an attempt to reduce the risk of stroke. There are approximately 140,000 deaths per year from stroke in the United States, which makes stroke the 4th leading cause of death (2). Carotid endarterectomy rates have varied significantly over the years, becoming quite high in the mid 1980's and then dropping substantially as there were significant efficacy questions raised. In the 1990's there were three substantial clinical trials performed that established the efficacy of CEA in reducing stroke rates in patients with symptomatic high-grade (70-99%) carotid stenosis (3,4,5) In the NASCET trial the risk of stroke was 26% in the medically managed group vs. 9% in the CEA group, a 65% risk reduction, and the number needed to treat with surgery to avoid one stroke was 6. In the European Carotid Surgery Trial CEA for symptomatic high-grade carotid stenosis led to a a six-fold risk reduction for future stroke. For comparative purposes it is important to note that the risk of stroke or death within 30 days of CEA in this study was 7.5%. The Asymptomatic Carotid Artery Study compared then optimal medical management with CEA for patients with asymptomatic carotid artery stenosis of 60% or greater and found a 47% relative risk reduction in stroke at 5 years with a 2.3% perioperative stroke rate. With proof of the effectiveness of CEA for both symptomatic and asymptomatic high-grade carotid stenosis, the frequency of surgery for carotid disease increased, and in 2009 there were approximately 140,000 carotid endarterectomies performed in the United States. While it is difficult to be very precise, it is likely that the majority of these procedures, perhaps as many as 90%, were performed on patients with asymptomatic carotid disease.

Carotid endarterectomy used to be the only procedure available for patients who required an intervention due to carotid stenosis. Carotid artery stenting (CAS) was introduced in 1994, and the FDA approved multiple stenting systems in 2004. There have been many technical advances in endovascular stent systems, mainly designed to trap atherosclerotic debris that would otherwise have been released into the brain with stent deployment. Multiple clinical trials comparing CEA and CAS have been done, with two of the most important the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) and the Asymptomatic Carotid Trial (ACT 1). The CREST trial, which was done in both symptomatic and asymptomatic patients deemed to be of average risk, and which now has 10-year follow up, the yearly risk of stroke post CAS was 0.7%, and the yearly risk of stroke after CEA was 0.6%. The results of CREST attest to the durability of treatment with CAS, and are often cited to prove the non-inferiority of CAS (8). In the ACT 1 trial, which involved asymptomatic patients with severe carotid stenosis who were not thought to be at high risk of surgical complications, and included 5 years of follow up, CAS was noninferior to CEA. The cumulative 5-year rate of stroke free survival was 93.1% in the CAS group and 94.7% in the CEA group. In many comments regarding these trials it was noted that it was not at all clear that the results of these trials could be generalized into wide clinical practice, given the likelihood that many practitioners of different backrounds and experience levels would likely begin to place carotid artery stents, and results when procedures are done at low frequency often do not match the results of carefully conducted clinical trials. Regardless, after these trials came out many thought that CAS would become more common as it is less invasive than CEA, and if results are equal patients will often choose the less invasive therapeutic option. Current indications for CEA that are generally accepted include high-grade (50-99%) carotid artery stenosis in a symptomatic patient, and 60-99% stenosis in an asymptomatic patient.

A significant factor that has complicated clinical decision making in the area of intervention for extracranial vascular disease is the changing effectiveness of what is typically abbreviated in the literature as BMT or best medical therapy. Over the years BMT has improved substantially, which makes BMT comparatively more attractive than CEA or CAS. In the 1990's 6% was thought to be an acceptable periprocedural stroke risk. As time has passed this "acceptable rate" has declined to 3% or perhaps even lower. Aggressive treatment of patients with asymptomatic carotid disease has reduced the yearly risk of stroke. Aspirin, or clopidogrel in patients intolerant to aspirin, statin therapy, and excellent management of hypertension and diabetes is changing the natural history of carotid artery disease. A recent synthesis of medical treatment strategies to reduce perioperative morbidity and mortality after carotid surgery lists many similar strategies, but also points out that neck hematomas are probably decreased if heparin is reversed with protamine. Another important point is that it is likely that postoperative

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hypertension will be more difficult to manage in patients who are treated within the first 7-14 days of symptoms, which will in all likelihood become more common. (9)

For a recent comprehensive literature review, the 2017 Practice Guidelines of the European Society of Vascular Surgery is an excellent place to start (10). These guidelines note that it appears that the highest risk of stroke in symptomatic patients is in the first 7-14 days after the onset of symptoms. We may well be asked to do more interventions in patients who are recently symptomatic or who even have recently suffered a small stroke. When the outcomes of CEA vs CAS in patients treated within 7 days of symptom onset are examined, the rate of stroke and death with CAS is 8.3%, while stroke and death with CEA was 1.3%, clearly favoring CEA. Early surgery is better than early stenting with regards to risk profile (11).

Concomitant with the improvement in BMT there has been an improvement in complication rates of CEA. In a single center study of 8743 patients undergoing CEA, perioperative stroke occurred in 1.04% of patients, and perioperative mortality was 0.32%, with myocardial infarction the most common cause of death (12). This report, while subject to the inherent limitations of a body of work that spanned 17 years at a single center, strongly suggests that very low complication rates are indeed possible with CEA in experienced hands. A recent metanalysis of the procedural risks of CEA and CAS notes that the procedural risks of CEA appear to have decreased significantly, while the procedural risks of CAS have not decreased over time. Risks for CEA were substantially lower in trials that recruited patients after 2005. Procedural stroke and death rates for CEA in symptomatic patients were 5.11% in trials before 2005 versus 2.68% in trials after 2005, and the same comparison in asymptomatic patients undergoing CEA is 3.17% before 2005 vs. 1.5% after 2005. Unfortunately, the procedural stroke/death rate after CAS did not change over time, 4.77% in symptomatic patients and 2.59% in asymptomatic patients (13). As clinical trials comparing CEA and CAS have continued, metanalyses of these trials have come to publication. A metanalysis of trials comparing CEA to CAS for stroke prevention concluded that while CAS and CEA were associated with similar composite rates of periprocedural ipsilateral stroke and death, the risk of long-term overall stroke was significantly higher with CAS (14). A metanalysis of CEA vs CAS for asymptomatic carotid stenosis concluded that due to increased rates of periprocedural stroke and death with CAS, CEA is the preferred option for the management of asymptomatic carotid stenosis (15). A metanalysis that pooled 7005 asymptomatic and symptomatic patients with 41824 years of follow up found that CEA is superior to stenting for short and long-term outcomes, although CEA was associated with a higher periprocedural rate of MI. their conclusion is that CEA is the first-choice treatment for carotid artery stenosis at present (16).

Regional versus general anesthesia for CEA has stimulated much debate over the years. There is little doubt that an awake patient is the best neurologic monitor available, but there is also little doubt that not every patient is a suitable candidate for CEA under regional anesthesia, and that not every surgeon enjoys operating on an awake patient. Patients who are significantly anxious or claustrophobic will likely be difficult to manage. Operative time varies significantly, at some centers 3 hours is routine, at other centers 1-hour skin to skin is the norm. It is much easier to do regional anesthesia for CEA when the surgical time is shorter. There are large case series documenting very low rates of conversion from regional to general anesthesia in centers that have very high functioning teams who perform the vast majority of their CEA's awake, but these results will not simply transfer to all settings. The regional block necessary to allow awake CEA is not at all difficult to perform, either a superficial or deep cervical plexus block will suffice. Intraarterial injections should be less common with a superficial cervical plexus block. The need for local anesthetic supplementation buy the surgeon is common. Intraoperative sedation during CEA must be performed judiciously to allow the patient to serve as a neurologic monitor. Special care must be taken to not mistake cerebral ischemia caused by carotid artery clamping as agitation that is treated with additional sedation. Many sedation techniques employing short-acting sedatives or analgesics can be effective. For many years it was assumed that carotid artery shunting was responsible for a higher incidence of perioperative stroke, which justified selective carotid shunting (only place a shunt is there is a neurologic change after cross-clamping) and made an awake patient or an effective neurologic monitor very important. A recent Cochrane review of carotid shunting practices finds a poor quality of clinical evidence on this topic, really inadequate to guide decision making (17). At this point in time surgical practice with regards to carotid artery shunting remains very variable, but overall it appears that routine shunting is more common.

Overall general anesthesia is used much more frequently for CEA, and there is little doubt that excellent results can be achieved with carefully performed general anesthesia. A recent report of CEA cases performed in the United States from the National Anesthesia Clinical Outcomes Registry shows that 94% of reported

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endarterectomies were performed utilizing GA, and the proportion of cases performed utilizing regional anesthesia had decreased over the years 2010-14(18). This decrease is puzzling given the lack of evidence of superiority of one anesthetic technique versus the other, and significant increases in regional anesthesia in other areas of anesthetic practice. The GALA trial, published in 2008, looked at 3526 patients undergoing CEA, and found no difference in outcome between general and local anesthesia for CEA when analyzed on an intention to treat basis (19).This conclusion is shared by a later Cochrane database review (20). There is no solid outcome data to suggest that the type of anesthetic technique utilized for CEA drives outcome- excellent results can be obtained with either general or regional anesthesia. With either technique careful attention must be paid to the maintenance of hemodynamic stability, which may not be easy or straightforward in this group of patients, who often have severe hypertension. A strategy for managing cerebral perfusion during crossclamping is mandatory- if no shunt is employed most would increase blood pressure with a vasoactive drug. Excellent communication with your surgical team will allow better anticipation of intraoperative demands. Some surgeons will measure a carotid pressure distal to the crossclamp and use that result to guide whether or not a shunt will be placed, others will shunt based on patient factors, and some will shunt everyone. If a shunt is employed there is little reason to raise blood pressure to improve collateral cerebral perfusion.

The question of what optimal neurophysiologic monitoring is during CEA performed with GA is an unanswered question. There are many options available, and as is typical when many options are available, there is no outcomes based clinical evidence to prove that a specific method of neurophysiologic monitoring is “the gold standard”. Common neurophysiologic monitoring techniques employed include EEG monitoring (both raw and processed), evoked potential monitoring (SSEP’s and MEP’s), transcranial doppler monitoring, and cerebral oximetry. Most strokes after CEA appear to be embolic in nature, which makes it difficult to generate an ironclad argument for routine neurophysiologic monitoring as a mechanism to reduce stroke rate. There have been literally hundreds of papers regarding the various available techniques for neurophysiologic monitoring during CEA, and no consensus as to what is best. With the continuing very rapid advances in computer technology and signal processing, an improved technique may well be about to enter clinical practice.

With regards to the future of CEA and CAS it is clear that CAS will continue to be performed in patients who are at high surgical risk. Up to date recommendations for indications for both CEA and CAS will be presented. There is no doubt that technical progress with therapeutic options and new options for carotid artery revascularization will enter widespread clinical practice. Transcarotid revascularization (TCAR) is a relatively recent advance that has a good chance of becoming widespread if initial low procedural stroke rates are confirmed in ongoing trials. This is a system that allows for brain protection from embolism while the carotid artery is exposed is currently in clinical trials. Reversal of blood flow from the brain to the femoral vein during carotid artery stenting ensures that atherosclerotic debris will mainly flow to the leg instead of the brain. This would address the achilles heel of previous CAS procedures, the persistently high procedural stroke rate. Proof of concept has been published on 208 patients in the ROADSTER trial, which achieved a stroke rate of 1.4%, comparable to the best results achievable with CEA. Anesthetic requirements for this procedure will be discussed (21,22). Exactly what to do for patients with asymptomatic carotid stenosis will continue to be a difficult question. Medical therapy for carotid artery disease has improved, so procedural stroke and death rates will have to be very low to justify widespread technical intervention in asymptomatic patients.

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Optimizing Safety, Communication, and Teamwork in and Around the Pediatric Operating Room

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"Everyone has two jobs: to do their work and to improve their work."
—Paul Batalden, M.D.

Abstract

The future of perioperative healthcare delivery, and anesthesiology services in particular, is bright. At the same time, the fundamental components of human interaction are being challenged in both predictable and unpredictable ways. Significant variations in quality of care provided to pediatric patients have been documented and lead to substandard care that contributes to diagnostic and medication errors. The quality of pediatric perioperative healthcare delivery is dependent on meaningful integration of past essential components of compassion, communication, caring, and curing into the future. This foundation of safety and reliability through prevention is essential by improving processes with a focus on customer service, evolving communication, enhanced teamwork, and through leveraging as well as understanding and respecting the human factors impositions of the culture, organization, and the limitations of technology.

All health care professionals caring for children should consider incorporating quality measurement and a focus on enhancing their team performance and safety into their practice. However, we need to focus on what is the right approach to take and the best questions to ask and address the challenges of aggregating scientifically imperfect tests of change. Effective teams use specific, structured techniques and behaviors that help communicate the appropriate messages in an efficient manner. These techniques and behaviors include: Checklists, Briefings, Debriefing, huddles, SBAR, I-PASS and tools to minimize distractions, critical language, and how to enable safe culture for psychological safety in the OR.

The future evolution of patient-centered care will need to focus on the best outcomes for the patient and address barriers to changes in the culture moving from the "be all" system where the patient adapts to the care model to one where the system is open to collaborating and redesigning the system with consideration of the patient and family's needs. We define continuous quality improvement (CQI) as the daily use of QI methods to improve outcomes while engaging all practice staff. Quality improvement (QI) should become a central part of the work of pediatric clinicians where the patient is the central focus of the service, and all members of the team are focused on optimal and safe care of the patient moving through the perioperative arena. Performance improvement can help pediatric anesthesiologists to ask the right questions when seeking to drive improvement, prevent child harm, and improve the value of care.

Introduction

Health care services have evolved from primitive forms where harm was pervasive, with advances in technology, understanding, economic policy, and outcomes. At the same time potential for harm continues to exist including anesthesia-related causes of preventable injuries and errors, such as from medication errors, that continue to occur even after 30 years of applied research. (1) Ineffective communication and teamwork are flagged by The Joint Commission and the Closed Claims Project as critical elements in causing harm to patients. Increasingly, colleagues, patients, payers and certifying agencies expect such measurement to achieve the Triple Aim of better health, better care and lower cost. In addition, new payment models increasingly pay providers for demonstrated value rather than volume, and they expect participation in continuous improvement. Perioperative care continues to improve with waves of change and innovation that include less invasive procedures, more rapid recovery and shorter hospital stays. Quality and safety have been thrust to the forefront stimulated by novel revelations and renewed attention to limitations of processes and services despite the technologic and therapeutic advances. The care of children is especially dependent on a continued focus and innovation as caring for children of different sizes and communication capabilities carries a unique set of risks and challenges, particularly in the fast paced procedural environment.

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The Clinical Microsystem: The Building Blocks of Safety

The building blocks for safe pediatric anesthesia care are the clinical microsystem. (2) The fundamental differences in quality of service to children are centered around the differences in provider interactions with the family unit and caregivers being of greater importance with respect to communication, engagement and satisfaction. Within this clinical microsystem is leaving a loved one, who may be incapable of effective communication, in the arms of a person who was met shortly before this transition. The microsystem is an organizing design construct in which social systems cut across traditional discipline boundaries. Because of its interdisciplinary focus, the clinical microsystem provides a conceptual and practical framework for simplifying complex organizations that deliver care that provides an important opportunity for organizational learning. Two separate and unique vulnerabilities meet when a child has surgery: The first is total reliance on a provider to care for and keep the patient safe during surgery and the second is the parent/caregiver trusting and completely relinquishing control/care of the patient. These together change the perspective and vision of quality and safety and put a premium on the importance of gaining swift trust and communicating with the family and the patient. Co-production of child perioperative care thus means inviting parents/caregivers into a meaningful decision-making collaboration while ceding control in order in an authentic family centered-care. (3) Younger children in particular have a limited ability to protect themselves and participate in care due to their inability to effectively communicate, but also due to a steep lack of knowledge and lack of understanding of the complex issues and environments in which we conduct pediatric anesthesia care. Most adults on the other hand can ask questions, express anxiety, answer questions and remind providers of allergies and report issues such as a leaking or a painful intravenous line, the need to urinate, or even the signs of a drug reaction such as shortness of breath and pruritis.

The complexity of healthcare production makes improvement in pediatric safety and quality virtually impossible using the same routines and approaches. In particular dealing with children and their families has long been recognized as an essential component of pediatric care. Effective and well designed communication is essential to convey important medical information from providers to providers through the system when the patient is unable to participate. The parent/family must be coopted as active team-members to help facilitate care, instructed what to look for and keep well informed to help keep the patient safe from ever present dangers including in successful activation of rapid response teams for improved outcomes. (4)

Advances in parental presence in the operating room and the importance of child life services have contributed to family and patient centered perioperative care and sense of security. At the same time the integration of the parent or caregiver into the procedural team can be leveraged to further the experience and quality of the perioperative interactions. While in manufacturing co-production has enhanced user satisfaction and integration, consumer ideas and input are highly sought for product enhancement, while the production of a service such as healthcare is dependent on the co-production between the provider and the patient and/or family to maximize the product/service. (3) In the perioperative period, improving integration of family centered care and communication can benefit from novel approaches to optimizing this relationship. Human factors and ergonomics, essentially engineering or redesigning the nature and quality of the interaction of people, technology and equipment, and tasks can create synergy using design as a stepping stone to foster greater team involvement of the family/caregiver in patient care delivery. (5) In the perioperative environment, elements of human factors can be used to redesign approaches to enhance communication and integration of teamwork to enhance satisfaction and improve care delivery.

The Role of Communication in Improving Safety and Quality

Communication in the workplace is the basis of effective, trusting and productive relationships. In the healthcare delivery arena, in particular, it is a critical component of all aspects of patient care and a fundamental tool for safeguarding and advancing the six domains of health care quality according to the Institute of Medicine: safe, effective, efficient, patient and family centered, equitable, and timely. (6) Communication is also the foundation for the triad of optimizing delivery of complex services such as healthcare: communication, teamwork, and customer satisfaction. However, barriers to effective communication can occur at any time, but broad categories of issues arise frequently. These include the impact of the digital domain and changes and challenges of education and learning from the generational divide. Understanding and addressing these human factors issues may enhance safety, help develop more meaningful processes that mimic the real work of anesthesia versus the imagined work, thus addressing real work and safety constraints, and enhancing the quality of the teamwork. (7)

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Communication manifests in four major ways to improve both safety and quality of pediatric perioperative care: a) family centered communication and teamwork, b) facilitating and enhancing communication through a climate to foster and enable family and health care providers to speak up, c) enhancing reporting or communication of issues, problems and events after they occur, and d) patient and family quality and assessment postoperatively (patient reported outcomes (PROM).(8) The first focus of family centered communication begins in including the family and the patient in the team. Including the family in rounds in the ICU improves satisfaction through connecting and generating comfort and confidence. (9) For the OR, the ideal place to involve the family could be in the pre-op area and during the surgical timeout. Since the timeout occurs in the operating room just prior to the procedure, this is not possible as we are not at the point of parent presence during operations, at least yet. One approach is to bring the OR to the family by using a "check-in" process immediately prior to going into the operating room in the pre-op area. This is effectively a redesign of the OR transition workflow to include the family and the patient in the a focused deliberate process. The OR nurse, holding room nurse, anesthesia providers, the patient and the family go over to the patient and discuss the issues, consents, sites, equipment needs and availability, allergies and all other issues in a team format and with a checklist. The patient and parents are directly engaged to verify correct procedure, identity and patient related issues and encourages their role in the peri- and post-operative care. This occasionally results in modification of the procedure, adding things such as blood draws or follow-up imaging studies, or even adding additional involvement of other providers. Inviting the family into this process directly engages the care team more meaningfully and facilitates the integration of equipment, procedures, and concerns prior to induction and when the family or caregivers are still present. This is likely most advantageous when the family is engaged through open-ended questions instead of statements about intent. (10) This directly impacts care through enhanced communication at the organizational wide level, addresses patient expectations and preparedness and engages with the family and care team members by improving family trust and confidence in the team. (11)

Creating a Culture of Trust: The Cornerstone of Safety

The second major way that quality and safety can be improved is by creating an environment where people feel empowered and safe to speak—the psychological safety. (12) This involves reducing or eliminating barriers to honest communication and building loyalty and trust versus the psychological danger of speaking up. A climate where asking questions is encouraged and fostered even if at times uncomfortable is essential to relieving the emotional burden of providers and meaningful communication where team members can honestly raise safety concerns and solutions. (13) This includes the family as well as all health care providers involved in the child's care. Mapping of the patient/family interactions can help or hinder the effective and respectful utilization of the family as part of the team. Bringing the "OR to the patient and family" changes the balance of the team from "we know what we are doing" and "we know best" to the concept that "we want you to be part of the team to help assure the patient gets the best and safest care." This acknowledgment by the surgical team of the primacy of the family in the surgical process can facilitate more attentive and respectful care and encourage team members to working more closely together at the outset. (14)

The Learning Organization: Capturing Process and Outcomes Failures

Outcomes in complex work depend on the integration of individual, team, technical, and organizational factors. A continuum of cascade effects exists from apparently trivial incidents to near misses and full-blown adverse events. Consequently, the same patterns of causes of failure and their relationships precede both adverse events and near misses. Getting clinicians to report these events requires an environment that fosters a rich reporting culture to capture accurate and detailed data about nuances of care. (15) This requires efficient and effective communication through multiple modalities to capture events or concerns of quality and safety that can lead to awareness and measurement of opportunities for process improvement. Information about quality and safety comes in many different forms. Data can come from the electronic medical record: this includes adverse event data that can be tracked, chart reviews with the use of an electronic QI template, and the MPOG and ASPIRE databases (currently working on pediatric specific outcome metrics). Data may also come from electronic event reporting systems and in unrelated verbal daily safety check-ins. Lastly quality and safety data can come from the patient experience assessment from postoperative telephone calls made to every outpatient from a PACU nurse (16), and data can come from the patient experience team in the form of Press-Ganey survey or free text comments both electronically or hand written. The issues that are reported on address all facets of care ranging from simple dirty floors to drug errors, sedation gone awry and inadvertent extubation and include changes in care acuity, readmission, and

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unexpected admissions. Patients and families have been shown to correctly assess the need for alerting rapid response teams. (4)

Any reported event or concern should be reviewed by at least 3 people to get a diverse assessment and evaluation of the reported data. In our hospital we use all of the previously mentioned methods for capture of events and concerns which are later reviewed by a nurse coordinator (for pediatric process improvement and patient safety), a surgeon and an anesthesiologist. A determination is made regarding what intervention is needed including but not limited to, initiating a multidisciplinary review with suggested process redesign and revised training in relation to process improvement, operational problems or personnel issues. Lack of retaliation, fear and ease to report are important to maximize reporting. (17) From the standpoint of quality, deficiencies in patient and family experience and satisfaction should be addressed through a team dedicated to this outcome measure. The follow up is also critical to prevent people from getting discouraged and to encourage future reporting. The use of family stories and their incorporation into team feedback, advisory committee and incorporating families into hospital committees and Board is valuable for their perspective. (18) We believe that many reporting channels are needed to ensure the system is aware of the safety and quality concerns that could pose harm to patients. Honest and timely communication of irregular events and concerns drives front-line ongoing engagement and improvement.

Tools to Measure Reliability, Teamwork and Effective Communication

The science of continuous quality improvement offers a powerful way of thinking about how to transform clinical operations and healthcare teams and how to measure reliability, teamwork and communication. There are five main quality improvement tools that we recommend every anesthesiologist should master— process maps, checklists, Ishikawa diagrams, run charts, and control charts—to improve the process, flow and outcomes of surgical care. (19) The tools help visualize, analyze, and track process and outcome data for both individual and groups of patients and should be used routinely by clinicians and healthcare systems to evaluate and improve care as well in the design of the built environment. (20) The tools can be used to achieve measurable improvements in the efficiency, effectiveness, performance, accountability, and outcomes of quality in services or processes of care. We know there is a tightly coupled relationship between non-routine events, teamwork and patient outcomes. (21)

We are going to focus here on the process map which is, in our minds, the most important quality improvement tool. The other tools can be seen here (22). A process map or a flowchart as in figure 1 is a visual representation of the care process that is created with information provided by team members. The process mapping exercise can help clinicians clarify through visualization what they know about their environment and determine what they want to improve about it. The process maps use common flow chart symbols and can describe the current state or baseline; the improved state in transition, and the optimal state. This exercise helps clinicians make assumptions and expectations explicit and can provide transparent insights on reflecting on their current state and importantly, into how to improve the process of care or to overcome barriers they perceive to its improvement. (2) Working with clinicians to understand their clinical sense-making is essential to sustain their interest and engagement in long-term continuous improvement. (23)

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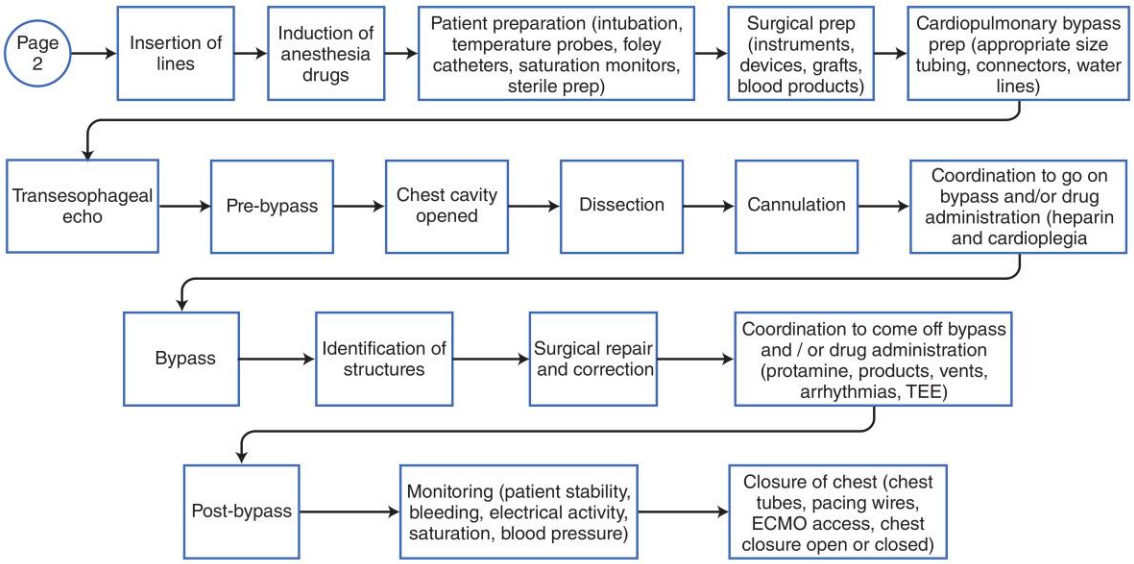

Figure 1. A process map of a pediatric cardiac surgical care operative processes (part of a larger perioperative process map that starts at the prehospital phase and continues through discharge). (22)

A high degree of process awareness often drives the design changes needed to sustain improvement at the individual and team levels. (24) Process mapping describes precisely what an individual provider is required to do and when, in terms of cognitive processes, actions, or both, to achieve the system's goal. Data are collected from observations or interviews that carefully break down complex clinical processes into discrete, measurable, and clear tasks. Team members can gain insights into how they and their colleagues perceive the same tasks and hopefully come to a shared understanding of the process.

Ultimately, improving patient outcomes requires appreciating the inherent links between process and results. Process maps help focus improvement efforts, not for the individual, but for the entire clinical microsystem. Visualizing the process can also help identify inefficiencies (e.g., parallel or redundant processes that have emerged for whatever reason), clarify roles, and reduce ambiguity among team members, all of which can help coordinate patient care across services and microsystems. This process is particularly useful in improving surgical patient transitions of care and avoiding readmissions and bounce back to the intensive care and high-dependency units. (25)

Process maps show how interactions occur, uncover variations, and make the invisible perioperative processes visible. Process maps can be created at different levels of detail to illustrate the major phases or detailed activities in that process. It is important to map the current process, not the desired process, to identify opportunities for improvement. We have used process mapping in multiple surgical and non-surgical settings to better understand the processes of care, including pediatric cardiac surgery and to summarize the data on near misses and adverse events. (26)

Tools and Approaches to Overcome Unseen Barriers to Change

Most serious pediatric adverse patient events or industrial and banking disasters (i.e, NASA Challenger space shuttle disaster, the Italian Cruise Costa Concordia ship wreck, the Wall Street 2008 meltdown, etc), do not arise from single point errors, but from many people committing multiple seemingly innocuous errors over time that breach reasonable practice standards. Vaughan describes allowing such unseen process and decision errors to go unattended as 'normalized deviance'. (27) By deviance, we mean organizational behaviors that deviate from normative standards or professional expectations. Outside people see the situation as deviant, whereas inside people get accustomed to it, seeing it as 'routine, rational, and entirely acceptable'. Low hand-washing compliance before patient contact, minimal attending oversight of OR care at nights or on weekends, suppressing information about poor care, and the poor handoff communication between OR and ICUs and wards are examples of normalized deviance. (28)

Discussion of this sensitive matter using terms such as 'normalized deviance' frequently leads to defensive reactions that halt conversation and require deeper refection and examination. Ashforth and Anand have described organizational normalized deviance as arising from three mutually reinforcing processes: institutionalization,

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rationalization, and socialization. (29) During the institutionalization phase, repetitive practices are enacted without significant thought about the nature of the behavior. The cause of the behavior is often external to any one person; instead it emerges from group interaction and socialization.

A few of these barriers and potential solutions are listed in Table 1, which is based on input gathered from healthcare practitioners. Any of these factors may hold back an organization, but strong leadership cannot be overemphasized as one of the critical elements for effectively driving change initiatives in intensive care. To increase efficiency and close the chasm between optimal patient care and that which actually exists, leaders must abandon adherence to obsolete management models.

Table 1 Barriers to Perioperative Change and Potential Solutions*

Factors Inhibiting Change	Potential solutions
Lack of leadership support	Facilitate contact with peers successful in deploying the methodologies
Resistance or scepticism from staff	Develop stakeholder analysis and use a team-based problem-solving approach.
Hesitancy to invest time and money	Create a business case supported by sound data (i.e. if the project is to focus on reducing infections, document the costs associated with such occurrences including length of stay, supplies, and added labour).
Shortage of internal resources to lead change initiatives	Enlist outside help to drive initial projects or receive training and mentoring in conjunction with projects that produce immediate results
Waning commitment or flavour of-the-month syndrome	Implement a solid communication plan that reaches all levels of the organisation, and build momentum through early, visible wins
Uncertain roles and/or lack of accountability	Adopt management systems and structures that clearly link projects and performance with overall strategies.
This is how we do things here	Addressing actions or care practices that deviates from guidelines, standards or professional society (i.e, ASA) in non-punitive manner

* Adapted from Barach P. Addressing barriers for change in clinical practice. In: Guidet B, Valentin A, Flaatten H, editors. Quality management in intensive care: a practical guide. Cambridge: Cambridge University Press; 2016. ISBN 978-1-107-50386-1. (30)

Successful change in operating room practices will be a function of a willingness to adopt new changes, and challenge dogma and the widespread normalized deviance. Dissatisfaction with the present, a shared vision of the future, and mastery of a core set of process improvement tools are needed. Each of these elements is key and needs to be fully leveraged to bring about change. Change leadership is about tirelessly working on each of these elements. Change leadership is also about ensuring all the people in and around the operating room and those that oversee the surgical pathways in the organization understand the changes, believe in the personal and organizational impact, and have the capabilities and confidence to flourish in the necessarily changing environment.

There are, however, a number of barriers to successful change – both in terms of implementation and equally, if not more importantly, in sustaining it. Why are both kinds of change not more successful? Often, the failures can be traced to a few missing ingredients:

a) A fundamental acceptance or realignment in thinking.
b) Appropriate guidance or knowledge.
c) Clear strategies and tactics for maintaining long-term results.

The upside to past improvement project failures is that they usually provide some valuable lessons for the future. For instance, organizations currently contemplating ERAS programs, introducing Surgical Site Infection prevention initiatives, as one aspect of transformation can learn from the experiences of other units, both inside and outside their hospital or healthcare system. While avoiding a ‘cookie cutter’ approach to change initiatives, such examination can provide useful insights into what worked well, and what gaps may have been overlooked.

The Science of Continuous Quality Improvement

Recognizing the barriers to change of clinical practices requires appreciating the heterogeneity and complexity of interventions implicit in improvement science, including rapid-cycle improvement methods, such as Plan–Do–Study–Act (PDSA) cycles that involve iterative cycles of planning, design, evaluation, and refinement of improvement strategies. (31) The Avedis Donabedian structure–process–outcome model provides the fundamental conceptual framework for delivery improvement evaluating the culture, service innovation in the delivery, and organisation of healthcare, and is encapsulated in the well-described PDSA cycle of quality improvement. (32) It is widely understood today that the first step towards improving the safety and quality of care is addressing the varying

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mental models held by care providers and managers. (33) Because mental models "limit us to familiar ways of thinking and acting," every planning procedure must, at some point, expose and challenge the organization's mental models. This does not mean that all mental models will be changed by a planning procedure and some of our mental models will have to change before we can improve our patient's outcomes.

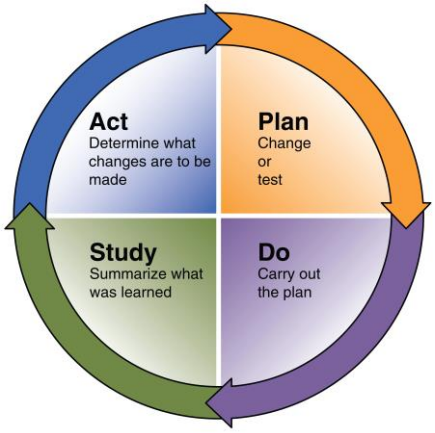

Figure 2. The plan-do-study-act cycle (22)

The implementation and evaluation of changes in structure and process are bound together in a recursive learning cycle of continuous quality improvement, at the heart of highly reliable organizational systems. (34) These HRO inspired systems are considered to be the most reliable and safe social technical systems in the world. Figure 2 shows a PDSA model builds on the Donabedian framework and provides clinicians with a structured theory–praxis methodology for routinely evaluating performance and answering the following questions:

a) What are we trying to accomplish?
b) Are we achieving what we claim and how effective and efficient are we?
c) From where we are now, what changes can we make that will result in improvement?
d) How will we know that we have achieved the change and that it is an improvement?

The PDSA continuous quality improvement cycle is founded on a thorough understanding of the process being evaluated, gained by detailed mapping of the process of interest, selection of appropriate measurement tools, and identification of an acceptable range of variance including in the physical design of the pediatric operating room and equipment and the reduction of hospital and ICU readmissions. (20, 35) The PDSA consists of a four-stage implementation process:

1. Plan: What is to be changed, in what way, and how is subsequent performance to be measured and recorded?
2. Do: Implement the plan and collect measurement data on process and outcome.
3. Study: Analyse the data and amend the plan to address the results of the analysis. Rework the process map to identify new nodes, connections, and issues.
4. Act: Implement the amended plan and collect the measurements again in an iterative recursive manner.

Summary

The most progressive view to define quality is that it is defined entirely by the customer, in our case the child and their parents/caregivers, and it is based upon evaluation of their entire perceived customer experience. (36) Improving teamwork is an important factor in the professional education of physicians in effort to produce insight, provide feedback, engage the team members, and track patient progress. Further integration of human factors and ergonomic redesign with the intent of better approaches to maximize the utility and effect improve patient outcomes. (37) In fact, it is a requirement for using CQI tools effectively. Indeed, ongoing quality improvement efforts are not about which tools are used but about how these tools can of the tools is essential, and this includes communication.

Teams that do not communicate well cannot deliver effective care but are merely groups of individuals working side by side. Effective teamwork and communication are critical to functioning safely in health care. They help groups navigate competing priorities, overcome issues associated with human factors, and reduce the risk of error. Anesthesia training must focus more intently on providing clinicians with the core competencies—the knowledge, skills and attitudes to more effectively communicate with the family and other providers and function as high reliable teams. (38) Anesthesiologists have been and will continue to be leaders in ensuring safe and reliable pediatric care. However, continued vigilance with regard to human factors and a deep and robust focus on systematic rather than personnel issues are vital to ensuring safe pediatric anesthesia. Continued research on how to improve the safety and quality of pediatric perioperative care will be driven by honest and respectful dialogue with providers. This will eventually lead to a deeper understanding of the systemic causes and mechanisms that cause harm and how best to develop resilience to help mitigate this harm and develop more reliable systems of care.

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Preoperative Evaluation in the 21st Century

Each year, over 200 million people undergo surgery worldwide and this population is becoming increasingly medically complex.[1] In the United States, 26% of all inpatient adverse events within the Medicare population are attributable to surgery and procedures.[2] Further, the number of ambulatory procedures performed now exceeds those done on an inpatient basis.[3-4] In such a progressively challenging environment, with an estimate that 44% of adverse perioperative events are preventable, it is essential that the risk of perioperative complications be mitigated. Also, the financial solvency of operating rooms in a fragmented health care system may be jeopardized by incomplete patient information that leads to delayed and cancelled surgeries.[5] As a result, having a sound preoperative process or preoperative clinic creates the ideal setting to optimize the patient's medical condition, ensure patient safety, selection, and maximize economic efficiency within the pre-procedural arena.

Appropriate Pre-Procedural Testing

David L. Hepner, M.D., M.P.H. **Boston, MA**

Preoperative Assessment Testing Clinics coordinate preoperative surgical, anesthesia, nursing and laboratory care. Such clinics have been noted to lead to efficiencies in perioperative care by seeing most patients days before the surgery. The prior history, medical records, previous tests and consultations are reviewed, and a medical history and physical examination are conducted. Laboratory testing, electrocardiogram, and chest x-ray should be ordered if necessary, and it is essential to determine which patients need further workup or consultations in order to assess the patient's readiness for surgery.

The perceived benefit of risk stratification based on results of preoperative testing may be considered to vary with surgical risk. What is the potential that screening tests will assist in risk stratification and management? A number of institutions vary preprocedure testing guidelines based on the risk of the procedure, on the assumption that routine screening is unlikely to impact risk stratification for low risk procedures. Preoperative testing should be based on patient's comorbidities (physical status), on the type of surgery (operative risk) and on findings from the history and physical examination. It is important to avoid repetition of prior testing if there is no change in the patient's condition, and to avoid testing in healthy patients having minimally invasive procedures. Routine testing does not increase safety or the possibility of surgery cancellation, even in elderly patients with multiple comorbidities, for minimally invasive procedures. In a study randomizing approximately 20,000 patients, Schein et al demonstrated that routine screening testing had no impact on risk management and outcome in cataract surgery.[6]

There is no value for ordering laboratory tests solely because of planned surgery. Common tests ordered include urinalysis, hematocrit, white blood cell count, platelet count, general chemistry labs (serum sodium, potassium, chloride, bicarbonate, glucose, and blood urea nitrogen), prothrombin time, partial thromboplastin time, chest x-ray, and electrocardiogram. It has been demonstrated that in close to 50 percent of cases, these tests have been ordered for patients without recognizable clinical indications. Despite twelve percent of these routine tests being abnormal in one study, only 0.5% led to a change in management.[7]

It has been estimated that the annual cost of preoperative medical testing for all types of surgery in the United States was as much as $30 billion in the 1980s with unnecessary diagnostic testing being a substantial component.[8] The value of routine preoperative medical testing has also been questioned.[6] In a study of nearly 20,000 patients undergoing elective minor surgery, patients were randomized to no testing or a standard battery of tests, including ECG, CBC, electrolytes, urea nitrogen, creatinine, and glucose. There were no differences between the two groups in the overall rate of intraoperative complications. Therefore, routine preoperative medical testing does not increase the safety of minor procedures.

Chest X-rays are ordered frequently as part of a routine admission or preoperative evaluation even though available data does not support this practice. Chest X-ray is one of the most expensive tests ordered, it is not predictive of inpatient or postoperative pulmonary complications and very rarely leads to a change in management or cancellation of elective surgery.[9,10] For these reasons, the American College of Radiology recommends against routine admission and preoperative Chest Radiography.[11]

Many physicians express the fear of increased medicolegal risk if they do not routinely order screening or preoperative tests. It could be argued from a medicolegal standpoint that it is better not to order an unnecessary test if the next step to take in the event of an abnormal result is unclear. Should a clinically insignificant abnormal laboratory test finding be uncovered but nothing done, legal action may result at a later time. A complication unrelated to the abnormal result may develop at some point in the future and be blamed on the lack of follow-up.

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In a recent population-based study evaluating preoperative blood work prior to low risk surgeries including ophthalmologic surgery, Kirkham and colleagues report that routine blood work was done prior to nearly a third of low-risk, mainly ambulatory, surgeries.[12] They demonstrate that comorbidities, age, and preoperative medical consultation were associated with routine blood testing. More importantly, they also found that there was significant variation between institutions. Geographic location of surgery was the strongest predictor for preoperative laboratory testing.[12] Similarly, Chen et al. recently demonstrated that preoperative testing before cataract surgery was more likely to be associated with the practice patterns of the ophthalmologist and whether patients had a preoperative visit rather than with patient comorbidities.[13] Over fifty percent of patients underwent a preoperative test prior to cataract surgery,[13] despite significant evidence and national guidelines against the utility of routine preoperative testing.[14,15] The authors suggest that providing institutions and individual providers feedback about rates of testing has the potential to reduce low value care.[12]

Recently, multiple primary care and specialty physician groups joined forces to create the '*Choosing Wisely'* campaign, aimed directly at decreasing the burden of unnecessary testing.[16] Each of the participating professional physician societies provided a list of five tests that should be performed less often, and the necessity of which should be questioned by physicians and patients when suggested. The American Society of Anesthesiologists is a partner in the Choosing Wisely Campaign, and is encouraging ongoing dialogue between patients and anesthesiologists to eliminate unnecessary tests and procedures.[17] Common low-value tests to question in anesthesiology include baseline laboratory studies in healthy patients without significant systemic disease when blood loss is expected to be minimal.[18] Even though baseline laboratory studies are discouraged in low risk patients based on low impact on quality, high cost of care, and weak evidence for their recommendation, they were still ordered in a third to half of patients in recent studies.[12-13]

The problem is not only the unnecessary test, but the actions taken as a result of an abnormal test. A false positive result, or an abnormal result that may not affect the anesthetic or surgical management, can lead to further testing, consults, and procedures that incur additional costs and potential complications. In an era of value-based medicine, the only justification of preoperative screening is that the health benefits outweigh the health risks and are worth the dollar costs. Laboratory tests are not good screening devices.[19]

Preoperative Evaluation

The most recent revision of the ACC/AHA perioperative guidelines provides an algorithm for evaluation and testing.[20] Current guidelines for cardiac risk stratification rely on urgency of procedure, stability of disease, clinical risk predictors including relative risk of surgery and functional capacity. Perioperative testing should only be conducted if it will impact decision making towards the surgery or perioperative care.[20] However, routine clinical evaluation is neither completely sensitive nor specific for cardiac risk estimation due to the inability to assess the functional capacity in some patients with orthopedic, vascular or thoracic disease.

Cardiac risk factors are generally utilized as clinical predictors for coronary artery disease and are elicited based on the history and physical examination. The most recent perioperative guidelines continue to use the revised cardiac risk index (RCRI) developed by Lee and colleagues for the prediction of heart disease for stable patients.[21] The RCRI identified six independent risk correlates, including ischemic heart disease, congestive heart failure, cerebral vascular disease, high risk surgery, diabetes mellitus (insulin dependent) and chronic renal failure (creatinine>2.0 mg/dL), where increasing number of risk factors correlated with increased risk for major cardiac complications. Not only is it essential to take into account the patient's cardiac risk factors, but also the relative risk of surgery in order to appropriately develop guidelines for preoperative testing. For this reason, the algorithm combines medical conditions and surgical risk for perioperative major adverse cardiac events. The relative risk of surgery is based on the risk of developing cardiac death and myocardial infarction during noncardiac surgery and is now divided into low and high risk procedures (previously low, intermediate and high). The risk of cardiac events ranges from <1% for low risk procedures to ≥1% for high-risk procedures. The most recent perioperative guidelines only considers intraperitoneal, intrathoracic, or suprainguinal vascular as high risk procedures.[20] The presence of two or more of the above named risk correlates place the patient at high risk for perioperative adverse cardiac events. For high risk procedures, one or more risk factors place the patient at high risk for major adverse cardiac events.

The probability of silent cardiovascular disease could be elicited by the presence of obvious symptoms during the history taking. The patient's functional capacity is assessed by daily living activities and exercise capacity, and is used to evaluate symptoms of potential cardiovascular disease such as shortness of breath and chest

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pain.[22] Functional capacity is also a predictor for perioperative cardiac events. It is necessary to determine the patient's functional capacity for those patients at elevated risk for major adverse cardiac events. Patients that can do at least 4 METS can reasonably proceed to the operating room without further cardiac testing. Patients at elevated risk with poor functional capacity may benefit from further cardiac testing (pharmacologic stress testing). However, this should only be done if the results will change decision making or the perioperative care plan. If testing will not impact decision making or management care, then it is reasonable to proceed to surgery according to guideline directed medical therapy. Alternatively, consider alternative management strategies such as noninvasive treatment or palliation.

ADDITIONAL CARDIAC TESTING

Perioperative assessment for prevention of cardiac complications is an important task of the anesthesiologist. Cardiac preoperative evaluation of the noncardiac patient relies on information from multiple sources: the medical record, history, and physical examination; and findings from medical tests, including electrocardiogram (ECG). As outlined above, other factors to be considered include coexisting medical disease, clinical risk factors, and the patient's functional capacity.

Since risk assessment relies on a medical history and physical examination, it is important to be more selective in the ordering of cardiac tests. A test is likely to be indicated if it can identify abnormalities and change the diagnosis and management plan, or the patient's outcome.[23] Excessive cardiac testing is expensive, and it may delay the operation and place the patient at risk for unnecessary interventions. It has been shown that an efficient anesthesiologist-directed preoperative clinic can decrease non-invasive diagnostic testing.[24]

Electrocardiogram

Routine ECGs have been reported to be abnormal in 7.0-42.7% of cases in 12 different studies but led to changes in management in only 10% of these cases.[25] The rate of ECG abnormalities and changes in management increased when the ECG was ordered based on the history and physical examination. Important clinical characteristics to consider when making a decision to order an ECG include cardiovascular or respiratory disease, multiple cardiac risk factors, and the surgical risk. There is currently no consensus regarding a minimum age for obtaining an ECG prior to a noncardiac surgery.[25] Patients at higher risk of having a significantly abnormal ECG are those older than 65 years of age or who had a history of heart failure, high cholesterol, angina, myocardial infarction, or severe valvular disease.[26] The ACC/AHA 2014 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery discourage preoperative ECGs in asymptomatic persons undergoing low-risk surgical procedures regardless of age.[20] Even though ECG abnormalities are more common in older patients, they are not predictive of postoperative complications.[27] Therefore, a preoperative ECG ordered routinely in those older than 50-60 years does not seem to add any value in predicting postoperative complications beyond cardiac risk factors. The ACC/AHA 2014 perioperative guidelines state that preoperative resting 12-lead electrocardiogram (ECG) is reasonable for patients with known coronary heart disease, significant arrhythmia, peripheral arterial disease, cerebrovascular disease, or other significant structural heart disease. Furthermore, they state that a preoperative resting 12-lead ECG may be considered for asymptomatic patients, except for low-risk surgery.

Echocardiogram

A preoperative echocardiogram is recommended in patients with clinically suspected moderate or greater degree of stenosis or regurgitation if there is any progression of clinical status or worsening of the physical examination. Even if there have been no changes in clinical status, an echocardiogram is recommended if it has been at least a year since the last one.

The current guidelines consider assessment of left ventricular function reasonable for patients that have dyspnea of unknown origin or worsening dyspnea with a history of heart failure. It is also reasonable to repeat echocardiography in patients with heart failure that have not been reevaluated during the last year.

Pharmacologic stress test

Patients at high cardiac risk with poor or unknown functional capacity may benefit from further cardiac testing to assess for myocardial ischemia if the results may lead to a change in management. It is also reasonable to perform a stress test in patients at high cardiac risk with unknown functional capacity to assess for functional

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capacity if it will lead to a change in management. Routine screening with noninvasive stress testing is not useful for patients at low risk for noncardiac surgery.

SUMMARY

The preoperative assessment provides an invaluable opportunity to stratify, manage and optimize risk. Risk stratification, management, optimization, documentation, and communication to the care team will allow all providers involved in preoperative care the opportunity to ensure the best possible patient outcomes. Additional tests, evaluations and consultations should only be done if the information to be obtained will result in changes in the perioperative management of the patient.

Moving away from preoperative testing to the practice of preoperative medicine

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Major surgery is associated with significant physiologic stress and adverse outcomes short- and long-term.[28] Approximately 15% of patients having in-patient non-cardiac surgery are at risk for serious complications including disability or death. Worldwide, 200-250 million patients have surgery yearly; many are aged with severe comorbidities and advanced disease. Up to 2.5 million patients will die (1% risk) and 12.5 million will have costly adverse events (5% risk).[29] A little over 12% of patients account for 80% of postoperative deaths.[30] Mortality rates vary widely across hospitals and countries. Evidence suggests that high-risk patients are often not identified preoperatively, and proven strategies to lower risk are not implemented. Risk assessment can lead to changes in medical management, planned anesthesia and surgery, postoperative care, or recommendations to avoid surgery. Advanced age is a strong predictor of postoperative mortality and morbidity from cardiovascular (CV), pulmonary, and infectious causes.[31] Elderly patients >75 years have twice the risk of serious morbidity and 3-7 times the risk of dying compared to younger patients. The frail elderly and those undergoing cancer procedures are at particular risk. Frailty independently predicts postoperative complications, length of stay (LOS), and discharge to an assisted-living facility.[31] Determination of a frailty score supplements other risk models. Impaired cognition, low albumin, previous falls, low hematocrit, functional dependence, and multiple co-morbidities are associated with 6-month mortality and inability for discharge home postoperatively.

Most patients with chronic dyspnea of unclear etiology have one of four diagnoses: asthma, COPD, interstitial lung disease, or cardiac dysfunction . Miscellaneous conditions, including deconditioning, account for the rest. The history and physical examination leads to diagnoses in two thirds of cases. Initial testing includes an ECG, hematocrit, arterial blood gases, thyroid function tests, chest radiograph, spirometry, and oximetry (resting and after walking several feet).

Postoperative pulmonary complications (PPO) incur the highest costs. PPO reduce median long-term (5-10 years) survival by 90%. Established risk factors for PPO include a history of cigarette use (current or exceeding 40 pack-yrs); ASA-PS $\geq$ 2; age $\geq$ 70 years; COPD; neck, thoracic, upper abdominal, aortic, or neurologic surgery; procedures $\geq$ 2 hours, general anesthesia (especially with intubation); albumin concentration < 30 g/L; inability to walk 2 blocks or climb 1 flight of stairs; or a BMI $\geq$ 30.[32] Heart failure (HF) is one of the strongest predictors of PPO. Asthma, arterial blood gas, chest radiograph or pulmonary function test (PFT) results are not predictive of PPO. Risk is greater with recent exacerbations, prior PPO, recent hospitalizations, or intubations for asthma. Some risk factors for PPO are modifiable. Exacerbations or infections must be improved whenever possible. Antibiotics, bronchodilators and steroids, or delay of surgery are important in high-risk patients. Delaying surgery up to one month before lung resection in high-risk, cancer patients with respiratory compromise for “prehabilitation” is associated with short- and long- term survival. Changes in management, including altering the surgical procedure, alternatives to general anesthesia, and epidural pain management are effective in decreasing PPO.

Exposure to tobacco, directly or second-hand, increases perioperative complications.[28] Smoking is associated with 40% increased odds of 30-day mortality and 30%-100% increased odds of morbidity, including surgical site infection, unplanned intubation, pneumonia and sepsis. Smoking decreases macrophage function, negatively impacts coronary flow reserve, and causes vascular endothelial dysfunction, hypertension and ischemia. Smokers require longer hospital stays and need postoperative intensive care more than non-smokers. A recent systematic review found no increased adverse events with quitting smoking soon before surgery (i.e., within 8 weeks).[33] Benefits are evident with cessation 3-4 weeks before surgery. Patients should be encouraged to quit smoking at any point preoperatively. Soon after quitting, toxic substances and carbon monoxide and cyanide levels decrease, improving wound-healing and oxygen delivery and utilization. Lower nicotine levels improve vasodilatation.

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Renal disease increases perioperative risk, especially cardiovascular complications. Chronic kidney disease (CKD) is included in several risk scores. A creatinine ≥ 170 µmol/L is an RCRI risk factor equivalent to known stable ischemic heart disease in predicting cardiac risk.[20-21] Estimated glomerular filtration rate (eGFR) is a more accurate measure of renal function, especially for less severe disease. The eGFR predicts short- (< 30 day) and long-term mortality.[34] Even mild disease (eGFR <60 mL/min/1.73 m^2) is associated with a threefold risk of death within 30 days and mortality and CV events long-term. Preoperative kidney disease is the strongest predictor of postoperative renal failure. Risk factors for CKD include age ≥55 yrs, smoking, diabetes, hypertension, dyslipidemia and HF.

Severe liver disease increases perioperative risk, especially with major surgery. Predictors of increased risk include Child-Pugh-Turcotte class C, MELD (Model for End-stage Liver Disease) score >15, acute liver failure, acute alcoholic hepatitis and a serum bilirubin >188 µmol/L. Renal insufficiency in association with hepatic disease causes a particularly poor prognosis. The highest risk surgeries are abdominal (including cholecystectomy), cardiac and emergency procedures, and those with high blood loss. Complications in surgical patients with cirrhosis include pneumonia, infections, and renal and respiratory failure. MELD scores can be calculated with creatinine and bilirubin levels and the INR.[35]

Malnourished patients have significantly higher rates of morbidity or mortality especially poor wound healing, increased LOS and infections. Low albumin levels predict mortality and morbidity. Adequate perioperative nutritional support decreases postoperative complications. Even mild preoperative anemia is associated with increased 30-day mortality.[36] Hemoglobin <8 g/dL is associated with a 16-fold increase in mortality. Morbidity is increased with mild-moderate anemia. In patients with CV disease, diabetes, or CKD and anemia, the perioperative mortality is twice that with the underlying disease alone. Perioperative transfusions are associated with increased morbidity and mortality. A restrictive transfusion strategy (maintaining hemoglobin 7-9 g/dL) is as effective, if not superior, to a liberal approach (hemoglobin of 10-12 g/dL) in critically ill patients, with the possible exception of those with unstable coronary syndromes. Efforts to diagnose and correct anemia preoperatively, especially for elective surgeries, in the elderly, in patients with other diseases or for surgeries with significant blood loss is necessary.

Assessment of a patient's preoperative risk must extend beyond an assessment of their medical conditions and physical status. Patients at the highest risk for surgical complications often have a poor understanding of their health status and overestimate their ability to manage their comorbidities. These patients commonly have poor health literacy, are under- insured, and are of lower socioeconomic status.[37,38] The Institute of Medicine defines health literacy as the degree to which individuals have the capacity to obtain, process, and understand basic information and services needed to make appropriate decisions regarding their health.[39] The Brief Health Literacy Screen (BHLS) is a 3-item self-reported measure of health literacy, developed to rapidly detect patients with inadequate health literacy.[40] Its brevity makes it feasible to apply in clinical practice. Lower health literacy levels are independently associated with longer hospitalization lengths of stay for patients who are undergoing major abdominal surgery.[41]

Patients who exhibit a higher level of catastrophization are at greater risk of poor pain control in the acute postoperative period. Poor pain control leads to longer length of stay, and higher levels of patient dissatisfaction. Furthermore, catastrophic thinking related to pain may increase the risk of developing a chronic pain condition. The pain catastrophizing scale is a validated tool used to identify patients who are at greatest risk of poor pain control in the acute postoperative period.[42] Referrals to integrative health, pain management and psychiatry are all useful components to optimizing the patient's postoperative course while potentially reducing the overall length of time that opioid pain medications are required to manage the patient's postoperative pain.

SUMMARY

Optimal preoperative patient preparation is essential if risks are to be lowered. Further research and development of evidence-based protocols are needed. Optimal results require a multidisciplinary approach with care providers with various clinical skills. A starting point is to use a combination of age, type of procedure, co-morbid conditions, biomarkers, and levels of health literacy and pain catastrophization to stratify patients. Low-risk patients can proceed to surgery without special preparation. High-risk patients must be evaluated by a specialist in preoperative medicine and undergo advanced testing and prehabilitation, as well as health –coaching if needed before proceeding to surgery in specialized centers.

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Organizing and Managing the Preoperative Process

Angela F. Edwards, M.D. **Winston Salem, NC**

The primary goal of a preoperative process is to provide safe, reliable, risk reduction and medical optimization in a comprehensive manner. In order to do so, preoperative clinics have been developed to enhance operating room efficiency, decrease day of surgery cancelations, reduce hospital costs and improve the overall quality of patient care. Although preoperative programs differ in structure, staffing, financial support, and daily operations, they share the common goal of preoperative risk reduction in order for patients to proceed safely through the perioperative period. Effective preoperative evaluation occurs if processes are standardized to ensure clinical, regulatory, and accreditation guidelines are met while keeping medical optimization and patient satisfaction at the forefront. With careful triage based on comorbidities, functional status, and medications, certain low risk patients can often avoid unnecessary clinic visits while higher risk patients receive the necessary evaluations, consultations, and laboratory testing to ensure medical optimization. Well-resourced clinics in centralized locations have the ability to seamlessly provide preoperative services, ancillary testing (e.g. ECG, echocardiogram, laboratory testing and/or prehabilitation), and patient education in addition to maintaining effective communication across the surgical continuum. Collaboration and teamwork in a multidisciplinary context is paramount to such a program's success.

Several models of preoperative care have been previously described in the literature.[43] While, no current universally accepted standard model exists, key components and leadership are necessary to establishing and maintaining a successful preoperative process. The first of which is to determine which patients are recommended to have in-person visits to a preoperative clinic. Triage systems have been developed to assist referring surgeons and proceduralists to choose appropriate patients for in-person clinic visits. Such tools may be either paper or electronic, depending on the resources of the health care system. Historically, triage has been proposed using medical comorbidities and/or American Society of Anesthesiology classification to assess physical status and optimization.[44] With this, ASA class 1 and 2 patients could be triaged to phone screens, whereas ASA class 3 and 4 patients require in person consultation. Phone screening nurses may collect critical information on the ASA 1 and 2 type patients to confirm demographic information, medical optimization, as well as providing pre-procedural education. Higher risk patients with complex medical and social issues can be identified and triaged to in person visits with a trained physician or advanced practice provider. During this time, risk stratification and medical optimization of comorbidities can be ensured such that postoperative risks are minimized. Preoperative identification and management of high-risk patients with complex medical and social issues prior to their surgical admission has been shown to increase patient safety and satisfaction,[45-46] as well as improve efficient utilization of operating room resources.[47] Preoperative clinic visits have been shown to reduce unnecessary testing, subspecialty consultations, and decrease hospital stay.[48-49] Further, preoperative interventions that reduce risk of postoperative complications have led to significant cost savings. It has been well documented that centralizing and standardizing even part of the preoperative process through obtaining outside records, completing history and physical examinations, finalizing surgical, anesthesia, and nursing assessments increases operating room efficiency and decreases costs. The direct and indirect savings achieved by minimizing redundancy, avoiding day of surgery delays and cancellations, and ensuring appropriate documentation and coding offset direct expense of establishing and maintaining a preoperative assessment clinic.[50]

Benefits to developing an effective preoperative clinic include the following:

- Decreased surgical delays and cancelations due to non-medical issues
- Decreased perioperative morbidity and mortality
- Reduction in excessive and unnecessary testing and subspecialty consults
- Increased patient and surgeon satisfaction
- Increased regulatory compliance and operating room efficiency
- Improving information transfers; clean charts (consents, history and physical exams, etc.)
- Ensuring patient readiness promotes efficient operating room turnover times
- Improved patient satisfaction and education; opportunity for shared decision making
- Improved compliance with preoperative instructions (surgical & anesthesia)
- Implementing care coordination in a multidisciplinary context

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Well-established preoperative clinics can coordinate services such that most, if not all, components of perioperative care are brought to the patient and discharge planning can be initiated before the patient leaves the clinic. Medical optimization, chart completion, shared decision making and postoperative care coordination can all be addressed early in the preoperative process. Ideally, the preoperative clinic sets the standards for care and is the model of delivery for all preoperative processes in a given healthcare system.

The operational plan is the specific action plan developed to meet goals and objectives of the preoperative program. The goals noted in the following tables can be used as a springboard for determining which services will be delivered by the preoperative program, keeping current and future scope in mind. Furthermore, the design and development of the preoperative clinic must serve the goals and objectives of the program well.

Goals of the Preoperative Process

Direct Patient Care

Provide comprehensive preoperative evaluation

• Identify, communicate, and minimize the patient-specific risks of surgery and anesthesia
• Consistently apply evidence-based, standardized, consistent, condition-specific protocols for preoperative testing
• Use goal-directed patient medical optimization to reduce case delays and cancellations
  – Develop and implement individualized perioperative care plans
• Perform detailed review of patient medications and give patient-friendly preoperative medication instructions
  – Include any new preoperative medications and maintenance of the patient's chronic medications

Initiate transitional care planning

• Plan the appropriate postoperative level of care
• Provide case management services to plan for post-discharge needs

Provide patient education and counseling

• To reduce anxiety, increase participation and enhance recovery after surgery

Obtain or confirm consent - Confirm the presence of anesthesia & surgical consent prior to surgery

Indirect Patient Care and Non-Clinical Goals

Model Process Improvement

• Create standardized protocols to improve patient outcomes and decrease unnecessary testing
• Distribute protocols as the standard of care for all periprocedural patients

Centralize medical information and coordinate perioperative care

• Provide leadership in the perioperative services across service lines and department
• Manage tasks associated with perioperative patient care
  - Coordinate chart readiness, control information systems, other pertinent tasks
  - Comply with regulatory standards

Improve Perioperative Efficiency and Finance

Perform Research and Provide Education

Surgical Appropriateness

Angela M Bader M.D., M.P.H. **Boston, MA**

Most efforts to improve the quality of surgical care in the United States have been programs to either credential and certify providers, or measure and reduce surgical complications. The greatest unmet challenge in surgical quality is how to address *appropriateness*, i.e., to ensure that every decision to perform an operation fully reflects the conditions, circumstances, and values of individual patients. Appropriateness in surgery requires: 1) the best clinical evidence (right operation), 2) a qualified surgeon (right provider); 3) a healthcare facility that has the necessary resources to perform the operation safely (right place), and 4) a patient who is well-informed and meaningfully involved, and who is undergoing surgery that meets his or her individual preferences and values (right patient). Institutions and programs exist to address the appropriateness of provider and place, including board certifications, hospital privileging procedures, certification, and "center of excellence" designations. In contrast, the need to ensure that decisions for surgery reflect individual patients' values and preferences (right patient) is not as easily addressed with a programmatic or institutional approach, and has thus received inconsistent attention. While surgery often offers symptom relief or improved health status (e.g. reducing chance of heart attack or stroke), surgery is not without risk. Individual patients vary in how much they are bothered by their symptoms, how much

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they desire to reduce the chance of future health problems, and how much risk of surgical complications they are willing to accept. Given this variability, clinicians, healthcare consumers, and researchers have recognized that surgical decision making must be "patient-centered" and shared between patients and providers to ensure that decisions are of high quality, and procedures are selected appropriately. Health care organizations caring for patients undergoing surgical procedures must develop effective systems to ensure that all information, both clinical and nonclinical, is available throughout the episode to ensure high quality decision-making that integrates patient preferences, values and goals.

To achieve patient-centered care, providers need to ensure that patients are well informed and that medically appropriate treatments address patients' needs, wants and preferences. Decision quality is an important indicator of patient-centered care and an outcome relevant for surgical decision making. Prior research suggests that the patient's viewpoint is often absent when treatment decisions are made. In a study assessing the quality of decision making by surveying orthopedic surgeons (and not patients), reported deficits were related to fostering the patient's involvement in making the decision, and making attempts to ensure the patient's understanding.[51] Patients with chronic multiple comorbidities are particularly at risk; in a study of outpatient discussions of primary care doctors and surgeons regarding clinical decisions, only 9% overall met the criteria for complete informed decision making; less than 0.5% of intermediate or complex patients met this criterion.[52] Physicians rarely explored patient preference or whether patients understood the discussion. In summary, improving surgical decision making so that it is oriented toward the outcomes that patients value most should have a significant impact on decreasing inappropriate surgical care.

The reported incidence of poor surgical decision-making ranges from 15-50%. Postoperative studies in general and orthopedic surgery populations testing patients' knowledge of risks of surgery after signing informed consent paperwork have generally found understanding to be poor. Approximately 50% and 42% respectively were unable to name any potential complications. Analysis of data regarding medical decision making during office visits showed that fewer than 10% fulfilled minimum standards for informed decision making.[53] These studies are limited because they address only a few specific procedures, have small sample sizes, and are of inadequate scope to elucidate the reasons for low quality decision making. In the absence of available data, it is difficult for clinicians, consumers or payers to determine the quality of decisions made about most common medical tests and treatments.

Preliminary studies by our research team

Our pilot data showed that about 13% of patients exhibited deficits in their informed consent process before surgery, and over 33% exhibited other types of deficits.[54] Informed consent deficits refer to not knowing the procedure being performed or the risks and benefits of the procedure. Other deficits related to not having addressed patient values, preferences and goals. For example, 11% of patients expressed doubts about whether in fact they wanted to undergo surgery at all, 76% had not completed advanced directives, and 25% of patients reported that they would have benefited from further discussion.[54] Non-English language and lower educational level were suggestive of higher risk for these deficits. Also, because those scheduled for the intensive care unit postoperatively seemed to be at higher risk of deficits, we have undertaken additional projects to improve communication and concordance in medical decisions for high-risk surgical patients. This includes a grant funded by FAER to develop a training program for communicating with patients who are having surgery and have a DNR order. The purpose is to elicit patient expectations, preferences, goals and values around postoperative care and use of life-sustaining therapy to should they be required to make decisions in the postoperative period.

A recent review outlined the historical approaches to ensuring appropriateness in surgery, and noted that the absence of concordance with patient values and preferences may not be considered sufficiently.[55] In addition, we have reported that within our normal preoperative clinic structure, there are patients who are considered inappropriate for surgery for nonmedical as well as medical reasons.[56] Some of these patients were referred to palliative care.

SUMMARY

A consideration of patient indications for surgery must be assessed in the context of complete assessment of comorbidities as well as concordance with patient values and preferences (figure below). Ongoing work is needed to develop frameworks to ensure that these conversations occur.

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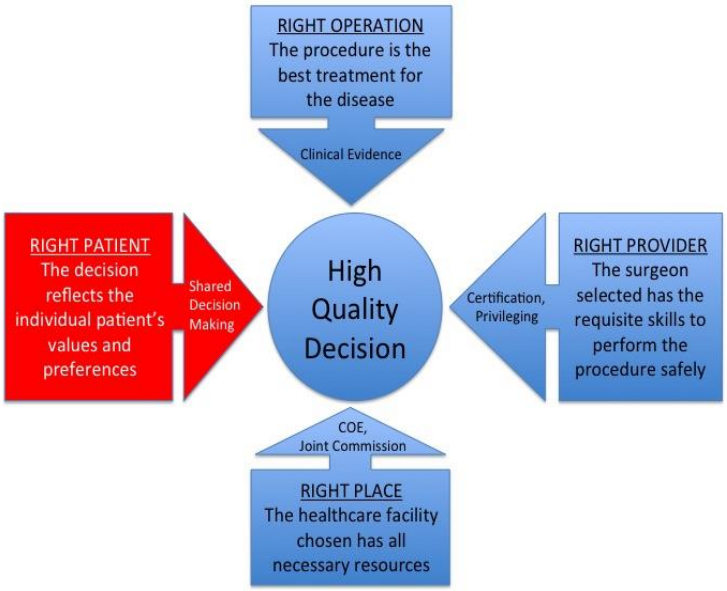

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Aging brain and age-dependent cognitive impairment

Zhongcong Xie, M.D., Ph.D. **Boston, Massachusetts**

Aging brain has changes in both structure and function. The structure changes include loss of neural circuits and brain plasticity, thinning of the brain cortex, decreases in dendritic arbors and dendritic spines of the neurons, and certain degree of DNA damage [1-3]. Generally, there is shrinkage of brain volume, decreased communication between nerve cells and reduced brain blood flow. The function changes of aging brain include the reduction in the ability of findings words and recalling names, paying attention and doing several things at the same time among others.

Age-dependent cognitive impairment generally includes postoperative delirium and postoperative neurocognitive disorder. Postoperative delirium and postoperative neurocognitive disorder are increasingly recognized common phenomena after major surgery, and have become important research areas in the field of geriatrics and aging [4-12]. Delirium occurs in 25 - 50% of geriatric surgical patients, and is potentially associated with Alzheimer's disease, greater postoperative complications, higher mortality, prolonged hospital stay, and higher discharge rates to nursing homes [13-17]. The U.S. healthcare costs attributable to delirium exceed $182 billion per year [18,19]. One to two million Americans over the age of 65 may suffer from postoperative neurocognitive disorder each year [4,9,20-22], and postoperative neurocognitive disorder could be associated with Alzheimer's disease [9,23-26] and Alzheimer's disease pathogenesis [27-30] while discrepant findings also exist [31-36]. At the present time, the lack of sufficient postoperative delirium and postoperative neurocognitive disorder mechanistic studies leads to insufficient knowledge regarding postoperative delirium and postoperative neurocognitive disorder pathogeneses. Consequently, there is no prevention or treatment for postoperative delirium and postoperative neurocognitive disorder. This is particularly alarming given the expected increase in postoperative delirium and postoperative neurocognitive disorder patients as the population of geriatric surgical patients grows, and the potential association between these disorders and Alzheimer's disease [17,23], daily functioning impairments [7], government assistance dependency [37], and increased morbidity and mortality [[4,12], reviewed in [38]]. The pathogenesis of both postoperative delirium and postoperative neurocognitive disorder could include neuroinflammation, apoptosis, accumulation of β-amyloid, Tau phosphorylation and dysfunction of blood brain barrier [15]. However, the exact reason why patients develop postoperative delirium and postoperative neurocognitive disorder remain largely to be determined, especially, why only certain percentage of patients, but not everybody, develops postoperative delirium and postoperative neurocognitive disorder is not known [15]. Finally, there have not been satisfied treatments or preventions for postoperative delirium and postoperative neurocognitive disorder at the present time. More research, including both clinical investigation and basic studies, is needed to understand the pathogenesis of postoperative delirium and postoperative neurocognitive disorder, and to develop the targeted interventions of the postoperative delirium and postoperative neurocognitive [15].

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Practical Management of High-risk Geriatric Patient: Brain, Heart-Lung and Kidneys - *Perioperative Cardiopulmonary Complications in Elderly Patients: More than Just the Heart*

Shamsuddin Akhtar **New Haven/ CT**

Introduction:

The incidence of cardio-pulmonary complications after surgery increases significantly in elderly patients. This is attributed to many factors, which include higher incidence of comorbidities, age-related changes in cardiopulmonary system, frailty, polypharmacy, drug-drug interactions, altered pharmacodynamics and pharmacokinetics, and alteration in immunological and stress response to surgery. Though prevention, evaluation, diagnosis and management of cardiovascular complications has been stressed in the past, it is important to know that the frequency of pulmonary complications far exceeds the incidence of major adverse cardiac events (MACE). In elderly patient who have limited reserve minor decompensation of pulmonary system, for example, atelectasis, pneumonia and hypoxia could lead to cardiovascular stress (MACE, atrial fibrillation), altered mental status, delirium and subsequent complications. This section of the panel will concentrate on cardiopulmonary changes with aging, anesthetics effects on cardiopulmonary system and perioperative cardiopulmonary complications.

Aging and the cardiovascular system:

The elastic component of tissues decreases with aging, while the proportion of collagen increases. Elastin becomes fragmented, because of increased activity of matrix metalloproteinases and collagen becomes increasingly cross-linked. These changes lead to increased stiffness of the tissues causing significant structural and physiological changes in the cardiovascular system.

Two broad structural effects are noticed in blood vessels with aging. One is the natural change in the composition of blood vessels with decreasing amount of elastin and increasing collagen. Cumulative effects of free radicals and glycosylation of proteins also leads to progressive stiffness of the arteries. The vessels become stiff, thicken, though aortic lumen increases with age. The second is the effect of atherosclerosis, which compounds the problem related to aging vessels. These processes occur simultaneously but are different. Atherosclerosis is a heterogeneous process compared to age-related changes that happen quite uniformly throughout the conduit arteries. The severity of blood turbulence and shear stress provide nidus for the process of atherosclerosis. Inflammation is the hallmark of atherosclerosis, while increased cholesterol is a co-factor for the process. Atherosclerosis causes occlusion of the arteries while age-related changes typically cause dilation. Functionally, the arteries become less responsive due to changes in the endothelium. Decrease in nitric oxide production has been noted. However, the effect of direct nitric oxide donor is not affected. Though, the levels of endothelin-1 (which is a potent vasoconstrictor) are increased, the effect of other vasoconstrictor agonists, norepinephrine, ephedrine, phenylephrine is attenuated.

The functional consequence of stiff arteries is that the pulse wave of the ejected blood travels faster. Positive velocity increases by twofold from the age 20 to 80 years independent of the blood pressure. Stiffer arteries also allow pressure to reflect from the periphery to the heart quicker while the aortic valve is still open and the heart is ejecting, thus effectively increasing the afterload on the heart [figure]. Thus, the systolic pressure is augmented. Data from the Framingham heart study shows that systolic blood pressure increases by 5 mmHg per decade until the age 60 and then increases by 10 mmHg per decade, while the diastolic pressure remains the same. The net effect is increase in the systolic blood pressure and no effect on the diastolic blood pressure.

These changes lead to alterations in ventricular-vascular coupling. The heart responds to increased impedance by left ventricle hypertrophy. Left ventricular mass increases by 15% from age 30 to 70 years with subsequent effects on systolic and diastolic function. The incidence of diastolic dysfunction increases with age and this has been proven by detailed echocardiographic studies. Any systolic dysfunction in the elderly should be considered abnormal, especially if it is accompanied by wall motion abnormality. Increased wall thickness also

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makes the myocardium more prone to ischemia. Though the cardiac myocytes continue to multiply during life, their ability to keep pace with apoptosis and necrosis decrease. Consequently, there is a net loss of 50% cardiac myocytes across the lifespan. Older myocytes are stiffer and lack the ability for ischemic preconditioning. The incidence of heart failure increases significantly with age [figure]. With heart failure, the ratio beta-1 and beta-2 adrenergic receptors also change. Typically, left ventricle has 80% beta-1 adrenergic receptors and 20% beta-2 adrenergic receptors. However, in heart failure the ratio changes to 60% beta-1 receptors and 40% beta-2 receptors. This can have significant impact on how the adrenergic agonists and blockers impact the cardiovascular function.

Ventricular septal thickness increases with age as does the thickness of the aortic and mitral valve leaflets. Annular dilatation is very common and 90% of healthy 80-year-old demonstrate some form of mild multivalvular regurgitation, which is typically mild, central and present with normal appearing leaflets. Left atrial chamber size also increases. The incidence of aortic sclerosis and stenosis increases with age.

The electrical system of the heart also declines with age. The number of pacemaker cells reduced by 90% by the age of 70. Prolongation of the PR interval, QRS duration, and QT interval is noted. The incidence of arrhythmia, especially atrial fibrillation, increases significantly with aging. There is no change in the resting heart rate with aging. However, marked decrease in maximum heart rate in response to exercise noted. Response to atropine is halved when compared to younger individuals. While decreased chronotropic response to beta-adrenergic drugs, and inotropic and lusiotropic response to dobutamine has been noticed in the elderly. Heart rate variability, that is variation in instantaneous heart rate, RR interval (which is considered a marker of physiological reserve) is also decreased in the elderly.

Normal age-related changes in the cardiovascular physiology include decrease in peak heart rate, peak cardiac output, peak ejection fraction. In addition, there are changes in autonomic tone and baroreceptor reflex activity. There is an overall dampening of autonomic and baroreceptor activity with aging. This results in a decreased resting heart rate (HR) and a decreased ability to increase cardiac output with changes in heart rate. As compared to younger patients, increases in cardiac output in the elderly are achieved by increasing end-diastolic volume, as opposed to increasing heart rate. This results in an increased reliance on atrial filling for maintenance of cardiac output. Overall, the ability of the cardiovascular to withstand stress is significantly decreased.

Cardiovascular management in the elderly should be governed by the fact that geriatric patients have decreased reserve to tolerate cardiovascular stress and acute hemodynamic changes. Furthermore, they are more prone to ischemia, arrhythmias, and heart failure. Acute cardiovascular management typically involves optimization of the following components of the cardiovascular system: maintenance of optimal vascular tone, optimal fluid volume, adequate contractile function of the heart, prevention of ischemia, and maintenance of an optimal heart rate with atrial-ventricular synchrony.

The use of inhalational anaesthesia is associated with myocardial preconditioning and their use, especially sevoflurane, is recommended in patients with coronary artery disease. One of the key factors to keep in mind is that for all inhalational anesthetics, the minimal anesthetic concentration (MAC) decreases by approximately 6–8 per cent per decade after 40 years. Thus, MAC for an octogenarian is some 30 per cent lower than their younger counterpart. Intravenous anesthetics have a more pronounced hemodynamic effect, with smaller doses being required to achieve the same anesthetic level. This is due to pharmacokinetic and pharmacodynamic changes in the elderly. The dose of induction agents should be decreased by 25 per cent and opioid doses may need to be reduced by 50 per cent. Adjusting the anesthetic dose for patient age may help reduce unnecessarily deep anaesthesia, associated hypotension and potentially reduce adverse outcomes.

Aging and the respiratory system:

Age-related physiological changes can be grouped into 3 broad categories: (i) mechanical changes; (ii) changes in gas exchange and (iii) changes in the sensing mechanisms. Progressive decrease in the elastic component of the tissues changes the respiratory mechanics and alveolar architecture. The chest wall becomes stiffer and the lung tissue loses its intrinsic elastic recoil. Thus, chest compliance decreases, while the lung compliance and the respiratory system resistance increases. With aging total lung capacity remains the same, however, residual volume increases while, vital capacity decreases with aging. Mechanical changes lead to increased work of breathing and make elderly more prone to respiratory failure. Due to progressive decline in diaphragmatic strength [25%] in healthy elderly person and changes in the airway, expiratory flows (FEV_1, FEV1/FVC, and FEF 75%) all decrease.

Complex changes at the alveolar pneumocyte level cause a reduction in arterial oxygen tension with age. It is estimated that the arterial partial pressure of oxygen (PaO_2) decreases by an average rate of 0.35 mmHg per year. These aforementioned changes are caused by an increased degree of ventilation/perfusion (V/Q) mismatching and to

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a lesser extent, pulmonary shunting. There is an overall reduction of elastic tissue presence in the interstitium of alveolar tissue. This results in emphysematous-like changes in airway architecture. As a result, there is an increased tendency of airways to close at equivalent lung volumes (closing volume). Closing volume reaches closer to tidal breathing, which makes them more prone to atelectasis. Furthermore, protective cough mechanisms may be attenuated, which may decrease their ability to clear secretions and increase aspiration risk. The endurance of the respiratory muscles also decreases. Functionally, there is reduced respiratory drive in response to hypoxia, hypercarbia and resistive load. Increased airway reactivity is also noticed in the elderly.

Age-related reductions in organ function, muscle mass, and ability to regulate temperature can significantly prolong the effects of many NMBAs in patients over the age of 65 years. In addition, the efficacy of anticholinesterases in reversing neuromuscular blockade may be reduced in this patient population. Clinical studies have demonstrated that when steroid-based NMBAs are administered to the elderly, the duration of action of neuromuscular blockade is increased, and the variability of recovery times is greater. In contrast, no significant differences are observed in recovery times between younger and older patients when cisatracurium is used. Clinical trials have revealed that patients over the age of 65 to 70 years of age are at increased risk of incomplete neuromuscular recovery (TOF ratio < 0.9) in the PACU. In addition, the aged have a higher incidence of complications related to postoperative residual neuromuscular blockade (hypoxemic events, airway obstruction, symptoms and signs of muscle weakness) in the early period after anesthesia and surgery. Careful management of neuromuscular blockade is essential in avoiding complications in this high-risk patient population.

Perioperative cardio-pulmonary complications and perioperative brain health

Perioperative surgical outcomes are dependent on many factors. The two most important factors that are recognized are: (1) surgical risk of the procedure, and (2) number of defined clinical factors in a patient. As the number of clinical risk factors increase and the risk of surgical procedure increases, the overall risk of poor outcomes will also increase. Surgeries performed in high-volume centers specialize staff and resources may also have better outcomes. One should be careful and extrapolating these results to wider populations.

Based on the physiological changes, one would expect that the outcomes in the elderly would be poorer than their younger counterparts. However, this has not been shown clearly. One of the reasons for this unexpected observation is that though the aging process occurs, the rate of decline or function varies significantly between individuals. The rate of decline is dependent on genetic factors, diseases and environmental insults. Thus ‘a healthy’ 80 years old may the more physiologically robust than a 70-year-old with co-morbidities. Epidemiologically, it may be difficult to differentiate between their outcomes. That is the reason that advanced procedures cannot be denied to elderly patients solely on the basis of age. One should consider co-morbidities and functional level of the patient.

The probability that an octogenarian will be completely healthy is remote. According to 2011 American Heart Association statistics, the prevalence of cardiovascular disease in patients older than 80 yrs was 78 - 85%. The incidence of hypertension is more than 65%, coronary artery disease is 23 - 37% and congestive heart failure is 13 - 15%. Furthermore, the incidence of diabetes, renal insufficiency, atrial fibrillation and chronic obstructive pulmonary disease increases significantly with aging. In a study involving 1000 patients 80 years and older who underwent cardiac procedures, 23% had diabetes, 82% had hypertension, 23% had coronary artery disease, 11% had congestive heart failure, 30% had a serum creatinine greater than 1.3 mg per deciliter and 20% had atrial fibrillation[1].

These patients have significantly poorer outcomes than their younger counterparts. This has been shown its national database and individual studies. In one study involving 1000 octogenarians, the overall 30-day mortality was 8.4%; 7.9% for AVR, 7.4% for CABG, and 10.1% for AVR + CABG, differences between procedures were not statistically significant. The operative mortality of octogenarians undergoing cardiac surgery is reported in the literature to range from 5.8% to 11%, compared with 2.7% to 4.1% in younger patients. The national database also show that the operative mortality is 2-5 times higher in octogenarians than younger patients. This is also true for non-cardiac surgery. Though vascular procedures are known to have high risk of adverse events (5-20%), the risk after orthopedic procedures is also significant. According to one study, urgent hip fracture surgery can have 5-7% risk of adverse events while the risk after elective knee and hip arthroplasty is 1.5-3%.

Postoperative complications, as high as 60- 63%, have been reported in some studies[7,8]. Pulmonary insufficiency or infection was one of the leading causes of postoperative morbidity. 21% of the patients suffered from prolonged (>24 h) mechanical ventilation. Similarly, octogenarians have a significantly higher risk for any complication with cardiac surgery, including neurologic events, pneumonia, dysrhythmias, and wound infection. Atrial fibrillation and surgical wound infection happens more frequently. Stroke rate is also twice (5.7% versus

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2.6%)[12]. Delirium as part of post-operative complication is observed more frequently in the elderly patients. Neuro-cognitive dysfunction is very common after cardiac and non-cardiac surgery. Acute confusional state and delirium is very common in the elderly (5 to 45%) after major surgery the incidence of long-term decline, in cognitive function is also very common. This has been most clearly demonstrated after coronary artery bypass surgery [20-40%]. The incidence of cognitive dysfunction is about 3 - 9 times higher after non-cardiac surgery compared to their nonsurgical counterparts. Many of these complications are common for increased hospital length of stay and subsequent increase in cost.

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Anesthesia for Patients With Pulmonary Hypertension: Pearls, Pitfalls and Pott Holes!

Mark D. Twite MA MB BChir FRCP **Denver, Colorado**

Key Points

- Pulmonary hypertension is defined as a mPAP ≥ 25mmHg at rest. There are different definitions for pulmonary hypertension in children compared to adults, including separate definitions for biventricular and univentricular circulations.
- The current 2013 Nice classification of pulmonary hypertension has 5 groups which may also be considered physiologically with respect to the pulmonary vascular bed as *Precapillary* (elevated PA pressure and PVR with normal PAWP), *Postcapillary* (elevated PA pressure and PVR with elevated PAWP) or a mix of both.
- A comprehensive evaluation of patients with newly diagnosed pulmonary hypertension is essential to determine management and prognosis
- Measuring hemodynamics in the cardiac catheterization laboratory is the 'gold standard' for diagnosis and monitoring therapeutic response
- Three classes of pulmonary vascular vasodilating drugs are available for the treatment of pulmonary hypertension: prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors.
- End stage therapies include; atrial septostomy, Pott's shunt and lung transplantation.
- Patients with pulmonary hypertension are at increased risk of cardiac arrest and death under anesthesia. Those with suprasystemic pulmonary hypertension are at greatest risk.
- Acute pulmonary hypertensive crisis can occur in patients with pulmonary hypertension and is life threatening.
- There is no single ideal anesthetic agent for patients with pulmonary hypertension. It is essential to understand the different hemodynamic effects of anesthetic agents and adopt a balanced anesthetic technique.

Definition of Pulmonary Hypertension

Pulmonary hypertension is defined as a mean pulmonary artery pressure (mPAP) ≥25mmHg at rest. A normal mPAP is around 15mmHg at rest and it is independent of age, gender and ethnicity. During exercise, as cardiac output increases, there is a corresponding small increase in mPAP due to the large capacitance of the pulmonary vascular bed. This increase in mPAP during exercise is dependent on the level of exertion and on age. However, a mPAP >30mmHg during exercise suggests the diagnosis of pulmonary hypertension. Pulmonary hypertension is a progressive illness, and the main cause of mortality is right ventricular (RV) failure. Non-invasive imaging to estimate PA pressures and measure RV function, are essential to monitor response to treatment and determine prognosis. Both echocardiography and cardiac MRI are non-invasive imaging techniques which can measure global and regional cardiac function and estimate PA pressure. Both techniques have their advantages and disadvantages.(1) However, the 'gold standard' is to directly measure hemodynamics in the cardiac catheterization laboratory. Echocardiography may reveal changes associated with pulmonary hypertension, such as right ventricle hypertrophy, dysfunction and interventricular septal flattening. If there is a regurgitant jet through the tricuspid valve due to elevated pulmonary artery pressures, then it is possible to estimate the PAP using the modified Bernoulli equation as follows:

$$\text{sPAP} = 4v^2 + \text{RAP}$$

$$\text{mPAP} = (0.61 \times \text{sPAP}) + 2$$

v = tricuspid regurgitant jet velocity
RAP = right atrial pressure

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Limitations to this estimation include the need for a regurgitant jet to be present, and it assumes good alignment between the Doppler beam and jet, which may be operator dependent.(2)

In the cardiac catheterization lab, hemodynamics of the circulatory system may be measured directly and pulmonary vascular resistance calculated from Ohm's law:

$$F = \Delta P / R$$

Rearranging the equation $R = \Delta P / F$

$$PVR = (Pin - Pout) / \text{Pulmonary flow}$$

$$PVR = mPAP - LAP / CO$$

F = Flow
P = pressure
R = resistance
LAP = left atrial pressure
CO = cardiac output
PVR = pulmonary vascular resistance

A normal PVR is 90 – 120 dynes/s/cm^5, reported using the international system of units. However, many cardiologists will convert this number to Wood units by dividing it by 80, to make a normal PVR 1 – 1.4 Wood units. (3) In addition to calculating the PVR from directly measured hemodynamics, the cardiac catheterization laboratory allows vasoreactivity testing of the pulmonary vascular bed. Short acting pulmonary vasodilators, such as inhaled nitric oxide (iNO), are typically used. Patients who demonstrate a response to a vasodilator, may benefit from a calcium channel blocker. (4)

Classification

Interest in pulmonary hypertension as a disease, became prominent in the early 1970s when many young women were being diagnosed with the condition. It turned out that many of them were taking an appetite suppressant, Fen-Phen (a combination of two anorectic drugs fenfluramine and phenteramine), which was later linked to pulmonary hypertension and withdrawn from the market by the FDA. The first world symposium on Pulmonary Hypertension took place in Geneva, Switzerland in 1973. The most recent fifth and sixth world symposiums took place in Nice, France in 2013 and 2018 respectively. The fifth symposium gave rise to the currently used 'Nice Classification'.(5) This system classifies pulmonary hypertension into 5 groups as follows:

1. Pulmonary arterial hypertension
2. Pulmonary hypertension from left heart disease
3. Pulmonary hypertension from lung disease and hypoxia
4. Pulmonary hypertension from chronic thromboembolic disease
5. Pulmonary hypertension from unclear mechanisms

These broad five groups have many subgroups. PH classification may also be considered physiologically with respect to the pulmonary vascular bed as *Precapillary* (elevated PA pressure and PVR with normal PAWP), *Postcapillary* (elevated PA pressure and PVR with elevated PAWP) or a mix of both.(6) There is also a separate 2011 Panama classification system for children with pulmonary hypertension, which accounts for chromosomal, post-natal course and other factors on lung development. (7) There is a refined definition of PH for patients with single ventricle circulation, where a transpulmonary pressure gradient >6mmHg or a PVRI > 3 Wood Units m^2, defines PH even if the mPAP < 25mmHg.

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Medical therapy for Pulmonary Hypertension

The current treatment strategies for PH are aimed at three pathological processes.(8) Vasodilators treat reactive vasoconstriction, anti-proliferative drugs attenuate vascular remodeling, and anti-coagulation may be used to treat and prevent thrombosis from forming in narrowed vessels. On the basis of the understanding of abnormalities of the vascular endothelium, three classes of pulmonary vascular vasodilating drugs have been studied for the treatment of PH: prostacyclin analogues, endothelin receptor antagonists (ERA), and phosphodiesterase-5 inhibitors (PDE5-inhibitors). General supportive measures include; physical activity and rehabilitation, birth control, diuretics, oxygen and the control of arrhythmias. The beneficial effects of these drugs and supportive measures, are an improved quality of life and increased survival.

Calcium Channel Blockers (CCB)

Acute responders to vasodilator testing are treated with CCB such as amlodipine, nifedipine and diltiazem. CCB inhibit the calcium influx through the slow channel into the cardiac and smooth muscle cells, causing relaxation of the pulmonary vascular smooth muscle. Adults with idiopathic PH, who were acute responders to vasodilator testing and treated with CCB, showed improved 5 year survival (94%) compared to those not treated with CCB (55%).(9)

Prostanoids

Patients with PH have reduced expression of prostacyclin synthetase in pulmonary arteries. The prostanoids, which are prostacyclin analogues, act via cyclic AMP in the smooth muscle cell to produce vasodilation. They may also have some anti-proliferative effects.

Epoprostenol (Flolan®)

This prostacyclin analogue has a very short half-life (3-6 minutes) and needs to be administered continuously, usually through a permanent central venous catheter. Side effects include facial flushing, headache, jaw pain and abdominal pain.

Treprostinil (Remodulin®, Tyvaso®)

This prostacyclin analogue has a longer half-life (4-5 hours) but needs to be administered by subcutaneous injection. Pain at the injection site severely limits the use of this drug in children. For those able to tolerate frequent subcutaneous injections the side effects are similar to epoprostenol. Other administration routes are under investigation, and the inhaled route has been shown to be effective.

Iloprost (Ventavis®)

This prostacyclin analogue is delivered by the inhaled route, and because of its short half-life (20-30 minutes) it needs to be administered 6-9 times per day. This frequency of administration, in addition to the side effect of increased lower airway reactivity, has limited its use in the chronic treatment of patients with PH.

Endothelin receptor antagonists (ERA)

Endothelin is a potent endogenous vasoconstrictor that acts via the endothelin type 1 receptor (ET). This ET receptor has two subtypes, ET_A and ET_B, which are present in pulmonary vascular smooth muscle cells, producing vasoconstriction when activated. ET_B receptors are also present in the pulmonary vascular endothelium and when activated produce vasodilation. Despite the differences in receptor subtype activity depending on location, both non-selective ET_A/ET_B receptor antagonists [*Bosentan* (Tracleer®)] and selective ET_A receptor antagonists [*Ambrisentan* (Letairis®) and *Macitentan* (Opsumit®)] are similarly effective in patients with PH. ERAs may be administered via the oral route and require close monitoring for hepatic toxicity.

Phosphodiesterase-5 inhibitors (PDE-5i)

Nitric oxide acts via a cyclic GMP (cGMP) pathway in the pulmonary artery smooth muscle cell to produce vasodilation. This pathway may be stimulated directly with iNO or the breakdown of cGMP may be inhibited by PDE-5i, resulting in increased cGMP and pulmonary vascular vasodilation. These inhibitors also have antiproliferative effects.

Sildenafil (Revatio®)

Sildenafil is an oral PDE-5i usually administered three times daily. Pediatric PH treatment with sildenafil has changed significantly since the STARTS 1 and 2 trials (Sildenafil in Treatment Naïve Children with PAH).(10) These trials were worldwide, randomized, double-blind, placebo controlled studies of oral sildenafil monotherapy in low, medium and high doses. The studies found that functional capacity only improved with high dose sildenafil,

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PVR improved with medium and high dose sildenafil, but mPAP was lower only with medium dose sildenafil. However, hazard ratios for mortality were 3.95 for high versus low dose and 1.92 for medium versus low dose. Review of these data by the U.S Food and Drug Administration (FDA) and the European Medicines Agency (EMA) resulted in different recommendations. Sildenafil was approved for use by the EMA in 2011 with a warning on avoiding higher doses. In 2012, the FDA issued a warning against the use of all doses of sildenafil for children with PH.(11, 12)

Tadalafil (Adcirca®)

Tadalafil is an oral PDE-5i that has the advantage of once daily administration. Its side effect profile is similar to sildenafil including headache, flushing, nausea, myalgia and nasal congestion.

End stage therapies for Pulmonary Hypertension

1. Atrial septostomy

This should be considered when pulmonary hypertension is not improving despite maximum medical therapy. This procedure is performed in the cardiac catheterization laboratory, via a balloon atrial septostomy.(13) While the resultant right to left shunt will improve cardiac output and decompress the RV, it does so at the expense of causing worsening hypoxia. Periods of excessing right to left shunting may result in severe hypoxemia and there is a high incidence of spontaneous septal closure. However, a septostomy is often used as a bridge to lung transplant.

2. Pott's Shunt

This surgical procedure, creates a shunt between the left pulmonary artery and descending aorta. It creates a permanent post-cardiac right to left shunt for continuous decompression of the right ventricle into the systemic circulation. There is a predictable level of cyanosis with preservation of the most oxygenated blood being ejected into the aorta supplying the brain and myocardium. A Potts shunt may be created via a thoracotomy with or without cardiopulmonary bypass.(14, 15) Some centers have even performed this procedure in the cardiac catheterization laboratory using covered stents to create the shunt.(16)

3. Lung transplantation

The advent of PH-specific therapies has reduced and delayed patient referral for lung transplant. Nevertheless, the absolute number of transplants for PH has remained relatively constant over the years. Currently, most patients worldwide receive a double lung transplant. Heart-lung transplantation is reserved for patients with coexisting left-sided heart disease or complex congenital cardiac disease. Recent data show that 5-year survival after transplantation is 52%-75%. Despite the recent implementation of the lung allocation score algorithm, the incidence of death on the wait list remains high for PH patients. Concerns remain that delayed recognition of patients in crisis and timely referral will increase mortality for patients with PH. Lung transplantation, which becomes the only therapeutic option for patients with uncontrolled disease despite maximal therapy, thus remains an essential component of the treatment algorithm of PH.(17, 18)

Perioperative risk

Patients with pulmonary hypertension are at increased risk for complications while undergoing general anesthesia for procedures. In adults the risk of mortality is around 10% for major surgery. Risk factors for adverse events in patients with PH having non-cardiac surgery include patients factors and surgical factors. Patient risk factors are New York Heart Association functional class >2; a six-minute walk distance less than 300m; history of coronary artery disease, pulmonary embolus and/or renal insufficiency; right ventricular hypertrophy with severe systolic dysfunction and a high mPAP. Surgical risk factors are: emergency surgery; intermediate and high risk surgeries; duration of anesthesia greater than 3 hours and the intra-operative use of vasopressors.(19) Children are at similar increased risk, and this risk appears to be greatest for those with systemic and suprasystemic PH.(20)

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Anesthetic management

The goals of anesthetic management are to AVOID INCREASING PVR and AVOID DECREASING SVR. PVR may be increased by hypoxia, hypercarbia, metabolic acidosis and sympathetic stimulation secondary to noxious stimuli (intubation, endotracheal tube suctioning). A decrease in SVR will lead to decreased coronary artery perfusion which can lead to myocardial ischemia and ventricular dysfunction. A rapid rise in PVR may lead to acute RV failure especially if there is no way for the blood to shunt right to left via a patent foramen ovale or created atrial septostomy.

There is no single ideal anesthetic agent which can safely achieve an adequate depth of anesthesia and analgesia without increasing PVR or decreasing SVR. Therefore, it is necessary to use 'sub-anesthetic' doses of multiple drugs which in their sum create an adequate anesthetic while minimizing their detrimental hemodynamic effects. Table 1 summarizes the effects of the commonly used anesthesia drugs. Those drugs in the lower half of the table are most widely used for the PH population.

Even in experienced hands, it is possible for a pulmonary hypertensive crisis to develop (figure 1). The key in this situation is to quickly address the cause if possible, decrease PVR and augment cardiac output by optimizing the heart rate and rhythm and supporting cardiac function to maintain myocardial perfusion. Table 2 demonstrates a series of steps which can be taken to reverse the PH crisis.

Summary

Pulmonary hypertension has a wide range of etiologies, with the common final pathway of elevated mPAP which eventually leads to right ventricular failure. An acute exacerbation of mPAP during a pulmonary hypertensive crisis can be a life threatening occurrence. It is important for the anesthesiologist to plan carefully to mitigate the chances of a PH crisis occurring, both with the anesthetic technique, and choice and dose of drugs. However, even with optimal perioperative anesthetic management, a PH crisis can occur, and it is essential the anesthesiologist responds quickly and appropriately to stop the downward spiral of the patient.

Figure 1. The cycle of a pulmonary hypertensive crisis

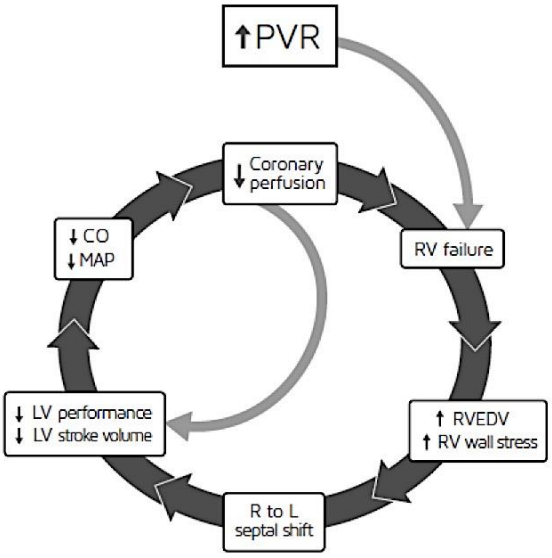

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Table 1. Hemodynamic effects of common anesthetic agents

	Contractility	MAP	SVR	PAP	PVR	HR
Halothane	↓↓	↓↓	↓↓	↓	↓	↓↓
Isoflurane	→	↓	↓↓	↓	↓	↑
Sevoflurane	↓	↓	↓	↓	↓	↑
Desflurane	→	↓	↓	↓	↓	↑
Propofol	↓	↓↓	↓↓	↓	↓	↓
Ketamine	→[a]	→	↑	↑→	↑→	↑
Etomidate	→	→	→	↑	↑	→
Dexmedetomidine	→	↑[b]	↑	→	→	↓↓
Opioids	→	→	→	→	→	↓
Benzodiazepines	→	→	→	→	→	→

[a]Ketamine can depress contractility *in vitro* and in catecholamine depleted patients

[b]Dexmedetomidine can increase MAP during loading dose administration

MAP mean arterial pressure
SVR systemic vascular resistance
PAP pulmonary artery pressure
PVR pulmonary vascular resistance
HR heart rate

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Table 2. Management of a pulmonary hypertensive crisis

Treatment	Rationale
Administer 100% O_2	↑ P_AO_2 and P_aO_2 can ↓ PVR
Hyperventilate	PVR is directly related to P_aCO_2
Exclude pneumothorax	Optimize ventilation
↓ mean airway pressure	Avoid $P_{alv} > P_{art}$
Correct metabolic acidosis	PVR is directly related to H^+ level
Administer pulmonary vasodilators	iNO
Support cardiac output	Adequate preload and inotropic support, ECMO
Support coronary perfusion	Maintain SVR with epinephrine, NE or Vaso
Analgesia	Decrease sensory/sympathetic mediated ↑ PVR

PVR pulmonary vascular resistance
SVR systemic vascular resistance
iNO inhaled nitric oxide
ECMO extracorporeal membrane oxygenation
NE norepinephrine
Vaso vasopressin

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Title: Opioid and Other Substance Use Disorder in Pregnancy: ***Strategies for Success***

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Despite a lower prevalence of substance use disorder in pregnant versus non-pregnant women of child-bearing age, recent national statistics reveal that 6.3% of pregnant patients used illicit substances, with the highest prevalence in the youngest age group (18-25 years; 8.6%).[1] This use is highest in the first trimester (11.2%) and lowest in the third trimester (3.7%). According to a recent retrospective analysis of the Healthcare Cost and Utilization Project (HCUP) data, over the 13 year period (2002-2014), there was a 300% increase in opioid use during pregnancy, stable amphetamine use, and a significant decrease in cocaine use.[2] By 2013-2014, substance use disorder was more prevalent in rural versus non-rural dwelling women.[3]

Opioids

Introduction

Worldwide, the United States accounts for 80% of the opioids consumed. As opioid use and misuse has grown, the total number of deaths in the general population from opioid overdoses increased by almost three-fold.[4] Opioids have traditionally been prescribed liberally by physicians during pregnancy for common complaints such as back pain, headache, and abdominal pain; 14.4% of pregnant women with commercial insurance[5] and 21.6% of pregnant women with governmental insurance[6] were recently found to have filled an opioid prescription in retrospective reviews. In addition, hydrocodone and oxycodone are commonly prescribed for post cesarean delivery pain management. Collectively, these medications have historically been thought of as being low risk in pregnancy. In 2016, the Federal Drug Administration (FDA) issued a back-box warning on immediate-release opioids, highlighting the risk of "misuse, abuse, addiction, overdose and death". These opioids of abuse include the non-medical use of oxycodone and diamorphine (heroin), both semi-synthetic opioids, and more recently, of the synthetic opioids fentanyl, and of the elephant tranquilizer, carbofentanyl. Fentanyl and other synthetic opioids are the fastest growing sector of opioid misuse; the high potency (100x more potent than morphine) and ease of synthesis make it a particularly dangerous drug of misuse. Fentanyl is being used as an independent drug of misuse and is also being mixed with heroin. A recent analysis in Canada showed that fentanyl was present in 89% of seized counterfeit oxycontin tablets.[7]

Other opioids of abuse include other oral (e.g. oxycontin) or IV morphine formulations and medication assisted therapies (MAT) such as buprenorphine and methadone. Crossover between prescription opioid and heroin abuse has also been observed. Studies have shown that the nonmedical use of multiple opioids has been associated with a transition to heroin and heroin users were almost four times more likely to report nonmedical use of opioids in the previous year.[8-10]

On April 20th 2017, the FDA issued an additional warning advising that breastfeeding mothers should not receive codeine or tramadol.[11] This caution was based on evidence that the use of these medications in women who are genetically CYP2D6 ultra-metabolizers can cause excessive amounts of morphine in maternal breast-milk, with the resulting potential for neonatal overdose and respiratory depression.

Further investigation has yielded insight into how changes in prescribing habits can impact maternal opioid use. A recent prospective study demonstrated that there was an association between the number of tablets dispensed and the number of tablets consumed postpartum. Women who were prescribed 31 or more opioid tablets upon discharge consumed significantly more tablets than those who were prescribed 30 or fewer tablets (incidence rate ratio 2.01, 95% Confidence Interval (CI) 1.48-2.76 and 1.35, 95% CI 1.10-1.65, respectively).[12] It is interesting to note that the amount of opioids dispensed was not directly related to pain control, patient satisfaction or the need to obtain prescription refills; however the greater the number of tablets prescribed, the greater the number of tablets that were used by the patient. To better address pain medication needs after cesarean delivery, a follow-up study used shared decision-making between providers and patients to enable patients to choose the number of opioids (less

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than 40) to receive at discharge. The result was a 50% reduction in the number of opioids prescribed, compared to the standard hospital prescription, without increasing refill rates or decreasing patient satisfaction.[13]

Fetal and Maternal Effects

There are several potential negative effects of opioid use in the antepartum period. A retrospective study in women exposed to a variety of opioids in the first trimester of pregnancy suggested a higher incidence of neural tube defects (aOR: 2.2, 95% CI: 1.2-24.2).[14] Though well designed and corroborating animal study findings, this study was subject to recall bias. In addition, pregnancies associated with opioid use/dependence during pregnancy were found to have an increased risk of cesarean section (aOR: 1.2, 95% CI: 1.1-1.3), oligohydramnios (aOR: 1.7, 95% CI: 1.6-1.9), preterm labor (aOR: 2.1, 95% CI: 2.0-2.3), and IUGR (aOR: 2.7, 95% CI: 2.4-2.9). In the same study, these pregnancies were also associated with an increased risk of an extended length of stay (aOR: 2.2, 95% CI: 2.0-2.5) and in-hospital mortality (aOR: 4.6, 95% CI: 1.8-12.1).[15] The odds of having a cardiac arrest or an acute MI were found to be 1.8 times higher in opioid than in non-opioid users in another recent retrospective review, even when adjusting for institutional and individual confounders.[2]

Pregnant women with opioid use disorder are more likely to engage in smoking and other polysubstance use, and are more likely to have concomitant infectious disease (e.g. HIV or Hepatitis B or C). As with substance use disorder in general, these women often have untreated psychiatric disorders and sexual promiscuity, which leads to more frequent pregnancies. The subsequent lack of prenatal care is then associated with more frequent pregnancy complications.

Acute detoxification is generally not recommended during pregnancy, primarily due to concern for relapse, and for maternal and fetal opioid withdrawal. The American College of Obstetricians and Gynecologists (ACOG) instead recommends medication assisted therapy (MAT) with methadone or buprenorphine coupled with associated counseling and optimal prenatal care.[16] Although methadone was historically the MAT of choice, the relative ease of patient access to buprenorphine (i.e. the receipt of a multi-day supply rather than a daily visit to the clinic) and the apparent decreased duration and severity of neonatal abstinence syndrome, have made buprenorphine an increasingly popular choice during pregnancy.[17] Rarely a pregnant patient may receive opioid antagonist therapy (ie naltrexone) which is now available in a long-acting, intramuscular injectable form.

Breastfeeding is also endorsed in postpartum women who are on stable MAT program with either methadone or buprenorphine, so long as they are not using illicit substances, and are not HIV positive. Increased availability of the reversal agent, naloxone, is credited with helping to combat the growing numbers of overdose deaths.

Anesthetic Management

The altered physiology of pregnant women with opioid use disorder and the pharmacology of their MAT therapy contribute to challenges in peripartum anesthetic care. Whenever feasible, a pre-delivery anesthetic consultation can help to establish trust between the woman and her providers, and provide an opportunity to discuss the multi-modal menu of care options. Women who take opioids chronically are typically tolerant to the analgesic effects, likely through a combination of chronic changes in pain pathways, and, in those receiving buprenorphine, the very high μ receptor affinity of the drug. The competition at the μ receptor between buprenorphine and other opioids inhibits pain management, in both buprenorphine (Subutex) and the formulation that incorporates a small amount of naloxone with low oral bioavailability (Suboxone) to discourage intravenous injection. It is crucial that patients on MAT therapy NOT receive the mixed agonist/antagonist medications (e.g. nalbuphine) commonly used on labor floors for labor analgesia or management of neuraxial analgesia side effects as their use may precipitate maternal and fetal withdrawal. Self-administered nitrous oxide for labor analgesia is not contraindicated in these patients.

Neuraxial analgesia for labor, or anesthesia for cesarean delivery, is highly desirable if not otherwise contraindicated. Studies show that the intrapartum pain scores for parturients on methadone and buprenorphine with neuraxial labor analgesia are like those of their respective controls. However, post-cesarean delivery pain management needs between patient populations were dramatically different from controls not on MAT. Specifically, obstetric patients on methadone therapy needed 70% more opiate analgesic and those on buprenorphine needed 47% more opiate analgesic.[18,19] These patients are not, however, necessarily tolerant to the sedative effects of additional opioids or adjunct medications, likely increasing their risk of respiratory compromise and perhaps contributing to the observed increased risk of cardiac arrest and death.

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MAT or chronic opioid therapy does not contribute significantly to acute pain management, but should be maintained to satisfy chronic requirements. A patient's methadone dose should be confirmed with the primary prescriber and should only be adjusted during pregnancy in collaboration with them, if needed. There are several options for peripartum buprenorphine management, outlined below.

Tips and Pearls

- Vaginal delivery is typically preferred, unless there are obstetric indications for cesarean delivery
- Avoid agonist-antagonist therapy for labor analgesia (e.g. nalbuphine) or for management of neuraxial analgesia-related side effects
- Options for intrapartum buprenorphine management:
    - Opioid replacement prior to admission
        - Advantages: better μ receptor availability for analgesic opioids
        - Disadvantages: logistical challenge; withdrawal/relapse risk; possible difficulty reintroducing buprenorphine therapy postpartum
    - Stop Dose on admission
        - Advantages: better μ receptor availability for analgesic opioids
        - Disadvantages: withdrawal/relapse risk; possible difficulty reintroducing buprenorphine therapy postpartum; increased intrapartum opioid requirements
    - Usual Dose
        - Advantages: continuity of MAT therapy; less relapse risk
        - Disadvantages: interferes with efficacy of intrapartum opioids
    - Divided Doses
        - Advantages: may confer some analgesia
        - Disadvantages: may miss doses

- Implement multi-modal therapy (Be creative!)
    - For labor:
        - Early initiation of epidural, combined spinal-epidural or dural puncture epidural analgesia can facilitate optimal labor pain management and provide an in-situ epidural if a cesarean delivery anesthetic is needed
        - Breakthrough pain during labor or cesarean delivery is most likely a sign of an ineffective epidural catheter rather than related to patient factors
- For post-cesarean delivery pain management:
    - Scheduled non-steroidal anti-inflammatory agents (NSAIDs) & acetaminophen are highly desirable unless contraindicated
    - Transverse abdominal plane (TAP) blocks or catheters may be beneficial
        - Although the additional benefits of TAP blocks in the setting of long acting intrathecal opioids (e.g. duramorph) are not clear, results in this population are not known.[20]
        - Some have advocated reduced doses and/or more posterior placement of TAP blocks given reports of block-related seizures or toxic blood levels in pregnant patients [21,22]
        - Consider neuraxial opioid (e.g. duramorph) +/- local anesthetic (e.g. PCEA) for first 12-24 hours
            - If elective cesarean delivery, consider "split CSE", with lumbar spinal anesthesia and low thoracic epidural catheter for optimal post-operative pain management
        - Consider adding low dose intravenous ketamine infusion
        - Perioperative gabapentin may have some utility in these patients at risk for high intensity post-operative pain (not investigated in this subpopulation)
        - If additional opioids are needed (e.g. po or IV PCA), consider additional respiratory monitoring.
- If receiving adjunct medication with sedative effects (e.g. po gabapentin or epidural clonidine), these patients may be at increased risk for respiratory depression.
- Discharge planning should ideally include:
    - An early postpartum visit with the patient's obstetric provider (e.g. at 2 weeks)

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- Continuation of opioid maintenance therapy with clear instructions regarding dosing
- If opioids have been used for postpartum pain management, then a taper schedule should be provided

Cannabis (marijuana)

Introduction

In 2016, 4.9% of pregnant women reported using cannabis in the past month, with the highest percentage during the first trimester (10.4%) compared to the second (2.5%) and third (2.3%)[1]. Prevalence of use among pregnant women increased 62% from 2002-2014.[23] Recently, synthetic cannabinoid use has also been increasing, associated with more emergency room visits.[24]

Cannabis contains more than 400 compounds (>60 Cannabinoids) with THC responsible for most of psychotropic effects. Cannabis activates two G-protein coupled receptors, one found in the central nervous system, and one in the periphery. [25] Because cannabis is a highly lipid-soluble drug that is sequestered in fatty tissues, it has a long elimination half-life (7 days or 1 month for its metabolites) (Table).[26-28] As cannabis use is often associated with polysubstance use, it can be difficult to separate out the cannabis-specific effects.

Maternal and Fetal Effects

Cannabis produces psychoactive effects including primarily euphoria, anxiolytics, analgesia, and appetite suppression.[25,29] It also has medicinal effects which include antiemesis, pain relief, and treatment of spasticity.[30,31] There is a biphasic effect on the autonomic system with low doses producing a sympathetic effect and high doses, a parasympathetic effect.[32,33] Maternal effects center primarily on disruption of the airway and lungs due to smoking inhalation. A mild maternal abstinence syndrome including anxiety, restlessness, nausea, and insomnia can occur within 1-2 days of discontinuation of the drug. A recent meta-analysis demonstrates that women who use cannabis during pregnancy are at greater risk of anemia.[34] Synthetic cannabis use results in an acute intoxication syndrome characterized by sympathomimetic effects including hallucinations, delirium, and psychosis; acute renal injury, acute ischemic stroke and death have also been reported in association with its use.[24,35]

Multiple animal and some human studies have investigated the fetal effects of maternal cannabis use, although the conclusions are limited by confounders and possible lack of generalizability. More studies are needed to assess the maternal and fetal risks of cannabis as its use in the general population is increasing[1] and as many as 70% of pregnant and nonpregnant women believe marijuana use is safe in pregnancy.[36] Out of concern for impaired neurodevelopment and smoking-related impairment, ACOG recommends that both recreational and medicinal use of marijuana be avoided during pregnancy and breastfeeding.[37]

Current data on the effects of marijuana in pregnancy are conflicting. Studies have shown an association between marijuana use and increased risk of stillbirth and preterm birth.[38-40] In a secondary analysis, marijuana use was associated with an increased risk of neonatal morbidity, after controlling for confounders such as tobacco use, race, and use of other illicit drugs. However, a retrospective cohort study of 8,138 pregnancies at a single institution did not find an association between marijuana use in pregnancy and poor neonatal outcomes, after controlling for confounders.[41]

Data on the long-term effects of marijuana exposure in pregnancy are sparse. However, in a prospective study of 646 prenatally exposed infants at 6 years of age, heavy maternal use of marijuana during pregnancy was negatively associated with memory and intelligence scores on the Stanford-Binet Intelligence Scale.[42] In a follow-up study of 524 children prenatally exposed infants at 14 years of age, a significant negative relationship was found between prenatal exposure to marijuana and the Wechsler Individual Achievement Test composite and reading scores.[43]

Anesthetic Implications

As is true in obstetrics in general, neuraxial anesthesia is preferred to general anesthesia if not otherwise contraindicated.

Tips and Pearls

- Hemodynamic perturbations are typically minimal, except in the case of synthetic cannabis
  - Atropine, ketamine may exacerbate tachycardia
- If general anesthesia, expect:

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- Increased airway secretions
- Impaired mucociliary clearance
- Increased airway reactivity

- Produces an additive effect with other sedatives
- May have effect on pain perception[44]
  - Low dose- no effect Medium dose- decrease pain High dose- increase pain

Alcohol

Introduction

Per a meta-analysis, the global prevalence of alcohol use during pregnancy was estimated to be 9.8% (95% CI 8.9-11.1). [45] Alcohol use during pregnancy is likely underreported, with recent population-based meconium assay study showing rates as high as 15% in the inner city of Scotland.[46] Maternal alcohol use occurs throughout pregnancy, with the highest percentage in the first trimester (16.5%) compared to the second (3.7%) and third (4.8%) trimesters.[1] The higher likelihood of alcohol use during the first trimester of pregnancy is most likely because many women were unaware of the pregnancy at the time[47] or may not be aware of the prenatal effects of alcohol.

Maternal and Fetal Effects

Alcohol use acts as both a stimulant and a depressant to the maternal central nervous system through a variety of neurotransmitters; endogenous opioids further reinforce alcohol use. Alcohol and metabolite (acetaldehyde) are directly toxic to the brain. Heavy consumption can lead to cirrhosis with encephalopathy, coagulopathy, and esophageal varices, each of which can complicate anesthetic management. Withdrawal from alcohol can produce the syndrome of tremor, confusion, electrolyte abnormalities, and seizures (i.e. Delirium Tremens) which can be modulated by benzodiazepines with or without dexmedetomidine, haloperidol, or clonidine.

Alcohol use causes the *single most preventable fetal birth defect*, most specifically fetal alcohol syndrome (FAS), which exceeds all other birth defects in the United States. [45] The global prevalence of FAS is estimated as 14.6 per 10,000 people.[45] A recent cross-sectional study of 6639 children in 4 U.S. communities estimated a weighted prevalence of fetal alcohol spectrum disorders (FASD) as 31.1 (95% CI, 16.1-54.0) to 98.5 (95%CI, 57.5-139.5) per 1000 children.[48] Mental and behavioral disorders, chromosomal abnormalities, congenital deformities and malformations have been identified as comorbid conditions co-occurring in individuals with FAS.[49] Paternal as well as maternal alcohol use has also been associated with FAS.[47]

Anesthetic Implications

As is true in obstetrics in general, neuraxial anesthesia is preferred to general anesthesia if the patient is otherwise an appropriate candidate.

Tips and Pearls:

- Airway
  - Aspiration risk
    - Decreased lower esophageal sphincter tone
  - More colonization with pathologic bacteria
- Effect on minimum alveolar concentration (MAC)
  - If acute intoxication, decreased MAC
  - If chronic intoxication, increased MAC
    - High risk of awareness
- Effect on P-450
  - Short-term consumption- competes with P-450
  - Long-term consumption- increases P-450 (associated with decreased levels of diazepam, labetalol)
  - Causes decreased pseudocholinesterase levels, although not clinically significant

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Stimulants

Introduction

Stimulants include cocaine, and the amphetamine analogues such as methamphetamine (i.e. "speed"; methyl radical), ecstasy ("MDMA"; methylenedioxy group confers hallucinogenic effects), ɣ hydroxybutyric acid (GHB), 3, 4-methylenedioxypyrovalerone (MDPV or bath salts). These drugs of abuse are of important to anesthesia providers because of their intense activation of the sympathetic nervous system through release of relevant neurotransmitters and the block of their reuptake. The half-life of amphetamines is approximately 12 times longer than cocaine (12 vs. 1 hour). Cocaine is unique in its local anesthetic effects, although it is rarely, if ever, still used for this purpose.[32]

Maternal and Fetal Effects

Both cocaine and amphetamines can produce pathologic multi-organ sympathetic stimulation resulting in myocardial ischemic, cardiac arrest, and stroke.[32] Drug-induced hypertension can mimic severe preeclampsia.[50] Maternal cocaine use has decreased from 0.4% in 2014 to 0.1% in 2016, according to the National Survey on Drug Use and Health.[1] Fetal effects of antepartum use of stimulants are associated with placental abruption, preterm delivery, and the need for urgent cesarean delivery.[51-53] Initial concern for congenital birth defects with antepartum cocaine use has not been corroborated in the literature. Associations between prenatal methamphetamine exposure and childhood behavioral problems are thought to be highly associated with exposure to early adversity.[54]

Anesthetic Implications

Neuraxial analgesia or anesthesia has several advantages in parturients that have consumed stimulants. Advantages include decreasing circulating catecholamines, addressing pain management in a population where changes in μ and κ opioid receptors and altered endorphin levels may increase pain, and providing an in situ epidural catheter for conversion to surgical anesthesia in this high-risk population. The thrombocytopenia initially associated with cocaine use has not been confirmed in follow up studies.[55] Challenges include potential for hemodynamic instability. Although refractory hypotension in a long-time amphetamine user has been reported, use of IV fluids and, if needed, direct-acting vasopressors are typically successful.[33,55,56]

Tips and Pearls

- If hypotension, consider direct-acting rather than indirect acting vasopressor (e.g. phenylephrine).
- Avoid selective β-blockers leaving unopposed α blockade. Labetalol (an α receptor and non-selective β receptor blocker) in combination with nitroglycerine may be effective in treating severe hypertension.
- Dexmedetomidine has been used in the setting of hypertension and agitation
- Cocaine could compete for available plasma cholinesterase
- For General Anesthesia:
    - Induction:
        - Airway
            - Rotten teeth ("meth mouth")
            - Nasal septal defects
            - Airway burns
            - Delayed gastric emptying
        - Avoid ketamine in an acutely intoxicated patient
        - Blunt hemodynamic response:
            - If hypertension, as above, consider nitrates +/- labetalol
    - Maintenance:
        - Changes in μ and κ opioid receptors and altered endorphin levels may increase pain
        - Acute ingestion increases MAC per animal studies
        - Chronic ingestion decreases MAC
        - Monitor for hyperthermia

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Summary

Pregnant women with substance use disorder should receive coordinated antepartum intrapartum and postpartum care. The provision of safe and effective maternal and fetal care is facilitated by a non-judgmental culture of trust and an understanding of the physiologic effects of the ingested substances. Whenever possible, an early anesthesia consult should be undertaken as it can facilitate intra-, ante- and postpartum/discharge planning. Opioid maintenance therapy (MAT) should be continued for the parturients' chronic needs, with additional acute pain management tailored to the delivery plan. In most instances, neuraxial anesthesia is the technique of choice for labor analgesia and cesarean delivery anesthesia if not otherwise contraindicated. If a parturient suffers from opioid use disorder or takes opioids chronically, then she is not a candidate for the mixed agonist-antagonist opioid medications frequently used for systemic labor pain management or treatment of neuraxial labor analgesia side effects. If she has persistent labor pain despite labor epidural analgesia, then she most likely has a dysfunctional epidural catheter. Multimodal therapy for post-cesarean analgesia can facilitate opioid-sparing therapy.

Table. Detection of Licit and Illicit Drug Use

	Detection in Urine	**Detection in Hair**	**Detection in Blood**	**Detection in Oral Fluid**
Opioid:				
Oxycodone	2-4 days	Up to 90 days		
Heroin	48 hours	Up to 90 days	20 hours	0.5-8 hours
Methadone	3 days	Up to 90 days		
Marijuana	Single use: 3 days Chronic use: 30 days	Up to 90 days	5 hours	34 hours
Alcohol	7-12 hours			
Stimulant:				
Amphetamine	48 hours	Up to 90 days	46 hours	20-50 hours
Cocaine metabolites	2-4 days	Up to 90 days	12 hours	5-12 hours
Methamphetamine	48 hours	Up to 90 days	48 hours	24 hours

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Pain Perception and Treatment: We Are Not All The Same

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Introduction

Chronic pain, or pain lasting or recurring for more than three to six months [1], has a high prevalence rate in the United States. There are currently 120 million chronic pain patients [2], which is greater than those suffering from cardiovascular disease (85.6 million [3]), diabetes (29.1 million [4]), or cancer (14.5 million [5]). This costs $600 billion annually due to health care costs, lost productivity, and long-term disability [6]. The perception of pain is derived in most cases from the interaction between ascending peripheral nociceptive signals and CNS modulation of those signals. If any one component is removed, the perception of pain correspondingly diminishes. For example, surgical interventions often focus upon removing or blocking peripheral nociception. It is possible, however, that the central processing of pain can become dysregulated in such a way that removal of the peripheral input fails to diminish the perception of pain. In such cases, the perception of pain is maintained predominantly by dysregulated CNS factors. A broad range of variables, including sex/gender, stress, trauma, psychosocial factors, and physiologic and neurobiologic parameters can contribute to an individuals' pain response.

The Influence of Sex and Gender on Pain

Sex is a critical factor in modulating the experience of pain and a growing body of research demonstrating that males and females experience experimental and clinical pain differently and respond differentially to specific classes of analgesic medications. There is also some evidence that men and women are treated differently by physicians or care givers with regards to recommended pain treatments.

Population-based research has consistently demonstrated higher pain prevalence among women compared to men. Large-scale epidemiological studies across numerous geographic regions have shown that pain is reported more frequently by women than by men[7]. It has also been reported that for each of 10 different anatomical regions, a larger proportion of women than men reported pain in the past week, and that women were significantly more likely to report widespread pain[8]. Finally, the prevalence of many common chronic pain conditions is greater for women than men, including fibromyalgia, migraine and chronic tension-type headache, irritable bowel syndrome, temporomandibular disorders, and interstitial cystitis[7,9].

In addition to the data that has demonstrated that pain is reported more frequently by women compared with men, another relevant issue is whether the clinical severity of pain differs by sex. This concept is surprisingly more difficult to address through subjective research. Several investigators have examined sex differences in pain severity among samples of patients seeking care for their chronic pain. While some studies have reported greater levels pain severity among women than men[10-13], other studies have found no sex differences in subjective pain severity among treatment-seeking patients[14-16].

The inconsistencies in the findings of subjective pain severity between males and females have been further investigated in an objective manner using experimental pain testing to elicit sex differences in pain thresholds. Sex differences in responses to experimental pain have been investigated using a wide variety of stimulus modalities including mechanical, thermal (heat and cold), electrical, chemical, and ischemic stimuli. Other experimental pain models have been used in recent years to characterize complex and dynamic pain modulatory processes, such as conditioned pain modulation (measure of pain inhibition) and temporal summation of pain (pain facilitation). Pain responses to these experimental pain models have been assessed by a number of different outcome measures including pain threshold (defined by time or intensity to the first sensation of pain) and tolerance, as well as self-report measures of pain intensity. General conclusions from these studies are that that women display greater

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sensitivity to multiple pain modalities compared with men, and that women show greater temporal summation of pain while men display greater conditioned pain modulation[7,9,17-19].

A variety of mechanisms underlying pain perception between males and females have been reported and include differences in psychosocial and biologic factors. A variety of psychosocial constructs may play a role in the sex-related differences in pain. Differences in coping strategies, catastrophizing, self-efficacy, abuse history, sociocultural beliefs and expectations have all been described as being different between the male and female sexes[18,19]. Sex hormones, cortical processing and activation, endogenous opioids, and genetic factors are the biologic mechanisms that have been reported as potentially explaining the differences in pain between men and women[9,18,19].

Finally, clinical interpersonal characteristics have been shown to vary as a function of sex both on the part of the physician and the patient. Sex differences have been found in the diagnosis and treatment strategies that physicians choose for their patients who report pain. A study has found that male and female physicians tend to prescribe more pharmacologic agents and diagnostic tests for female pain patients whereas males were offered more physical modalities including surgical referral or interventional procedures[20]. Both male and female physicians have been shown to prescribe higher doses of hydrocodone for "same-sex patients", however the same study showed that female physicians have been shown to prescribe more to blacks and male physicians prescribed more to Caucasians[21]. Another study however showed no physician-based sex difference in prescribing patterns of opioids in at least one Emergency Room study[22].

How Stress and Trauma Influence Pain

Stress is defined as an alteration in homeostasis that can be caused by a psychological, environmental, or physiological threat [23]. It has long been known to affect the perception of pain, in both acute and chronic settings. Acute stress is crucial for the survival of an organism: individuals are alerted to dangerous and life-threatening situations and can subsequently respond to the perceived or anticipated stress. However, stress can become detrimental when experienced in the long-term, especially early in life, and is associated with the development of chronic pain disorders [24-26].

There is increasing evidence to suggest that exposure to stress, abuse, or traumatic events during development can result in a broad range of lasting effects on neurophysiology. An altered Hypothalamic-Pituitary-Adrenal (HPA) system has been reported as a neurobiological sequela of early life stress[27-30]. A large body of research suggests that children exposed to abuse have diurnal cortisol patterns that are different from the cortisol patterns exhibited by their non-maltreated peers[31]. Specifically, children exposed to abuse tend to exhibit low cortisol reactivity to stress even when they exhibit intense behavioral distress and negative emotionality[32,33]. With regard to diurnal cortisol patterns, children who are abused tend to exhibit less day-to-day variation in cortisol levels as compared to their non-maltreated counterparts[34]. Specifically, these biological data suggest that the stress system of children exposed to abuse may be re-regulated to have little internal control (blunted cortisol response to stress system activity). Without this control, maltreated children are more likely to exhibit undifferentiated, low to extinguish and maladaptive "fight, flight or freeze" reactions in response to novel stressors, which can have implications on the developing brain when neuronal plasticity is greatest. Even if the traumatic experience(s) occurred only in childhood, it has been reported that this neuroendocrine dysregulation can persist into adulthood[35]. Changes in neurotransmitter systems, including the corticotrophin-releasing hormone (CRH) circuits can occur as well[36,37].

Pain sensitivity, processing, and circuitry can potentially be also be altered after early life stressors or noxious insult, and these alterations can persist into adulthood[38-40]. In rat models, neonatal noxious insult or non-noxious stress can increase the duration and magnitude of nociceptive responsivity in adulthood[41-44]. Electrophysiologic and anatomic studies identified persistent alterations in central nervous system nociceptive mechanisms resulting from neonatal pain that likely underlies these pain behavioral effects, including increased density and distribution of nociceptive afferents to the spinal cord and hyperexcitability of dorsal horn neurons at rest and in response to non-noxious and painful stimuli[41,43,45]. Brain imaging studies have shown a reduced

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hippocampal volume in adults who reported childhood stress[46,47] and a recent study has reported that a significantly smaller amygdala volume and reduced cortical thickness in the rostral anterior cingulate cortex exists in adolescents with a history of traumatic event[48].

Using Patient Phenotyping, Quantitative Sensory Testing, and Neuroimaging to Identify Altered Pain Processing

There is a growing appreciation of the importance of augmented central nervous system (CNS) pain processing and centralized pain in many chronic pain states.[49,50] The term "centralized pain" has been used to describe any CNS dysfunction or pathology that may be contributing to the development or maintenance of chronic pain.[50-52] The pain experienced by individuals with centralized pain is typically multifocal (with a high current and lifetime history of pain in many bodily regions), rated as more severe, and characterized by neuropathic pain descriptors. Beyond pain, co-existing somatic symptoms including memory difficulties, fatigue, and sleep disturbances as well as cognitive/affective symptoms (e.g., catastrophizing, anxiety, depression) are frequently observed.[51,53,54]

Another hallmark of the centralized pain phenotype is the frequent presence of hyperalgesia and/or reduced or absent endogenous analgesia.[55-57] Data from quantitative sensory testing (QST) studies suggest a wide, bell-shaped distribution in pain sensitivity across the general population. Most, but not all, individuals with centralized pain fall on the right side of this curve and have QST findings consistent with notable hypersensitivity (hyperalgesia and allodynia).[51,58-64] Some of the chronic pain conditions where QST evidence of widespread hypersensitivity is consistently seen include fibromyalgia (FM), irritable bowel syndrome, tension headache, low back pain, temporomandibular joint disorder, interstitial cystitis, and vulvodynia.[65-75]

The prominent role of central factors in chronic pain is substantiated by the fact that there is no chronic pain condition in which the extent of tissue damage or inflammation alone (e.g., as evaluated by an X-ray or MRI) accurately predicts the presence or severity of pain.[76-80] Many people have "normal" radiographs or MRIs yet report unbearable pain, while others have significant radiographic or MRI findings yet report no pain. It has been theorized that this discrepancy exists because individuals with chronic pain display variable degrees of CNS pain amplification and the current 2011 Fibromyalgia (FM) Survey[81] is hypothesized to be a surrogate measure of the degree of centralized pain. Wolfe coined the term "fibromyalgia-ness" (FMness) to describe the phenomenon that where an individual lies on this FM continuum markedly influences how much pain they will experience in response to peripheral nociceptive damage or an inflammatory process.[82] Recent well-powered, prospective studies (described in detail below) have shown that increasing FMness strongly predicts poor analgesic outcomes *and* decreased responsiveness to opioids after surgery meant to improve pain.[83-85]

Although there are no definitive laboratory tests or single biomarker of pain centralization, multiple constructs can be used to infer its presence. Neuroimaging has been shown to corroborate QST findings of diffuse hyperalgesia and altered endogenous pain modulation in centralized pain states.[50,69,86-88] Recent neuroimaging studies provide additional insight into the underlying CNS changes in centralized pain, and demonstrate notable structural, chemical, and functional changes in pain-related brain areas. Structural alterations in gray matter are seen in pain processing regions such as the thalamus, insula, cingulate, and somatosensory cortices.[89] Neurochemical changes include increased levels of excitatory neurotransmitters (e.g., glutamate) and decreased levels of inhibitory neurotransmitters (e.g., γ-aminobutyric acid (GABA)).[90] Finally, increased resting brain network connectivity to pro-nociceptive brain areas and reduced connectivity to anti-nociceptive brain areas are also commonly present.[91-94]

In summary, a variety of factors including sex, trauma/stress, physiologic, psychosocial, genetics, and neurobiologic have been shown to be associated with and likely influence the differences that are seen not only clinically but experimentally in male and females and pain patients. Continuing to perform innovative research on these constructs will hopefully continue to move the field forward in pursuing the ultimate goal of being able to provide personalized analgesia to all acute and chronic pain patients based on their phenotype, genotype, and physiologic characteristics.

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Pediatric Patients With Congenital Heart Disease for Non-Cardiac Emergency Cases

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With improvements in the management of children with congenital heart disease, the size of this patient population continues to grow. This has resulted in a greater number of these patients undergoing anesthesia for non-cardiac surgery. However, multiple studies have demonstrated that they are at significantly increased risk of anesthetic complications.[1-6] Additionally, the need for surgery to occur in an emergent manner further complicates the situation. This review will:

- Outline a structured approach to children with congenital heart disease
- Review which pediatric patients are at increased risk for cardiac arrest under anesthesia
- Describe appropriate anesthetic management of these patients for non-cardiac emergency surgery

An Approach to Congenital Heart Disease

For all patients with congenital heart disease, it is important to understand the precise anatomy as well as what pressures impact the direction and amount of blood flow. Blood flow will follow the path of least resistance, which is almost always from left (systemic) to right (pulmonary). However, the amount of flow will depend on how restrictive the shunt is. In an unrestrictive shunt, the flow will depend on the relative vascular resistances of the two vascular beds and can result in a significant amount of blood flow into the pulmonary system. This is in contrast to a restrictive shunt in which some level of physical stenosis will be the point of maximal resistance and thereby limit the amount of shunting that can occur.

Unrestricted Shunt **Restricted Shunt**

Ultimately, the goal is to determine the relative pulmonary (Qp) to systemic (Qs) blood flow in order to establish how well "balanced" the circulation is (Table 1). The Qp:Qs ratio will most often be determined in the cardiac catheterization lab through the use of the Fick Principle. However, this data is not always attainable in an emergency situation or readily available on all patients. Therefore, when a patient is on room air (and without significant lung disease), the Qp:Qs ratio can be estimated using arterial oxygen saturation (SpO_2). In a patient with no level of shunting, the Qp:Qs ratio should be equal to 1. In a fully mixing lesion, in which the blood going to the aorta is a mixture of blood from both the systemic and pulmonary venous return (i.e. single ventricle physiology), the SpO_2 on room air should be 75-85% if the Qp:Qs is 1.

Qp:Qs ratio	Relative Blood Flow	Clinical Picture
< 1	Right to Left Shunt	Cyanosis
1-1.5	Minimal Left to Right Shunt	Asymptomatic, murmur, normal ECG
1.5-3	Moderate Left to Right Shunt	+/- symptoms; mild CHF
3-5	Large Left to Right Shunt	Very symptomatic with CHF; failure to thrive

In the preoperative period, it is extremely important to determine and understand the precise anatomy of the patient's congenital heart disease. The vast majority of patients will have an echocardiogram in their recent past that will be key to review. The presence of shunts, conduits, and valve gradients should be noted. Importantly, the heart function should also be determined. The patient's previous cardiac surgeries will need to be reviewed as well in order to determine which palliative or corrective procedures have already been undertaken.

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Once this data is reviewed, it is important to validate that this data correlates with the patient's vital signs and SpO_2. If there is a significant discrepancy, is there something else that explains this? For instance, if a patient with single ventricle physiology awaiting their stage I palliative cardiac surgery has a significantly lower saturation than expected, there could be several explanations for this, including an intrinsic pulmonary issue (pneumonia, pulmonary hypertension) or increased right-to-left shunting across a fenestration. On the other hand, if the SpO_2 is significantly higher than expected, there could be pulmonary over-circulation at the expense of systemic circulation, which can lead to a metabolic acidosis from poor perfusion. In each of these scenarios, one must then determine what effect, either positive or negative, the administration of oxygen will have.

Finally, it is important to consider what impact the proposed surgery and anesthetic will have on the patient's physiology. As in all patients, prolonged NPO times, dehydration, anesthetic agents, and systemic infectious disease will cause a decrease in systemic vascular resistance (SVR) while pain, hypoxia, hypercarbia and atelectasis can increase pulmonary vascular resistance (PVR). The relative ratio of pulmonary to systemic blood flow in the presence of shunts can change in these scenarios and potentially complicate the perioperative management of the patient. In emergency surgery situations, there is often not an option to delay surgery in order to fully optimize the patient. Therefore, the anesthetic plan needs to monitor, treat and mitigate these issues.

Pediatric Cardiac Patients at Increased Risk

In 1994, the Pediatric Perioperative Cardiac Arrest (POCA) Registry, a multi-institutional database, was formed to determine the cause of cardiac arrest in anesthetized children.[7] While initial reports from the registry showed significant medication-related morbidity, the causes of arrest have evolved over time with improvements in anesthetic agents. Hypovolemia, transfusion-related hyperkalemia, and respiratory events accounted for the majority of arrests in the latest report from 2010. However, 34% of cardiac arrests occurred in children with congenital heart disease. Of those, over 50% occurred in children with single ventricle physiology, shunting lesions, or obstructive lesions, especially aortic stenosis. Seventy-five percent of deaths were also accounted for in the following three groups: single ventricles, cardiomyopathy, and aortic stenosis. Furthermore, these arrests were more likely to occur in the general operating rooms rather than the cardiac operating room or the catheterization lab.[1] Patients with pulmonary hypertension also are at increased perioperative risk.[3]

Compared to children with low RACHS (Risk Adjustment in Congenital Heart Surgery) scores, those in higher categories 4-6 are more likely to have non-cardiac surgeries.[8] Patients with single ventricle physiology, in particular, undergo various types of non-cardiac surgery, most commonly placement of peripheral or central venous lines, insertion of gastrocutaneous tubes (percutaneous or laparoscopic), and airway procedures.[6] In this subset of patients, anesthesia-related complications typically range between 11-15% but are as high as 31% in older Fontan patients.[6, 9-10]

Due to the increased risk in these patient populations, several centers have stratified patients into risk categories based on age and/or complexity of disease to help standardize preoperative evaluation as well as determine whether sub-specialized cardiac anesthesiologists are needed to care for the patients in the perioperative period.[5, 11-12] While specific criteria may vary between centers, some stratification should be developed based on the comfort level and training of each group's anesthesiologists. In emergency situations, however, there may not be an option to wait for a sub-specialty team before proceeding, and it is imperative that the general anesthesiologist understands the complexity of these patients' baseline status and applies that knowledge in his/her care until the sub-specialty team arrives.

General Principles of Perioperative Management in Patients with Congenital Heart Disease

Preoperative: As in all patients for surgery, a thorough preoperative evaluation is imperative to best care for patients with congenital heart disease in the perioperative period. While this can be difficult in an emergency situation, at a minimum, the echocardiogram and any cardiology notes that are available should be reviewed (as described above). Again, the clinical picture of the patient should match the data that these studies provide, and if there is a discrepancy, the cause of this should be determined. Consultation with the team managing the patient

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preoperatively can be extremely helpful in shedding light on the patient's current findings and is strongly encouraged.

As complete a review of systems as possible should be done during initial evaluation of the patient. Many patients with cardiac disease can also have significant co-morbidities, such as pulmonary disease, airway abnormalities, liver or kidney dysfunction, and neurologic delays. These may affect the anesthetic in numerous ways, including drug uptake and metabolism, the ease of intubation, and ventilation. Review of medications is also imperative. Many patients will be on medication for anti-coagulation at baseline. This needs to be taken into account to determine if it is necessary (or possible) to reverse its effects prior to proceeding and thereby reduce intraoperative blood loss. Furthermore, in emergency situations, medications such as dopamine, epinephrine, or vasopressin may be infusing due to hemodynamic instability. If not started already, induction of anesthesia and the surgery itself may warrant the need for an inotrope, so emergency medications at appropriate concentrations should be available for immediate use.

The effects of a prolonged NPO time need to be considered. In general, patients in the higher risk groups (single ventricle, pulmonary hypertension, LVOT obstruction) should have intravenous fluids to prevent significant dehydration. As time allows, any fluid deficits should be corrected, beginning preoperatively and then continuing into the intraoperative period. Maintenance fluids can then be initiated. In younger age groups, maintenance fluids should include dextrose at an appropriate concentration for the patient's age.

Beyond the standard ASA monitors, the need for additional invasive monitoring such as an arterial line or central venous catheter will depend on the patient's underlying cardiac disease, their functional status, and the nature of the surgery. In many shorter and less invasive procedures, no additional monitors are needed if there is a well-functioning non-invasive blood pressure cuff and accurate pulse oximeter. However, if there is a high likelihood to need inotropes intra- or postoperatively, most practitioners will elect to place additional monitors preemptively.

Intraoperative: As with any anesthetic, the choice of medications and type of anesthesia will be guided by the underlying cardiac disease and the proposed surgery. Agents such as etomidate, opioids and ketamine have a favorable hemodynamic profile that allows for smoother intravenous inductions of patients with even the most complex congenital heart disease. Volatile agents can then be used at lower MAC values (0.5-1 MAC) for maintenance of anesthesia. While intubation with positive pressure ventilation is often undesirable in second and third stage single ventricle physiology, many surgeries require intraoperative paralysis for best conditions to be present. If so, limiting the peak inspiratory pressures and PEEP so that venous return is not impeded is key.

Because abdominal surgery is one of the most common non-cardiac procedures done in this patient population, the question of whether laparoscopic surgery is safe has been investigated extensively. With insufflation, changes in systemic vascular resistance as well as decreases in venous return have the potential to cause hemodynamic instability, especially in the patients with single ventricle physiology. Gillory et al. performed a 10-year retrospective review of 121 laparoscopic vs. 50 open procedures in children with congenital heart disease. They found no difference between groups with respect to instability.[13] Other studies have also demonstrated safety with laparoscopy in patients with a single ventricle, noting that insufflation pressures should be kept between 8-12 mm Hg and low flow.[14-15]

Postoperative: Finally, the decision to extubate the patient is multifactorial and depends on the length of the surgery, the amount of fluids administered, intraoperative hemodynamic stability, and postoperative pain management. Postoperative disposition needs to be considered as well. Depending on the complexity of the surgery and the patient's status, many patients should recover in an intensive care unit due to the potential for hemodynamic instability and the need for postoperative ventilation. When in doubt, the default should be to send the patient to the intensive care unit for closer observation following most emergency surgeries.

Anesthetic Management of Specific High Risk Pediatric Cardiac Patients

Single Ventricle: Patients with single ventricle physiology are some of the most high-risk patients to care for during non-cardiac surgery.[16] While there are many different anatomical variations that fall within the category of

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single-ventricle physiology, all of them have both systemic and pulmonary blood flow mix completely before leaving the heart. In the course of their management, these patients will undergo three staged cardiac surgical procedures, which result in varying sources of pulmonary and systemic blood flow. Consequently, following each stage, there will be different physiologic consequences and management principles.

Post-Stage I Palliation: In this shunt-dependent physiology, a systemic to pulmonary connection allows for pulmonary blood flow. This is most commonly either a Sano shunt (right ventricle to pulmonary artery) or a modified Blalock-Tausig shunt (subclavian artery or carotid artery to pulmonary artery). In order to maintain patency of the shunt, these patients are often on some form of anti-coagulation. This is considered a somewhat fragile circulation, in which even small changes in oxygen, ventilation, pH, or temperature can tip the balance of pulmonary and systemic blood flow. The goal is to maintain SpO_2 in the range of 75-85%. It is important to avoid high FiO_2, which can result in increased pulmonary blood flow at the expense of the systemic blood flow. Furthermore, since the single ventricle handles both the systemic and pulmonary venous return and outflow, it is very preload dependent, and increases in afterload are not well tolerated. Therefore, these patients should not be subjected to unduly long pre-operative fasting. Careful attention should be given to fluid management with regard to third space losses as well as blood loss. Maintaining appropriate SVR with inotropes and adequate intravenous fluids is imperative.

Post-Bidirectional Glenn and Fontan: The second stage of palliation, the Glenn operation, diverts the venous return from the superior vena cava (SVC) to the pulmonary arteries. The desaturated blood from the inferior vena cava (IVC) continues to mix in the common atrium with the saturated pulmonary venous return, yielding an arterial oxygen saturation of approximately 85%. Partial diversion of the venous return to the pulmonary circulation significantly reduces the volume load on the ventricle, resulting in improved hemodynamics over the stage I palliation. In the third stage, the Fontan operation, the IVC blood flow is also diverted to the pulmonary bed, resulting in even higher pulmonary blood flow and higher saturations (85-92% while a fenestration is present).

Since passive flow from the SVC (Glenn) or the SVC and IVC (Fontan) is the source of pulmonary blood flow, it is more likely to be affected by increased intrathoracic or intra-abdominal pressure, volume status, PVR, and hemoglobin levels. While spontaneous ventilation is ideal with this physiology to allow for improved venous return, the nature of many surgeries requires paralysis and positive pressure ventilation. Therefore, limiting peak inspiratory pressures and PEEP so that venous return is not impeded is key. Oxygenation is actually improved with mild hypoventilation ($PaCO_2$ of approximately 40-45 mm Hg). By improving cerebral vasodilation, there is better blood drainage from the cerebral vasculature into the SVC and ultimately the pulmonary bed for increased oxygen exchange.[17]

The goals of management, therefore, include the maintenance of adequate intravascular volume and appropriate PVR. Conditions that decrease venous return, such as hypotension, hypovolemia and tachycardia should be treated with appropriate fluid therapy. Factors that increase PVR, such as hypoxemia, hypercarbia, acidemia and excessive airway pressures, result in decreased pulmonary blood flow and hypoxia and therefore should be avoided.

Pulmonary Hypertension: Pulmonary hypertension is secondary to one of the following causes:

- Left-sided heart disease in which high pressure is transmitted back to the pulmonary bed
- Increased left-to-right shunting resulting in significant pulmonary overflow
- Intrinsic pulmonary disease
- Idiopathic

In all of these scenarios, intrapulmonary vascular changes develop with thrombosis, ultimately leading to fibrosis and obliteration of arterioles. This then places the patient at increased risk for a pulmonary hypertensive crisis. With sudden increases in PVR (due to hypoxia, hypercarbia, acidosis or sympathetic stimulation), the pulmonary artery pressure exceeds systemic blood pressure, and there is an acute drop in right ventricular function. In patients with an atrial level shunt, the patient will become cyanotic with right-to-left shunting. When no shunt is present, however, decreased pulmonary blood flow will result in decreased cardiac output and biventricular failure.[3]

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Multiple studies have demonstrated that pediatric patients with pulmonary hypertension are at increased anesthetic risk.[18-19] The frequency of major complications is associated with the severity of baseline pulmonary hypertension. In patients with systemic or supra-systemic pulmonary pressures, the incidence of complications is significantly higher than those with sub-systemic pressures.[18] Predictors of perioperative mortality with pulmonary hypertension include a history of syncope, poor functional status, dysrhythmias, SpO_2 less than 85%, severe right ventricular dysfunction and Trisomy 21.

In patients with pulmonary hypertension, prevention of acute increases in PVR while under anesthesia is key. The time of induction can be especially difficult. Agents such as etomidate, opioids, or ketamine have all been shown to provide hemodynamic stability.[20] Active measures to avoid hypercarbia, hypoxia, and acidosis should be undertaken, including early controlled ventilation when appropriate. Adequate fluid resuscitation is also important. No specific anesthetic agent or technique will prevent pulmonary hypertensive crises in all patients. Rather, a balanced technique is used so that the detrimental effects of a higher dose of any one specific agent are avoided. In the event of a hypertensive crisis, a FiO_2 of 1.0, hyperventilation, correction of acidosis, and nitric oxide are the treatments of choice. Hemodynamic support and agents to improve right ventricular function are also needed.

Cardiomyopathy: Cardiomyopathy, an abnormality of the myocardium, is classified by etiology and physiology into the following categories:

- Dilated cardiomyopathy (DCM)
- Restrictive cardiomyopathy (RCM)
- Hypertrophic cardiomyopathy (HCM)
- Arrhythmogenic right ventricular cardiomyopathy (ARVC)
- Unclassified.[21]

Each of these subtypes has a specific clinical picture, with the vast majority eventually developing heart failure. In the POCA registry report from 2010, there was 50% mortality in patients with cardiomyopathy.[1] Patients with cardiomyopathy at highest risk of cardiac arrest under anesthesia are those with a shortening fraction of less than 16% on echocardiogram.

In many forms of cardiomyopathy, baseline blood pressure is relatively low secondary to diuretic therapy, use of ACE inhibitors, beta blockade and poor cardiac function. In the perioperative period, this is further exacerbated with dehydration when there is fasting. This dehydration and relative hypotension can complicate anesthetic induction and maintenance secondary to the vasodilatory effects of almost all anesthetic agents and the resulting decrease in preload. Kipps and colleagues, looking at anesthetic management in 26 patients with heart failure, found that approximately 38% had complications under anesthesia, the most common being significant hypotension requiring inotropic agents.[22] As with pulmonary hypertension, the choice of anesthetic technique will most often be a balance of several agents at lower doses to avoid the negative effects of larger doses of any agent alone. Inotropic support is key in these patients to prevent worsening ischemia or the development of arrhythmias.

Obstructive Lesions: Obstructive lesions can occur anywhere along the ventricular outflow tract, including at the valve itself, above or below it. Certain disease states, such as Williams Syndrome, can be associated with both left and right ventricular outflow tract obstruction. Looking specifically at left ventricular outflow tract obstruction, which tends to cause more significant complications, there are several mechanisms whereby cardiac arrest occurs. With severe obstruction, the left ventricle becomes hypertrophied, increasing wall tension and oxygen consumption. The hypertrophy can also compromise coronary blood flow leading to subendocardial ischemia.[5]

In these patients, any agents that decrease coronary blood flow (decrease SVR or cause myocardial depression) or increase myocardial oxygen consumption (tachycardia or dysrhythmias) will potentially worsen ischemia and lead to cardiac arrest. Furthermore, anesthetic induction and emergence are associated with an increase in sympathetic activity, which can cause hypertension, tachycardia and increased oxygen consumption.

Anesthetic goals in these patients include the following:

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- Maintenance of preload, contractility, and SVR
- Continuation of normal sinus rhythm
- Preventing increases in PVR
- Avoidance of anesthetic agents that cause tachycardia or significant vasodilation.

Adequate hydration is key, with fluid boluses often given prior to induction. Etomidate and opioids are common induction agents. Ketamine, though it can cause some tachycardia, has been successfully used in pediatric patients with severe stenosis.[5] Dexmedetomidine, which will decrease heart rate and increase SVR, can be used as part of a balanced anesthetic technique. In case of worsening ischemia, seen as ST segment changes or dysrhythmias on ECG, prompt treatment with an alpha-agonist such as phenylephrine is critical. Improvement of the balance in myocardial oxygen supply and demand should be immediate as well. ECMO availability in the highest risk patients should be arranged prior to surgery to allow for the most rapid response possible if needed.

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Leadership Touchstones and Behaviors and Enhancing Your Abilities

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INTRODUCTION

Many of us operate under the belief that success in leadership involves an innate skill. However, the qualities and behaviors of great leaders can be learned, practiced and refined. Additionally, there is no one best style of leadership as everyone has a different set of strengths and weakness that relate to their abilities as a leader. Independent of our specific job description or role, we are all leading others in some respect as a member of a team. Even though anesthesiology is often the practice by an individual, we are in almost all circumstances a part of a team as an inherent part of our jobs. Additionally, our specialty lends itself to enormous leadership opportunities in health care at the departmental, hospital and national levels.

TRAITS OF SUCCESSUL CEOS

One place to look for leadership qualities that produce successful and some unsuccessful outcomes would be to analyze the inner workings of Chief Operating Officers. Certainly, by definition, these individuals would exemplify leadership in practice. A recent article analyzed and described the successful traits of CEOs and found that Decision-making, Engagement, Adaptation and Reliability were all determinates of success as a leader. Anesthesiologists have traits that are aligned with many of these qualities and can be developed further for an impact outside the operating room.

The first striking revelation was making decisions in a timely manner with conviction was more important than making the exact right decision. The context is important, as in clinical practice, we must make rapid decisions and they must be correct with consequences of poor patient outcomes for a hasty decision. The key here is that with ambiguity, the top CEOS are about to make decisions with conviction and are comfortable in unfamiliar domains. This type of process is a contrast to our training as physicians as we seek very targeted decision-making processes and strive for familiarity and consistency in our environment. One concept that might also be difficult to grapple with as a physician is that as a leader an incorrect decision may be better than no decision at all. Our propensity for intellectual complexity may cause a struggle with decisiveness. Slow decisions from a leader can produce bottlenecks and teams may become frustrated or model a cautious approach which can limit the ability of the organization to act. As an anesthesiologist, we often can relate to the premise that we may not always have perfect information and so we analyze the risks and benefits and move forward. This is aligned with the early decision making with conviction as a leader outside the operating room.

Engagement starts with gaining insight the priorities of others and working on the delivery of good outcomes. Doing so with calmness under pressure is also important and within the skill set of anesthesiologists. One needs not necessarily try to be liked by everyone, but respect for stakeholder interests and instilling confidence will lead to high-performance as an engaged leader. Sometimes this requires making uncomfortable decisions that are unpopular and negotiating conflicting viewpoints, but in a respectful manner helps engagement. Engaged leaders engage in conflict, but in the most respectful manner allowing all points of view to be expressed, but not necessarily driven by consensus for a final decision.

Another area where our skills as anesthesiologists are particularly suited is for proactive adaptation. Comfort with facing new situations that require creativity and adjustment to changing conditions is a critical skill. A different challenge to our roles as anesthesiologists would be to spend the majority of our time considering the long-term goals and strategies. Our planning in the operating room usually involves short periods on time from seconds to minutes to hours. Even those in management positions usually deal with days and weeks for OR scheduling, not timelines of months and years. Looking at a longer timeline allows for the recognition of early signs rather than a

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reactive set of behaviors. It is also important to recognize mistakes and use them as part of adaptation to learn how to deal with them. Much as we analyze a patient complication and try to learn from it, our focus on improving patient safety can be applied as part of a strategy in the development of leadership qualities.

Of all the four essential traits of CEOs the most powerful is the ability to reliably produce results. Predictability and reliability build trust in our teams and our stakeholders. We know this to be true in our operating room environment and those of us who set reasonable expectations and deliver on them are successful. The skills in predictably planning and delivering a reliable anesthetic can be applied as a leadership quality in the context of managing a team.

Success in leadership is not a function of permanent and unchangeable qualities, but of behavioral modification.

INPIRATIONAL LEADERSHIP

Inspiring leaders use unique combination of their strengths to motivate individuals and teams to take on bold missions plus hold those individuals accountable for producing results.

Likely one of the most important concepts is that a successfully inspirational leader must be true to themselves. It may be tempting to look at other leaders to imitate, but that will not produce authenticity. Certainly, observing and considering the experiences of others is part of learning leadership, to for the trust of others, your genuine self must be presented. One place to start is with your own life story and a reflection upon your own personal experiences. Through that context you can find a place for inspiration for your impact upon the world.

You have your own set of beliefs and convictions and the first step in discovering them is to see how you hold to them under pressure. When things are going well, they may be easy to list and abide by, but in the face of adversity, your values will be tested and this circumstance will expose what is truly most important and what you are willing to sacrifice. Ultimately, your leadership principles are values translated into action determined by your behaviors. One exercise would be to observe yourself under conditions of stress and see which principles you use for leading. Ask for feedback from others. As a corollary, you cannot be an inspirational leader alone. Empowering others on your team and leaders at all levels of the organization will be inspired by your actions and then inspire those around them.

One needs only one strong attribute of inspiration to be successful in this domain. The right inspirational leader for motivation is contextual to the needs of the organization and that are right for motivating leader's specific strengths. There are is one universal set of qualities for inspirational leaders which includes remaining calm under stress, empathizing, listening, and remaining present.

To help gain these qualities a great deal of attention has been focused recently on emotional intelligence. Travis Bradberry and Jean Greaves have outlined some of the habits of highly emotionally intelligent people which can all be strengthened through insight and practice. They are relentlessly positive and release what they can't control. They have power in attention and effort and a robust emotional vocabulary. Unlabeled emotions will be misunderstood and lead to irrational choices. Emotionally intelligent people make specific word choices and focus on more directed actions. Assertive is important, but balanced with good manners, empathy, and kindness with an ability to assert and establish boundaries. This is ideal for handling conflict. Curiosity about other people will provide empathy and an ability to listen. One can forgive, but without forgetting. However, it is key to forgive to prevent a grudge. Making things fun and finding joy where you are able fights off stress and builds lasting resilience. Be difficult to offend with a firm grasp of whom you are, self-confident and open-minded. This can be facilitated by squashing negative self-talk. One method is to stop pessimistic things by writing them down which will slow down negative momentum to be more rational and clear.

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CHARISMA

One does not have to be charismatic to be an inspirational leader, but for those of you who inspire to refine your own charismatic traits there are some tips to consider:

1. You don't have to be the most attractive person in the room.
2. Always be present.
3. Be an excellent listener by pausing and asking questions deliberately.
4. Don't compare yourself to others.
5. Combine your power with warmth to create a full, charismatic package.

Just as there is no one form of inspirational leadership and one must remain authentic, there is also no one charismatic style.

Charismatic Styles:

Focus: People to feel like they're the only ones in the room with you.
Visionary: This style makes other people feel inspired.
Kindness: Based mostly on warmth and body language
Authority: Powerful charisma style, but not likeable all the time.

No matter what you choose as your style indicators that you can consider are the use of body language, a choice in your appearance, your title and reflection of the reactions of others.

In her commencement speech at the Stanford University School of Business Mary Barra, the CEO of General Motors summarized what every business school graduate should know and shared leadership lessons she's learned along the way. "Leaders Listen, Leaders Care, Leaders Inspire, Leaders Work."

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Lung Isolation: Clilnical Challenges and Strategies for Success

Jerome M. Klafta, MD **Chicago, Illinois**

Success in the context of one-lung anesthesia means that lung collapse is both complete *and* well tolerated by the patient. Although the concept is simple, a number of clinical details frequently make the difference between success and failure. Lung isolation (functional lung separation) allows us to ventilate one lung independent of the other (airtight seal) or to restrict passage of blood or fluids (watertight seal) from one lung to another. One-lung anesthesia requires *not only* functional lung separation *but also* adequate one-lung ventilation and oxygenation. Figure 1 depicts the three clinical end points integral to one-lung anesthesia:

- Optimal position of double-lumen tube (DLT) or bronchial blocker (BB)
- Functional lung separation
- Adequate one-lung ventilation and oxygenation

Various overlapping subsets of these conditions can and do occur. For example, adequate position of the DLT or BB does not ensure functional lung separation (condition A), and adequate one-lung ventilation can sometimes be achieved with *suboptimal* DLT position (condition C). Table 1 lists examples of causes and solutions for each clinical condition in Figure 1. By identifying the exact nature of the difficulties, the anesthesiologist can implement appropriate therapy without wasting time on maneuvers (DLT repositioning, cuff volume manipulations, or ventilation changes) that are not part of the problem.

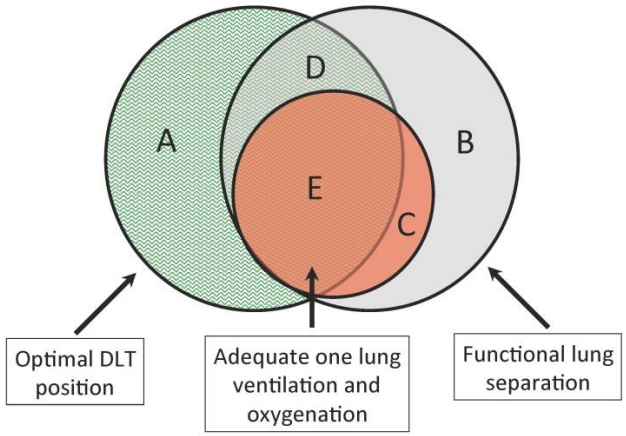

Figure 1. Overlap of clinical end points in one-lung anesthesia. *A, B, C, D,* and *E* represent different clinical end points as described in Table 1.

Design Characteristics of Double-Lumen Tubes and Bronchial Blockers

Common adult DLT sizes are 35, 37, 39, and 41 French (F). Some manufacturers also provide 26, 28, and 32F sizes. The particular dimensions and design characteristics vary somewhat between manufacturers (Rüsch, Portex, Sheridan, Mallinckrodt, and Fuji Systems). The resting bronchial cuff volume (defined as the smallest cuff volume beyond which a 0.5 cc increase results in more than a 10 torr increase in cuff pressure) can differ between sizes (35F = 3.7 cc; 41F = 2.0 cc).[1] Inflation of the bronchial cuff beyond its resting volume (or even less than its resting volume if fitted tightly inside a bronchus) may result in dangerously high intracuff pressures and should be avoided.[1,2]

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Table 1. Clinical Conditions during One-Lung Anesthesia

Area [a]	*Example Situation*	*Typical Solution*
A	No airtight cuff seal – lungs not separated	More air in cuff or larger DLT
B	Left DLT inserted too far, occluding left upper lobe orifice	Position DLT optimally
C	Right DLT cuff occluding right upper lobe orifice	Position DLT optimally
D	• Hypoxemia • Obstruction of the ventilating lumen of the DLT	• 100% oxygen/CPAP/PEEP/TLV • Consider alternative lung separation technique
E	No problem!	

[a] See Figure 1.
CPAP, continuous positive airway pressure; *DLT*, double-lumen tube; *PEEP*, positive end expiratory pressure; *TLV*, two-lung ventilation.

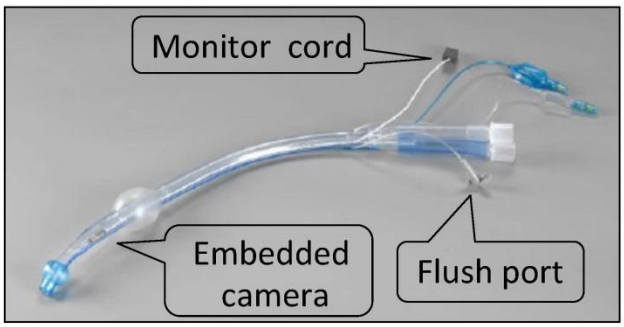

Figure 2. The VivaSight™-DL double-lumen tube (ETView, Misgav, Israel). A high-resolution camera is embedded below the tracheal cuff. Next to the balloons of the bronchial and tracheal cuffs, a white cable connects the camera to an external monitor. An extra side-port is available for flushing the camera lens with saline.

A new left-sided DLT with integrated camera, the VivaSight™-DL (Figure 2), allows for continuous visualization of the tracheal carina, once correctly placed.[3] In a study comparing this device with conventional DLTs placed blindly, intubation time was faster (63 *vs.* 97 sec) and correct initial positioning was facilitated.[4] In another study, loss of video image quality because of secretions occurred in 30% of patients despite use of the integrated flushing mechanism.[5] It appears that this device can provide helpful continuous visual monitoring of DLT position but is unlikely to supplant use of the fiberoptic bronchoscope.

The Univent Torque Control Blocker (Figure 3) is shaped like a standard single-lumen tube (SLT) but has two lumens: one housing a retractable BB and the other used for gas exchange. Typical cuff inflation volume of the blocker balloon is 5 to 6 cc.

Figure 3. The TCB Univent torque control blocker (Fuji Systems, Tokyo, Japan).

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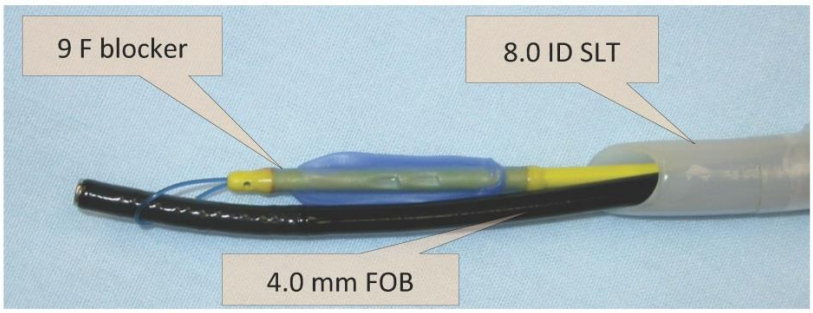

Figure 4. Coaxial use of the Arndt Endobronchial Blocker (Cook Critical Care, Bloomington, IN) illustrating the critical interdependence of the BB, SLT, and FOB sizes.

The Arndt Endobronchial Blocker (Figure 4) was the first of several additions to our current armamentarium of lung separation devices. This system minimizes some of the traditional difficulties associated with the use of Fogarty embolectomy catheters as independent BBs and with Univent tubes. A patient's lungs can be conveniently ventilated while the blocker is fiberoptically positioned through the Arndt multiport airway adapter. The guidewire loop that protrudes through the blocker's tip is used to couple the blocker to the fiberoptic bronchoscope, which can be directed fiberoptically to the desired location in the bronchial tree. The blocker's 1.4-mm lumen can be used to insufflate oxygen or suction gas from the blocked lung after the wire loop is removed. The smallest SLT for use with this blocker coaxially (≥7.5 mm ID) has a corresponding outer diameter that compares favorably with that of the typical DLTs and Univent tubes used for small adults.

Cook Critical Care has made several design modifications to the Arndt blocker since its introduction in 1999. Characteristics of available blockers are described in Table 2. A midsize 7F catheter permits the use of a larger-diameter fiberoptic bronchoscope *or* a smaller-diameter SLT for coaxial use. "Murphy eye" side holes have been introduced into the distal end of the 9F adult catheter to circumvent suctioning difficulty if the end hole abuts the bronchial mucosa, and the guidewire loop of the 9F blocker can now be reinserted if needed.

Table 2. Arndt Endobronchial Blockers

Size (F)	*Smallest SLT ID for Coaxial Use (mm)* [a]	*Length (cm)*	*Cuff Shape*	*Average Cuff Inflation Volume (cc)*
9	7.5	78	Spherical	4–8
7	6.5	65	Spherical	2–6
5	4.5	50	Spherical	0.5–2.0

[a] With 3.4 mm fiberoptic bronchoscope (data from www.cookmedical.com).
ID, inner diameter; *SLT*, single-lumen tube.

The Cohen blocker is similar to the Arndt blocker except that its distal tip is directed by way of a proximal control mechanism instead of coupling to a bronchoscope. The Uniblocker is an independent BB controlled similarly to the one integral to the Univent tube. The use of BBs in adults for routine cases[6] and for selective lobar blockade[7] has been reviewed.

The Y-shaped, dual-balloon Rüsch® EZ-Blocker™ (Figure 5) is the newest BB design. When compared with left-sided DLTs in 100 patients, an SLT plus EZ-Blocker performed similarly (intraoperative malposition, speed and quality of lung collapse, gas exchange) and took only slightly longer (25 *vs.* 13 sec) to place.[8] Importantly, the incidence of airway injury as assessed by an independent bronchoscopist was less with the EZ-Blocker, as were postoperative hoarseness and sore throat. A horizontal orientation in the supine position facilitates correct initial placement of this device.

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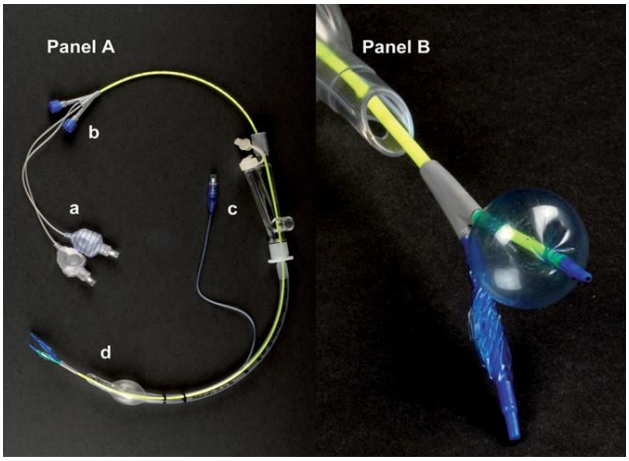

Figure 5. The Rüsch® EZ-Blocker™ (Teleflex, Morrisville, NC) placed through a single-lumen tube (7 mm ID). (A) An overview of the EZ-Blocker, a 7F, 75-cm, 4-lumen catheter. (B) Close-up view of the distal end. The blocker is protruding from the endotracheal tube. Photographs taken by Anja Prischmann, medical photographer, and used with permission. From Mourisse *et al.*[8]

Size Selection of Double-Lumen Tubes

Assuming that the main body of a DLT will fit through the glottic opening and the trachea, an appropriately sized DLT is the largest tube that will fit in the main bronchus with only a small air leak detectable when the cuff is deflated.[2] The presence of some air leak ensures that the tube is not tightly impacted in the bronchus. Thus, the goal is to select a DLT with an outer bronchial diameter that is 1 to 2 mm smaller than the diameter of the intubated bronchus to allow for the size of the deflated cuff.[2] Although some practitioners use 35F DLTs for *all* patients,[9] many select 41F and 39F DLTs for tall and short men, respectively, and 39F and 37 or 35F DLTs for tall and short women, respectively. There is considerable variability in the diameters of left main bronchi, however, and the relatively weak predictive value of gender and height has been repeatedly demonstrated.[2,10] Because prediction is imprecise, measurement of the left main bronchus diameter is most reliable. On chest x-ray it is discernible only 50% to 69% of the time,[2,11] but it is reliably identified on chest CT.[12] *Checking the radiograph to identify unexpectedly large or small bronchi (i.e., significant outliers) is probably most important.*

One critically important assumption is that we clinicians know the dimensions of the different sized DLTs. Russell and Strong[13] independently measured the dimensions of DLTs from four manufacturers and found marked variations, even within the same tube size for each manufacturer! (Figure 6). Thus, any effort to predict appropriate DLT size has this important limitation. Although attempting to select an appropriately sized DLT is important, it is equally important clinically to recognize when a DLT is too large (bronchial lumen will not fit in the bronchus or forms an airtight seal with no air in the cuff) or too small (requires more than ~3 cc of air in the bronchial cuff to create a seal), and adjust accordingly.

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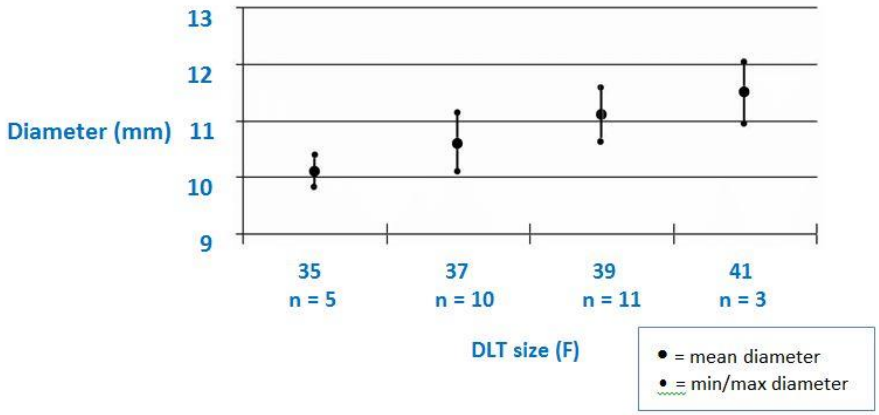

Figure 6. Variation in bronchial outside diameters of Mallinckrodt double-lumen tubes (DLT). Modified from Russell and Strong.[13] Reproduced from *Anaesthesia and Intensive Care* with the kind permission of the Australian Society of Anaesthetists.

Right-Sided Double-Lumen Tubes

The perceived or real difficulty in achieving adequate one-lung ventilation with right-sided DLTs is evidenced by the fact that they are used much less frequently than are left-sided DLTs: currently, 96% of sales of the Broncho-Cath™ (Medtronic, Minneapolis, MN) are for the left-sided device (Erich Weiss, personal communication, 2016). Use of left-sided DLTs is generally encouraged because of the greater margin of safety in positioning them, but a retrospective analysis of 691 cases demonstrated indistinguishable oxygenation, ventilation, and airway pressure performance between right- and left-sided DLTs.[14] Moreover, in the hands of *infrequent* users of DLTs, the three aforementioned performance criteria were *less favorable* with left-sided tubes.[15]

When right- and left-sided DLTs were compared for left-sided thoracic surgery in 40 patients, no right upper lobes collapsed and the difference in the time to place the tubes was clinically insignificant (3.37 *vs.* 2.08 min).[16] Although their routine use in thoracic surgery is controversial,[16,17] right-sided DLTs are indicated when a patient requires a DLT but also has an anatomical abnormality of the left main bronchus such as an exophytic or stenotic lesion or left main bronchus disruption. Regardless of the reasons for use, right main bronchial length of at least 23 mm best accommodates the bronchial cuff and facilitates successful use.[18] This length can be determined bronchoscopically or from a chest x-ray or CT. Attempts to position a right-sided DLT in patients whose right main bronchi are too short are almost certainly doomed to failure.

Fiberoptic Placement and Positioning of Double-Lumen Tubes

Precise positioning of a DLT is most reliably achieved with the benefit of a fiberoptic bronchoscope. In comparisons of fiberoptic positioning of DLTs with conventional methods, more than one-third of left DLTs were malpositioned after blind intubation and the inspection and auscultatory method.[19] In a study of 200 patients, the incidence of malposition (0.5 cm deviation from ideal position) was 39.5% with 14% of them deemed "critical."[20] Critical malpositions were those in which the left endobronchial limb allowed no clear view of the left upper or lower lobe bronchus, the right endobronchial limb allowed no clear view of the right upper lobe bronchus, or there was intratracheal dislocation of more than one-half of the endobronchial cuff. Visually unassisted placement of left DLTs may result in initial intubation of the wrong bronchus 7% to 30% of the time.[20-23]

Ovassapian described a reliable and reproducible method for placing left-sided tubes (and right-sided, with slight modification) on the first attempt.[22] The technique involves first inserting the DLT through the glottis with direct laryngoscopy, rotating it 90° leftward, and advancing it *only until* the proximal edge of the tracheal cuff is past the vocal cords. This limited advancement ensures that the tip of the bronchial lumen is supracarinal. After the tracheal cuff is inflated, ventilation through both lungs is initiated. The fiberoptic bronchoscope is then placed through the *bronchial* lumen and advanced until the carina and main bronchi are clearly identified. The posterior membranous portion of the trachea, the 5 cm left main bronchus, and the characteristic trifurcation of the right upper lobe bronchus are reliable anatomical landmarks to facilitate directional orientation. The fiberoptic bronchoscope is then

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advanced into the left main bronchus to a position just proximal to the left upper and left lower lobe bronchi. After deflation of the tracheal cuff, the entire DLT is slid over the fiberoptic bronchoscope until its bronchial lumen comes into view beyond the tip of the device. Confirmation of a patent left upper and left lower lobe bronchus ensures that the DLT is not in too far. Finally, the fiberoptic bronchoscope is passed through the tracheal lumen to check for a carinal or subcarinal position of the bronchial cuff and ensure patency of the right main bronchus.

Initial passage of left-sided DLTs through the glottis can sometimes be difficult using the typical 90° counterclockwise rotation. In a recent study, 164 patients were randomly allocated to 90° or 180° left-sided DLT rotation once the tip of the bronchial lumen passed the glottis. The 180° rotation facilitated DLT passage through the glottis and reduced the incidence of postoperative sore throat (20% *vs.* 40%) and vocal cord trauma (19% *vs.* 47%). All 9 of the 84 DLTs that could not be advanced after 90° rotation were successfully placed with 180° rotation. The authors acknowledged that attention to re-rotating 90° *clockwise* in the 180° group is important, lest the posterior membranous wall of the trachea be injured.[24] Another recent study using three-dimensional chest CT reconstructions demonstrated that *the left main bronchus branches not only horizontally, but posteriorly as well, at an average of 108° to the sagittal midline*.[25] This finding was consistent with those authors' clinical experience that "over-rotating" left-sided DLTs to ~110° results in more successful placements. While intriguing, this radiological finding and its clinical correlation have not yet been demonstrated prospectively.

When 50 thoracic surgical patients with left-sided DLTs were positioned from supine to lateral, the tubes tended to move outward by an average of about 1 cm.[26] Inflation of the endobronchial cuff before lateral positioning *did not* decrease the incidence of this movement or the amount of overall distance change. Because of the tendency for carinal shift and DLT movement upward with lateral positioning, *there is an advantage to keeping the bronchial cuff 5 to 10 mm inside the left main bronchus before turning the patient laterally.* In another study, of 61 patients, the incidence of proximal repositioning was reduced significantly (43% *vs.*16%) after turning from supine to lateral when the left Broncho-Cath was initially inserted with the proximal edge of its bronchial cuff 5 mm beyond the tracheal carina.[27] Initially positioning the DLT without a headrest may minimize the displacement.[28] This same tendency toward outward movement was also recently demonstrated in cadavers.[29]

Confirming Lung Separation

Of the techniques described to achieve a minimum occlusive seal,[30-32] I routinely use the positive pressure test or bubble test depicted in Figure 7. There are a number of reasons to use a "just seal" technique to inflate the bronchial cuff of a DLT or BB

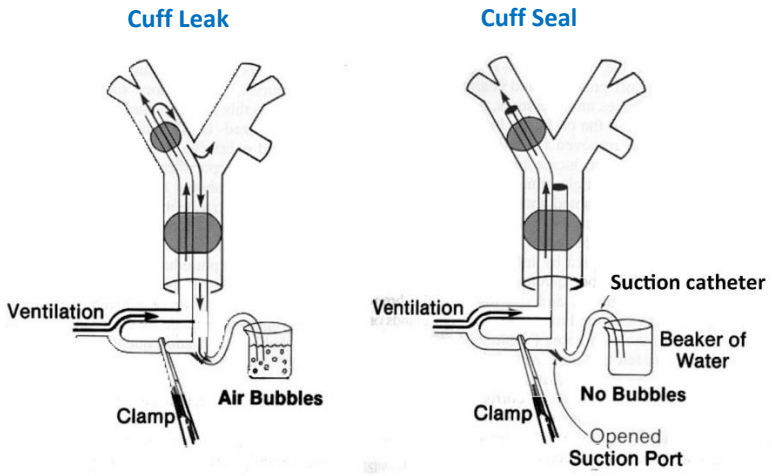

Figure 7. Air bubble method for detection of cuff seal/leak. Modified from Benumof.[30]

First, a cuff that is inflated beyond a minimum occlusive pressure may result in ischemia or even rupture of the bronchial mucosa.[31,33] Second, an overinflated bronchial cuff or BB is more likely to herniate over the tracheal carina and interfere with contralateral ventilation. Third is the ability to immediately and definitively verify lung

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separation. That "moment of truth" when the thoracoscopic port is inserted or the hemithorax is opened is *thoroughly predictable*. If lung collapse is slow or incomplete, documented lung separation assures the anesthesiologist that manipulation of the DLT or BB or their cuffs will not improve the situation. Attention can be focused on other maneuvers that will improve the surgical exposure: manual compression, suction, additional time, or intra-hemithoracic CO_2 insufflation.[34]

Facilitating Lung Collapse

Once functional lung separation is confirmed and one-lung ventilation begins, collapse of the nonventilated lung occurs in two phases. The first phase is secondary to lung elastic recoil and commences with pleural opening when ambient air enters the pleural space. This phase is terminated by small airways closure. The second, slower phase is caused by absorption atelectasis.[35] This atelectasis was achieved most rapidly with DLTs using an N_2O/O_2 mixture (FiO_2 = 40%), then 100% O_2, and then air/O_2 (FiO_2 = 40%) because of the diffusion differences of these gases.[36,37] Moreover, lung collapse will be most rapid if lung separation is initiated at end expiration (at functional residual capacity), especially when using a BB that has a small or absent lumen.[30] The use of 50% N_2O prior to the initiation of one-lung ventilation using BBs has also been shown to facilitate lung collapse without compromising oxygenation.[38] Most recently, in a study comparing BBs with DLTs in patients with normal lung elastic recoil undergoing video-assisted thoracoscopic surgery procedures, instituting two periods of apnea (the first prior to initiating one-lung ventilation, the second coincident with opening the pleura) resulted in significantly faster and more complete lung collapse with BBs than with DLTs.[39] Despite the frequent use of suction to facilitate lung collapse, data supporting its utility are not compelling.

Comparison of Lung Isolation Techniques

Campos and Kernstine[40] prospectively compared the effectiveness of lung isolation with a left Broncho-Cath, Univent Torque Control Blocker tube, and the Arndt Endobronchial Blocker through an SLT in 64 elective right- and left-sided thoracic surgical cases. There were no statistically significant differences among the three groups in frequency of tube malpositions, number of required bronchoscopies, or overall quality of lung isolation as assessed by the surgeon (blinded to technique) once lung isolation was achieved. The Arndt blocker took slightly longer to place (3 min, 34 sec) compared to the DLT (2 min, 8 sec) or Univent (2 min, 38 sec) groups, inclusive of time to place the SLT, although 86- and 46-sec differences are hardly of clinical significance. Complete lung collapse took longer with the Arndt blocker (26 min, 2 sec) than with the DLT (17 min, 54 sec) or Univent (19 min, 28 sec), and more frequently required suction assistance.

Campos *et al*.[41] also studied the success with which the occasional thoracic anesthesiologist (<2 cases per month) correctly placed and positioned these same three devices in 66 patients with favorable airways. They found an astonishing overall failure rate of 38% with no differences among devices! When successful, placement times averaged between 6 and 9 minutes regardless of the device used. *Their observations suggested that unfamiliarity with tracheobronchial anatomy and lack of skill in fiberoptic bronchoscopy were most responsible for the difficulties.* An excellent web-based resource for self-assessment and learning of tracheobronchial anatomy is the Bronchial Anatomy Quiz and Bronchoscopy Simulator developed by Drs. Kanellakos, Dugas, Wong, and Slinger.

When a left Broncho-Cath DLT was compared to the Arndt BB for port-access cardiac surgery, more laryngoscopy attempts (2.3 *vs.* 1.1) and additional time (105 sec) to replace the DLT at the end of the case were trade-offs for slightly better right lung deflation with DLTs.[42] More recently, a comparison of three different BBs to left DLTs for left-sided surgery, all four devices provided equivalent surgical exposure at 10 and 20 minutes after pleural opening.[43] Postoperative hoarseness was prospectively found to be more common with DLTs (44%) than with BBs (17%).[44]

A 2015 meta-analysis sought to determine the efficacy and adverse effects of BBs and DLTs.[45] Of 39 RCTs published between 1996 and 2013, 13 met inclusion criteria. Overall, DLTs were quicker to place than BBs (mean difference = 51 sec) and were less likely to be incorrectly positioned (odds ratio = 2.70). However, patients managed with BBs had fewer sore throats (odds ratio = 0.39), less hoarseness (odds ratio = 0.43), and fewer airway injuries (odds ratio = 0.40) than with DLTs.[45]

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Lung separation and the difficult airway
In the patient with a difficult airway who requires lung separation, the concern for providing lung separation is subordinate to securing the airway. Several options exist for achieving lung separation once an SLT has been successfully placed. BBs are especially useful in these situations, particularly when a nasal intubation is required.[46] An algorithm for airway management options is presented in Figure 8.

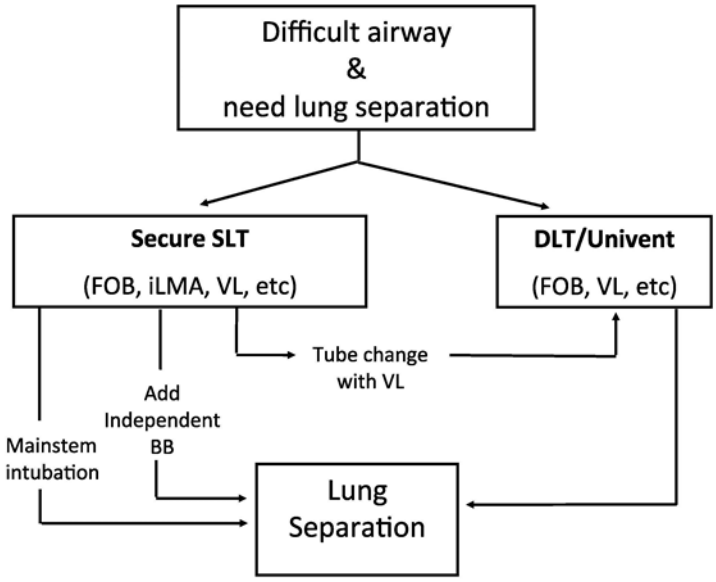

Figure 8. Approach to lung separation options in the patient with a difficult airway. *BB*, bronchial blocker; *FOB*, fiberoptic bronchoscope; *iLMA*, intubating laryngeal mask airway; *SLT*, single-lumen tube; *VL*, videolaryngoscope. From Klafta and Ovassapian.[47]

Upper and Lower Airway Difficulties
Airway difficulties may arise from the upper airway (more common) or the lower airway. Anatomical or pathological features of the upper airway that render conventional rigid laryngoscopy difficult for placement of SLTs are even more problematic for the placement of DLTs and Univent tubes because of their size and shape.[48] Awake fiberoptic intubation with an SLT or DLT may be the best option in cases of known or anticipated difficult intubation and ventilation.[21,47,49]

Lower airway difficulties can be encountered because of anatomical variation (*e.g.*, aberrant or supernumerary tracheal bronchi),[50] distortion of the tracheobronchial anatomy from prior surgery (*e.g.*, apically retracted left main bronchus following left upper lobectomy),[51] or strictures, extraluminal compression, or intraluminal masses. These changes may require creative solutions to lung separation and will influence the selection of the targeted bronchus and choice of a BB or DLT. Lower airway difficulties can be detected or predicted by diagnostic bronchoscopy before intubation or by imaging studies performed preoperatively.

Options for Lung Separation
Double-Lumen Tubes. The literature on videolaryngoscopy to facilitate DLT insertion has blossomed and now contains more comparative trials rather than just case reports or series. One recent study randomly allocated 60 patients *with normal airways* to intubation with a DLT using a GlideScope® (Verathon Inc., Bothell, WA) or Macintosh direct laryngoscope. Although duration of intubation was longer with direct laryngoscopy (63 *vs.* 46 sec), the success of the first intubation attempt (87% *vs.* 100%) was not significantly different.[52] A 2018 meta-analysis of 14 studies found videolaryngoscopy provided a higher first pass success rate, a lower incidence of oral, mucosal, and dental injuries, similar intubation times, but a higher incidence of malposition when compared with Macintosh laryngoscopy *in patients with normal airways*[53] Critical analysis of all comparative studies must consider

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patient characteristics (e.g., degree of airway difficulty), design features of the particular videolaryngoscopes, and importantly, the experience of the operators with both videolaryngoscopy *and* DLTs.[54]

Oral fiberoptic intubation with a DLT is well described in both awake and asleep patients.[49,55,56] A patient's mouth opening and oropharyngeal size must be large enough to accommodate a DLT for orotracheal intubation. Awake placement requires good topical anes-thesia, adequate conscious sedation, and assistance in maintaining soft tissue support. Soaking a DLT in a warm-water bath just before intubation and using sufficient lubrication will minimize its rigidity and has recently been shown to decrease the incidence of postoperative sore throat and vocal cord injuries (but not hoarseness).[57] Concurrent direct laryngoscopy may be required to elevate the supraglottic tissues to facilitate passage of a DLT through the glottic opening after the fiberoptic scope is in the trachea.[56] Videolaryngoscopy may add further benefit.[58]

Univent Tubes. Some anesthesiologists consider a Univent tube easier to place and position than a DLT,[59] particularly in patients with upper airway abnormalities.[60] The internal diameter of the ventilating lumen in a size 8.5 or 9.0 Univent tube will accommodate an adult 5.0 mm bronchoscope,[59] which then precludes the need to change tubes after diagnostic bronchoscopy. Although it is also suitable for fiberoptic intubation, the Univent tube has several limitations. First, unlike the polyvinylchloride of the SLT and DLT, the Univent tube is constructed of a polymeric silicone material that will not soften in a warm-water bath. As such, its curved shape is relatively fixed, and this may be a disadvantage when sliding it over a bronchoscope. Second, the fixed concavity often makes the leading edge of the tube impinge upon the vocal cords, impeding its passage into the trachea. A successful nasal intubation with a 7.0 Univent tube has been described, despite its size and rigidity.[61]

Endobronchial Blockers. See earlier discussion.

Single-Lumen Endotracheal Tubes. Using an SLT to intubate a main bronchus is another option for achieving lung separation and is frequently the preferred technique for children who are too small for DLTs or coaxial BBs.[62] Advantages of this approach include its simplicity and the rapidity with which lung separation can often be achieved, particularly when the right lung must be ventilated. Blind advancement of an SLT will rarely result in intubation of the left main bronchus, but rotating an *in situ* SLT 180° while turning the patient's head to the right will improve the success rate of left main bronchus intubation to about 92%.[63] Fiberoptic guidance of an SLT into the appropriate main bronchus is probably the easiest and most reliable technique. If significant amounts of blood or secretions preclude bronchoscopic visualization, using fluoroscopy to visualize and direct the radiopaque bronchoscope is another option.[64]

Disadvantages of the use of an SLT for lung separation include frequent exclusion of right upper lobe ventilation when an SLT is in the right main bronchus. Left upper lobe ventilation can also be excluded when the left main bronchus is relatively short.[65] Regardless of which lung is ventilated, neither independent suctioning nor application of continuous positive airway pressure to the nonventilated lung is possible. Lastly, if the nasotracheal route is used, most SLTs will not be long enough to provide reliable intubation of the main bronchus.

SLT to DLT Exchange. Exchange of an SLT for a DLT is a strategy commonly employed to achieve lung isolation when insertion of a DLT is difficult. In a simulator study comparing three different DLT designs, the Fuji-Phycon tube (Silbroncho®, Fuji Systems, Tokyo, Japan) was faster and easier to pass over an airway exchange catheter (AEC) than DLTs manufactured by Rüsch or Mallinckrodt when using an AEC plus GlideScope technique.[66] The authors attributed this difference to the Fuji-Phycon's more beveled bronchial tip, softer silicon material, and more angulated bronchial limb. Successful tube exchange is never a guarantee, especially when changing SLTs to DLT. A single-center retrospective analysis of 1,177 airway exchanges found an overall 13.8% failure rate, with 43 of 110 (39.1%) of SLT to DLT exchanges unable to be completed as intended.[67] Cook Critical Care manufactures AECs specifically designed for DLT exchanges. These differ from conventional AECs in that they are longer (100 cm), have centimeter markings that extend to 50 cm, and are extra firm with a 7-cm flexible tip. The 11F and 14F sizes will fit inside small and large DLTs, respectively.

Concurrent videolaryngoscopy will elevate the supraglottic tissues and provide visual guidance should the DLT need to be manipulated to successfully pass through the larynx. Continuous manual control of the AEC throughout

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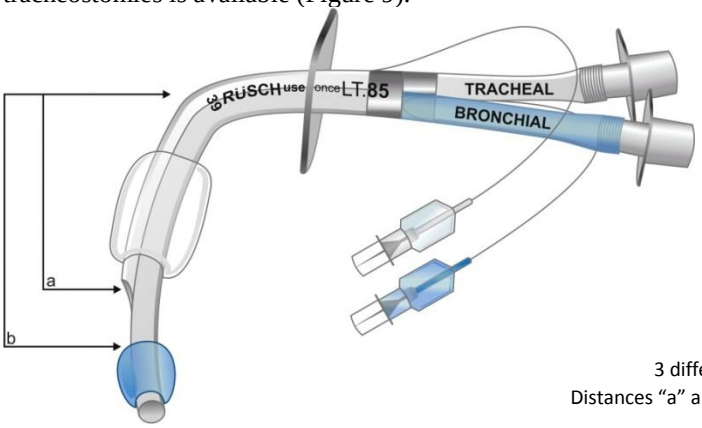
the entire exchange will help ensure it neither loses its intratracheal position nor advances too distally, causing trauma.

The Patient with a Tracheostomy

Although the presence of a tracheostomy greatly simplifies airway management for most anesthetics, it presents an interesting challenge when lung separation is required. As with orotracheal intubation, options include a DLT,[21] Univent tube,[68] or BB through the tracheostomy stoma. Depending upon the details of a patient's anatomy, such as stomal diameter, distance between the skin and the anterior tracheal wall, and stoma-to-carinal distance, DLTs and Univent tubes may be difficult to place and position precisely and atraumatically.

Another way to achieve lung separation in a patient with a tracheostomy is using a BB, either coaxially or alongside an SLT or tracheostomy tube through the stoma[69] or through the mouth.[70] Blind or bronchoscopically directed intubation of the main bronchus with an SLT inserted through the stoma is yet another option, although it has the usual limitations associated with intubations of the main bronchi. A short DLT specially designed for use with tracheostomies is available (Figure 9).[71]



3 different sizes are marketed.
Distances "a" and "b" differ according to DLT size.

Figure 9. The Rüsch Tracheopart® (Teleflex, Morrisville, NC) double-lumen tube for a tracheostomized patient.

Extubation and Postoperative Intubation

When the decision is made to leave a patient intubated after a procedure involving lung separation, some special considerations need to be addressed. The possibility of the recurrent need for lung separation should be considered a reason to leave a patient intubated. Occasionally, an airway that was not difficult initially may become difficult after a lengthy procedure involving large fluids shifts that contribute to upper airway or head and neck edema. An anticipated need for postoperative intubation should therefore inform the preoperative choice of lung separation technique. If an SLT with a BB was used, then all that needs to be done at the end of the procedure is to remove the BB. If a Univent was used, then its blocker should be fully retracted and the Univent can function as an SLT.

If a DLT was used for lung separation, then the risks and benefits of changing to an SLT must be carefully weighed. The main advantage to leaving the tube in place is that the hazards associated with a tube change with a difficult airway are avoided. In this case, one can leave the tube positioned and ventilate both lungs through both lumens. Alternatively, the tube can be withdrawn to the point at which the tip of the bronchial lumen is just above the carina, which will position the tracheal cuff just below the vocal cords.[72] Increased flow resistance leading to obstructed expiratory flow or increased work of breathing is probably not clinically significant with 37F or larger Rüsch or Sheridan DLTs.[73]

CONCLUSION

Keys to success in one-lung anesthesia:

- Understand the physical details of DLTs and BBs. Select them appropriately.
- Use the fiberoptic bronchoscope! Optimize conditions (antisialagogue, suction), learn the tracheobronchial anatomy, and practice!
- Employ a "just seal" test every time. Avoid trouble and identify problems early.

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Choosing the Right Med for Mom

Pamela Flood Stanford, California

Chronic pain is unfortunately common among young women. According to the 2016 Health, United States Report, among women of childbearing age (18-44), 25% reported migraine, 26% low back pain, and 15% neck pain.[1] An increasing prevalence in recent years has been attributed to risk factors including obesity, sedentary lifestyle, social and socioeconomic circumstances. The increasing incidence of chronic pain tracks with an exponential increase in opioid use and neonatal opioid withdrawal syndrome over recent years . This change is not a problem restricted to the United States. As far back as 2001, Blyth and colleagues reported a 10-15% prevalence of chronic pain in women of childbearing age in Australia, with doubling predicted by 2050[2].

Any painful condition that occurs in young women can coexist with pregnancy, and pregnancy itself has variable impact on chronic pain conditions. Common chronic pain conditions with increased prevalence in women include headache, fibromyalgia, pelvic pain, rheumatoid arthritis and back pain. [3] While migraine and autoimmune disease-mediated symptoms often improve or even resolve in pregnancy, back pain and pelvic girdle pain frequently worsen as a direct result of the pregnancy.[4, 5] In a prospective study of women recruited in the 3rd trimester of pregnancy, 38% reported a chronic pain condition or pain prior to pregnancy, and 55% reported pain during the current pregnancy. At two weeks after delivery, 43% reported pain that persisted and pain was maintained in 25% of the original cohort at 3 months postpartum.[6]

Back Pain

Preexisting chronic back pain is reported in 2% of women who become pregnant but increases to more than two-thirds of women over the course of pregnancy.[4] It persists postpartum in approximately 25% of women and there is significant relapse in subsequent pregnancies.[7-11] Proposed etiologies include weight gain, increased lumbar lordosis and inefficient muscular control. [7-10] Thus, pregnancy is a significant life event that is associated with the onset of chronic back pain in many young women.

A 2015 metanalysis provided moderate quality evidence that an 8-12 week exercise program during pregnancy, whether land- or water-based reduced the percentage of patients who reported back pain and also reduced functional impairment and sick leave.[4] Pain and functional disability were also reduced by a multimodal intervention that included exercise, manual therapy and education. One study small study evaluated the efficacy of transcutaneous electrical nerve stimulation (TENS) found that it was associated with reduced pain and functional disability without adverse effects. [12] The same study showed a small effect from acetaminophen. In spite of their common use, studies have provided little evidence to support the use of rigid pelvic support belts for back pain.[13] There is broad agreement that there is inappropriately high use of imaging, rest, opioids, spinal injections, and surgery. Despite emphasis on these modalities in recent years, there has been an increase in reports of and disability from back pain.[14] These modalities are even less desirable during pregnancy due to fetal exposure to potentially dangerous medications and radiation. Better outcomes are achieved through promotion of activity and function, including work participation.

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Basic early management does not differ from that outside of pregnancy with recommendation for biopsychosocial management with initial non-pharmacological treatment, including education supporting self-management, resumption of normal activities and exercise.[14] Psychological programs and judicious pharmacological intervention are indicated for those with persistent symptoms. Pharmacological management of moderate to severe pain follows the WHO ladder with acetaminophen and other non-opioid drugs (indications in pregnancy are discussed below) making the foundation of treatment with supplementation by opioid analgesics judiciously as required. Cauda equina syndrome and preexisting cancers are red flags for immediate imaging and more acute intervention. Imaging during pregnancy is made more difficult due to concerns about radiation exposure to the fetus, however MRI is safe and useful in diagnosis of back pain in pregnancy and advances are being made with the use of ultrasound in diagnostic and therapeutic pain management.[15-18]

Pelvic Pain

Approximately 20% of women report pelvic pain during their pregnancy. A long-term follow-up study found that 10 percent of women with pelvic girdle pain in pregnancy continued to suffer up to 10 years later.[19,20] As such, pregnancy is again a setting that may initiate long term chronic pelvic pain. Pelvic pain can originate from various elements of the pelvic girdle including the sacroiliac joints and pubic symphysis, held together by thick ligaments that usually don't allow for much motion. Increasing estrogen and progesterone in pregnancy allow for softening of the ligaments to allow for important skeletal reconfiguration to support the enlarging pregnancy and future delivery. Perhaps not surprisingly for pain due mainly to ligamentous stretching, metanalysis did not find that exercise programs were associated to a reduced incidence of pelvic pain.[7, 21] Individual studies showed that acupuncture or craniosacral therapy improved pelvic pain more than usual prenatal care. However, studies of complementary therapies are controversial due to persistent questions about establishing causality with sham controls and dose responsiveness to therapy. Women with pelvic girdle pain had more anxiety and depression and scored higher on a pain catastrophizing scale than controls. It is not known whether psychological intervention would affect the incidence or long-term consequences.

Management of pelvic pain in pregnancy is a common problem. Like low back pain, integration of a biopsychosocial model and identification of addressable risk factors such as fears about delivery are important. Unlike back pain, there is no role for exercise therapy as the causes are largely ligamentous rather than muscular. Pain is relieved by rest. The FABER (Flexion, abduction, and external rotation) sign is commonly positive and over-extension during delivery, particularly in the setting of regional analgesia that can mask pain, should be avoided. Pharmacological treatment is similar to that for back pain following the WHO ladder. [22, 23]

Fibromyalgia

Fibromyalgia is a common pain syndrome in young women, associated with central nervous system sensitization to pain.[21] Current criteria for diagnosis include myofascial pain in multiple body regions, fatigue, and cognitive symptoms. In a population based study of more than 12 million pregnancies, mothers with fibromyalgia were more commonly older, obese, and users of alcohol, tobacco, and illicit drugs.[24] Pregnancies among mothers with fibromyalgia are more likely to be complicated by intrauterine growth restriction but not preterm birth compared to

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the general population.[25] Symptoms of fibromyalgia, especially pain in various parts of the body and generalized fatigue, may be difficult to differentiate from normal symptoms of advancing pregnancy. In one study, 27% of otherwise healthy women had symptoms which would technically meet criteria for fibromyalgia in term pregnancy. Therefore, fibromyalgia should not be diagnosed during pregnancy. Pain due to fibromyalgia may increase in pregnancy and was associated with increasing depression scores in a large prospective case control study.[26] Lifestyle modification including sleep hygiene and exercise are mainstays for the treatment of fibromyalgia during and outside of pregnancy. Migraine headache is frequently comorbid with fibromyalgia and if so management of migraine is helpful.[27, 28] Pharmacological management should be used with care as it often includes modalities such as antidepressants that have known side effects in pregnancy.[29-31]

Management- A Multimodal Approach

Multimodal analgesia, also known as "balanced analgesia," has been used effectively in treatment of cancer and chronic pain for many decades. The rationale behind its use is the optimization of additive and/or synergistic analgesic effects between different modes of analgesia or drug classes, while reducing doses and minimizing the side effects of each drug.[32] Various combinations of opioids, NSAIDs, acetaminophen, and local anesthetics, and other drugs, have been used with varying degrees of success in patients with chronic pain.[11, 12]

A primary goal of multimodal analgesia for the pregnant patient is to provide adequate analgesia with minimum side effects to the mother balanced by minimal risk to the fetus. Important concerns postpartum include minimizing transfer of drugs to breast milk and reducing maternal side effects that may interfere with breast feeding or caring for the neonate. In general, medications for which transfer is less than 10% are considered safe. The use of non-pharmacological interventions including techniques in pain psychology and physiotherapy are particularly useful for the pregnant woman with chronic pain to reduce the amount of medication required and support a positive pregnancy experience. Interventional techniques including nerve blocks, and radiofrequency techniques are limited by the requirement to avoid radiation exposure from fluoroscopy. Many of these procedures can now be accomplished with ultrasound guidance, and there is no contraindication to local anesthetic and minimal steroid exposure during pregnancy.[33, 34] Used peripartum in the short term, currently available anesthetic and analgesic drugs are transferred in the breast milk, the amounts transferred are almost always clinically insignificant and pose little or no risk to the nursing infant.[35] There is no need to "pump and dump" after an anesthetic. Specifically, acetaminophen, low-dose aspirin, NSAIDs, codeine, morphine and propoxyphene are considered compatible with breastfeeding.[36-39]

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Update on Cardiac Anesthesia 2018

Martin J. London, MD, FASE **San Francisco,CA**
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Coronary Artery Bypass *(MJ London)*

CABG vs. PCI: Which is Best for Whom?

A recent meta-analysis using pooled individual patient data from 11 RCT's of 11,518 receiving either CABG or PCI followed for at least one year postop reported a significant benefit of CABG on 5 yr survival (overall 9.2% vs. 11.2%) in patients with multivessel disease (hazard ratio 1.28) but in diabetics only (HR 1.48). Patents with higher vessel complexity (SYNTAX score) also has improved outcome, but surprisingly no benefits were noted in patients with left main disease. [1]

Conduit Controversies for CABG: All Arterial or Hope for Vein Grafts?

Despite recommendation in guidelines and publication of a specific STS guideline according a IIa recommendation to use, [2] adoption of a multiple arterial graft strategy incorporating the right internal mammary or radial artery for CABG has been limited. This is partly related to fear of sternal complications as well as a paucity of RCT data. Analysis of Medicare data from 2009 – 2014 found that the rate of BIMA use was low (6.9% of LIMA claims) and remained flat over time but was correlated with the regional volume of LIMA use. [3] Guadino et. al. performed a patient level analysis of six RCT's comparing radial artery vs. saphenous vein grafting, evaluating a primary composite outcome of death, myocardial infarction or repeat revascularization and a secondary outcome of graft patency on follow-up angiography. [2] Data was obtained on 1036 patients (534 radial artery, 502 saphenous vein). The frequency of adverse events was significantly lower in the radial artery after a mean of 60 months (hazard ratio 0.67) and graft patency at follow-up angiography (mean 50 months) was higher (HR 0.44). Radial grafting was associated with lower incidence of MI (HR 0.72), repeat revascularization (HR 0.50), but not all-cause mortality. These data suggest that use of radial artery grafts for CABG results in lower rates of adverse cardiac events and higher patency rates at 5 years postoperatively. Although arterial graft use is being heavily encouraged at surgical meetings, at least one leading surgeon has stated that there is promising data on the use of mesh-supported saphenous vein grafts and that if clinical trials pan out, this could obviate the need for multiple arterial grafts. [4] However, data at this point remains very limited and it is likely that in absence of longterm data over 10 – 20 years that a major shift will occur.

On Pump vs. Off Pump CABG: Which is Better?

The OPCAB controversy is of great interest to all involved and for anesthesiologists involves a different "mind-set" and set of reflexes relative to traditional on-pump. Of note, a variety of hybrid approaches are also becoming more common such as on-pump beating heart revascularization. However, many surgeons tend to heavily favor one or the other technique. A variety of meta-analyses of the RCT and observational data have been published. Filardo et. al. analyzed 42 RCT's and 31 OBS studies comparing short term outcomes (N = 1.2 million patients, 36 RCT, 26 OABS) and longer term outcomes (up to 10 yrs N = 59,125, 5 OBS). Although RCT data showed no differences, OBS studies suggest that OPCAB offers lower short but worse longterm mortality. [5] Somewhat similar results were reported by Smart et. al. in a meta-analysis of 6 RCT's reporting longterm data (8,145 patients), mortality was 12.3% with on-pump and 13.9% with OPCAB. [6] Prevention of stroke with CABG is a high priority. Zhao et. al. performed a network meta-analysis comparing different approaches to minimizing manipulation of the ascending aorta (anaortic OPCAB, OPCAB with Heartstring device, OPCAB with partial cross clamp and traditional CABG with cross clamp) evaluating 13 studies (12 OBS retrospective, 1 RCT). [7] The risk of stroke increased with each level of approach, complete anOPCAB had a 52%, 66% and 78% reduction in stroke risk compared to the other categories respectively). Avoiding CPB reduced risk of short-term mortality and morbidity as noted above.

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Controversies in Cardio (and other organ) protection: Can Any Nonsurgical Methods Improve Outcome?

A working group of European clinical and cell biology experts affiliated with the European Society of Cardiology has recently published a position paper on type 5 MI following CABG (Universal Definition Grouping). [8] Aside from a comprehensive review of clinical literature linking biomarker elevation with mortality, etiologies, and predictors the aim of this group was to better define levels of troponin following CABG that are prognostically significant and thus should prompt further clinical evaluation. Type 5 MI is defined as an elevation of cardiac troponin > 10x 99th percentile URL in patients with a normal baseline level along with either 1.) new Q waves or LBBB, 2.) angiographic evidence of new graft or native vessel occlusion, 3.) imaging evidence of loss of viable myocardium or regional wall motion abnormality. The group recommends that isolated elevations in cTnT > 7 x URL and/or cTnI > 20x URL in the 48 hr postoperative period may indicate the presence of prognostically significant PMI prompting the clinician to exclude "actionable" Type 5 MI etiologies (injury related to primary myocardial ischemia, unfavorable hemodynamics or oxygen supply, surgical issues unrelated to ischemia and multifactorial or indeterminate causes).

The value of volatile agent pre (and possibly post-) conditioning has been hotly debated for over 2 decades since the first reports of beneficial effects in animal models were first reported in 1997. [9] In the ensuing decade, a number of small clinical RCT's of varying quality were reported, most of which reported significant reductions in biomarkers of cardiac and renal injury along with reduction in a variety of process outcomes such as length of stay, etc. However, subsequent studies in both cardiac (and noncardiac) surgery reported minimal if any benefits and despite earlier guideline recommendations encouraging preferential use of volatile agents in high risk patients, the latest iteration of the AHA/ACCF Guidelines backed away from the initial recommendation. [10] A more recent meta-analysis of 68 RCT's of 7104 patients reported significant reductions in mortality, pulmonary and other complications in cardiac surgery patients (45 RCT's, 4890 patients) but not in non-cardiac surgery. [11] Another meta-analysis of 30 studies, 2578 patients evaluated both on pump and OPCAB including a "trial sequential analysis" approach considering troponin release as the endpoint. [12] They report a significant reduction for on pump CABG, but not for OPCAB. Considering the TSA approach, adequate numbers were present for on pump, but had not yet been attained for OPCAB. These types of meta-analyses suffer from pooling of data from different volatile agents and heterogeneity in how they are administered (dose, timing, wash-in or washout periods, etc.) and assessment of outcomes. In an attempt to more definitively answer this question, Landoni et. al. are currently conducting a single-blinded, multicenter, international "pragmatic" RCT comparing any use of any contemporary volatile agent in any manner to any type of TIVA (thus, the term pragmatic as there is no rigidly imposed protocol only suggested strategies) in patients undergoing on pump or OPCAB. [13] A sample size of 10,600 patients is based on the hypothesis that volatile agents will reduce 1 year mortality (all cause, the primary outcome) from 3% to 2%. A variety of secondary outcomes will be tracked as well. This approach should allow enrollment of the most patients but will rely very heavily on a variety of prespecified subgroup analyses, an approach with potential statistical pitfalls.

There has been considerable interest in the potential cardio- and neuroprotective of the anesthetic noble gas, xenon over the past two decades despite its considerable cost and logistical problems in the surgical, cardiology and out of hospital cardiac arrest settings. The largest cardiac surgical cohort to date was recently published by the Xenon-CABG Study Group involving 17 university hospitals in Europe evaluating either xenon, sevoflurane or propofol anesthesia in low-risk, elective on-pump CABG patients (492 patients) with postoperative troponin release as the primary outcome (using a non-inferiority design). [14] Although xenon was found "noninferior" to sevoflurane, troponin release was significantly lower with its use relative to propofol. Other outcomes including safety, were similar across groups. Another recent study evaluated the addition of 30% xenon to propofol anesthesia for OPCAB (50 patients) versus propofol alone, considering the total intraoperative dose of norepinephrine required to maintain MAP > 70 mm Hg. [15] Xenon was associated with a statistically significant decrease. Other outcomes were similar between groups.

The topic of remote ischemic preconditioning (RIPC) has attracted substantial interest and more recently notoriety in this setting given its ease of application and lack of expense (aside from time). Publication in the NEJM in 2015 of 2 large RCT's reporting a lack of effect of this intervention (with the suggestion of increased risk in patients with

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unstable coronary plaques) was a great disappointment to many but the potentially inhibiting action of propofol on the signaling pathways involved in RIPC, has kept the flame alive since then, along with conflicting data with regards to potential benefits on renal protection reported in JAMA earlier that year. Pierce et. al. reported a meta-analysis of cardiac surgery RCT's through 2015 (21 trials, 5262 patients). [16] No significant effects were noted for mortality, acute kidney injury, or postop MI. A subgroup analysis considering studies without use of propofol (434 patients), noted a significant reduction in AKI (RR 0.70). A meta-analysis of 14 on-pump CABG studies (2830 patients) also failed to note differences in mortality, any morbidity, or LOS. [17]

Use of high doses of insulin while providing exogenous glucose (with supplemental potassium) has been the subject of research interest for a number of years since it was recognized that glucose-insulin-potassium (GIK) therapy may be of value in patients with acute MI or undergoing CABG by promoting myocardial glucose uptake and utilization. [18] In the largest study of its kind, Duncan et. al. randomized 1,493 patients at 2 centers to either a standard glucose management regimen with low dose insulin infusion targeting glucose > 150 mg/dl or a hyperinsulinemic, normoglycemic regimen targeting glucose 80 – 110 mg/dl. [19] The primary outcome was a 30-day composite of mortality or selected morbidity, secondary outcomes include atrial fibrillation, LOS and 1 yr mortality. Patients in the hyperinsulinemic group has a lower rate of the composite variable (6.9 vs 11.2%), however there were significant differences between the 2 sites which used different forms of cardioplegia and there were not differences in any of the secondary outcomes. Severe hypoglycemia occurred in 0.9% of the hyperinsulinemic group. This study is suggestive, but clearly not definitive, that such a laborious approach may be of value.

Other Controversies in Perioperative Management

Cerebral injury associated with cardiac surgery using cardiopulmonary bypass is an important problem. Overt stroke occurs in 1 – 2% of patients while silent infarction detected by diffusion weighted magnetic resonance imaging is found in up to 50% of patients. The role of perfusion pressure during CPB on these outcomes is unclear. In the Perfusion Pressure Cerebral Infarcts (PPCI) trial, a patient and assessor blinded trial, patients were randomized to a high (70 – 80 mm Hg) or low (40 – 50 mm Hg) pressure target for mean arterial pressure during CPB. [20] Pump flow was fixed at 2.4 l/min/m2 and a maximum dose of phenylephrine boluses up to 2.0 mg followed by a 0.4 mcg/kg/min infusion of norepinephrine was allowed during CPB with normothermia (temp > 36.5 C). No vasodilators were used in the low target group. Adult patients undergoing CABG or left heart valve surgery were studied. Patients with a history of neurologic or cerebrovascular disease were excluded. The primary outcome was difference in the total volume of ischemic cerebral lesions from preop to repeat imaging postop day 3 – 6. One hundred ninety-seven patients were enrolled (99 low target, 98 high target) with a mean age of approximately 65 yrs in both groups. There was no difference in new cerebral lesions between groups (52.8% low, 55.7% high, P = 0.76) nor in the primary outcome (25 mm3 low, 29 mm3 high), nor in the number of new lesions (1 in each affected patient per group). No significant differences were noted in the frequency of severe adverse events.

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Valvular Heart Disease, Heart Failure, Transplantation *(NJ Skubas)*

Transcatheter AVR

Patients with aortic stenosis (AS) are frail and have many co-morbidities. Among them, pulmonary hypertension from backward transmission of increased left ventricular and left atrial filling pressures may result in secondary pulmonary vaso-constriction and remodeling of pulmonary vasculature. Patients with baseline pulmonary hypertension who undergo surgical aortic valve replacement (AVR) have increased morbidity and mortality. This holds true for patients undergoing trans-catheter AVR (TAVR). In a meta-analysis of 16 studies enrolling 9,204 patients with AS who underwent TAVR, all-cause mortality was significantly increased for 30-day, 1-year and 2-year all-cause mortality compared with those without PH. A higher risk of stroke and acute kidney injury were also noted. Despite the limitations (increased heterogeneity, observational retrospective cohorts and variable techniques to detect pulmonary hypertension), the importance of baseline pulmonary hypertension to postoperative outcome should not be overlooked. This becomes even more important in the current era, when monitored anesthetic techniques or sedation are the anesthetic techniques of choice, and undetected hypercapnia may further exacerbate underlying pulmonary hypertension. *Tang M, et al. Meta-Analysis of Outcomes and Evolution of Pulmonary Hypertension Before and After Transcatheter Aortic Valve Implantation.Am J Cardiol. 2017;119:91-99*

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Diabetes mellitus (DM) is frequent amongst patients undergoing TAVR but has not been associated with worse outcome than TAVR patients without DM. The mortality and complications for 30-day and 1-year was similar in 13,253 patients included in a meta-analysis.
Sun Y, et al. Meta-Analysis of Impact of Diabetes Mellitus on Outcomes After Transcatheter Aortic Valve Implantation Am J Cardiol. 2017;119:623-629

Decompensated AS is a condition characterized by high mortality if treated medically and a significantly increased risk of perioperative mortality and morbidity in case of surgical AVR. Catheter-based emergency balloon valvuloplasty is considered a treatment option. In a German multicenter observational study of patients with decompensated AS (cardiogenic shock requiring catecholamine therapy, severe acute dyspnea (NYHA IV), requiring cardiac resuscitation or mechanic respiratory support) immediate procedural and 30-day mortality of emergency TAVR (n=23; 24%) and emergency balloon aortic valvuloplasty (n=118; 33%) were high, and mortality of secondary TAVR subsequent to emergent balloon aortic valvuloplasty (n=32) was higher than expected (16%). In the TAVR group, there was an unexpectedly high rate of cerebral events and vascular complications. The major limitations of the study are its retrospective nature, evolution of TAVR prostheses and non-randomized treatment. Whether emergent TAVR is viable option for such patients remains to be proven. *Bongiovanni D, et al. Emergency treatment of decompensated aortic stenosis. Heart 2018;104:23-29*

Initial clinical trial evidence comparing TAVR to surgical AVR was mainly limited to patients at high risk of death during surgery. Data from large national registries have now indicated a global trend towards TAVR being used in lower-risk populations despite little rigorous clinical trial evidence for this practice. In a propensity matched patients with moderate AS, TAVR with SAPIEN 3 was found to be superior to surgery at 1-year follow-up with lower rates of all-cause mortality, stroke, and the composite endpoint of mortality, stroke, and moderate or severe aortic regurgitation, but higher rates or moderate or severe regurgitation. The new generation SAPIEN 3 TAVR prosthesis has different geometry of the leaflets, longer frame and a fabric skirt sewn to the bottom portion of the interior and exterior of the frame, providing an external circumferential seal to reduce paravalvular leaks) and comes in four different sizes. However, the two groups were from different, historical registries and included patients from various north American and Canadian centers. *Thourani VH et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet. 2016;387:2218-25.*

Thrombosis in Valvular Surgery

Aspirin (COR IIa) and vitamin K antagonism for 6 months (COR IIa) are indicated for prophylaxis against thrombosis following AVR or mitral valve replacement. In a meta-analysis of randomised and observational studies of vitamin K antagonists versus anti platelet/no treatment in patients undergoing bioprosthetic valve implantation (vast majority AVR), there was no benefit of adding a vitamin K antagonist regarding thromboembolism or mortality (no significant differences in rates of thromboembolism, all-cause mortality or redo surgery/re-exploration). Use of a vitamin K antagonist was associated with increased risk of major bleeding. *Masri A, et al. Anticoagulation versus antiplatelet or no therapy in patients undergoing bioprosthetic valve implantation: a systematic review and meta-analysis. Heart 2017;103:40-48.*

Symptomatic thrombosis represents the extreme end of the spectrum of bioprosthetic aortic valve thrombosis and is probably under-reported (prevalence of 1–2%). In contrast, subclinical leaflet thrombosis with no associated symptoms is more frequent (prevalence of 10–15%) than is symptomatic bioprosthetic aortic valve thrombosis. Reduced leaflet motion detected with high-resolution CT in bioprosthetic aortic valves has been attributed to subclinical leaflet thrombosis in previously reported series. In 931 patients who had CT scans done (at a median interval of 83 days [IQR 33–281]) after surgical AVR or TAVR to assess reduced leaflet motion, frequency and severity of reduced leaflet motion was lower in surgical AVR than in TAVR. In addition, anticoagulation with novel anticoagulants or warfarin was effective in prevention or treatment of reduced leaflet motion, but dual anti platelet therapy, which is the standard of care, was not. Patients with reduced leaflet motion had a small, but significant, increase in valve gradients (~10 mmHg). The rates of neurological events, including transient ischemic attacks and strokes or transient ischemic attacks associated with reduced leaflet motion were increased, although the rates of strokes were not significantly different. These findings should be considered when treating patients with recent

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AVR. Despite excellent outcomes after TAVR with the new-generation valves, lack of symptoms does not necessarily indicate a normally functioning AVR. A short course of anticoagulation may be shown to be more appropriate than anti platelet therapy in future, ongoing randomized trials to further improve clinical outcomes and hemodynamics.
Chakravarty T, et al.Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet. 2017;389:2383-2392

The lack of anticoagulation therapy post-TAVR influenced TAVR hemodynamics and was associated with a higher risk of valve hemodynamic deterioration due to thrombosis at 1-year follow-up (but no clinically significant complications). *Del Trigo M, et al. Impact of anticoagulation therapy on valve haemodynamic deterioration following transcatheter aortic valve replacement. Heart. 2018;104:814-820*

NeoChords in Mitral Valve surgery

A new technique for less invasive MV repair is the transapical, off-pump implantation of artificial chordae under TEE–guidance. Anesthesia for NeoChord implantation is a standard anesthesia for off-pump cardiac surgery with 2- and 3-dimensional TEE playing crucial role for the guidance, safety, and effectiveness of the procedure. The perioperative morbidity and mortality are low and blood transfusions rare.
Samalavicius RS, et al. Anesthetic Management and Procedural Outcomes of Patients Undergoing Off-Pump Transapical Implantation of Artificial Chordae to Correct Mitral Regurgitation: Case Series of 76 Patients. Anesth Analg 2018;126:776-84

Strain Imaging

Strain is a new technique to evaluate myocardial function. Based on the relative position of echocardiographic markers ("speckles") it is available in both transthoracic and TEE systems. Left ventricular speckle-tracking strain did not change and right ventricular strain decreased immediately following surgical AVR. [*Duncan AE, et al. Early Left and Right Ventricular Response to Aortic Valve Replacement. Anesth Analg 2017;124:406–18*]. Decreased pre-procedure intraoperative global longitudinal strain was associated with prolonged hospitalization (>7 days), after adjusting for predefined confounders in patients undergoing AVR surgery. [*Sonny A, et al. Reduced Left Ventricular Global Longitudinal Strain Predicts Prolonged Hospitalization: A Cohort Analysis of Patients Having Aortic Valve Replacement Surgery. Anesth Analg 2018;126:484-93*] A larger, retrospective analysis also found an independent association between reduced global longitudinal strain and low cardiac output syndrome, but without an incremental prognostic value over established risk factors. [*Amabili P, et al. Preoperative Three-Dimensional Strain Imaging Identi es Reduction in Left Ventricular Function and Predicts Outcomes After Cardiac Surgery.Anesth Analg 2018;126:1476-83*] A three-dimensional global strain analysis, performed with transthoracic echocardiography in cardiac surgery patients found acute reduction in postoperative left ventricular function as well as, an independent association between preoperative three-dimensional strain with acute and long-term postoperative clinical outcomes. [*Howard-Quijano K, et al. Preoperative Three-Dimensional Strain Imaging Identi es Reduction in Left Ventricular Function and Predicts Outcomes After Cardiac Surgery Anesth Analg 2017;124:419-28*]

Organ transplantation

Cold storage has been the gold standard for heart preservation with excellent clinical outcomes. Side effects of cold storage include time-dependent ischemic and subsequent reperfusion injury of the donor heart, which can impair heart function after transplantation. A prolonged cold ischemia time is an important risk factor for early dysfunction of the donor heart and death of the recipient. The limited time of cold ischemia can limit use of donor hearts and possible organ sharing. A proprietary system (Organ Care System) preserves the donor heart in a warm, beating, near-physiological state ex vivo during transportation from the donor hospital to the recipient hospital. The coronary arteries of the donor heart are perfused with warm oxygenated blood, which is pumped into the aorta. The coronary sinus flow then passes through the tricuspid valve (as both the superior and inferior vena cava are sutured closed) and is ejected by the right ventricle into a pulmonary artery catheter, and returned to the blood reservoir. The mean aortic pressure is kept between 60 mmHg and 90 mmHg, and coronary blood flow between 650 mL/min and 850

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mL/min. Arterial and venous lactate samples are taken regularly from the system perfusate to assess the adequacy of perfusion. At the recipient hospital, the donor heart is arrested with the centre's standard heart preservation solution and disconnected from the Organ Care System for implantation into the recipient. 130 patients were randomized to receive cold storage or Organ Care System donor and had similar patient and graft survival rates. The clinical outcomes of donor hearts adequately preserved with the Organ Care System platform were non-inferior to the outcomes of those preserved with standard cold storage. Of note, five donor heart were discarded while preserved with Organ Care System, because of rising total perfusate lactate concentrations, which indicated persistent myocardial ischemia despite optimization of myocardial perfusion.
Ardehali A et al. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. Lancet 2015;385:2577-84.

Organ failure

In patients with advanced heart failure, a fully magnetically levitated centrifugal-flow pump (HeartMate 3) was superior to a mechanical-bearing axial-flow pump (HeartMate II) with regard to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device. The centrifugal-flow pump also resulted in a lower risk of stroke than the axial-flow pump, while averting pump thrombosis–related device malfunction. *Mehra MR, et al. Two-Year Outcomes with a Magnetically Levitated Cardiac Pump in Heart Failure. N Engl J Med 2018;378:1386-1395*

Vasopressin in vasoplegia

Vasoplegia is common after cardiac surgery and due in part to insufficient endogenous vasopressin, especially in patients previously treated with β-blockers or ACEi. Patients with vasoplegic shock (defined as MAP <65 mmHg resistant to fluid challenge and cardiac index greater than $2.2\ l \cdot min^{-2} \cdot m^{-2}$) after cardiac surgery were randomized to receive vasopressin (n=149; 0.01-0.06 U/min) or norepinephrine (n=151; 10-60 µg/min) to maintain MAP. The primary outcome was a composite of mortality or severe complications (stroke, requirement for mechanical ventilation for longer than 48 h, deep sternal wound infection, reoperation, or acute renal failure) within 30 days. The primary outcome occurred less frequent in the vasopressin patients (unadjusted HR=0.55; 95% CI 0.38-0.80; $P = 0.0014$), who also encountered a lower occurrence of atrial fibrillation (63.8% *vs.* 82.1%; $P = 0.0004$); no difference was found between groups in the rates of digital ischemia, mesenteric ischemia, hyponatremia, and myocardial infarction. Vasopressin use was associated with a shorter duration of inotropic and vasopressor therapy and shorter lengths of ICU and hospital stay.
Hajjar LA et at. Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery. The VANCS Randomized Controlled Trial. Anesthesiology 2017;126:85-93

Inhaled Vasodilators

In a systematic review and meta-analysis aerosolized vasodilators for the treatment of pulmonary hypertension in cardiac surgery patients were compared to intravenously administered agents and to a placebo (n=434 patients from 10 studies). Aerosolized vasodilators were no better to placebo in terms of decreasing mortality, had no effect on length of hospitalization and were associated with an increased ICU duration of stay. Apart from an increase in RV ejection fraction (along with decreased PVR and increased mean arterial pressure) with aerosolized agents, data was insufficient to compare other outcomes to intravenous vasodilators. Whether or not treatment of pulmonary hypertension with inhaled vasodilators during cardiac surgery alters clinically important patient outcomes remains unanswered. [*Elmi-Sarabi M, et al. Aerosolized Vasodilators for the Treatment of Pulmonary Hypertension in Cardiac Surgical Patients: A Systematic Review and Meta-analysis. Anesth Analg 2017;125:393–402*]

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Postoperative Delirium: The Known Knowns, Known Unknowns, and Unknown Unknowns

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INTRODUCTION

Delirium occurs when a patient experiences fluctuation in mental status caused by acute cerebral dysfunction. All hospitalized patients are at risk for the development of delirium, and patients in the perioperative setting are no exception. The risk of developing delirium appears dependent on age, preexisting comorbid conditions, severity of concurrent illness, and severity of the surgical process.[1] Studies in surgical patients focusing on delirium in the first few postoperative days have found significant associations with increased length of stay, higher cost of care, readmission to the hospital, higher rates of institutionalization after discharge, prolonged cognitive decline, dementia, and increased mortality.[2-6] Because delirium occurs commonly and is associated with worse outcomes, an understanding of its disease process, risk factors, and management is essential for an anesthesiologist.

DEFINITION AND DIAGNOSIS

To diagnose perioperative delirium, it is important to understand the definition: a disturbance in the ability to direct, focus, sustain, and shift attention coupled with a change in cognition (memory deficit, disorientation, or perceptual disturbances) which cannot be accounted for by a neurocognitive disorder or a severely reduced level of arousal.[7] Changes in attention and cognition are acute in onset, fluctuate, and may include hypoactive and/or hyperactive psychomotor activity. Hypoactive delirium is characterized by slowed mentation, lethargy, and a decrease in movement. It is found more commonly in the elderly and typically requires delirium assessment tools to diagnose since it is less clinically apparent than the agitation and restlessness of hyperactive delirium. Hyperactive delirium is characterized by agitation and restlessness. Another form of delirium common in the perioperative setting is emergence delirium, which typically refers to agitation after discontinuation of an anesthetic. PACU delirium is mental status changes that occur after emergence but before PACU discharge criteria are met. Postoperative delirium occurs when mental status changes take place after the patient meets PACU discharge criteria, whether on the hospital ward or in the ICU.

The diagnosis of delirium is very important but can be challenging in the perioperative setting due sedative and analgesic medication administration and emergence from general anesthesia. Importantly, most delirium goes undiagnosed without using a regular screening tool. Further, a positive test on a delirium instrument should alert the provider to an exacerbation of a primary insult (e.g., shock, stroke, hypoxemia) or the development of new secondary insult (e.g., infection, medication administration). Common signs of delirium are listed in **Table 1**. The gold standard for delirium diagnosis is to have the patient evaluated by a psychiatrist using *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* criteria.[7] Since this is not routinely feasible in most hospitals, there are validated instruments to aid clinicians in the diagnosis. There are no validated instruments, however, specifically focusing on assessment of delirium in the PACU setting. The key components of these validated instruments can be used to aid in the diagnosis no matter the perioperative stage. The first thing a clinician must do is assess a patient's level of arousal. Delirium assessment cannot occur if the patient is unresponsive to voice. The most common arousal scales used are the Richmond Agitation Sedation Scale (RASS)[8] and the Sedation Agitation Scale (SAS).[9] After the patient has achieved a level of arousal that allows for response to verbal stimuli, the Confusion Assessment Method (CAM),[10] the 4AT,[11] the Nursing Delirium Symptom Checklist (NuDESC),[12] the Confusion Assessment Method for Intensive Care Unit (CAM-ICU),[13] the Intensive Care Delirium Screening Checklist (ICDSC),[14] or another validated assessment tool can be utilized. Importantly, most delirium goes undiagnosed if a regular screening tool is not used. The NuDESC and CAM-ICU tools have been the most studied tools in the PACU, but neither is very sensitive for PACU delirium.[15] Their

TABLE 1. SIGNS OF DELIRIUM
Acute onset of mental status altered from baseline
Mental status fluctuation
Altered level of consciousness from baseline
Inattention, inability to focus, easy to distract
Disorganized thinking, incoherent thought process
Hypoactive and/or hyperactive motor activity

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specificity, however, was found to be >90%. Therefore, if a patient tests positive on one of these assessment tools, the diagnosis of delirium is very likely to be correct. Finally, current research is examining delirium severity scales through modification of these assessment tools. The CAM-S tool to quantify the severity of symptoms has been validated, and severity as determined by the CAM-S has been associated with both in-hospital and post-discharge outcomes.[16] The CAM-ICU-7 severity tool has been validated in critically ill patients, and severe delirium on the CAM-ICU-7 has been associated with higher odds of death.[17] Educational materials on these tools can be found at www.icudelirium.org.

PREVALENCE

Delirium prevalence in the perioperative setting varies widely depending on the patient population, definition, and assessment tool utilized. In a cohort of 400 patients undergoing non-cardiac surgery, hyperactive agitated arousal from anesthesia was found to occur in 19% of patients.[18] When using the CAM-ICU, 37% of patients had delirium upon on arrival to the PACU, 47% of whom had hypoactive signs and 53% of whom had hyperactive signs. During the PACU stay prior to meeting PACU discharge criteria, 16% of patients had delirium, 92% of which had hypoactive signs. After meeting PACU discharge criteria, 5% of patients had delirium.[18] In a smaller study of patients > 70 years old, 45% of patients had delirium *after* completing recovery from anesthesia.[2] Postoperative delirium has been reported at approximately 50% after cardiac, orthopedic, and major non-cardiac surgery (**Table 2**) and typically occurs on the first or second day after surgery.[1] If patients are admitted to an ICU after surgery and require mechanical ventilation, delirium prevalence can be as high as 80%. On the ward and in the ICU, hypoactive delirium is much more common than the more clinically apparent hyperactive delirium.

TABLE 2. RATES OF DELIRIUM PER SURGERY CLASSIFICATION

Surgery	Rate
Otolaryngological	12%
General	13%
Aortic	29%
Orthopedic	40%
Major Abdominal	50%
Cardiac	51%

ETIOLOGY AND RISK FACTORS

The pathophysiology of delirium is poorly understood with many proposed mechanisms depending on the patient and the clinical situation. This includes systemic inflammation, nervous system inflammation, endothelial and blood brain barrier dysfunction, cholinergic deficiency, and disturbances in neurotransmitters such as serotonin and norepinephrine.[19] Studies have also shown neuroanatomical changes associated with delirium, including brain atrophy and white matter changes, which may lead to subsequent cognitive decline.[20,21]

TABLE 3. DELIRIUM RISK FACTORS AND PRECIPITANTS

Risk Factors	Precipitants
Increasing age	Infection
Pre-existing cognitive impairment	Dehydration
Frailty	Electrolyte abnormalities
Congestive heart failure	Acute kidney failure
Acute myocardial infarction	Acute liver failure
Mechanical ventilation	Hypoxemia
Poly-trauma	Ethanol/drug withdrawal
Metabolic acidosis	Fragmented sleep
ASA >3 classification	Central nervous system insults
Emergency vs. elective surgery	Benzodiazepines, incl premedication
Open vs. endovascular surgery	Deep sedation
Increased surgical duration	Poor pain control

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Existing coma or delirium	Opioid administration?

There are known risk factors that are important for identifying high risk patients (**Table 3**). In general, these include, and are not limited to, increasing age, pre-existing cognitive impairment, and increasing comorbid medical conditions.[22] Thus, patients with lower cognitive and physical reserve possess decreased capacity to maintain normal brain functioning in response to the stress of surgery. Short preoperative screening tests can identify patients with previously undiagnosed cognitive impairment and predict postoperative complications, including delirium.[23] Understanding the precipitants can also be extremely important to change clinical strategies in order to minimize the occurrence of delirium. In addition, risk factors of postoperative delirium reported in the literature appear to be influenced by the severity of the surgical insult and by the exposure to sedative and/or analgesic medications during the perioperative period. Benzodiazepine exposure is known to be associated with an increased risk of emergence and postoperative delirium.[24,25] Opioid administration has been associated with delirium in the postoperative and ICU settings;[18,26,27] however, data on this association is inconsistent as others have shown opioids to be protective (or have no effect) with regard to delirium when used to appropriately control pain.[28-30] One thing that has been shown to increase perioperative delirium rates, repeatedly, is increasing pain scores.[31]

DELIRIUM PREVENTION

Many risk factors for delirium are unable to be modified by perioperative providers, but several preventative strategies have been demonstrated to reduce the incidence of delirium. Prevention of delirium is of utmost importance because the number of evidence-based treatment options for delirium is minimal.

Anesthetic Techniques

The evidence is inconclusive regarding the effects of anesthesia type on the development of postoperative delirium. There was not any difference in delirium rates when comparing total intravenous propofol general anesthetic compared to desflurane.[32] Similarly, no difference was found in early cognition when comparing total intravenous propofol general anesthetic and sevoflurane[33] or when comparing sevoflurane and desflurane.[34,35] The use of xenon was studied in older patients undergoing hip fracture surgery, but no difference was found in postoperative delirium between xenon and sevoflurane.[36] In a Cochrane review, regional anesthesia in patients undergoing hip surgery resulted in a potential decrease in postoperative confusion when compared to general anesthesia.[37] However, a large prospective study of elderly hip surgery patients did not find a decreased risk of postoperative delirium with regional anesthesia vs. general anesthesia,[38] and neither did a meta-analysis.[39] Importantly, the results of these studies in patients with lower extremity orthopedic procedures may not be generalizable to other surgical procedures. Current clinical guidelines[40] for postoperative delirium prevention in the elderly state that regional anesthesia can improve pain control and help prevent delirium, as studies have shown an association between poor pain control and higher rates of delirium. A study of femoral nerve blockade in addition to patient controlled analgesia demonstrated a lower incidence of postoperative delirium after total knee replacement.[41] The addition of non-opioid adjuncts for perioperative pain control may reduce rates of perioperative delirium, but data are limited. A randomized controlled trial in older patients undergoing spine or joint replacement surgery found no difference in delirium incidence with administration of gabapentin preoperatively and over the first 3 postoperative days. [42] In fast-track knee and hip arthroplasty, however, patients whose primary pain management plan was gabapentin, acetaminophen, and celecoxib were found to have low incidence of delirium.[43] This multi-modal analgesic plan is a key component of any enhanced recovery after surgery (ERAS) pathway, and lower rates of delirium have been reported in colonic surgery patients when on a ERAS pathway with low opioid exposure.[44] Thus insuring adequate pain control through regional techniques and non-opioid adjunct medications seem beneficial with regard to delirium outcomes.

Several studies have investigated depth of anesthesia with regard to delirium. Spinal anesthesia combined with lighter sedation in elderly patients undergoing hip surgery was shown to decrease the incidence of postoperative delirium when compared to spinal anesthesia with deeper sedation.[45] Other research has shown that monitoring depth of anesthesia was associated with less over sedation and also with less postoperative delirium.[46] It appears, however, that duration of burst suppression and low anesthesia dose requirements may be more predictive of postoperative delirium than low values on processed electroencephalography.[47]

Pharmacologic Prophylaxis

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Studies investigating whether prophylactic medication administration reduces the incidence or duration of delirium have had mixed results but are mostly negative. Perioperative haloperidol prophylaxis for up to 6 days (up to 3 days prior to and 3 days after surgery) did not affect delirium incidence but did decrease delirium duration compared to placebo in a randomized controlled trial in elderly hip surgery patients at intermediate or high risk for postoperative delirium.[48] The choice of anesthetic was not reported or accounted for in the analyses. In elderly elective surgery patients, haloperidol prophylaxis for 3 days in the postoperative period *increased* the incidence of delirium (severity and duration were unaffected).[49] Perioperative olanzapine prophylaxis decreased the incidence but did not affect the duration or severity of delirium in elderly elective joint replacement surgery patients.[50] In a randomized controlled trial in elderly patients admitted to the ICU after non-cardiac surgery, low dose haloperidol bolus followed by an infusion decreased the incidence of delirium compared to placebo only after intra-abdominal surgeries.[51] A more recent, large, multicenter study of prophylactic haloperidol versus placebo performed in ICU patients found no difference in delirium incidence, delirium-free days, length of stay, or survival.[52]

Prophylactic dexmedetomidine infusion (as opposed to dexmedetomidine infusion for sedation) has been studied as a method to prevent postoperative delirium. A study randomized elderly patients with normal cognition or mild cognitive impairment undergoing joint replacement surgery to dexmedetomidine or normal saline infusion during surgery.[53] Both normal and cognitively impaired patients had decreased incidence of postoperative delirium with dexmedetomidine vs. normal saline. A randomized controlled trial of intraoperative dexmedetomidine versus placebo in elderly patients undergoing major elective noncardiac surgery found no difference in PACU or postoperative delirium or in cognitive performance at 3 or 6 months.[54] A large double-blind, placebo-controlled trial in two tertiary-care hospitals enrolled patients >65 years old admitted to the ICU after non-cardiac surgery and randomized them to either a sub-sedative, low dose dexmedetomidine infusion or placebo.[55] Patients requiring mechanical ventilation received propofol or midazolam to achieve sedation targets prior to study drug administration. Patients received study drug from ICU admission until 8:00 AM the following morning. They found that the incidence of postoperative delirium was significantly lower over the first 7 days of their hospitalization in the dexmedetomidine group.[55] Interestingly, the patients receiving the low dose dexmedetomidine infusion had lower pain scores, and the reduction in delirium remained when stratifying patients by whether or not they required postoperative mechanical ventilation.

Though cholinergic depletion is thought to play a role in delirium development, acetylcholinesterase inhibitors such as rivastigmine and donezepil have had disappointing results with regard to delirium.[56-59] They have not been shown to decrease incidence or duration of delirium. Ketamine has been studied to prevent delirium due to its anti-inflammatory properties and ability to improve postoperative pain. In a large trial of older patients undergoing major cardiac and noncardiac surgery, ketamine administration after induction of general anesthesia did not affect the incidence, duration, or severity of postoperative delirium compared to placebo.[60] In fact, patients receiving ketamine had more postoperative hallucinations and nightmares. The pleiotropic anti-inflammatory effects of statin medications have been of interest given the potential role of inflammation in delirium, but data are conflicting with regard to the effects of statins on delirium. In cardiac surgery patients, preoperative statin use has been associated with a reduced incidence of postoperative delirium in one study,[61] but another found no difference in delirium according to preoperative statin use.[62] A randomized controlled trial of perioperative statin versus placebo found no difference in delirium incidence or duration.[63] In elderly elective surgery patients, preoperative statin use has been associated with an increased risk of postoperative delirium.[64] Preadmission statin use did not affect delirium in a cohort of critically ill patients,[65] but statin therapy while in the ICU has been shown in two studies to be associated with lower overall risk of delirium.[65,66] Also, increasing duration of statin discontinuation in chronic statin users increased the odds of developing delirium, potentially from a rebound pro-inflammatory state from statin discontinuation.[65] Randomized controlled trials of statin versus placebo, however, have not shown a decreased risk of delirium.[67,68]

Numerous studies have examined methods to prevent delirium after cardiac surgery. Use of intraoperative cerebral oximetry monitoring does not appear to prevent postoperative delirium.[69] Administration of dexamethasone upon induction of anesthesia to potentially reduce the subsequent inflammatory response to cardiopulmonary bypass and surgery did not reduce the incidence or duration of delirium after cardiac surgery compared to placebo in a large randomized controlled trial.[70] To test the hypothesis that increased cholinergic activity would decrease delirium after cardiac surgery (since low cholinergic activity and anticholinergic medications have been associated with delirium), a randomized controlled trial of prophylactic rivastigmine vs. placebo starting the night prior to surgery was performed but found no difference in the incidence of postoperative delirium.[56] One study found that a single dose of sublingual risperidone, once the patient had regained consciousness in the ICU, reduced the incidence of delirium

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when compared to placebo.[71] Another study of risperidone in elderly patients requiring cardiac surgery found that repeated doses could prevent the development of delirium in patients already exhibiting some signs of acute brain dysfunction (referred to as subsyndromal delirium).[72] These positive results with risperidone need to be confirmed in additional larger cohorts before routine administration can be recommended. Finally, the use of dexmedetomidine for sedation after cardiac surgery has been shown to improve delirium outcomes when compared to morphine- or propofol-based sedation regimens.[73-75]

Intensive Care Unit Management

One hospital setting with established successful prevention techniques for delirium is the ICU. Sedative regimens that focus on targeted arousal levels and light sedation have positively affected the rates of delirium, and exposure to sedative medications and deeper levels of sedation have been associated with increased risk of delirium.[22] The use of dexmedetomidine for sedation during mechanical ventilation has improved delirium outcomes in randomized controlled trials when compared to lorazepam, midazolam, propofol, and morphine.[74-77]

Sleep hygiene is important to the prevention of perioperative delirium, as fragmented sleep has been associated with increased rates of delirium.[22] A decrease in the incidence of ICU delirium has been demonstrated when sleep disruptions are minimized and normal circadian rhythms are promoted.[78] No association was seen, however, between daily perceived sleep quality rating and transition to delirium.[79] Dynamic light application has been shown to restore circadian rhythms but was ineffective in reducing delirium in ICU patients.[80] Non-pharmacological sleep aids should be used when capable and alternative sleep medications used only when necessary. Interest in the role of sleep disturbances in delirium has led to studies investigating melatonin as an agent for delirium prevention. Studies investigating the benefit of prophylactic melatonin for delirium have had conflicting results.[81] In the perioperative setting, a double-blind randomized controlled trial of melatonin vs. placebo in patients with hip fracture did not demonstrate a difference in incidence of delirium.[82] A systematic review concluded that sleep interventions may be a promising means by which to improve delirium but that current research is limited by varied methodologies and significant bias.[83]

Early physical and occupational therapy has been demonstrated to reduce ICU and in-hospital delirium. Therapy typically progresses from passive range of motion to active range of motion, exercise in bed, sitting, standing, and walking depending on a patient's sedation level and physical abilities. A randomized controlled trial of daily sedation interruptions paired with physical and occupational therapy vs. usual care in hemodynamically stable medical ICU patients found a reduction in ICU and hospital duration of delirium by 2 days in the early therapy group.[84] More recently, a randomized controlled trial of early goal-directed mobilization vs. usual care in surgical ICU patients found a reduction in the incidence of ICU delirium and an increase in ICU delirium-free days.[85]

Multicomponent Intervention

Multicomponent bundles combining evidence-based prevention techniques have also been shown to reduce delirium rates even further. Multicomponent prevention protocols that include reorientation, continuity of caregivers, decreased use of restraints, removal of catheters, providing hearing aids and eye glasses, and geriatrics consultation have been found to reduce delirium incidence and the total number of days of delirium in multiple studies of surgical and medical non-ICU patients.[81,86,87] Similarly, hospital elder life programs in the perioperative setting have been shown to reduce delirium and length of stay.[88] In the ICU, bundles involving frequent assessment and control of pain, awakening and breathing trial coordination, light sedation, minimizing benzodiazepine use, delirium monitoring and management, and early mobility (i.e., the ABCDEF bundle) have been advocated to improve outcomes associated with delirium. A before-after trial of the implementation of this type of bundle found less delirium with a significant independent effect of the bundle on decreasing delirium.[89] A large scale implementation study of the ABCDEF bundle across multiple hospitals found that increased bundle compliance was associated with improved survival and increased the number of days alive without delirium or coma.[90]

Recommended strategies to reduce delirium in the perioperative setting are listed in **Table 4**.

TABLE 4. PERIOPERATIVE CARE STRATEGIES TO REDUCE DELIRIUM
Avoid or minimize precipitating medications (e.g., benzodiazepines, meperidine, anticholinergics)
Insure adequate pain control through regional techniques and non-opioid adjuncts
Light sedation for monitored anesthetic care when able
Avoidance of oversedation or burst suppression with general anesthesia

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Restore hearing aids and eye glasses, prompt removal of catheters and restraints
Attention to hydration and electrolytes
Dexmedetomidine use and light-sedation techniques for sedation
Early mobilization
Multicomponent prevention bundles
Consultation services for elderly high-risk patients

DELIRIUM TREATMENT

Specific pharmacological agents for the treatment of delirium are not supported by definitive guidelines or large clinical trials. Their use should be restricted to the patient who has failed non-pharmacologic prevention strategies and who is a risk to self or others. The most popular pharmacologic treatments are antipsychotic medications (e.g., haloperidol, olanzapine, quetiapine) and dexmedetomidine. However, none of those agents are FDA-approved for the treatment of delirium. In one pilot study of ICU patients, there was no difference in delirium-free days amongst placebo vs. haloperidol vs. ziprasidone.[91] When haloperidol was compared to olanzapine for delirium treatment, there was no difference in length of delirium.[92] In a small study of patients who required intravenous haloperidol, subjects were randomized to receive placebo vs. quetiapine in addition to the haloperidol.[93] The quetiapine group had a faster resolution of the first episode of delirium.

A randomized controlled trial compared dexmedetomidine to placebo in patients with critical illness that had otherwise resolved but for whom weaning from mechanical ventilation was prevented by hyperactive delirium.[94] Patients treated with dexmedetomidine had increased ventilator-free hours and faster resolution of their delirium symptoms. A non-randomized study examined the effectiveness of dexmedetomidine as a rescue therapy for non-intubated ICU patients with hyperactive delirium.[95] Patients whose agitated delirium failed to be controlled with intravenous haloperidol received dexmedetomidine. Patients whose agitated delirium improved after haloperidol received a haloperidol infusion. Patients receiving dexmedetomidine had a higher percentage of time at target sedation, less over-sedation, and a shorter ICU length of stay without increased incidence of hemodynamic side effects. The other key conclusion from this study was the overall failure rate of haloperidol (43%), demonstrating the limited efficacy of antipsychotic agents in the treatment of delirium.[95]

The treatment strategies for delirium are sparse, and the evidence is lacking for a single pharmacologic approach. Prevention with non-pharmacologic means remains the best course of action. Agents that tend to be used to prevent or treat delirium affect the sensorium and have significant side effects. For example, antipsychotic agents can cause sedation, respiratory depression, prolonged QT intervals, and neuroleptic malignant syndrome; dexmedetomidine is administered by infusion often requiring ICU admission and can cause bradycardia. Additional studies are needed to examine the effectiveness of dexmedetomidine as a first-line therapy for the treatment of delirium and with other alpha2-agonists administered orally or by intermittent intravenous bolus (e.g. guanfacine, clonidine) on delirium prevention and treatment.

SUMMARY

Delirium is a common problem in the perioperative setting associated with important clinical outcomes. An understanding of delirium risk factors, precipitating factors, and management is essential for an anesthesiologist in the perioperative care of patients. Importantly, screening and assessment tools are readily available for delirium diagnosis by non-psychiatric trained personnel to identify patients with delirium, including hypoactive and hyperactive subtypes. Prevention of delirium is of utmost importance because the number of evidence-based pharmacological options for delirium treatment is minimal, and those that exist have significant limitations.

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Economics of Anesthesia Care Urban Legends

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"Healing is an Art, Medicine is a Science, and Healthcare is a Business"
Author Unknown

Objectives: By the end of the presentation, you should be able to

1. Determine if the urban legends discussed are "True", "Mixture", or "False"
2. Discuss different strategies to improve OR throughput
3. Explain how anesthesia care is billed and paid and how surgical duration affects the charges
4. Show how comparing simply yearly compensation of different anesthesia providers results in wrong conclusions of the cost of care
5. Show why using "per provider" measurements can lead to inaccurate benchmarking of clinical productivity.

Economics of Anesthesia Care Urban Legends

Personally, I visit Snopes.com when confronted by a claim or story (especially via social media or email) to determine the validity. Based on their research, Snopes.com will rate a story from "True" to "Mixture" to "False".

In a similar way, in today's presentation, I will examine 4 urban legends concerning anesthesia economics and try to determine if they are true, a mixture of true and false, or false. The legends that will be discuss are the following:

- Focusing on turnover time will improve OR throughput.
- Because anesthesia revenue includes time, anesthesia providers prefer longer surgeries.
- Going from physician-only staffing to medical direction staffing will reduce staffing costs.
- Using "per provider" (aka FTE) measurements allow for accurate benchmarking of productivity.

Focusing on turnover time will improve OR throughput.

More frequently, you will hear the complaint "If turnover time was shorter, we'd do more cases!" My first response to this statement is "Stop beating a dead horse!" Research has established the fact that further reducing reasonable turnover times will not increase the number of cases that can be done in a workday.(1,2) For instance, for an OR in a non-ambulatory surgical center hospital, a reasonable maximum turnover time between procedures might be 35 minutes. Reducing this number by 20% would only result in a 7-minute time saving between cases. If 3 cases were done per OR, this would mean a 14-minute saving. Compared to the average surgical duration of one's hospital, reducing turnover time by 20% will not allow for one more surgical case to be done. Obviously, in an OR where more cases are being done in a day (e.g., 7-10 cataract or pediatric otolaryngology surgeries), reducing turnover time by 7 minutes per case may be significant. But in these specific ORs, the turnover time will already be much lower than in the rest of the ORs (e.g., 15-20 minutes) and further reduction may not be possible.

In contrast, focusing on reducing any delays—defined as a turnover time greater than the reasonable maximum turnover time—will result in large time savings. For instance, if a turnover time is 90 minutes in an OR with a the maximum time set at 35 minutes, then a 55-minute delay has occurred. Focusing on the etiologies of this type of delay could result in a reduction of 55 minutes per occurrence.

Finally, anesthesiologists should point out that they cannot bill for turnover time and therefore are also interested in decreasing it. Although decreasing the downtime will not allow an anesthesiologist to bill more per OR for that day (because of the previously mentioned inability to perform even one more case in a regular day); such efforts may result in the anesthesia provider(s) going home earlier, which can reduce overtime payments.

Traditionally, OR throughput improvement initiative has been to focus on how to have current number of people work more efficiently. (3,4) An interdisclipinary work flow assessment and redesign has been to work. It is

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important to note that all the efforts must include all participants, including surgeons. Further, anecdotal experience is that the initiatives work as long as there is a focus on the effort. After "people are not looking at", old habits will come back into existence. So the major lessons from this traditional approach is that one must include everyone and that the initiative must be publicized every 3 months to remind workers that it is still important.

In additional, traditional methods have a limited potential improvement. On the other hand, three studies published in *Anesthesiology* (August 2005 issue) describe successful attempts at redesign the non-surgical time.(5-7) Each study examined the movement of non-surgical time from series to parallel processing – that is moving from performing all activities in the OR where the surgery is done to performing some or all the non-surgical activity in another room while the surgery from the previous case is ongoing. In this way, turnover time activities are not reduced but done at another time. In all three studies, more staff (anesthesia and non-anesthesia) were required. This process is not new. In the past, ORs use to provide two ORs for fast surgeons – that is two complete OR teams for one surgeon. Presently, this is not as common, but with the emergence of preoperative regional block "rooms", a form of parallel processes already exist in some OR suites. A form of parallel processing (either block room or ones described in the studies) makes economic sense if the increased costs is offset by increased revenue (i.e., more cases) (which is dependent on payer mix and staffing costs (as described in the previous section) or a reduction in overtime staffing costs.

In July 2008 *Anesthesiology*, Smith et. al. showed how parallel processing and the use of regional anesthesia successfully allowed for an increase in OR throughput over a several year period.(8) As noted in the accompanying editorial (9), several important factors contributed to this success including (a) commitment of increased staff (both anesthesiology and nursing, especially an extra surgical technician), (b) commitment of increased facilities (no new ORs were built, but a place to set-up the equipment for total joint replacements was provided outside the actual OR), and (c) patient selection bias (not all patients were done in the high volume rooms).

To put it all together, Cima et al. from the Mayo Clinic presented their experience at improving OR efficiency and throughput.(10) I strongly recommend this paper as pre-reading for any committee or group that wants to do this at their own institution and the committee or group should begin any discussion by looking at Table 1 of this paper describing the 5 key work stream issues focused on in the improvement projects are

1. Unplanned surgical volume variation
2. Streamlining the preoperative process
3. Reducing non-operative time
4. Reducing redundant information collection
5. Employee engagement

Urban Legend: Mixture. It is possible to improve OR throughput, *but one must focus on the whole perioperative experience*, like described by Cima et al. If one only looks at turnover time, then this legend would be false!

Because anesthesia revenue includes time, anesthesia providers prefer longer surgeries.

Charges for anesthesia care differ from those of other medical specialties, in that time directly influences the amount charged. For instance, surgeons bill for cholecystectomies using relative value units (RVUs) independent of case duration of the surgery. In contrast, as noted above, anesthesiologists bill using ASA units, including time units. Thus, anesthesiologists do bill more for longer cases than shorter ones.

At first glance it would appear to be in the best financial interests of an anesthesiologist to have longer cases because he or she could bill more per case. Upon further analysis, it becomes clear that longer cases are not financially beneficial. Anesthesiologists actually bill more providing care for many short cases than for a few long cases. Instead of examining billed units per case, one should evaluate the hourly billing productivity (defined as total ASA units billed per hour of care = tASA/h).(11-14) This measurement is calculated by dividing the sum of total base units and total time units by the total hours of care (for 15-minute time units, hours of care will equal time units divided by 4). For instance, if one assumes that 8 billed hours of care are provided to 2 different surgeons, then the difference in hourly productivity (tASA/h) is dependent solely on the basic units billed. The basic units billed for

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these 8 hours is related to the number cases done and the base units per case. Therefore, for similar cases, a greater number of cases that can be done in 8 hours will result in more billed units. In other words, the shorter the case duration, the more advantageous it is for an anesthesiologist. Hence, there is actually an incentive to work faster!

A further incentive for wanting surgical cases to be shorter is that for most anesthesiology groups, the revenue from the additional surgical time does not cover the staffing costs for that time. In particular, the cases that finish after regular hours result in a net loss to the anesthesiology group due to the higher staffing costs.(14) That is the situation of finishing the same number of cases, but finish at 6 PM or 5 PM. If the difference is delays, then it is a "no-brainer" since any delay of a case is non-billable and the revenue is identical but the anesthesiologist is leaving the hospital an hour later. On the other hand, let's examine the situation where the additional hour is intraoperative time and hence an additional hour of billed time. So there is a difference in revenue, but only for an hour of billed time and no difference in base units since the same number of cases are done. Therefore the difference is revenue can be calculated by multiplying the conversion factor for one unit by 4 (assuming 15-min time units). Calculating a weighted average depending on payer mix, the results are shown in Table 1 and range from $80 (poor payer mix) to $176 (good payer mix).

Table 1: Hourly Revenue due to Time

	Commercial	MediCAID	MediCARE	Indigent	Ave CF	Hourly Revenue (CFx4)
CF	$55.00	$15.50	$18.50	$0.00		
Good	71%	2%	24%	3%	$44	$176
Average?	44%	20%	32%	4%	$33	$132
Poor	15%	35%	32%	18%	$20	$80

The next step is to ask if this increase revenue is worth it. That is if the revenue covers staffing costs, then the answer is "yes, it makes sense to want to stay an extra hour." On the other hand, if the staffing costs are more than the revenue, then "it makes economic nonsense to want an extra hour."

We originally did using 2001 compensation data (14). Since then, compensation for both anesthesiologist and nurse anesthetists have changed, I will use an estimate of staffing costs. Note that since the hour being considered is "after hours", there needs to be a increase costs. In studies, this increase is a multiplier of 1.75 to cover direct costs (actual payments out) and indirect costs (cost of poor moral and need to recruit new members). Using an estimate of working 44 weeks a year (that is 2 weeks holiday, 4 weeks vacation, and 2 weeks meeting) and an average of working 50 hours a week, an estimate of an average anesthesiologist works 2200 hours per year. In Table 2, the staffing cost per hour and per "after hour" is shown.

Table 2: Staffing Costs per Hour Estimate

Yearly Compensation	Hourly Cost	After-Hourly Costs (1.75x)
$400,000	$182	$318
$300,000	$136	$239
$250,000	$114	$199
$160,000	$73	$127

Comparing revenue expected (Table 1) for additional time with staffing costs (Table 2), it is easy to understand why for most groups, additional time in the OR does not pay for itself, especially for cases that run beyond regular hours. Simply stated, from an anesthesiology perspective, the provider would rather go home sooner than work the additional time (that is go home at 5 PM rather 6 PM).

Therefore, we do have an incentive to work faster and have an interest for the surgeon to work faster as well!

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Urban Legend: False. The way anesthesia care bill has an incentive to work faster and reduce non-billable time (turnover or delays).

Going from physician-only staffing to medical direction staffing will reduce staffing costs.

For a full discussion, please see the December 2010 ASA Newsletter article by A.Abouleish, S.Stead, and N.Cohen, entitled "Myth or Fact? Nurse Anesthetists cost less than anesthesiologists." Available on the ASA website, www.asahq.org (15).

Costs can be compared either using "Cost-effectiveness" or "Cost-minimization" analysis. In a cost-effective analysis, the underlying principle is that two items being compared do different functions or provide different benefits. Therefore, a item that costs more might be the better option because of the additional benefits. In a cost-minimization analysis, the underlying principle is that both items being compared do the same function or have the same benefits. Therefore, the best option is the lowest cost item.

In the case of staffing models, the correct analysis should be cost-effectiveness analysis because physicians (anesthesiologists) can provide additional functions and expertise than advanced nurse practioners (CRNAs). These include consultations, providing independent medical care and expertise, call and evening duties, additional training, acute pain and chronic pain expertise, and management of postoperative patients as well as medical staff committee membership work. In addition, in all states, physicians can work independently which allows for more efficient staffing in remote settings. Finally, in academics, physicians can provide clinical and didactic educational duties of residents. The full discussion of this analysis is beyond the time allowed in this presentation.

On the other hand, if the move from physician-only staffing to medical direction results in more costs than a cost-minimization analysis would show this. Hence, in any situation, the first thing is to do a cost-minimization. Unfortunately, this is often done incorrectly. Simply comparing costs of providers by yearly compensation will lead to inaccurate conclusions of staffing costs. On average, an anesthesiologist works 55 hours per week clinically, and a CRNA works 40 hours a week clinically. Further, the additional 15 hours the physician works is done after regular hours (evenings, nights, and weekends) which needs to valued per hour more than work done during regular hours.

Since the 2010 newsletter article, we have updated our model to include the need for "break" CRNAs once you have 4-6 CRNAs in the room. The cost of the medical direction models increases. In addition, the models discussed in the newsletter article were limited to care provided till 3 pm. If more than 20% of the sites are running after 3 pm, the cost of the medical direction model increase even more.

Urban Legend: False. Simply moving to medical direction staffing model does not necessarily mean reduction in staffing costs.

Using "per provider" (aka FTE) measurements allow for accurate benchmarking of productivity.

Hospital administrators or medical school deans who make this statement are mistakenly trying to apply outpatient clinic logic to anesthesia staffing. For instance, the administrator might use 30 patients a day as a benchmark for how many patients a pediatrician should see in one day. Thus, if there are 300 patients to be seen each day, then one needs 10 pediatricians to staff the clinic each day.

Unfortunately, as anesthesiologists well know, this logic does not work for determining staffing needs for operating rooms. The primary determinants of the number of anesthesia providers needed each day for a particular department are a) the number of clinical sites or ORs to be staffed; b) the staffing ratio (i.e., concurrency); and c) the numbers of persons both on-call and post-call.(16) What is not a direct determinant of anesthesia staffing is any type of productivity benchmark. Simply put, if the administrator wants the anesthesiology group to cover 20 ORs, then the group will need the same number of providers whether the cases finish at noon or 3 PM.

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In addition, the logic applied by the administrator in this situation compares anesthesiology group productivity using "per anesthesiologist" (i.e., per FTE or full time equivalent) measurements. However using "per FTE" measurements to compare anesthesiology groups with different staffing ratios leads to inaccurate conclusions.(17) An example in see when comparing a physician-only group and a group that uses anesthesia care team model (medical direction). When comparing tASA "per FTE", the medical direction groups appears to be more productive. But when the comparison is done by "per OR site", one finds that the physician-only group is identical to the medical direction group. (See Table 3) Administrators can more meaningfully compare anesthesia care done by groups (or by hospitals in which they work) by using tASA/hr and "per OR site" measurements.(12,18-19)

Table 3. Comparing Group Productivity

		Physician Only	Medical Direction
Cases	Per FTE	907	1653
	Per OR	933	915
tASA	Per FTE	8,769	16,647
	Per OR	9,157	9,323

tASA = total ASA units per FTE, from MGMA 2011 Cost Survey of Anesthesia Groups

Urban Legend: False. Using "per FTE" measurements will lead to misleading conclusions if there are differences in the staffing models/ratios.

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Percutaneous Approaches to Implantation and Repair of Aortic, Mitral, and Tricuspid Valves

Michael G. Fitzsimons, M.D.
John G. Augoustides, M.D.
Brandi Bottiger, M.D.
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Transcatheter Aortic Valve Technology: The Procedure and Latest Trials

John G. Augoustides, M.D.

The breakthroughs in transcatheter aortic valve replacement (TAVR) has been impressive since the first procedure was described from France in 2002.[1-2] Within a decade, seminal randomized controlled trials paved the way for commercial approval of these devices worldwide. In the contemporary era, there are two valve families for TAVR: balloon-expandable valves and self-inflating valves.[1-3] As a guiding principle, TAVR valves can be deployed successfully in the aortic valve position via various arterial access routes, most commonly via transfemoral access.[1-3] The detailed approach to the technology and procedural aspects for TAVR have been reviewed recently in the literature.[1-3]

There have been three major phases in the evolution of TAVR. The first phase was the emergence of TAVR as a reasonable alternative to surgical aortic valve replacement for severe aortic stenosis in patients at high perioperative risk, defined as a perioperative mortality risk above 8% as calculated by the Society of Thoracic Surgeons score.[1-3] The second phase has been the recent emergence of resulted of TAVR as a reasonable alternative to surgical aortic valve replacement in intermediate-risk patients, defined as a perioperative mortality risk in the range of (4-8)%, as calculated by the Society of Thoracic Surgeons risk score.[1-4] These developments have prompted a Class IIa recommendation for TAVR in symptomatic severe aortic stenosis in the 2017 valvular heart disease guideline from the American Heart Association (AHA) and American College of Cardiology (ACC).[5] The experts have recommended that TAVR is a reasonable therapeutic option in intermediate-risk patients with severe aortic stenosis, based on moderate quality evidence from randomized controlled trials (Level of Evidence: B – R).[5] The third phase is currently in progress, namely that TAVR could be a reasonable therapeutic intervention in low-risk patients with severe aortic stenosis, defined as a perioperative mortality risk < 4%, as calculated by the Society of Thoracic Surgeons risk score.[1-3] The large randomized trials to evaluate this indication are currently enrolling patients. In the 2017 AHA/ACC guideline, surgical aortic valve replacement is currently the recommended intervention for low-risk patients with severe aortic stenosis, based on moderate quality evidence from non-randomized trials (Class I recommendation; Level of Evidence B – NR).[5]

The progress in TAVR has also blossomed in important subsets of patients with aortic stenosis. A large recent registry trial has also demonstrated that TAVR is also a reasonable therapy for bicuspid aortic stenosis, a relatively common disease in the developed world.[6] In the past, landmark TAVR trials had excluded bicuspid aortic valves due to their anatomical variations. This clinical breakthrough further increases the impact of TAVR in aortic stenosis.[5-6]

Moderate aortic stenosis may also be target for TAVR, since in this setting of (defined as aortic valve area 1.0 cm^2 -1.5 cm^2), clinical outcomes are suboptimal, especially if combined with left ventricular systolic dysfunction (defined as an ejection fraction from 20% -50%).[7] This combination has been associated with significant mortality and morbidity in a recent trial: all-cause death or hospitalization for heart failure was 48%.[7] These concerning findings have prompted the randomized evaluation of TAVR in this high-risk population by the TAVR UNLOAD trial.[8] In the perioperative setting, arena, TAVR could become a reasonable

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intervention in patients with significant aortic stenosis before elective major non-cardiac surgery, given that this disease confers high perioperative risk in non-cardiac surgery.[9]

The modern practice of TAVR has also focused on frailty as an outcome determinant and the evolution of anesthetic technique. Frailty is a geriatric syndrome that impairs resiliency to perioperative stressors to confer a high risk of adverse outcomes after invasive procedures.[10-11] Recent trials have demonstrated that frailty is a significant predictor of mortality after TAVR, suggesting frailty should be considered by the multidisciplinary heart team in the preprocedural risk assessment.[10-12] This comprehensive approach to patient selection has also been emphasized in the 2017 ACC/AHA guideline (Class I recommendation; Level C evidence).[5]

The anesthetic for TAVR has also evolved steadily away from general endotracheal anesthesia with full invasive monitoring towards monitored anesthesia care with less invasive monitoring.[13] This evolution of anesthetic technique has been facilitated by multiple factors such as advances in TAVR hardware, less reliance on intraoperative transesophageal echocardiography, heart team experience, and the rarity of major complications.[13] Although there are no major randomized trials to compare TAVR outcomes as a function of anesthetic technique, recent meta-analysis has suggested that the major outcomes appear equivalent.[13-14] If monitored anesthesia care is chosen, it appears to proceed best in the setting of a mature program with an experienced team who have designed a perioperative pathway for these cases that includes screening criteria, a sedation protocol, and fast-tracking of postoperative care.[13-15] The continued progress in this arena has established TAVR as a mainstream therapy for aortic stenosis in the setting of a multidisciplinary heart team model that includes the anesthesiologist.[16-17]

Given this success in aortic valve disease, transcatheter valve therapies have now been expanded.[5] In the setting of severe bioprosthetic valve dysfunction, a transcatheter valve-in-valve procedure may be a reasonable alternative to surgery.[5] Transcatheter mitral valve repair has been recommended in selected patients with severe mitral regurgitation.[5] There is also considerable interest in the development of transcatheter platforms both for repair and replacement in tricuspid valve disease.[18-19] These paradigm shifts in valvular heart disease will include the anesthesiologist both for anesthetic care and precise imaging guidance with real-time echocardiography, including three-dimensional technology as a vital adjunct for clinical decision-making during these challenging procedures.[20-23] These aspects will be considered in further detail in the rest of the panel.

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Ultrasound for Percutaneous Valve Technology

Brandi A Bottiger, MD

Ultrasonography is an invaluable real-time imaging modality for patients undergoing percutaneous valve placement. Both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are readily available at many centers in the US, and provide real-time feedback to the interventionalist and multidisciplinary team to help guide decision-making. Advantages of this technology over other imaging modalities include its accessibility, portability, relative safety, and real-time feedback in the setting of hemodynamic and procedural changes (1,2)

Echocardiography is key in planning the interventional approach, monitoring during the procedure, and evaluating prosthesis quality and hemodynamic result. For transcatheter percutaneous valve procedures in the aortic position, practice guidelines for comprehensive intraprocedural echocardiographic imaging for procedural guidance has been established (1). A comprehensive review of key anatomic and hemodynamic features to assess during TAVR was recently published (3), and summarized in Table 1 for consideration across various perioperative time points.

Pre-procedure	Intra-procedure	Post-procedure
Identify aortic valve morphology, calcifications, confirm severity of AS, assess AI	Guidance of catheters, wires, balloon for valvuloplasty	Prosthesis placement, function (leaflet motion)
Aortoannular complex dimensions	Evaluation of prosthesis position and deployment	Quantify central or paravalvular leak
Aortic valve hemodynamics	Transapical cannulation	Reevaluate wall motion, assess patency of coronary arteries
Detection of associated valvular abnormalities (MS, MR)	Hemodynamic monitoring	Assess Hemodynamic profile of prosthesis (position, shape, peak/mean gradient, AVA)
Evaluate associated ventricular abnormalities (LV size, function,	Identify procedural complications (4,5)	Identify new pericardial effusion or focal rupture
Assess LVOT (calcifications), septum size and dynamic narrowing		Reassess ventricular and other valvular function

Table 1: Key echocardiographic assessment areas across the perioperative time period.

Paravalvular leak after TAVR, in particular, is correlated to postoperative morbidity and mortality in many large, multicenter outcomes studies and registries. (6-10) Standard endpoint definitions for paravalvular leak and quantification by echocardiography have been established. (11,12) Quantification of PVL in its relationship to outcomes is performed through the use of angiography, TEE, or TTE either as sole methods or in combination, depending largely on institutional practice. (13). However, interpretation of immediate post-deployment evaluation PVL as it relates to post-operative imaging remains unclear. A recent retrospective study found moderate correlation between the PVL quantified immediately postoperatively by TEE and PVL quantified by TTE (14). Variability in reporting of PVL attributed to team experience with the

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procedure, type, size and generation of prosthesis, imaging modality, imaging quality and timing of image acquisition (15)

Ultimately imaging goals must be set with members of the multidisciplinary team in the context of where the procedure is occurring, available equipment and expertise, and what other imaging modalities may be used. There is a huge amount of institutional variability in the US, with selection of TTE vs. TEE being centered on the following considerations:

Considerations for ultrasonography choice:
Patient habitus, predicted quality of imaging
Access to patient
Available expertise and equipment for performance, interpretation, and reporting
Setting (Operating Room or hybrid room vs cardiac catheterization lab)
Timing of ultrasound performance relative to the procedure
Anesthetic approach (16)

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Beyond TAVI: Percutaneous Repair of the Mitral and Tricuspid Valve
Joerg Ender, MD

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Among different percutaneous mitral valve repair techniques (1) so far the trancatheter mitral valve repair using the MitraClip® is by far the most often used treatment option for high risk patients with severe symptomatic mitral regurgitation (2). The five years results are comparable to surgical repair. It is recommended for primary mitral regurgitation based on the American Guidelines (3, 4) and for primary and secondary mitral regurgitation based on the European Guidelines (5). The five-year results are comparable with surgical mitral valve repair in the Everest Trial (6) and the results are comparable even when expanding the inclusion criteria I daily clinical routine (7). Transcatheter annuloplasty implantation with the Cardioband® is another transcatheter treatment option for mitral regurgitation with promising results (8).
Tricuspid regurgitation is frequent and associated with a poor prognosis if not treated (9). Transcatheter treatment options so far are promising but the experiences are still limited. Several devices are currently under investigation (10) but the number of patients included so far is limited (11-14). Imaging plays an important role in these procedures (15, 16).
In Europe the Cardioband® is the first device which received CE mark approval in May 2018 CE for the transcatheter tricuspid valve repair.
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Additional Information:

Anesthesia for TAVI: conscious sedation, general anesthesia or monitored anesthesia care. Where are we and where are we going

Nadia B. Hensley, M.D.

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Conscious sedation (CS) for TAVI is steadily increasing in the U.S. Hyman et al. examined data from 10,997 patients undergoing transfemoral TAVR between April 2014 and June 2015 using STS/TAVR registry data. CS increased from 11%/quarter to 20%/quarter during the 14 month period[1]. This study showed TAVI with CS was associated with reduced in-hospital and 30-day mortality. The need for intraprocedural inotropes, ICU length of stay were also reduced.

Another retrospective study by Babaliaros et al. conducted at Emory and published in 2014[2] initiated the discussion at many other institutions. Emory had adopted a minimalist approach (MA) with a catheterization laboratory nurse, under the direction of the interventional cardiologist, administered sedation with fentanyl and midazolam. Babaliaros et al. examined 142 patients and found a significant reduced length of stay (3 days vs. 5 days, $p<0.001$) in the MA compared to standard approach (SA) with general anesthesia, and cost ($45,485 +/- 14,397 vs. $55,377 +/- 22,587, $p< 0.001$).

There have been numerous observational and retrospective- designed studies examining conscious sedation vs. general anesthesia with the limitations of potential confounding bias. Even in the largest study by Hyman et al. and involving the NCDR STS/ACC TVT Registry was the most rigorous in analysis but still left questions of confounding. How sedation was defined can be troubling, since anesthesiologists all appreciate that it is a wide continuum that can easily cross into general anesthesia, with or without an airway device. Were the centers for sedation highly experienced centers in TAVR and therefore high use of CS may be a surrogate for expected excellent outcomes? The conversion rate in this study from CS to GA was not negligible at 5.9% and should be considered if one is considering the catherization laboratory model with nurse-administered sedation.

Another question to consider in determining whether or not CS is the best choice for your patient is TEE necessity? TEE is highly sensitive in detecting paravalvular leaks and because paravalvular leaks have been associated with increased late mortality, many argue that TEE is necessary, especially if TAVR transitions to low-risk patient populations.

Finally, if your center is considering transitioning to CS, define the patient variables that are important in considering which patients are best for CS. The first branch point in your algorithm should be access of approach. If the patient has favorable anatomy for transfemoral approach, then CS is reasonable. Any normal sedation concerns are also for consideration: airway, BMI, ability to lie flat, cooperation, anxiety, obstructive sleep apnea, baseline dementia, significant pulmonary hypertension and many more. Most centers use mild to moderate sedation and thus, cooperation is key. Ensure that your center is not on the steep learning curve of a TAVR program when transitioning to CS. Communication and being a part of the heart team to voice your concerns as the anesthesiologist is vital.

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Additional Tables and Information

Table 1– AHA TAVI Recommendation

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Recommendation	COR	LOE
Surgical AVR is recommended in patients who meet an indication for AVR with low or intermediate surgical risk	I	A
For patients in whom TAVR or high-risk surgical AVR is being considered, members of a Heart Valve Team should collaborate to provide optimal patient care.	I	C
TAVR is recommended in patients who meet an indication for AVR for AS who have a *prohibitive* surgical risk and predicted post-TAVR survival >12 mo.	I	B
TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR and have a high surgical risk.	IIa	B
TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from corrected AS	III: No benefit	B

Adapted from 2014 AHA/ACC Guidelines

Table 2 - TAVI Valve Characteristics

	Sapien Valve (Edwards)	Sapien XT (Edwards)	Sapien 3 (Edwards)	Evolute (Medtronic)
Height	15 mm	14-19 mm	15.5-22.5 mm	54 mm
Sizes	23, 26, 29 mm	20, 23, 26, 29 mm	20, 23, 26, 29, mm	25, 26, 29, 34
Valve leaflets	Bovine pericardial tissue	Bovine pericardial	Bovine pericardial	Porvine pericardium
Frame	Polyethylene terephthalate	Cobalt chromium	Cobalt chromium	Nitinol
Deployment method	Balloon Expansion	Balloon expansion	Balloon expansion	Self expansion
Approaches	Femoral artery Subclavian artery Axillary Transaortic Transapical	Femoral artery Subclavian Axillary Transaortic Transapical	Femoral Subclavian Axillary Transaortic Transapical	Transfemoral Subclavian Axillary Transaortic
Introducer size		16, 18, 20 Fr	14, 16 Fr	

Table 3 - Approaches for TAVI

Approach	Advantages	Disadvantages/ Difficulties/	Notes

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		Complication	
Transfemoral	Easy access Most common GA/MAC/Sedation Quick recovery Percutaneous	Peripheral disease Femoral aneurysm Arterial dissection	Most common approach
Transapical	Direct access Avoids femoral vessels	Requires GA	Needs close BP control
Transaortic	Direct access Avoids thoracotomy	Requires GA Requires partial sternotomy	
Subclavian/axillary	Avoids femoral vessels	Requires surgical cut down	
Carotid	Direct approach to the aorta	Cerebral embolization Compromised cerebral blood flow	

Table 4 - Risk factors for Heart Block After TAVI

Male sex Higher degrees of 1st degree AV block Left bundle branch block Right bundle branch block Intraprocedure heart block Use of the CoreValve

Table 5 – Indications for Post-operative ICU Admission over PACU Recovery

Pre-operative Factors indicating ICU Admission	Interoperative factors indicating potential ICU admission
Transapical approach Transaortic approach Pre-operative hemodynamic support Emergency case Pulmonary artery catheter needed post-op Pre-operative significant delirium Significant pulmonary hypertension High grade coronary artery disease	Expected post-op intubation Unexpected placement of a PA line Hemodynamic instability Conditions requiring close monitoring (pericardial fluid, aortic injury) Ischemia Significant arrhythmia Suspected complete heart block without adequate safe pacing

Panelists

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I'm Worried I'll Harm Him Before the Cancer Does: DNR, EOL, and Palliation in the Elderly

Perioperative management of advance directives, code status designation, and determination of decisional capacity.

Allen N. Gustin, M.D. Maywood, IL

Rebecca A. Aslakson, M.D., Ph.D. Stanford, CA

I. Demographics

The population of older adults in the United States is projected to double between 2012 and 2015 and to comprise more than 80 million individuals in 2015[1, 2]. Older adults frequently need surgery and perioperative complications and mortality progressively increase concurrent with increasing age[3, 4]. Thus, anesthesiologists must be prepared to care for ever increasingly older patients who need care during surgery.

Evidence supports that many Americans do not receive the treatments that they would choose or prefer at the end-of-life[5, 6]. In an attempt to prevent these discordant treatments at the end-of-life, individuals can complete an advance directive. Advance directives are documents that direct the medical treatments that a person may or may not desire in the future and are meant to inform future medical decisions should the individual lose decision-making capacity. These documents include living wills and/or health care proxy forms. Similarly, there is also support for advance directives as a scaffolding to ultimately promote better "in the moment" decision making for surrogate decision makers[7]. Recent evidence supports that 37% of US adults have an advance directive, that patients older than 65 years are significantly more likely to have an advance directive, and that patients with neurologic diseases, renal diseases, cancers, and/or cardiovascular diseases were also more likely to have advance directives[8]. Thus, anesthesiologists must also be prepared to care for older adults who present for surgery and who have a concurrent advance directive.

II. Treatment limitations – advance directives and code status definitions

One half of all Americans over the age 65 are disabled and living with major chronic diseases[9]. Also, as our American population ages, the Joint Commission requires that all patients receive information on treatment limitations of care on each admission to any healthcare facility[10]. Thus, treatment limitations of care are increasingly being seen more commonly among patients with complex medical conditions presenting for anesthetics within the peri-procedural environments. Treatments limitations of care are meant to ensure that the patient's goals of care are aligned with the medical or surgical care being provided. Treatment limitations of care ensure that patients who are unlikely to benefit from medical or surgical care are not subjected to burdensome futile treatments. Medical and surgical management must be aligned with the patients values and preferences. Two examples of treatment limitations of care are advanced directives and code status.

Advanced directives are instructions given to patients which spell out a patient's clinical decisions ahead of time in case of future decision-making incapacity[11,12]. Despite attempts to educate patients on advanced directives, adoption of advanced directives seems to be slow. In one study, 75% of all patients admitted to an emergency room did not have advanced directives[13]. Advanced directives are legally valid in all states and do not expire. Laws regarding advanced directives may vary from state to state. Advanced directives can be influenced by the patient's culture beliefs, clinical status, specific goals, and are specifically tailored to each patient. Alterations to the advanced directions can occur with changes in the patient's goals of care, on each readmission to a hospital, when significant changes in the patient's

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condition occurs, or when either the surrogate or the patients asks for changes to be made to the advanced directives. The Power of Attorney is a document that names a healthcare proxy who will make decisions for the patient if the patient is unable to do so. The power of attorney tends to be someone the patient trusts to make those decisions for the patient.

Code status is another treatment limitation of care which focuses on medical interventions that a patient would wish to have started if the patient's heart stops or if the patient stops breathing. Hoffman determined that as much as 30% of the American population who have a chronic illness do not want any form of resuscitation[14]. Unfortunately, physicians cannot predict a patient's preferences for code status unless he/she directly asks the patient. As a result, any physician is expected to provide all resuscitative effort unless the patient's code status specifically states that the physician should not do so.

III. How to handle perioperative treatment limitations

The automatic suspension of a patient's advanced directives or code status prior to any anesthetic, surgical procedure, or other procedure should be avoided. This automatic suspension of a patient's advanced directives without discussion with the patient does not respect an individual's autonomy. Rather, patients with active advanced directives presenting for an anesthetic should have a conversation with the anesthesia team regarding the goals of care and make any needed modifications to those advanced directives. Multiple national societies including the American Society of Anesthesiologists and the American College of Surgeons advocate for a "Forced Reconsideration" conversation with each patient[15-17]. From the guidelines published by the American Society of Anesthesiologists, a patient with active advanced directives who presents for anesthesia care can choose one of three possible pathways or outcomes: (1) full attempt at resuscitation, (2) limited attempt at resuscitation defined with regard to specific procedures, or (3) limited attempt at resuscitation defined with regard to the patient's goals and values. If the patient or surrogate decides to accept full resuscitation, then the current advanced directives are suspended during the anesthetic and during the immediate postoperative period[15]. If the patient or surrogate chooses to limit the attempts at resuscitation, then a "Forced Reconsideration" conversation must occur between the anesthesia provider and the patient/surrogate regarding aspects of anesthesia which are needed for success of the anesthetic and which are not[15]. For example, a patient with a "Do Not Intubate" directive who needs a laparoscopic cholecystectomy would need an intubation for the anesthetic goals of be successful. Finally, if a patient/surrogate chooses the limited attempt at resuscitation defined with regard to the patient's goals and values, then the anesthesia or surgical team may then determine which aspects of the anesthesia care and surgical care would be appropriate for the patient and which would not be appropriate[15]. In this scenario, the patient gives the either or both of the clinical teams the ability to make judgements in the patient's best interest during the procedure. More examples of clinical situations will be provided during the Refresher Course Lecture which will highlight different aspects of how to manage these perioperative discussions with these patients with advanced directives who present for a procedure.

IV. Assessing decisional capacity

Patients are assumed to have decisional capacity for medical decision making unless proven otherwise, although many clinicians don't receive formal training to assess that capacity[18, 19]. Consequently, it is not surprising that clinicians frequently fail to recognize impaired decisional capacity[21-26]. Although formal laws regarding medical consent vary by state, most are based on common law and the presence of three elements: (1) giving the patient sufficient information regarding the proposed treatment and its risks, benefits, complications, and the benefits and consequences of non-treatment; (2) freedom from coercion, and (3) the patient having medical decision making capacity[27].

To assess an individual's medical decision making capacity, there are four legal standards commonly used in the United States; these include a person's ability to: communicate a choice (*communicate*), understand information pertinent to the treatment decision (*understanding*), appreciate the magnitude of their condition, situation, and the decision in question (*appreciation*), and weigh the benefits and drawbacks of the varying treatment options (*reasoning*)[28, 29]. While any licensed physician can complete this assessment and physician evaluation is still considered the "gold standard" for

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determining a patient's decision-making capacity, multiple tools, most particularly the Mini-Mental Status Examination (MMSE)[16], exist to aid in determining a patient's medical decision making capacity[18].

A recent systematic review [18] highlights how the prevalence of impaired decision making capacity varies greatly by population and ranges from 2.8% among health older adults to 26% among hospitalized older adults on a medicine service. Moreover, decisional incapacity was correctly identified in 42% of cases. Use of the MMSE helped in determination of decisional capacity with an MMSE score of <20 significantly increasing the likelihood of the individual having incapacity for medical decision-making. Other validated tests of capacity found to be helpful and that are easy to administer included the Aid to Capacity Evaluation (ACE)[29], the Hopkins Competency Assessment Test (HCAT)[30], and the Understanding Treatment Disclosure (UTD)[31].

In conclusion, as licensed physicians, anesthesiologists are able and empowered to complete a competency exam. Moreover, given the higher prevalence of decisional capacity among hospitalized older adults, anesthesiologists should have a relatively low threshold for assessing medical decision making capacity. That assessment requires discussing and documenting in the medical record the patient's ability to *understand*, *appreciate*, and *reason* the risks and benefits of the decision and to *communicate* their decision choice. Should adjunctive and/or screening testing be desired for certain patient populations, anesthesiologists can also consider using the MMSE, ACE, HCAT, and/or UTD. Of note, the HCAT and UTD are more lengthly and can take upwards of 30 minutes to administer. ACE is freely available (https://www.aafp.org/afp/2001/0715/afp20010715p299-f2.pdf; accessed June 7, 2018), quick to administer, and rooted in the patient's own medical experience.

V. Conclusions

Patients presenting for an anesthetic and who have an active advanced directive in place can be a challenge for anesthesiologists. Anesthesiologists should be willing and prepared to engage each patient with a "Forced Reconsideration" conversation regarding the implications of the advanced directives. Each patient's experience with his/her advanced directive is different and in clinical practice one plan does not apply to all patients. Each patient situation should be approached truthfully with full respect for the patient's culture, the patient's personal beliefs, and the patient's desires. Each patient or surrogate should have a "Forced Reconsideration" conversation with the anesthesiologist. Anesthesiologists should avoid medical jargon and have honest conversations with each patient regarding the intersection of anesthesia goals of care and the patient's goals of care. If these goals between the patient and the anesthetic care are not aligned, then some or all of the treatment limitations of care can be held in place or fully suspended. Timing of when the advanced directives should be reactivated should always be discussed and decided upon at the time of each "Forced Reconsideration" conversation.

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Regenerative Medicine for Pain Physicians: Where We Are in 2018?

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Introduction

After years of experimental studies, regenerative medicine is inflowing into the clinical research, and promising to become one of the most ground-breaking and extraordinary trends in medicine today. An important factor that has made this transition achievable is a new understanding of the mechanisms of tissue repair. Today we will briefly discuss the fundamental concepts of regenerative medicine, as well critically assess samples of clinical evidence examining the current regenerative medicine options for treatment of such commonly encountered conditions as degenerative joint disease and tendinopathy.

We will start with the overview of the history of regenerative biology and medicine as well as the evolution of the basic science of regenerative biology as it relates to treatment of musculoskeletal conditions. We will proceed with the advances in regenerative biology, as and with a general review of the current state of regenerative medicine, including technologies being explored for treatment of musculoskeletal conditions.
There will be examples of experimental studies that have been translated into research of clinical applications which will be discussed in this presentation. It is important, however, to notice an important concept that regenerative medicine tools themselves (e.g., platelet-rich plasma, PRP) "are not synonymous with the practice of regenerative medicine." One of the leading regenerative medicine experts, Professor David B. Harrell suggested, and many agreed, that "PRP" and other regenerative medicine modalities are not sole "treatments" themselves, but "rather they are tools in the arsenal of the practicing physician."

History

The ancient texts confirm that regeneration is a long-known concept. The early medical and scientific texts point towards existence of ancient views on regenerative concepts in biology. It was not until 18th century, however, when the religious and metaphysical arguments made their way to the molecular revolution of 20th century. Goujon showed regenerative capabilities of bone marrow in 1869. At that time, there were also first attempts of organ transplants in animals. Later, Maximov suggested that stromal-hematopoietic cell interactions are vital for hematopoiesis. The first stem cell research report was published on neural cell differentiation in vitro using a hanging drop of lymph as a culture medium. The first published evidence of adult neuroplasticity in vitro by Joseph Altman and Gopal Das in 1965 was initially ignored by the scientific community. Their findings were published in the best scientific journals, but they did not overturn the scientific "fact" that no new neurons are born into the adult brain. In 1998, James Thomson and Jeffrey Jones demonstrated the pluripotency of human embryonic cells.
After that it was discovered that neovascularization has a vital role in tissue regeneration.

Despite regenerative medicine's ancient ties, and remarkable developments in this field, the clinical application of stem cells, growth factors and proteins is in its infancy in the modern clinical application. It has dawdled for a number of reasons, including safety, regulations, policy, ethics and other. At the same time stem cells "hypo" have caught the attention of physicians, patients as well as policy makers, and the media.
The term "stem cells" term is frequently used inappropriately, delineating a variety of regenerative medicine options, including platelet-rich plasma, bone marrow aspirate, or adipose tissue grafts, other cellular therapy, growth factors and proteins.
The clinical application of true "stem cell" therapies is limited to a very few conditions, including hematopoietic stem cell transplantation for repopulation of bone marrow in patients with a variety of blood cancers, using bone marrow transplant for treating rare blood disorders, and some others.

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However, there are recent significant advancements in the understanding of tissue biology, cellular and molecular biology, and practical applications of regenerative medicine which may help to apply regenerative medicine techniques for treatment of degenerative joint disease and tendinopathy.

These are few important concepts we have learned relatively recently.

1. In the past, adequate tissue restoration was believed to require primarily the presence of polypotent cellular material. Recently, however, the role of mesenchymal stem cells (MSCs), which are highly important in tissue regeneration, was found to differ substantially from what was initially taught. Beyond the traditional stem cell function of producing a “cloned” or self-renewed tissue, researchers have discovered signaling functions of the MSC. These cells serve as a “toolbox” for tissue repair, delivering a customized library of signaling molecules, rather than simply a “self-dividing” entity, leading to tissue restoration. The term “MSC” was coined in 1988 by one of the founders of modern regenerative medicine, Professor Arnold Caplan of Case Western Reserve University. These cells were named for their ability to transform into an assortment of mesenchymal phenotypes in culture. Recent evidence suggests that MSCs arise from pericytes, long-known perivascular cells, when blood vessels are broken or inflamed. Pericytes are situated on every blood vessel. They can sense the microenvironment of damage to the body and respond by producing site-specific growth and other factors that orchestrate reparative processes. Dr. Caplan recently suggested that MSCs are actually not "stem cells," but rather cells that serve as “medicinal signaling cells” or as intrinsic therapeutic agents. An additional important discovery is that MSCs cannot stimulate adequate restoration of injured or degenerated tissue without the availability of an appropriate matrix or “scaffold.” In some circumstances, the patient’s own tissues serve as a scaffold; in others, the scaffold must be delivered to the affected tissues as an advanced biomaterial or the patient’s own structural tissue (fibrin clot, adipose tissue, and others). In addition to the important role the microenvironment, and overall, paracrine effects of regenerative medicine agents, it was discovered that tissue regeneration occurs primarily through endogenous cells rather than transplanted cells. Stoichiometry (describing the quantitative relationships among substances as they participate in chemical reactions) can be also altered to control cellular recruitment, yield, differentiation, and activation. Stochasticity is predominant during the early cell cycle development, but then stem cells are greatly impacted by growth factors and signals determined by the microenvironment. The roles of other key elements of tissue regeneration in addition to cells are reemphasized. These include signals, scaffolds, physical environment, and angiogenesis. OA is a prevalent chronic disease impacting on quality of life and has societal and economic burden increasing with age. Yet, no confirmed pharmacological, biological or surgical therapy could prevent the progressive degeneration of joints. MSCs with paracrine activities emerged as a potential therapy. Here we will discuss some of the recent Phase 2 studies.

2. Prolotherapy, or fibroproliferative therapy, a regenerative injection treatment (RIT), was introduced in 1930s. The concept was to stimulate tissue regeneration by modifying the microenvironment through creating a controlled inflammatory reaction, and thereby promoting the body to initiate the healing process in the area where dextrose was injected. Interestingly, microfracture, and some cellular therapies work by changing the microenvironment via chemical signaling (growth factors, cytokines, and other cellular signals) to stimulate the paracrine effect. Essentially, they stimulate endogenous cells to repair and regenerate the damaged tissue. Many offer a new look at prolotherapy, and suggest using it for treatment of osteoarthritis, ligament instability, tennis elbow, temporomandibular joint dysfunction, rotator cuff disease, upper and lower back pain, whiplash injury, failed back syndrome, and other conditions. While recent publications explain why this older therapy may deserve renewed interest, prolotherapy has not become a routine method of treatment over its more than 80 years of application because of controversial efficacy. It did, however, help to shift attention of regenerative medicine science to heterogeneity, microenvironment, and paracrine effects, which produced a foremost departure from the previous concept of tissue regeneration.

3. Another method of stimulating tissues to restore their structure and function is via administration of PRP, which contains both the scaffold and growth factors. Although questions about the mechanism of clinical efficacy or failure of PRP are still being answered, PRP injections have been found to be helpful in restoring function in a variety of musculoskeletal injuries and chronic conditions, including joint pain, tendinopathy, muscle and ligament injury. At the same time, a number of studies have documented that PRP injections are not superior to conventional modalities for treatment of OA or tendinopathy. Now we will discuss examples of recent research.

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4. In addition to RIT and PRP, other autologous products, including bone marrow aspirate, and adipose tissue grafts, have all been studied in the field of regenerative medicine for a variety of conditions. Basic science suggests that intravenously transplanted MSCs can modulate the response of tissue to injury and disease located at a distance from the injection site. Intravenous transplantation of MSCs has the potential for safe and effective management of a number of chronic painful conditions, including OA and tendinopathy. Multiple publications demonstrated that adipose tissue grafts can serve as effective autologous regenerative medicine tools. However, it is uncertain how the recent US Food and Drug Administration (FDA) documents ("Draft Guidance") will impact practical applications of these methods of treatment. The detailed discussion on this issue will merit a special consideration and will not be discussed during this session.

Summary

Pain physicians are particularly qualified to practice regenerative medicine, based on the clinical skills they obtained during their training, including image guided targeted delivery of biological agents to the tissues affected by the pathological process. However, the current state of regenerative medicine does not yet support its routine use in management of OA and tendinopathy for a variety of reasons, primarily because of the limited number of high-quality clinical trials. Both continuing basic research and conducting high quality clinical studies, as well as creating new, and supporting existing registers of regenerative medicine cases are of are. Hundreds of studies of growth factors, PRP, and stem cells on OA and tendinopathy models, and in the clinical settings, are currently underway. These investigations should help to answer many of the questions that currently are limiting wider implementation of regenerative medicine techniques for OA and tendinopathy. Basic research and high-quality clinical studies on clinical and radiological evidence of cartilage restoration with MSC administration, PRP, prolotherapy and many other investigations have the potential to change current symptomatic pain management to definitive therapy in many cases. At the same time, the acquisition and preparation techniques of the proper bone marrow concentrate, autologous MSCs, PRP or other autologous biological agents, which may reflect on clinical outcomes, are being thoroughly studied as well. Overall, advancements in regenerative medicine technology and its clinical applications could redesign the way we treat chronic pain consitions.

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Common Pediatric Anesthesia Emergencies: Safety and Best Practice

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Introduction

Children commonly require anesthesia care for a variety of diagnostic and therapeutic procedures. In the United States alone, each year over 5 million children undergo procedures for which anesthesia is provided. These procedures take place in a variety of clinical settings, from tertiary care pediatric hospitals to rural general facilities. Despite the continued specialization among anesthesia providers and the proliferation of fellowship-trained anesthesiologists, the vast majority of pediatric cases are still performed by general anesthesiologists in the US and around the world. Children who present to community hospitals create uniquely stressful and challenging clinical demands. This review will discuss some of the commonly encountered pediatric surgical emergencies, and how the recent literature informs our approach to these clinical events. We will also discuss future trends that may impact the future provision of perioperative care for children.

The vast majority of pediatric diagnoses that result in hospitalization in children include respiratory diseases such as pneumonia, bronchitis, and asthma. Children will also frequently present to hospitals with surgical emergencies that require immediate attention. These emergencies include trauma, burns, aspiration of foreign bodies, appendicitis, and pyloric stenosis. These children will require specific resources in the emergency room, the operating room, the PACU, and floor. These resources include airway equipment for all ages of pediatric patients, systems for positive-pressure ventilation appropriate for infants and children, warming devices, appropriate equipment for intravenous fluid administration for children of varying sizes, and appropriate invasive and non-invasive monitoring equipment (1).

Many children who present emergently are previously healthy. The preoperative assessment should focus on the present illness, including the duration of symptoms. The presence of vomiting and difficulty taking liquids should be assessed. Other important elements of the medical history should include the following: 1) any prior anesthetic exposures and how they were tolerated, 2) a family history of anesthetic complications such as prolonged muscle weakness or malignant hyperthermia, 3) the presence of any other underlying diseases for which the child is being treated (this can frequently be assessed by inquiring about whether the child sees any specialists for any medical problems), 4) the presence of recent respiratory infection, in anticipation of potential perioperative complications when considering emergency surgery, and 5) the time of the last liquid and solid meal. While many of the following clinical entities demand either a rapid sequence induction (RSI), or modified RSI, NPO issues may influence the clinician's decision making during the perioperative period.

Common Pediatric Emergencies

Airway and Esophageal Foreign Bodies

Foreign body aspiration is a common indication for pediatric surgery. In 2016 there were almost 5000 choking deaths in the U.S. While most of those occurred in individuals over the age of 50, they also commonly occur in much younger children with a peak age of 1-2 years. We will first discuss airway foreign bodies, for which retrieval is essential to prevent atelectasis, pneumonia, or granuloma formation. We will then turn our attention to the recent rise in button battery ingestions.

Aspirated airway and esophageal foreign bodies present in numerous ways, depending on location, size, and timing. A foreign body obstructing the glottis will present dramatically with acute respiratory distress, stridor, and hoarseness, whereas a distal airway foreign body can go weeks or months without clear presenting symptoms. Coughing, wheezing, and recurrent pneumonias are frequently encountered. A choking or gagging event is highly suspicious for a foreign body aspiration, and a non-witnessed event may significantly cloud a clinician's diagnostic ability. Physical examination can be highly variable, from normal findings, to a complete lack of breath sounds. Chest radiography can provide a definitive diagnosis when the foreign body is radiopaque. However, most commonly aspirated foreign bodies are organic in nature and will not be visualized on a chest x-ray (2). Indirect findings suggestive of an airway foreign body may include hyperinflation of the involved lung.

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Intraoperative management of the child with an aspirated foreign body has traditionally focused on providing a safe induction without dislodgment of the aspirated material. It is prudent to obtain IV access prior to induction. Induction techniques include 1) mask induction with spontaneous ventilation with sevoflurane and oxygen, 2) induction utilizing TIVA with propofol and a narcotic allowing for spontaneous ventilation, and 3) the use of controlled ventilation or manual jet ventilation. The foreign body is typically removed with a rigid ventilating bronchoscope. This device allows the anesthesiologist to deliver gases to the patient during airway examination. Topicalization of the airway with local anesthetic is commonly performed when the FB is distal. While a rigid bronchoscope is commonly used, some clinicians now use a fiberoptic bronchoscope for retrieval. Every practitioner should be able to intervene if grip on the foreign body is lost during retrieval, resulting in complete tracheal obstruction. Children in this clinical setting will desaturate quickly and rapid intervention may be necessary. The FB should be advanced into one of the main stem bronchi with either the rigid bronchoscope or endotracheal tube, allowing ventilation to take place in the other lung.

One foreign body that deserves special consideration is the button battery. While the number of battery ingestions has been fairly stable over the past two decades the number of major or fatal outcomes has risen steadily over that time (3), and clinicians struggle with the risk posed to the child with an esophageal injury even after the battery has been removed. An additional complication is the broader use of both larger batteries, and batteries with higher voltage. Most significant button battery ingestions are now with batteries greater than 20 mm in diameter, and stronger 3V lithium batteries result in greater tissue injury. Among children under the age of six, almost 13% experienced a major complication due to the ingestion of a 20 mm battery including esophageal perforation, tracheo-esophageal fistula, major vessel damage, or esophageal stricture (4). When a battery ingestion is suspected, time is of the essence, as tissue damage can occur in as little as 15 minutes, and significant tissue injury has occurred by two hours (5).

The presentation of children with button battery ingestions is similar to that of children with other esophageal foreign bodies. Symptoms include drooling, chest pain, wheezing, or refusal to eat. As in other foreign body aspirations, unwitnessed battery ingestions can be diagnostically confusing. Every practitioner must have a high index of suspicion in this clinical setting, as the risk of esophageal injury, and damage to critical anatomic areas including the great vessels, rises quickly. It is critical to differentiate a button battery from a coin. On X-ray, button batteries appear as double-rings or halos. The presence of an esophageal button battery demands rapid attention, and should result in immediate endoscopic removal under general anesthesia. Induction for these cases is typically with a rapid or modified RSI with endotracheal intubation to allow for a FB removal and careful esophageal examination, as the esophageal mucosa will have to be carefully re-examined for mucosal damage following FB extraction. Esophageal injury can result in an aorto-enteric fistula that has tragically been associated with a number of pediatric deaths that occurred days to weeks following the removal of a button battery (6). Evidence of esophageal injury mandates hospital admission, with consideration of further observation and imaging studies including CT angiography or MRI to assess the potential for vascular injury (7).

Appendectomy

Appendectomy is the most common indication for abdominal surgery in childhood. The lifetime risk of appendicitis is about 8 percent, and presents most frequently in the second decade of life. Appendicitis is quite rare in young children, and fewer than 5% of cases are diagnosed in children less than 5 years of age. Despite this, the majority of cases of advanced appendiceal disease are present in children under 5 years of age, likely due to the myriad of diagnostic challenges in this age group. Furthermore, appendiceal perforation is negatively correlated with patient age, and occurs with greatest frequency in pre-school children.

Appendicitis classically presents with a constellation of symptoms that include anorexia, abdominal pain, vomiting, and fever. Pain typically begins in the peri-umbilical area and subsequently migrates to the right lower quadrant within one to two days. Children will commonly complain of pain with ambulation, coughing, or percussion. Younger children will have highly variable symptoms, and the diagnosis of a young child with appendicitis can be easily confused with gastroenteritis. Other common differential diagnoses include streptococcal pharyngitis, pneumonia, and pelvic inflammatory disease.

The management of appendicitis is determined by how early the disease is diagnosed. Early appendicitis is associated with an intact appendix, whereas advanced appendicitis has perforated, or is associated with a mass or abscess. Initial treatment includes rehydration, analgesia, and antibiotic administration. Appendectomy has been the standard approach to appendicitis for over 100 years, as removal of the diseased organ prevents rupture, peritonitis, and allows for pathologic examination to rule out other, rare diseases. In the past, appendicitis was often managed

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emergently at all hours. Recent evidence suggests that the rate of complications such as appendiceal perforation do not increase in children who receive intravenous antibiotics in a timely fashion and undergo surgery within 24 hours of diagnosis (8).

Preoperative preparation typically includes IV antibiotics and rehydration. Anesthesia is commonly induced with either a RSI, or a modified RSI when the patient does not present with significant vomiting. Surgery is increasingly performed with a laparoscope resulting in shorter hospital stays and diminished wound infection risk (9). There is insufficient evidence to say that laparoscopic appendectomy is associated with lower pain scores in children. Postoperative pain is managed with intravenous opioids, acetaminophen, and non-steroidals such as ketorolac (10). Recent studies have highlighted the use of transversus abdominal blocks (TAP) to reduce immediate perioperative opioid requirements (11). Patient controlled analgesia can be employed in the setting of complex open procedures, or perforated appendicitis with peritonitis.

Uncomplicated appendicitis results in very rapid recovery, and recent literature has described the success of same-day discharge for children with uncomplicated appendectomy treated with laparoscopy (12).

Testicular torsion

Testicular torsion is a common entity that results from vascular compromise of the testis resulting in necrosis. It classically presents in early pubertal males with the acute onset of significant scrotal pain, nausea and vomiting. Patients typically are afebrile, and have a normal urinalysis, which can help differentiate them from individuals with epididymitis. Rapid surgical treatment is required if there is hope to salvage the testis. Ultrasound will quickly evaluate blood flow; diminished flow should result in rapid surgical intervention. Outcome is excellent when blood flow to the testis is corrected within 6 hours of the onset of symptoms with testicular salvage rates as high as 90%; this rate falls rapidly to 50% at 12 hours, supporting the need for urgent surgical care.

The presence of nausea and vomiting in the patient with torsion frequently results in a RSI, and the procedure itself is short. Post-operative pain is managed with intravenous narcotics, or an ilio-inguinal nerve block, or local infiltration.

Pyloric Stenosis

Infantile hypertrophic pyloric stenosis is a common pediatric emergency that is frequently encountered in both urban and rural health care facilities. It occurs in approximately 2-3 per 1000 live births, and is four to six times more common in male infants. There is a general decline in incidence with increasing birth order so many cases occur in first-born infants. Infants classically present to health care providers at approximately 4 to 5 weeks of age with the onset of immediate post-prandial projectile, non-bilious vomiting. Classic presentation also includes significant dehydration and emaciation, with a palpable “olive” in the right upper quadrant. Laboratory values demonstrate a characteristic hypochloremic metabolic alkalosis secondary to the loss of gastric hydrochloric acid, with variable severity depending on the length of symptoms.

The presentation of the infant with PS has evolved over time, as clinicians have become increasingly familiar with its signs and symptoms and imaging techniques have improved (13). Vomiting is common, though significant electrolyte abnormalities are less frequently encountered as the diagnosis is typically made quickly. Most centers will utilize ultrasonography to confirm the presence of a hypertrophied pylorus due to the high accuracy of ultrasound in experienced hands.

It is imperative to remember that pyloric stenosis represents a medical emergency, not a surgical one. Preoperative re-hydration is the cornerstone of treatment, and evidence of euvolemia should be present before proceeding to the operating room. Residual signs of dehydration, including a sunken fontanelle, lack of tears, or poor skin turgor, should be evaluated. Laboratory values that confirm the adequacy of rehydration include a serum chloride of > 100 mEq/l and a serum HCO3 of < 30 mEq/L. Lab values outside of these limits should result in postponement of surgery until the infant is better hydrated. As is the case with all infants, the possibility of hypoglycemia should be considered, and corrected as necessary.

Prior to induction, due to gastric outlet obstruction, clinicians will commonly suction the stomach. Even with gastric suctioning, there is the potential for significant gastric residual content to be present. Infants should always be pre-oxygenated to mitigate against the common occurrence of hypoxemia. Many clinicians will perform either a RSI or modified RSI in this group of patients due to the risk of aspiration. It is this author’s opinion that given the propensity for infants to desaturate during induction, it is helpful (and less anxiety producing) to provide gentle bag-mask ventilation with low airway pressure following the administration of a non-depolarizing muscle

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relaxant. Some institutions describe the use of a mask induction following gastric suction (14) highlighting the various approaches to the perioperative care of infants with pyloric stenosis.

Studies comparing succinylcholine with a non-depolarizing muscle relaxant such as rocuronium demonstrate a slightly prolonged time to recovery with the latter (15). Infants are quite sensitive to non-depolarizing muscle relaxants, and the clinician should always carefully consider the use of a second dose of a muscle relaxant in these short cases. Sugammadex has been clinically available in the U.S. since 2015 and there is some evidence supporting its safe use in children. A recent report retrospectively described the use of sugammadex in infants under one year, with 3mg/kg effectively reversing rocuronium in just under 2 minutes (16) Regardless of medication choice, infants should be extubated fully awake at the end of these procedures.

Many surgeons now utilize laparoscopy to perform this procedure. Care must be taken to closely monitor cardiorespiratory function as insufflation pressures can impede venous return and reduce pulmonary reserve in infants. There is evidence that the use of laparoscopy for pyloric stenosis results in faster advancement to full feeding and shorter hospitalization when compared with an open approach (17). Maintenance of anesthesia is typically with either an inhalational agent such as sevoflurane or desflurane, or with total intravenous anesthesia. Post-operative care of infants after pyloromyotomy is managed with minimal narcotics, and the use of either po or IV Tylenol and ketorolac is common. Regional anesthesia in this setting is increasingly utilized, including either TAP or rectus sheath blocks. Emergence from anesthesia is rapid and infants are feeding within hours of surgery.

The Bleeding Tonsil

Tonsillectomy is a common pediatric procedure, and post tonsillectomy bleeding is a frequent indication for emergency surgery. Many factors contribute to post-tonsillectomy bleeding including infection, bleeding diatheses including von Willebrand disease, or early scar separation in the surgical field. Tonsillar hemorrhage occurs in two distinct phases. Early bleeding occurs in the first 24 hours, and is associated with poor surgical hemostasis, whereas secondary bleeding occurs around day 6. Bleeding rates can vary, but are typically in the 2-3% range. Rebleeding is highest in the teen years, and is lowest in children under the age of 3. The presentation of tonsillar hemorrhage can also vary, from parental report of blood associated with a completely normal physical exam to dramatic and profuse bleeding associated with hypovolemia, shock, and airway obstruction. Because one episode of bleeding raises the probability of a second bleeding episode, any child who presents with post-tonsillectomy bleeding should be carefully evaluated, and either observed in the ED or admitted to the hospital (18).

Pre-operative assessment can be challenging. Patients may have swallowed a significant amount of blood, making blood loss difficult to quantify. The degree of hypovolemia can be assessed through hemoglobin levels and vital signs. Children should have IV access secured and fluid resuscitation should begin promptly. Laboratory evaluation should include a CBC and coagulation profile, as well as a type and screen. It is uncommon for children in this clinical setting to require transfusion, but under some circumstances the clinician may want to have blood products available.

Anesthetic induction is commonly performed with a RSI, with strong suction readily available. Muscle relaxants include either succinylcholine or rocuronium, and induction agents include propofol or ketamine in unstable children. Clinicians should use a styletted cuffed endotracheal tube that is slightly smaller than normal. Having an extra set of hands available in the case of heavy bleeding can be helpful when securing the airway. Swallowed blood potently induces nausea and vomiting, and aggressive antiemesis is warranted. Postoperative pain is usually not significant, and children should be observed following surgery to be sure that bleeding has been controlled.

Other Developments in Pediatric Anesthesiology

In 2015, the American College of Surgeons (ACS) launched the Children's Surgery Verification program, designed to improve pediatric surgical care through the adoption of more uniform clinical standards. This program bears resemblance to the ACS Trauma Certification process, which has existed for more than 40 years. At the present time, there are almost 500 verified trauma centers in the US (Falcone, personal communication). As in trauma, many pediatric surgical specialists believe that the creation of a network of multidisciplinary expertise, including pediatric anesthesiologists, Neonatal and Pediatric Intensive Care, and a full array of pediatric subspecialty and nursing expertise represents the foundation for achieving improved surgical outcomes in children. The pediatric ACS program formally launched in 2017; numerous children's programs have already received verification, and over 100 have expressed an interest in becoming verified (19).

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A complete description of the ACS standards can be found on the ACS website (www.facs.org/quality-programs/childrens-surgery/childrens-surgery-verification). There are 4 elements to the verification process are as follows: 1) clinical standards, 2) infrastructure requirements including staffing and equipment, 3) ongoing data collection, and 4) an external verification process. While a full description of the ACS program is beyond the scope of this review, the ACS pediatric verification program will significantly impact clinical processes in institutions that seek certification and will create specific staffing standards for anesthesiologists. A summary of the Children's Surgery Scope of Practice can be found in Table 1. The guidelines call for three classifications of centers, ranging from pediatric institutions capable of managing highly complex multi-disciplinary problems to those that perform more routine single-specialty pediatric procedures. Of note, Level III centers are required to have anesthesiologists with pediatric expertise available within 60 minutes 24 hours a day who must serve as the primary anesthesiologist for all children two years of age or younger. The ACS standards also define the requirements of a pediatric anesthesiologist, including either board certification in the specialty or specific demonstrable experience and training.

Table 1. Summary of Children's Surgical Center Standards with Expected Scope of Practice (20)

Characteristic	Level I	Level II	Level III
Age of patient	Any	Any	>6 months
ASA	1–5	1–3*	1–2*
Multidisciplinary management of comorbidities	Multiple medical and surgical specialties; pediatric anesthesiology	Typically, single surgical specialties; neonatology; pediatric anesthesiology	None
Operations†	Procedures for major congenital anomalies and complex diseases, including those that are uncommon or require significant multidisciplinary coordination	Procedures for common anomalies and diseases that are typically treated by most children's surgical specialists and that do not require significant multispecialty coordination	Common, low-risk procedures typically performed by a single specialty
Ambulatory‡	ASA 1–3 Full-term and preterm infants may be cared for as ambulatory patients based on written guidelines established by the pediatric anesthesiologist in charge of perioperative care; institutional guidelines generally require full-term infants <4 weeks or preterm infants <50 weeks' PMA to be monitored for ≥12 hours postoperatively	ASA 1–3 Full-term and preterm infants may be cared for as ambulatory patients based on written guidelines established by the pediatric anesthesiologist in charge of perioperative care; institutional guidelines generally require full-term infants <4 weeks or preterm infants <50 weeks' PMA to be monitored for ≥12 hours postoperatively	Otherwise healthy (ASA 1–2) Age >6 months

It is unclear at the present time the impact the ACS program will have on the pediatric anesthesia landscape. Certainly ACS Trauma guidelines have been broadly promulgated throughout our clinical environment, and many believe that the ACS pediatric guidelines will be similarly disseminated. Healthcare providers should be aware of these multidisciplinary standards as they consider future strategic planning.

Cognitive Aids in Pediatric Anesthesiology

Numerous cognitive aids have emerged in our practice to enhance patient safety and provide structure in the event of critical events. These tools have been promulgated in part due to their effectiveness, and have also received significant media coverage, including the publication of the best-selling book "The Checklist Manifesto" by Atul Gawande. These aids range from simple "time outs" prior to the initiation of a procedure to more complex checklists to manage life-threatening processes.

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One of the most useful cognitive aids available is the Society for Pediatric Anesthesia Critical Events Checklist, available at: www.pedsanesthesia.org/wp-content/uploads/2018/03/SPACriticalEvents. The checklist provides pathways for the management of 23 perioperative events including MH, hyperkalemia, pulmonary hypertension, and local anesthetic toxicity. There is also a smartphone application that closely mirrors the above product (Pedi Checklist). The app was recently updated in March 2018. These tools are extremely useful, and clinicians should explore each of these products to evaluate their ease of use and practicality.

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Leading Change in Anesthesiology and Perioperative Medicine

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Objectives:

To Understand the Concept of Leadership in Relation to Change Management
To Recognize the Key Ingredients that are Part of Any Successful Change Initiative
To Illustrate how a Change Initiative can be Performed in Perioperative Medicine

Creating the Appropriate Environment
The role of Leadership is to create the appropriate environment which will allow clinicians to be successful in their individual and collective endeavors. As healthcare is becoming more a business than medical care, the role of the Anesthesiologist/Physician leader appears diminished (1) when it should in fact be enhanced. The goal of this lecture and summary is to empower the Anesthesiologist with the necessary leadership and change management principles to effectively lead a change initiative.

Ensuring Optimal Team Functioning
As perioperative care becomes ever more complex a leadership challenge is to develop interdisciplinary teamwork recognizing teams as "a small group of people with complementary skills who are committed to a common purpose, performance goals and approach, for which they hold themselves mutually accountable" (2).

Dealing with Change
The only constant in todays periop environment is change. To continue to be successful, individuals and anesthesiology groups need to be able to change as individuals, and collectively as a perioperative care team. This is because the external landscape is continually changing (3).

In the following text we will outline the concepts of Leadership and Management from contemporary business literature, and then describe a "framework" within which leadership can occur (4,5).
We will conclude with how Leadership and Management principles can be applied to the Perioperative Setting.

Definitions of Leadership
- "Leadership is the accomplishment of a goal through the direction of human assistants." (6)
- "The first responsibility of a leader is to define reality. The last is to say thank-you. In between the two, the leader must become a servant and debtor." (7)
- Leadership has also be defined as the electricity that runs through an organization.
- "Leadership defines what the future should look like, aligns people with that vision, and inspires them to make it happen despite the obstacles." (8)

Relationship of Leadership and Management
Leadership and management are interdependent and both essential to effective functioning. They are complimentary but not the same. "Managers do things right and leaders do the right thing"(9) is oft quoted. In fact managers create order, predictability and stability through planning and budgeting, organizing, staffing, controlling and problem solving. Instead leadership is about coping with and producing constructive change (11), in this process, Leaders are "chief disorganizers" through probing, challenging and finding better ways of doing things (12).

Attributes of Successful Leaders
Kouzes and Posner have identified the key characteristics that followers seek in their leader (13). In the course of their work, these investigators surveyed more than 75,000 people in 6 continents over a period of more than eleven years and asked; "what do you expect from a leader that you would willingly follow?" The four characteristics most

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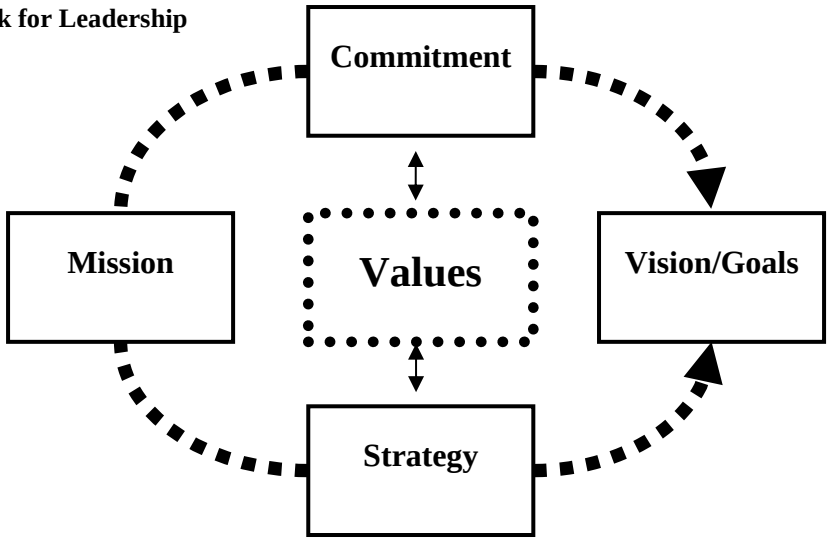
consistently identified by the highest percentage of respondents, were, that they wanted their leaders to be: Honest (88%), forward looking (71%), competent (66%), and inspiring (65%) (13).
Effective leadership is dramatically ordinary stuff according to a George Binney, a management consultant (14). The three leadership qualities that are most important in business are (i) A clear sense of direction and the ability to communicate this, (ii) A knack for motivating people, and (iii) a measure of adaptability (14).
Referring to our own specialty, in a survey of Chairpersons of Academic Anesthesia departments, we found that fully 64% had decided, as a career goal, that they wanted to take on the leadership of a department early in their career (when they were a fellow or Assistant Professor). Further, 30% had been Chairs previously and 29% had been previous Vice Chairs while 28% had been Division Directors. This suggests future academic leaders planned their career experience to prepare to lead Anesthesiology departments (15).

Emotional Intelligence (role modeling)

Some would say that the key leadership competency is that of emotional intelligence. This is because, the Leader's "emotional style" or mood is quite literally contagious (16). This sets the tone for the work environment and culture. Thus the leadership challenge is for leaders to regularly be optimistic, and energized so that through their chosen actions colleagues feel and act in the same way (16). More specifically, Goleman has defined leadership with respect to 6 leadership styles, namely, *visionary*, *coaching*, *affiliative*, *democratic*, *pacesetting* and *commanding*. Leaders use these styles to varying degrees at different times. In a survey of Anesthesiology Chairs in the USA, Chairpersons ranked Visionary and Coaching styles as most commonly used, while a Commanding style received the lowest rank order (34).

Framework for Leadership



A simple way to view the framework within which leadership occurs (17), is according to the adapted schema depicted above.

Our ***Mission*** in anesthesia may include clinical care, quality, education, research and possibly community outreach.

Shared Values (such as *respect*, *integrity*, *collegiality*, *compassion*, as well as *excellence* are the enduring beliefs that drive decisions and strategy in a department (8).

A key goal is developing a ***Vision*** for the endeavor based on established values (8). A vision is not something "mystical" but a practical embodiment of a goal, which is both inspiring and sets direction.

Strategy are the actions that will be taken to achieve the established vision and goals (21). An example of strategy in an academic department, defines not only what will be done, but more importantly determines what will not be

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done. So a department that has the Vision of being number one in National Institutes of Health (NIH) funding would not invest in research endeavors unlikely to result in NIH grant applications.

Commitment by an individual is the energy and creativity that people bring to the department to ensure success (20). Leaders cannot command commitment only inspire it. It is built through identifying an individual's passion and through the sharing of accountability and responsibility (13).

Teaming

The hallmark of a team effort is both individual and mutual accountability and a common commitment to a goal (2). A study of 16 cardiac surgery teams who together developed a new approach to cardiac surgery, the Heartport system, and comprising teams of surgeons, anesthesiologists, nurses and perfusionists has highlighted commonalities in successful teaming (24). This procedure which is complicated and involves, TEE monitored endovascular clamping, and minimal surgical incision size, required more interdependence and communication between clinicians than conventional cardiac surgery. An important lesson was that the most successful teams, (measured as the average improvement in procedure duration times) had team leaders who actively managed their teams learning efforts.

While the procedure initially took 3-4 times longer than usual; the pace of improvement differed dramatically from team to team. The authors (24) identified factors that improved team success. Important factors were found to be the selection of a consistent team of members based on competence, willingness to work with others and the willingness to accept ambiguous situations and converse with members of higher status. In addition, framing the challenge as organizational (rather than technical, vide infra) was also important. Finally, creating an environment of psychological safety and allowing "learning in action" sped team performance.

Change management

Change is difficult (8). This is so because often what we did in the past works, is comfortable and the need to alter is not clearly apparent. This leads to the quote so often heard as a counter to the wrenching process of change: "If it ain't broke don't fix it". The Center for Creative Leadership has conducted an inventory of the 10 flaws that can result in managerial derailment. The most commonly cited reason for derailment was the inability to adapt (change) and the most common cited success factor in North America was the ability to develop or adapt (26).

Understanding Technical vs. Adaptive Change

At its essence, it is important to define the Challenge of the required change as a *technical* or an *adaptive* challenge.

To understand this concept better, think of an individual who has just been diagnosed with coronary artery disease (CAD).

A technical solution to this problem would be to schedule him/her for a CABG operation. However an adaptive challenge would be asking the individual to change their behavior to improve the potential outcome from CAD, through a change in eating and smoking habits and through starting an exercise program to compensate for a previous sedentary life style.

Leadership Role

In such change initiatives the leadership role is complex. It is crucial that the leader is able to understand the problems on the ground i.e. the "dance floor" while also being constantly able to remove themselves from the action on to the "balcony" to see the big picture (27). The leader needs to regulate the inevitable distress that occurs keeping enough pressure so that people feel the need to change while avoiding colleagues from becoming overwhelmed (28). To achieve this the leader needs to attend to three areas (28). Firstly a "holding environment" must be established where the issues, norms and values needed are debated and shaped and from which these are communicated to the organization. The leader needs to establish priorities and focus, (not everything is important) and pace and sequence events. Secondly the leader must protect, orient, provide norms and reestablish values. Thirdly the leader should have presence and poise and should have the emotional capacity to withstand ambiguity, frustration and anguish. She will be observed by colleagues to see if she has the intestinal fortitude to hold steady and tackle the tasks ahead.

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Anatomy of a Change Initiative
The fear of change (Metathesiaphobia) is often a result of the fact that the benefits of the change are not clearly established or realized while the loss that change evokes is immediately felt. In addition there will be many who cling to the "old" way of doing things, while there may few supporting the new initiative because the outcome may not be certain. The leadership challenge lies in defining a compelling vision, setting and creating an urgency (not anxiety) around the change imperative, building a guiding coalition, communicating, addressing obstacles, and celebrating and noting short term wins (8). An adaptation of this universal approach has been described both in a Curricular Change initiative at UCSF (29) and in moving to Universal Start Times in the Perioperative environment in our own institution (30). The Table below is adapted from the latter work.

Table: Ingredients for a Successful Change Initiative
Development of trust
- Information Sharing
- Shared Values
- Role Modeling Change

Development of compelling vision
Creating an urgency.
Guiding coalition.
Communication
Short-term wins: monitor progress.
Don't declare victory too soon.

Parallels in Industry with respect to the Perioperative Setting
As there is little to no literature on how leadership principles might be applied to the perioperative setting, the aviation industry may serve as an example. This is an industry, (similar to the perioperative arena) that functions in a time pressured, stressful and highly regulated environment where a premium is placed on safety and quality. South West Airlines is a well known example of this industry. While many have filed for bankruptcy in the past or consolidated, Southwest Airlines, has remained profitable year after year and is considered one of the ten safest airlines. (31) *FORTUNE* listing Southwest Airlines as number five among America's Top Ten most admired corporations and the airline was named to *Business Week*'s first ever list of "Customer Service Champs" while being ranked as one of the top 50 Best Places to Launch a Career (32).
The leadership and management practices of this airline have been dissected to evaluate the leadership style of its founding CEO, Herb Kelleher. Herb has created a "culture of *commitment*" practicing as a servant leader with a very distinct customer orientation, both outward (passengers) and inward, to each employee (33). The airline has a clear *vision/mission*, "to the highest quality of customer service delivered with a sense of warmth, friendliness, individual pride and Company spirit" (32). Strong core *values*; "maintain principles, while changing practices" (33) and competitive *strategies*; by focusing on a point to point service, using a single plane type (737's) for efficiency.

Application of principles to Perioperative Medicine
It must be clear a cook book recipe for Leadership in Perioperative Medicine cannot be provided as each institution is different. Nevertheless a focus on Key Areas of Concern and Principles of Leadership may be of advantage (35).

Creating the Environment
Creating an environment for work that is collegial, respectful, equitable, safe (for patient and practitioner), adaptable and goal oriented, is a paramount concern for leadership. In order to create and sustain this environment, leadership does well to consider all participants volunteers. Leaders can and should:
(1) Be visible and role model the established values.
(2) Build trust and trustworthiness through transparency and their own actions
(3) Be ever mindful that their emotional style sets the tone for the environment
(4) Be goal oriented
(5) Be prepared to deal with problems, timeously and decisively
(6) Communicate, communicate, communicate, using all media at their disposal.

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Leadership shared at all levels

The view that there is a single leader at the top from whom all initiatives flow is insufficient to deal with today's complex perioperative environment. Leadership is about relationships (13). Thus, Leadership is created together. To be effective, leadership needs to occur at multiple levels (8). Leadership is an interchangeable phenomenon, "now you lead, now I lead" depending on the circumstance and the particular skill set required.

Leaders can and should:

(1) Foster leadership at appropriate levels
(2) Cede responsibility (and accountability) to allow leadership development

Building interdisciplinary teams

The case studies of 16 cardiac surgical teams illustrates the strength of interdisciplinary team development vs. the "command and control approach".

Leaders can and should:

(1) Decide where processes can benefit from the development of Teams
(2) Create an environment of psychological safety, allowing "learning in action" for such team development

Change management,

Leadership is about managing constructive change. As Mahatma Gandhi said, the Leader should "Be the change you want to see." Leaders can and should:

(1) Identify and articulate clearly the need for change and the advantages of the future state
(2) Establish what Adaptive Change is required and what values may need to be addressed to effect this
(3) Recognize that change is "loss"
(4) Set Priorities, re-iterate values, protect and support
(5) Maintain an urgency while regulating the pressure
(6) Recognize short term wins
(7) Don't declare victory, too soon

Conclusion

The concepts of leadership are universal and can be applied with advantage to the perioperative setting.

Leaders learn best by leading and learn best in the face of obstacles.
As weather shapes mountains, problems shape leaders."
Warren Bennis (9).

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Kicking Butts: How Helping Your Patients Quit Smoking Benefits Both Your Patients and Your Practice

David O. Warner, M.D. **Rochester, MN**

Anesthesiologists daily see the consequences of their patients' smoking. Not only are smokers at greater risk for perioperative morbidities such as pulmonary complications, myocardial ischemia, and wound infections, but often the disease that makes surgery necessary is related to smoking. Nevertheless, most anesthesiologists feel that there is little that they can do to help patients quit smoking, and do not consider that this is part of their responsibility as a physician. Few anesthesiologists have training in how to help people quit smoking, and few have extra time. The good news is that there are now many resources available to help patients who are facing surgery quit smoking. Anesthesiologists can quickly and easily connect their patients with these resources – and get credit for doing so.

Why should I care about my patients' smoking?
There are 2 good reasons why anesthesiologists should help their patients quit smoking.

Perioperative abstinence from smoking improves outcomes. The first reason is that smokers are at increased risk for perioperative respiratory, cardiac, and wound-related complications, and quitting smoking may reduce the risk of complications. Although smoking-related diseases increase risk, status as a current smoker itself increases risk, even when the effects of such diseases are accounted for. Smoking adds on average $5000 to healthcare costs after surgery, resulting in approximately $10 billion additional costs in the US each year. The risks of smoking extend beyond the smoker to those exposed to secondhand smoke; children and adults undergoing surgery who are exposed preoperatively to secondhand smoke have an increased risk of respiratory complications. Most smokers are aware that smoking is bad for their health, but most do not recognize the specific immediate risk of increased perioperative complications.

Fortunately, surgical patients can be successfully treated for their tobacco use. And if patients can maintain abstinence from smoking, it reduces their surgical risk. The most recent systematic review of randomized trials concluded that both intensive (defined as multi-session in-person counseling initiated at least four weeks prior to surgery) and brief interventions produced cessation at the time of surgery (pooled risk ratios (RR) of 10.8 [95% CI 4.5 to 25.5] and 1.3 [95% CI 1.2 to 1.5] for intensive and brief interventions, respectively). More intensive interventions reduced the incidence of any complication (RR 0.42 [95% CI 0.27 to 0.65]) and the incidence of wound-related complications (RR 0.31 [95% CI 0.16 to 0.62]); brief interventions did not. Subsequent studies found similar benefit with a preoperative intervention initiated at least 3 weeks prior to surgery consisting of a brief (< 5 min) counseling session by a trained preadmission nurse in the preoperative clinic, stop-smoking brochures, referral to a telephone counseling service ("quitline"), and a free 6-week supply of nicotine patches. This relatively simple intervention increased both short term (30 day) and long-term (one year) abstinence rates (RR 4.0 [95% CI 1.2 to 13.7] and 3.0 [95% CI 1.2 to 7.8], respectively). Thus, although even just brief advice to quit smoking has some benefit, it is best to get smokers referred to treatment specialists for the support that they need.

The duration of preoperative abstinence needed to maximally reduce perioperative complications is not known, and likely depends of the type of complication. The pharmacology of several smoke constituents such as nicotine and carbon monoxide suggests that even brief preoperative abstinence may be beneficial for some outcomes. A recent observational study found that smoking on the morning of surgery was associated with a significant increase in

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subsequent surgical site infections (odds ratio 1.8 [95% CI 1.1 to 2.8]), suggesting that even just morning abstinence could be beneficial. Lower carbon monoxide levels caused by acute abstinence also reduce the risk of intraoperative myocardial ischemia. Even if patients don't quit before surgery, just maintaining postoperative abstinence for some period of time may reduce risk. The pernicious myth that quitting smoking shortly prior to surgery increases risk is now debunked – quitting smoking shortly before surgery does NOT increase the risk of postoperative pulmonary complications, and ANY time is a good time for smokers to quit around the time of surgery.

Surgery is a "teachable moment" for smoking cessation. The second reason is that the perioperative period is a great time for smokers to quit for good. Some anesthesiologists worry that smokers will be offended if we discuss their smoking, but about 75% of smokers want to quit, and most have already made multiple attempts. Research show that in smoker will NOT be offended if you talk with them, and in fact want to know information that could help reduce their risk around the time of surgery. Interviews with smokers facing surgery show that they are aware of the general health hazards of smoking but that most are not aware how it may affect their surgery, and they do want to know. For many smokers, surgery represents a "teachable moment" for smoking cessation, providing a powerful motivation to quit. Undergoing a major surgical procedure will at least double the chances of successful quitting,2 and if patients quit, the average smoker will add 8 years to his or her life. Approximately 1 in 12 successful quit attempts in older Americans are associated with surgical procedures, representing a major contribution to public health. Many smokers worry about nicotine withdrawal if they stop smoking for surgery. Recent studies, however, show that quitting smoking around the time of surgery does not increase stress levels and only rarely produces nicotine withdrawal symptoms.

How is tobacco use treated?

Although most smokers agree that it is difficult to quit, the majority of Americans who smoke eventually succeed in doing so. Most of them quit without assistance, but tobacco treatment can more than double the chances of success. Treatment optimally incorporates two components –pharmacotherapy and counseling.

Pharmacotherapy. Several medications increase quit rates. Nicotine replacement therapy aims to provide a sufficient blood level of nicotine to avoid nicotine withdrawal symptoms. A variety of delivery devices are available, including gum, inhalers, lozenges, nasal spray, and patch. The most recently-approved medication, varenicline, is a partial agonist of the nicotinic acetylcholine receptor that may be the most efficacious of the available options. It is also possible to combine medications; for example, a baseline nicotine patch with gum as needed for cravings. All of these medications have potential side effects, but overall have excellent safety profiles. In particular, multiple studies have shown that nicotine replacement therapy is safe for patients with cardiovascular disease.

Surgeons have raised concerns about the potential effect of nicotine replacement therapy on the healing of surgical wounds. It is true that high doses of nicotine (higher than those used clinically to treat tobacco use) can impair the healing of experimental wounds in animals. However, there is no evidence of increased risk in surgical patients; indeed, studies suggest that quitting smoking with the use of nicotine replacement therapy significantly reduces the risk of wound-related complications. Thus, the use of nicotine replacement therapy in surgical patients should not be discouraged.

Counseling. Even just brief advice from clinicians to quit smoking can produce small increments in quit rates, but the efficacy of counseling increases with increases in the length and frequency of counseling sessions. Most counseling techniques are based on cognitive behavioral therapy (for patients ready to make a quit attempt) or

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motivational interviewing (exploring why individuals smoke in order to motivate a quit attempt). Optimally counseling will begin prior to a quit attempt and continue for several weeks afterward to provide support. Counseling can be delivered in person or via means such as telephone counseling ("quitlines"). The latter services are available in the US without cost via a single toll-free number – 1-800-QUITNOW. Treatment can be provided by a variety of individuals. Tobacco Treatment Specialists (TTS) are health care professionals specifically trained in counseling and the management of pharmacotherapy.

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Treatment combining pharmacotherapy and counseling will typically approximately double rates of successful quitting compared with unassisted attempts. This means that even with treatment, approximately 4 of 5 individual quit attempts will fail in a given attempt - but the majority of smokers will eventually succeed in quitting after multiple attempts. Thus, tobacco use is in this way analogous to chronic diseases that often cannot be "cured" with a single treatment, and both clinicians and patients should recognize that multiple treatments may be required.

What should I do to help my patients quit smoking?

Few anesthesiologists have either the time or training to themselves treat tobacco use. However, they can be very effective in getting patients to the help that they need to succeed. With only a few extra minutes, anesthesiologists can make a difference: just **ASK**, **ADVISE**, and **REFER**. It takes a minute or less to do all 3 steps.

- First, **ASK** all your patients if they smoke, even if you already know the answer, to show them that you think their smoking is significant.

- Second, **ADVISE** all your patients who smoke to stop smoking. The longer they can quit, the better. However, it's beneficial even if they can avoid just smoking on the morning of surgery, or if they can stay off cigarettes for a short time after surgery. Many patients who are not willing to quit for good may be willing to "quit for a bit" (e.g., from the morning of surgery until one week after surgery). You can advise them that, just like they fast from food on the morning of surgery, they should also "fast" from cigarettes.

- Third, **REFER** your patients who smoke to professionals who can help them quit. There may be referral resources, such as tobacco treatment centers, available in your practice setting. If not, every American has free access to a tobacco" quitline" at 1-800- QUIT-NOW. Quitlines provide extended, confidential counseling by trained specialists and, in some cases, free nicotine replacement therapy by mail. The American Society of Anesthesiologists can provide you with "quitcards" that include the quitline number which can be distributed to patients.

The preoperative clinic is a great place to **ASK**, **ADVISE**, and **REFER** – and evidence shows that it works. Anesthesiologists may devise creative ways for others, such as nurses or physicians' assistants, to provide this information as a part of the clinical routine that fits their practice. But even if anesthesiologists only see patients immediately before surgery, they can still **ASK**, **ADVISE**, and **REFER** because many patients are interested in quitting after surgery. Remember that because of smoke-free hospital policies, all smokers will be abstinent for some time around surgery—the only question is for how long.

For those patients who just are not yet ready to quit for good, encourage them to "quit for a bit" – from the morning of surgery until one week after surgery. Not only will tis reduce their risk of perioperative complications, but it may be the first step towards more prolonged abstinence.

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How can my practice benefit if I help my patients quit smoking?

The Merit-based Incentive Payment System (MIPS) now recognizes the critical importance of smoking in the perioperative period. There is now a quality measure related to perioperative smoking within the Anesthesiology-Specific Measure Set specified by the Center for Medicaid and Medicare Services (CMS) - MIPS #404: Anesthesiology Smoking Abstinence, designated as a "high priority measure". The outcome for this measure is self-reported or exhaled carbon monoxide-confirmed abstinence from smoking on the morning of surgery. Each practice is free to determine what intervention to apply in the preoperative period to achieve this goal.

You can also be separately reimbursed for providing tobacco treatment in your practice. For Medicare patients, there are two CPT codes that can be used to obtain payment – that are separate from any charges for providing anesthesia services. One covers counseling from 3 to 10 minutes duration (code 99406), and one covers counseling of greater than 10 minutes duration (code 99407). All Medicare patients are covered, regardless of whether they have yet developed any smoking-illnesses. Many private insurance plans also cover these services; coverage is required by the Affordable Care Act.

How can I learn more?

Both patients and anesthesiologists can learn more at www.quitforsurgery.com. Patients can get more information about why and how to quit smoking, and get connected with resources such as the quitlines and web-based quitting programs. Anesthesiologists can get more information about why and how to help their patients, including the evidence base supporting these efforts, training modules in tobacco control, and how to get reimbursed.

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ANESTHESIOLOGY 2018
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Extubation of the Difficult Airway with a Focus on Patient Outcomes

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Data from the American Society of Anesthesiologists (ASA) Closed Claims Project showed that 17 % of brain injuries and deaths occurred after extubation in the operating room or postanesthesia care unit (PACU). (1-2) After the introduction of guidelines for the management of difficult intubation, claims of airway-related injury at the induction of anesthesia significantly decreased, while the claims arising from airway injury at extubation remain unchanged. Among claims for failed extubation reported since 2000, death and permanent brain damage occurred in 15 of 16 claims (94%), and there were 8 claims with difficult airway management that occurred postextubation in the recovery period, all (100%) resulting in death/brain damage. (3)

Learning Objective 1: Formulate a stepwise approach to the safe extubation of patients with a difficult airway

Tracheal extubation is an elective process and should follow a stepwise approach. Before extubation of patients the following steps need to be followed:

1- Adherence to evidence based extubation criteria(table 1)
2- Identification of potential causes for extubation failure (table 2)
3- Decision on whether the patient will be extubated awake or deep. Patients with a difficult airway (difficult intubation and or ventilation), patients at risk of aspiration, patients with questionable baseline conscious level and obese patients may not be candidates for deep extubation
4- A preformulated plan for reintubation in case of extubation failure including access to all the required equipment and medications
5- Established institutional protocols that guide extubation timing after complex surgery with close communication of the perioperative team (surgical, anesthesia, respiratory therapist, nursing). Examples include anteroposterior cervical spine surgeries, maxillomandibular advancement surgery for OSA
6- Consideration for routine fiberoptic evaluation prior to extubation for evidence of resolution of laryngo-pharyngeal edema in select surgeries (4)

Table 1: Extubation criteria (5):

a- General criteria

Awake, cooperative patient
Hemodynamic stability on no or minimal vasopressors
Absence of surgical bleeding or coagulopathy
Temperature ≥ 36 °C

b- Mechanical criteria:

Tidal volume ≥ 6 ml/kg
Vital capacity ≥ 15 ml/kg
Negative inspiratory force ≥ 30 cm H 2 O
Rapid shallow breathing index (Respiratory Rate/Tidal Volume) <100

c- Chemical criteria:

PH ≥ 7.25
PaO 2 /FIO 2 ratio >300
PaO 2 ≥ 65 mmHg on FiO 2 ≥ 0.4
Minimal PEEP of 5–8 cm H 2 O
Acceptable PaCO2 (PaCO 2 ≤ 50 mmHg)
Stable metabolic status (serum HCO 3 ≥ 20 mmHg)

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Table 2: Risk factors for extubation failure (6):

a- Pharyngeal obstruction

Glossoptosis, low tidal volumes, reduced cough strength, accumulation of airway secretions, or retropharyngeal hematoma (anterior cervical spine surgery)

b- Laryngo-tracheal obstruction

Edema of the larynx, laryngospasm, vocal cord paralysis, tracheomalacia

c- Pulmonary etiology

Pulmonary edema (cardiogenic, noncardiogenic negative pressure), atelectasis, pneumothorax, pneumonia, ARDS,

d- Bleeding or mass lesions

External or internal hematoma/ bleeding compressing or obstructing the airway or presence of an airway, substernal or mediastinal mass

Learning objective 2: Correct performance and interpretation of the cuff leak test

Post-extubation stridor and upper-airway obstruction are multifactorial in etiology and can occur as a result of laryngotracheal edema, intubation trauma, excessive cuff pressure with mucosal ulceration, and prolonged intubation with secondary inflammation and granuloma formation.(7)

Cuff leak tests (CLTs) were introduced in an attempt to predict post-extubation upper-airway obstruction and reduce the incidence of extubation failure. Qualitative CLTs were performed by deflating the endotracheal tube (ETT) cuff, blocking the ETT opening, and listening for an audible leak around the ETT while patients were spontaneously breathing.(8) In an effort to increase the accuracy of CLTs in detecting post-extubation stridor, methods of quantifying a cuff leak were introduced. Miller and Cole (9) described the cuff-leak test with the ventilator set in assist-control mode at a tidal volume (VT) of 10–12 mL/kg. An inspiratory VT and 6 subsequent expiratory VT values were recorded after oropharyngeal suctioning and ETT cuff deflation. The cuff leak was measured as the difference between the preset inspiratory VT and the average of the 3 lowest of the subsequent 6 expiratory VT values. The threshold cuff-leak volume was determined by visual inspection of the receiver-operating characteristic plot. A leak of <110 mL was considered a positive result of the CLT and indicated that patients were at risk for post-extubation stridor secondary to laryngeal edema. (9)

This quantitative cuff leak has been expressed as an absolute volume or as a percentage of the inspired VT. When the cuff leak volume is < 110–130 mL (9, 10) or <10– 15.5% (11, 12) of the delivered VT, the risk for post-extubation stridor is significantly elevated. Other attempts have focused on quantifying a cuff leak volume in spontaneously breathing patients receiving CPAP. (13) The leak volume was calculated as the difference between the expiratory VT with inflated cuff and the expiratory VT with deflated cuff.

Even with quantifiable cuff leak volumes, studies reported a low sensitivity and a low positive predictive value of cuff leak volumes in detecting post-extubation stridor.(9,10,11,14) This was attributed to several factors, including the lack of standardization of the ratio of ETT size to the laryngeal diameter (a large ETT will result in a smaller cuff leak volume for the same laryngeal diameter), and the possible contribution of the exhaled limb of the breathing circuit and the ventilator to an increased airway resistance and therefore an increase in cuff leak volume.

Most studies on cuff leak volume document a high specificity and a high negative predictive Value, which means that patients with a cuff leak volume above a certain threshold (cuff leak volume >15% of VT or > 140 mL) have a low probability of developing post-extubation stridor. Incorporating the CLT into the clinical decision making tree may avoid unnecessary delays in extubating patients for fear of post-extubation stridor, once other extubation criteria are met. (15) While there is currently no evidence that delaying extubation of patients with a positive CLT improves outcomes, a positive cuff leak test should be considered a risk factor for extubation failure and should trigger the formulation of the stepwise approach to patient extubation outlined above under objective.

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Learning objective 3: Identify the correct and safe use of airway exchange catheters in the extubation of the difficult airway

Although the presence of an airway exchange catheter does not guarantee success at subsequent reintubation, a high success rate of reintubation has been reported with their use. 16, 17 In addition, oxygen insufflation through an airway exchange catheter (AEC) can maintain oxygenation until definitive measures are taken to secure the airway (e.g., tracheal intubation, cricothyroidotomy, and tracheostomy).
Numerous AECs are available, but these devices must be used correctly because airway complications can develop (e.g., perforation of the tracheobronchial tree, failure to pass the ETT over the AEC, barotrauma) when the wrong size, type, or technique is used. (18—24)
Suggestions for success include the following:

- AECs with a very small outer diameter should be avoided because they are prone to kinking, making railroading of the new ETT difficult
- Match the marking of the AEC with the centimeter markings on the ETT to avoid excessive advancement of the AEC, which can irritate the carina and cause bronchial trauma and bleeding
- Use an AEC with an inner hollow lumen that allows oxygen insufflation, whether by jet ventilation or a bag valve device.
- If resistance is encountered during the advancement of the ETT over the AEC, oral laryngoscopy (if feasible) can aid tube advancement. Rotation of the ETT in 90-degree increments also helps to pass the ETT tip past the arytenoids. ETTs with flexible tips serve the same purpose in that the tube tip is prevented from becoming caught against the arytenoids
- Avoid using force in advancing the AEC and the ETT because it may traumatize airway structures (21)
- Applying a silicone-based spray or a lubricant gel on the outside of the AEC can facilitate tube advancement
- The position of the new ETT should be confirmed before the AEC is withdrawn. This can be done by end-tidal capnography through a flexible bronchoscope adapter. (18)
- Longer AECs are available for double-lumen tubes and can be used with the same precautions

Learning Objective 4: Organize the steps required for management of the airway in patients with failed extubation, including patients with expanding neck hematoma

A preformulated plan for resecuring the airway in cases of extubation failure is an essential step in planning for extubation and involves (3):

1- A multidisciplinary approach that ensures immediate availability of experienced personnel (anesthesia and surgical teams, respiratory therapists)
2- Airway management equipment (oxygen source, suction, AEC, oral and nasopharyngeal airways, supraglottic ventilation devices, endotracheal tubes of different sizes, variety of laryngoscopes and fiberoptic scope, jet ventilation, cricothyroidotomy kit).
3- Resuscitation and induction medications
4- ASA monitoring including capnography
5- Extubation setting: OR, PACU, ICU, with bed controls that allow easy access to the patient's airway
6- Additional surgery specific strategies: (airway surgeries, neck surgeries, maxillofacial surgeries)
Table 3 outlines the steps in management of patients with an expanding neck hematoma (25)

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Table 3: Management of Postoperative Neck Hematoma (25)

1- Apply pressure to bleeding site
2- Notify surgery and anesthesia team (call for help)
3- Consider reversal of residual anticoagulation
4- Tight blood pressure control

Outcome:

A- No further hematoma expansion

- Communication with surgical team
- Mark the boundaries of the hematoma for early identification of further expansion
- Close observation and extended (8-12 hours) monitoring in a critical care environment

B- Continuous expansion of hematoma with no airway compromise

- Awake (fiberoptic) intubation either in the PACU or after immediate transfer to the operating room after topical anesthesia to the airway followed by general anesthesia for exploration of wound and drainage of neck hematoma.
- Assess neurologic status at the end of the case.
- Consider maintaining the patient intubated postoperatively until resolution of reactionary airway edema

C-Expansion of neck hematoma with rapidly progressive airway compromise

Emergent intubation (ASA algorithm):

- Cannot intubate Can Ventilate: using face mask, oral or nasal airways, laryngeal mask airway:
  - Consider immediate surgical drainage of the neck hematoma followed by further attempts to secure the airway
- Cannot intubate Cannot ventilate:
  - Surgical airway (Emergent cricothyroidotomy, percutaneous or surgical tracheostomy)
  - Evacuation of hematoma and wound exploration
  - Neurologic assessment
  - Maintain airway secured postoperatively

Learning objective 5: Recognize how safe extubation of patients with a difficult airway can impact patient outcomes using Kirkpatrick's 4th level of evaluation model

Most of the data on airway related complications occurring during extubation (including death and neurologic injury) arise from the ASA closed claims project database. (1) While this continues to be an important source of data, there are several limitations to the exclusive use of closed claims data for identifying trends in complications including:

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1- On average, it takes 5 years between the dates of an injury to the entry of a claim into the closed claims project database, creating a very long feedback loop.
2- Closed claims are biased towards more severe injuries, meaning that routine cases of extubation failure as well as near misses are not included in the database
3- Not all cases of severe airway related injuries result in a claim, meaning that the numbers in the data are an under-representation.

So how can we enhance patient outcome and reduce the number of extubation failures and extubation related complications:

1- Adopting evidence based extubation protocols (surgery specific in special situations)
2- A robust, accurate mechanism for identifying and reporting cases of extubation failure at the local (departmental) level with quality committee oversight that conduct peer review, and provide recommendations with a short feedback cycle
3- Adopting a universal definition for extubation failure that allows reporting of its incidence to national organizations concerned with quality and performance improvement including Aspire (Anesthesiology Performance Improvement and Reporting Exchange and AQI (the Anesthesia Quality Institute)
4- Sharing best practices and evidence based extubation protocols among anesthesiology departments and through peer reviewed publications
5- Avoiding unintended consequences of the use of extubation failure alone as a quality metric since this may result in a paradoxical increase in the incidence of patients being kept intubated at the end of surgery. Tracking other related quality metrics (e.g.: prolonged mechanical ventilation) should be considered.
6- Use of collected data on patterns of airway injury to update airway management algorithms

By addressing practice variations and tracking protocol adherence, identifying best practices, and providing a shorter ongoing feedback loop to departments, patient outcomes can be improved

Linking Kirkpatrick's Evaluation Model to Patient Outcomes

Level	Definition	Method of evaluation
1- Reaction	participants react favorably to the learning event	Participant survey
2- Learning	participants acquire the knowledge, skills and attitudes based on their participation	Pre and posttest questionnaires
3- Behavior	participants apply what they learned during the session when they are back on the job	Simulation activities, OSCEs, quality metrics, peer morbidity and mortality reviews, root cause analysis
4- Results	Patient outcome	Rate of extubation failure, rate of reintubation in PACU, rate of reintubation within 24 hours, rate of postoperative medical emergency team activation due to airway related issues

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Patient Blood Management: Improving Both Sides of the Value Equation

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Introduction

Preoperative anemia has been consistently associated with adverse perioperative outcomes in patients undergoing both cardiac and non-cardiac surgical procedures.[1] Historically, red blood cell (RBC) transfusion was viewed as an effective and acceptably safe intervention for the management of anemia. Similarly, platelet and plasma therapies have been viewed as safe and necessary interventions for the management of thrombocytopenia and altered coagulation parameters, respectively. However, blood transfusion has more recently come under increased scrutiny.[2-4] The three primary drivers of this renewed concern relate to questionable efficacy of some transfusion practices for the major blood component therapies (RBCs, plasma, platelets);[5-7] underappreciated risks of blood transfusion, including life-threatening respiratory complications such as Transfusion-Related Acute Lung Injury (TRALI) and Transfusion-Associated Circulatory Overload (TACO);[8-10] and increased recognition of the substantial associated health care costs (estimated to exceed $10 billion in the United States for RBC transfusions alone).[11-13] In aggregate, these concerns have resulted in increased interest in the optimization of patient's blood health as well as transfusion practice. The implementation of a Patient Blood Management (PBM) program has been advocated as the preferred approach to these optimization efforts.

In this refresher course lecture, I will highlight some of the persistent gaps in optimizing blood health and blood component utilization. I will then outline the role of PBM with specific emphasis on the perioperative environment. I will further identify gaps in our current understanding relating to both risks and benefits of transfusion therapies and will advocate for PBM as a cornerstone for optimizing future transfusion practices. The presentation will provide specific examples of PBM approaches that have led to meaningful change in transfusion practice with substantial impact on the quality of care delivered.

Perioperative Anemia

Background and Epidemiology

Anemia is defined as a total reduction in erythrocyte number, reduced amount of circulating hemoglobin (Hgb), or decreased circulating RBC mass, resulting in a pathological state where the oxygen-carrying capacity of blood is insufficient to meet physiological demand. The World Health Organization defines anemia as a Hgb level of less than 12.0 g/dL in non-pregnant adult women, less than 11.0 g/dL in pregnant adult women and less than 13.0 g/dL in adult men.[14]

Anemia is a common finding in preoperative patients with a prevalence ranging from 5% to 76% depending on patient age, presenting condition, and the planned operation.[15] Several large observational studies have associated preoperative anemia with increased risk of perioperative morbidity and 30-day postoperative mortality.[1] Evidence additionally suggests that the utilization of RBC transfusion to treat anemia further contributes to increased perioperative morbidity and mortality. The administration of RBC transfusion for the treatment of anemia has also been associated with increased cost when compared with preoperative elevation of the Hgb concentration with pharmacologic interventions (e.g., erythropoiesis-stimulating agents).[1]

Management of Preoperative Anemia

The American Society of Anesthesiologists' (ASA) Task Force on Perioperative Blood Management recommends erythropoietin with or without iron as an effective measure for reducing patients' exposure to allogeneic RBC transfusions (category A1-B evidence).[16] In contrast, the task force notes insufficient evidence to evaluate the efficacy of erythropoietin with iron compared with erythropoietin without iron. Furthermore, equivocal findings were noted when comparing preadmission iron supplementation to either placebo or no iron with the outcomes of preoperative Hgb levels and perioperative allogeneic RBC transfusions (category A2-E evidence).[16] Of note, the most common etiology underlying anemia world-wide is iron deficiency. In such patients, iron replacement is recommended with intravenous formulations showing improved tolerance and more rapid iron replenishment.[16,17]

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Red Blood Cell Transfusion

Background and Epidemiology

The number of RBC units transfused annually has fallen over the last number of years and was most recently estimated to be around 11.35 million in the United States for the year 2015.[18] Historically, more than a quarter of these transfusions have occurred in the perioperative environment.[19] Despite a growing number of clinical trials and evidence-based guidelines supporting restrictive RBC transfusion policies, liberal RBC transfusion practices remain commonplace. Furthermore, there continues to be tremendous variability in RBC transfusion practices, both for cardiac and non-cardiac surgical procedures.[20,21]

From a physiologic perspective, RBC transfusions are administered with the intent of improving end-organ oxygen utilization. Interestingly, the majority of basic physiologic studies fail to show improvements in physiologic parameters such as oxygen consumption or lactate clearance following RBC transfusion.[22]

Transfusion guidelines

A growing body of clinical trials evaluating RBC transfusion practices has now been completed and their results published. Although a clinical trial suggested the potential for improved outcomes with more liberal RBC transfusion practices in the setting of cardiac surgery,[23] the vast majority of trials support the safety of more conservative RBC transfusion practices.[24] These results appear robust, with similar results being consistently reported in a variety of surgical and medical populations including those undergoing Orthopedic and Cardiac Surgery, as well as those with traumatic brain injury, sepsis, and more heterogeneous critically ill populations.[25-30] In summary, the preponderance of data (both observational and experimental) support the implementation of restrictive RBC transfusion practices in hemodynamically stable, non-hemorrhaging patients.

Current guidelines recommend a Hgb threshold of 7 g/dL for RBC transfusion in hemodynamically stable, non-bleeding patients.[31] A higher threshold of 8 g/dL is often recommended for those with documented coronary artery disease or symptomatic anemia (e.g., active ischemia; orthostatic hypotension, syncope or tachycardia unresponsive to fluid therapy; congestive heart failure). For actively bleeding patients, RBC transfusion decisions should be based on the overall clinical context rather than strict adherence to a specific Hgb threshold.

Plasma

Background and Epidemiology

Data from the 2015 National Blood Collection and Utilization Survey suggest that approximately 2.7 million units of plasma were transfused in the United States in 2015.[18] A large proportion of these transfusion episodes occur in the perioperative environment, particularly in the setting of cardiac surgery. Despite efforts to educate care providers on the appropriate indications for plasma administration and limit the number of inappropriate transfusions, liberal plasma transfusion practices remain common. Indeed, it has been suggested that up to 50% of plasma transfusions occur outside of published guidelines,[32,33] with the most commonly cited reason for plasma transfusion being the correction of abnormal coagulation tests prior to an elective invasive procedure.[34] Importantly, the preponderance of studies performed to date have failed to show a consistent correlation between mild-to-moderate coagulation abnormalities [i.e., International Normalized Ratio (INR) $\leq$ 2] and bleeding complications in patients undergoing elective invasive percutaneous procedures.[7,35,36] In addition, plasma transfusion does not reliably normalize mild-to-moderate elevations in the INR.[37] As studies have failed to demonstrate a clear relationship between mild-to-moderate elevations in INR and increased procedural bleeding, plasma administration aimed at normalizing an elevated INR for the prevention of bleeding complications remains theoretical at best. Indeed, the available literature does not support prophylactic plasma transfusion in this setting.[11]

Transfusion Guidelines

Perioperative plasma product transfusion guidelines were published by the ASAs' Task Force on Perioperative Blood Transfusion and Adjuvant Therapies.[16] Indications for plasma administration in the perioperative setting include active bleeding related to coagulation factor deficiencies for which specific concentrates are not available as well as trauma-related massive hemorrhage as part of a fixed-ratio transfusion resuscitation protocol (e.g., 1:1:1,

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RBC:plasma:platelet). Additional clinical scenarios where plasma therapy may be warranted include the reversal of warfarin anticoagulation in a patient with active bleeding or need for emergency surgery (when prothrombin complex concentrates are not available) or the correction of excessive microvascular bleeding in the presence of an INR > 2.0. Plasma administration is also recommended as a replacement fluid when providing plasmapheresis for specific clinical indications (e.g., thrombotic thrombocytopenic purpura). As noted above, plasma transfusion is not recommended for the treatment of mild-to-moderate elevations in the INR (INR $\leq$ 2) when clinically significant bleeding is not present.

Platelets

Background and Epidemiology

Approximately 2 million platelet units were estimated to have been transfused in the United States in 2015.[18] An estimated 20% to 25% of these platelet transfusions occur in the perioperative environment with the majority being delivered in the setting of cardiac surgery.[19] In an observational study by Glance et al. evaluating patients undergoing non-cardiac surgery, thrombocytopenia was present in 1 in 14 patients without clinical indications for preoperative platelet testing.[38] Thrombocytopenic patients were more likely to be transfused and had higher 30-day mortality when compared to those with normal preoperative platelet counts. Less clear is the impact of perioperative platelet transfusion on mitigating these risks. A recent large observational study in the setting of non-cardiac surgery failed to identify reductions in bleeding complications or improved clinical outcomes when comparing those who received preoperative platelet transfusions to those who did not.[39] Similar findings were also recently noted in the setting of percutaneous procedures.[40]

Transfusion Guidelines

Although a number of clinical trials have evaluated platelet transfusion thresholds in the setting of hematologic disorders in patients undergoing chemotherapy or stem cell transplantation, surprisingly few studies have evaluated the impact of platelet transfusion on bleeding complications in the perioperative environment.[6] For those with hematologic disorders, platelet counts of 10×10^9/L (20×10^9/L for those on heparin or with evidence of increased platelet destruction) are advocated as transfusion thresholds. Although similar trials have not been performed in the perioperative setting, most guidelines recommend a platelet count transfusion threshold of 50×10^9/L (100×10^9/L for procedures involving a closed anatomic space) in this environment.[16] A lower threshold of 20×10^9/L is recommended for prophylactic platelet transfusion in a patient undergoing an elective central line placement (although lower platelet counts may be safely tolerated if the venous puncture site is compressible [e.g., internal jugular, femoral] and real-time ultrasonography is being used). Of note, evidence supporting the efficacy of platelet transfusion for the reversal of antiplatelet medication effects is very limited, and significant uncertainty remains regarding the benefit of this practice.[6,41]

Transfusion Risks

As with all medical therapies, blood transfusion is not without risk. Historically, concerns have been centered on the vertical transmission of infectious disease. Although significant progress has been made in mitigating the risk of transfusion-associated infectious complications, additional risks have since come to light. TRALI remains the leading cause of transfusion-related death in the United States.[10] This is closely followed by a second transfusion-related pulmonary complication known as TACO. While the incidence of TRALI is believed low (< 1%), the condition has significant associated mortality, estimated to range from 15% to 20%.[42] TACO is a more frequent complication with an estimated incidence of approximately 4%.[8] Though TACO's attributable mortality is less well-defined, clear associations with increased respiratory support requirements, intensive care unit admission, and hospital length-of-stay have been noted.[8] Importantly, a growing body of literature has begun to highlight concerns associated with under-diagnosis and under-reporting for both TRALI and TACO.[43]

Additional transfusion-related complications can include febrile transfusion reactions (the most common transfusion-related complication with rates reported up to 30% with platelet transfusions), allergic and anaphylactic reactions, hypotensive transfusion reactions, and hemolytic transfusion reactions (acute and delayed). Additional rare transfusion complications include transfusion-associated sepsis, graft-versus-host disease and post-transfusion purpura.

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Transfusion Costs

Expenses related to the acquisition of a blood component (acquisition costs) represent a fraction of the overall costs associated with a transfusion episode. Additional transfusion-related costs include those associated with labor, component processing and storage, and supplies for storing, testing, and administering the blood component. These "activity-based" or "direct variable" costs have been quantified for both RBC and plasma transfusions.[12,13,44] Results of these analyses suggest that total transfusion costs can be up to 4.8-fold greater than the cost of simply acquiring the blood component. Notably, these cost considerations also fail to account for expenses related to transfusion-related adverse events. Regardless, with an estimated cost of $761 per RBC unit (activity-based costs), it is estimated that total annual RBC transfusion expenditures may have historically approached $10.5 billion in the US alone.[17,44] Prior observational studies have also associated liberal perioperative transfusion practices with significant excess perioperative costs.[45] Similarly, after adjusting for potentially confounding variables, the administration of transfusion(s) to multiday acute care inpatient admissions was associated with 1.83-fold higher mean inpatient cost.[46] Though the precise impact of PBM activities on overall institutional economics is often be difficult to determine, it is clear that the impact can be significant.

Transfusion Education

Perioperative training programs have done a poor job of incorporating PBM education into the medical curriculum. It has been reported that less than 20% of anesthesiology residents receive formal training in PBM.[19] The frequency of formal training in best transfusion practice is only slightly improved at institutions with PBM programs, estimated at less than 30%.[19] Similar numbers have been reported for our surgical colleagues as well. Unfortunately, recent work suggests numerous knowledge gaps remain in the space of blood management.[47,48] Clearly, education of health care providers on optimal transfusion practices remains an essential element of PBM programs.[49]

Patient Blood Management for the Optimization of Transfusion Practice

Definitions

AABB: Patient blood management is an evidence-based, multidisciplinary approach to optimizing the care of patients who might need transfusion. PBM encompasses all aspects of patient evaluation and clinical management surrounding the transfusion decision-making process, including the application of appropriate indications, as well as minimization of blood loss and optimization of patient red cell mass.[50]

Society for the Advancement of Blood Management (SABM): PBM is the timely application of evidence-based medical and surgical concepts designed to maintain Hgb concentration, optimize hemostasis, and minimize blood loss in an effort to improve patient outcome.[51]

Pillars of Patient Blood Management

Perioperative PBM generally focuses on three pillars of care in surgical patients: the detection and treatment of hematologic derangements (e.g., anemia, thrombocytopenia, or coagulopathy); the reduction of perioperative blood loss; and harnessing and optimizing the patient-specific physiological reserve of anemia, thrombocytopenia, and coagulopathy (including restrictive transfusion triggers and use of pharmacologic hematologic adjuncts such as anti-fibrinolytic therapies and Prothrombin Complex Concentrates when appropriate).[52-54]

Pillars of a Patient Blood Management Program

Clinical champions and institutional "buy-in": A key element with most of health care's change management initiatives is the identification of a clinical champion who can lead the effort. This individual will serve many key roles in the PBM process as they must educate institutional leadership regarding the importance of the effort while marketing PBM as the approach to address the problem. This initial effort should not be under-appreciated as it is required to garner the resources needed for the success of the PBM program. The clinical champion will also oversee the interactions with the clinical practice. Effective leaders must be skilled in many areas including

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business acumen (vision, strategic planning, human resource management), change management (project management, problem solving, decision making), interpersonal skills (communication, team building, negotiations), and health care leadership (operational excellence, health care policy, health care quality).[55]

Organizational structure: Implementation of a PBM program must take into account the key stakeholders. Success depends on a robust PBM "team" inclusive of members who represent the clinical service lines that will be impacted by PBM-related interventions. Examples of key stakeholders include Emergency Medicine, Internal Medicine/Family Practice, Surgery (e.g., Cardiothoracic, Trauma, and Orthopedic), Anesthesiology, Critical Care Medicine, Hematology/Oncology, Transplantation, Transfusion Medicine, Pediatrics, and Nursing. Additional stakeholders also include administrative partners and Information Technology personnel. These participants will have unique and essential perspectives on the "culture" of the environments that they represent. Changes to clinical workflows are often better accepted when the rationale is delivered by a respected colleague. These key stakeholders can also greatly facilitate the dissemination of best practices guidelines, performance metrics, and quality concerns.

Data-driven approach to understanding transfusion practices: Health care providers often have perceptions regarding their clinical practice. However, when valid clinical data are available, it often contradicts these clinical impressions. As with so many other areas of health care, data-driven approaches to understanding the transfusion landscape can prove impactful.[56] Moreover, data detailing the impact of specific PBM interventions can add significant value to a PBM program. As an example, Cohn and colleagues have shown that a data-driven approach to PBM can markedly reduce the proportion of inappropriate transfusion orders and the number of overall transfusion events.[57] Whenever possible, data detailing the transfusion practice, adherence to best practice guidelines, and occurrence of adverse events should be made available to help guide the PBM program.

Defining and disseminating best practices: Having developed and implemented the necessary infrastructure to support a PBM program (e.g., people, processes, technology), a key early PBM activity is the development of best-practice guidelines that can be disseminated to the clinical practice. In addition to best-practice guidelines for preoperative evaluation/optimization and use of blood components therapies, consideration of strategies that can minimize perioperative blood loss and reduce the risk of exposure to allogeneic blood products should be considered. Examples of evidence-based intraoperative interventions include point-of-care testing and pharmacologic interventions (e.g. antifibrinolytic therapies, prothrombin complex concentrates, topical hemostatics), as well as additional strategies such as acute normovolemic hemodilution, and intraoperative autologous RBC recovery.[16] These strategies should be specifically considered in patient at high risk for excessive bleeding (e.g., major cardiac, orthopedic, thoracic, or liver surgery). Information related to the risks of blood transfusion as well as the economic implications of liberal transfusion practices should also be disseminated broadly.

Optimizing clinical decision support and implementing innovative informatics approaches: When evaluating the individual components of a PBM program, implementation of well-thought electronic clinical decision support (CDS) tools have been shown to meaningfully impact transfusion behaviors. CDS implemented at the time of order entry can assist clinicians by helping to guide them towards appropriate transfusion behaviors or alternatively steering them away from the administration of blood components when potential recipients are unlikely to benefit. Even apparently simple interventions such as defaulting the transfusion "dose" to a single unit of RBC, as opposed to multiple units, can have very meaningful impacts on overall transfusion practice.[58] A recent systematic review highlighted the impact of electronic decision support on transfusion practice.[59] Although the Mayo Clinic transfusion practice has noted a significant impact with the meaningful implementation of CDS for all of the major transfusable blood components, the published evidence in support of non-RBC blood components is less robust than with RBC transfusions.[59,60]

Operationalizing performance metrics and quality indicators: Generally speaking, clinicians are competitive individuals who continually strive to outperform. This competitive nature can be leveraged to support meaningful change in transfusion practice. To this end, a number of behavior modification interventions for the optimization of transfusion practices have been recently assessed.[61] In addition to the development of formal transfusion protocols/algorithms, multiple studies have highlighted the importance of providing data back to the practice ("audit and feedback") on how they are performing in terms of optimizing transfusion practices.[57] As with the CDS approaches outlined above, delivery of meaningful transfusion performance metrics or quality indicators to the clinical service-lines appears to be a key element to optimizing transfusion practice.

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Relating the intervention to patient-important outcomes: Ultimately, health care personnel strive to provide the best outcomes possible for their patients. As such, an essential final component for PBM programs is the development of strategies which tie changes in transfusion practice back to patient-important outcomes. Though seemingly straightforward, linking PBM activities to clinically relevant outcomes can be challenging and remains underdeveloped in most PBM programs. As we move forward, key steps include identifying the relevant outcomes to assess as well as the appropriate methods for their measurement. Candidate outcomes include mortality, morbidity, level and duration of care, and resource utilization.[53,62-63] Notably, multiple groups are currently working to further identify key outcomes to be assessed in this domain. Encouragingly, recent work suggests that PBM not only reduces blood product utilization with associated cost savings but, indeed, is also associated with improved patient outcomes.[53,54]

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Neuromodulation: Advancements and Enhancements in Patient Outcomes

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Neuromodulation in 2018 and the Future: Understanding the Advancement - Lawrence Poree, MD PhD

Neuromodulation and Spinal Cord Stimulation; 50 years of the gate control theory and beyond:

In 1965, Melzack and Wall published their seminal paper on the mechanism of action of A-beta mediated inhibition of wide dynamic range (WDR) nociceptive neurons via GABAergic interneurons[1]. They termed this theory the Gate Control Theory. Shortly thereafter, the first spinal cord stimulator (SCS) was implanted for pain control utilizing stimulation parameters in the 40-60 hertz(Hz) range capable of activating A-beta fibers and eliciting mild paresthesias.[2] The working hypothesis was that these overlapping paresthesias were required to achieve analgesia. For the subsequent 50 years, SCS research focused primarily on device design aimed at improving ease of usage, patient satisfaction, and patient safety. Amongst the most significant advances were the introduction of multi-contact percutaneous placed electrode arrays to better control the targeting of the electric field, implementation of rechargeable batteries to extend the battery replacement interval, and MRI compatibility to allow for safer MR imaging. During this period, little attention was given to investigating the consequences of expanding the stimulation paradigms to better understand the physiological basis of neurostimulation analgesia and the impact various stimulation parameters have on clinical effectiveness.

However, in the past 5 years, a renaissance in the field of neuromodulation has emerged with a resurgence of interest in the mechanism of action (MOA) of neurostimulation induced analgesia spurred by the publication of a series of randomized controlled trials (RCTs) that demonstrated improved analgesia with stimulation parameters outside the conventional stimulation parameters. The first study in this new era of alternative stimulation was a randomized clinical trial comparing perception free high frequency stimulation (10 kHz) with the more conventional physiologic paresthesia-based stimulation parameters (40-60 Hz, 1-10 milliamps, 200-400 pulse width).[3,4] The results of this study revealed significantly greater analgesic response for both back and leg pain in patients treated with 10 kHz frequency as compared to conventional stimulation. Similarly, another RCT study investigated the impact 500Hz burst stimulation delivered in trains of 5 at 40 Hz.[5] This study also reported greater analgesic efficacy of burst stimulation over conventional stimulation. In addition to new stimulation paradigms, new spinal targets have also been the subject of investigation in this era of novel approaches to spinal stimulation. A RCT comparing dorsal root ganglion (DRG) stimulation to conventional SCS demonstrated significantly greater analgesic response in the DRG group vs the conventional arm in patients with nerve injuries in the lower extremities.[6]

A common theme among these new stimulation paradigms was that analgesia could be achieved independent of paresthesia, thus raising the question, is the gate control theory sufficient to fully explain these observations? Consequently, a series of in-vivo and in-vitro

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cellular experiments were subsequently published that implicated a variety of additional potential mechanisms of action of neurostimulation analgesia such as subthreshold hyperpolarization of dorsal horn neurons[7], modulation of glial cell activity[8,9], and enhancement of T-junction filtering of action potentials in the DRG[10, 11].

A recent animal study reported that, in a nerve injury animal model of neuropathic pain, SCS elicited anti-nociceptive behavior greater in animals when SCS elicited a larger evoked compound action potential (ECAP) versus a smaller ECAP[12,13]. These results suggest that greater neural recruitment was correlated with greater anti-nociceptive behavior. These basic science studies have provided greater insight into the various potential physiological mechanisms involved in SCS induced analgesia, however, until recently, these physiological responses could not be measured in real time in patients and subsequently used to modify stimulation parameters to maximize analgesic benefit. This technological barrier was broken by a recent publication of a clinical trial that used measurement of ECAPS to control SCS output in a real time closed loop fashion in much the same way that evoked compound muscle potentials (EKG) are used to control the output of pacemakers in a closed loop fashion.[14] The results of this study revealed that conventional stimulation parameters were able to elicit analgesia similar to the newer higher frequency stimulation parameters. A double blind RCT comparing stimulation with and without ECAP closed loop feedback control is currently underway[14]. This breakthrough of using a patient's own physiology to drive stimulation settings will not only lead to greater understanding of the physiological determinants of SCS induced analgesia but may also translate into greater long-term effectiveness of SCS by allowing physiology to drive therapy and technological innovation. This is a noteworthy step in meeting the challenge set forth by the 2005 IMMPACT guidelines to "provide the foundation for a mechanism-based treatment approach in which therapeutic interventions target the specific mechanisms of a patient's pain."[15]

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Enhancement in Patient outcomes – David Provenzano, MD

Over the last 40 years, the utilization of neuromodulation to treat chronic pain states has substantially grown. Currently, the annual worldwide SCS system implantation rate is between 35,000 and 50,000 units.[1-3] In addition, neuromodulation has been introduced earlier in the pain treatment algorithm. As the utilization has increased, significant efforts have been taken to highlight barriers to treatment, complication management, and methods to enhance patient outcomes. In this refresher course, we will define the role of neuromodulation for the treatment of pain, explore technological advancements, define best perioperative practice management strategies, and discuss patient selection variables known to influence outcomes.

One of the major factors involved in the success of neuromodulation in treating chronic pain states is patient selection. Patient selection variables to consider include type of pain state, trial response rate, timing of intervention, and psychosocial comorbidities.[4] Recently, emphasis has been placed on employing neuromodulation earlier in the treatment algorithm. A retrospective review over a 22-year clinical practice examing 410 patients demonstrated that the success of SCS was inversely proportional to the time between the initial pain diagnosis to SCS implantation.[5] When SCS was initiated within the first two years of the responsive pain diagnosis the success rate was 85%. The success rate significantly declined with time. Therefore, an emphasis has been made to trial individuals with chronic pain states that may respond to neuromodulation within the first two years of the chronic pain diagnosis. Identified points of delay in the use of neuromodulation include referring physician, patient awareness and the efficiency of the implantation process. On average, the organization of the implantation processes has been shown to take approximately 3.3 months. [1,6] When comparing SCS to other forms of treatment, a Safety, Appropriateness, Fiscal Neutrality and Effectiveness (S.A.F.E.) analysis has been proposed. Utilizing this approach to therapeutic decision making, SCS is deemed to preferred over some repeat spine surgeries and for earlier treatment of complex regional pain syndrome (CRPS).[7-9]

The neuromodulation trial is also important in patient selection and defining future implant steps. Initially during trialing, lead position is optimized. The information and data collected during the trial phase help guide the decision to progress to permanent implant. A multicenter analysis evaluating 244 patients who underwent a SCS trial at two academic medical centers examined the factors involved in long-term implantation outcomes.[10] One variable associated with a negative permanent SCS outcome was a prior history of substance abuse. The strongest predictor of a negative SCS outcome was attaining less than 50% pain relief during the trial period even if functional outcomes improved. A factor also associated with a positive SCS long-term implantation outcome was the presence of allodynia and hyperalgesia on physical examination.

Although emphasis has been placed on the importance of a psychological evaluation in patient selection, further research is needed to determine the optimal psychological parameters assessed. A systematic review on pretreatment psychological variables as predictors of outcomes following lumbar surgery and spinal cord stimulation, only identified four SCS studies that met inclusion criteria of which none were randomized controlled trials.[11] Although insufficient empirical evidence for a psychological screen before surgery was found to improve outcomes, the current literature did suggest that certain psychological factors should be considered that

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often result in poor outcomes including uncontrolled somatization, depression, anxiety and insufficient coping.

Technology selection also is critical. For example, the size of the generator and the recharging capabilities influence patient satisfaction levels. Depending on the study, the incidence of implant site pain has been reported in the range of 0.4 to 35%. A recent observational study examing 278 responses, reported that 64% of patients experienced battery site pain with 8% reporting severe pocket pain.[12] Therefore, further attention is needed on methods to reduce patient burden with regards to generator site pain by optimizing technological advancements including miniaturizing the size of the implantable pulse generator. Improvements in recharging need to continue to occur. A retrospective study examining 35 patients demonstrated that 23.3% of recharging attempts were problematic and included difficulties with the coupling, heat generated, and the pressure and weight of the charging system.[13]

Complication mitigation and its ability to influence surgical outcomes has recently received much attention. In 2017, the Neurostimulation Appropriateness Consensus Committee (NACC) published recommendations for infection prevention and management (35 consensus points), reduction of severe neurological injury (22 consensus points), and bleeding and coagulation management in neurostimulation devices (22 consensus point).[14-16]

Surgical site infections have been shown to significantly increase mortality, prolong hospital length of stay and reduce health-related quality of life.[17,18] Specifically, spinal cord stimulator SSIs may result in significant clinical, humanistic and economic consequences. A recent analysis of the Anesthesia Closed Claims Project database for complications associated with advanced implantable pain therapies from 1990 to 2013 identified infection as the most common damaging event (23% of all claims) for surgical device-related claims.[19] The Center for Disease Control (CDC) estimates that approximately half of SSIs are deemed preventable using evidence-based strategies.[20] Defined methods to decrease the rate of implantable pain therapy SSIs are shown in Table 1.

Table 1: Methods to Decrease the Rate of Implantable Pain Therapy Surgical Site Infections.[15,21]

Preoperative	Intraoperative	Postoperative
Identifying patient risk factors	Appropriate agent selection for skin antisepsis	Occlusive dressing for a minimum of 24 to 48 hrs.
Optimization of immune and nutritional status	Operating rooms with laminar flow & HEPA filters	Close postoperative wound surveillance
Preoperative screening and decolonization for SA carriers	Limit OR traffic	Continued comorbidity optimization
Prophylactic antibiotic therapy	Wound irrigation	
Appropriate hair removal	Adequate hemostasis	
Surgical hand washing	Limit tissue trauma	
	Limit surgical time	

**SA = Staphylococcus aureus*

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Neurological injury may also occur with neuromodulation procedures. Direct trauma to the spinal cord may occur through ischemia, compression, device volume, infection and iatrogenic processes. The rates of serious neurological complications in case series have been shown to vary between 0.54% to 2.35%.[14] Recommendations made by the NACC include the review of preoperative imaging in the area of lead placement, the treatment of postdural puncture headache initially with conservative measures, management of anticoagulant therapy and providing feedback during the placement of either a percutaneous or surgical lead by an alert patient or with intraoperative neurological monitoring including motor and sensory evoked potentials.

Bleeding complications with neuromodulation-based therapies can be significant and result in devastating neurological injuries. Multisociety guidelines have been published on methods to mitigate and manage anticoagulant concerns during the perioperative period. [16,22] In the NACC guidelines, a neuromodulation procedure classification was developed according to the potential risk of serious bleeding. Spinal cord stimulation was classified as a high to an intermediate risk neurological procedure with regards to bleeding. When bleeding surrounding the neural axis does occur, appropriate and rapid medical treatment is required.

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Anesthetic Considerations for Neonates: Term and Preterm

Jennifer K. Lee, MD **Baltimore, MD**

Neonates born prematurely or at full-term gestation have unique physiology that renders them vulnerable to cardiovascular compromise and end-organ injury during the perioperative period. This course is written for the general pediatric anesthesiologist who cares for neonates with two cardiac ventricles. We will not review single-ventricle physiology. Infants born prior to 37 weeks of gestation are classified as preterm, whereas infants born at 37 weeks of gestation or later are considered term. The neonatal period refers to the first month of life. This course will discuss the physiology of term and preterm neonates, review the anesthetic management of common emergent and urgent surgical procedures, and provide strategies to improve perioperative safety for neonates.

Bronchopulmonary Dysplasia

Premature neonates have surfactant deficiency and underdeveloped lungs that cause **respiratory distress syndrome** with tachypnea and hypoxia. Treatment with oxygen and positive-pressure ventilation promotes airway inflammation and remodeling in neonates with **bronchopulmonary dysplasia.** This is one of the most common complications of preterm births. The etiology of bronchopulmonary dysplasia is multifactorial, and severity is increased by sepsis and a patent ductus arteriosus. The most common predictors of bronchopulmonary dysplasia include lower gestational age and the requirement for mechanical ventilation. The severity of bronchopulmonary dysplasia decreases as gestational age increases.[1]

Though avoiding excessive oxygen administration and ventilation may decrease respiratory disease severity, minimizing oxygen delivery is generally not safe in the operating room for neonates without cyanotic cardiac disease. Little evidence supports specific arterial oxygen saturation (SaO_2) thresholds in the perioperative period for preterm or term neonates. Thus, we turn to the general neonatology literature for guidance. A Cochrane review examined outcomes from almost 5000 neonates born at less than 28 weeks' gestation from 5 randomized controlled trials. The premature neonates were randomized to have a clinical goal SaO_2 ≤90% or >90% for 2 weeks. Neonates with SaO_2 ≤90% were significantly more likely to die by 18-24 months, suffer major disability or death at 18-24 months, or die before hospital discharge. The main benefit conferred by targeting SaO_2 >90% was a reduced risk of retinopathy of prematurity. Thus, we can assume that a goal SaO_2 >90% is safest during the perioperative period in neonates without cyanotic cardiac disease. A higher SaO_2 also permits time for the anesthesiologist to respond to hypoxic events during surgery.

Transitional circulation

The transition from fetal to “adult” circulation includes closure of the foramen ovale and ductus arteriosus. The fetal circulation may persist, however, with early hypoxia, acidosis, or hypothermia. Continued fetal circulation may cause persistent pulmonary hypertension of the newborn, which worsens the hypoxemia and acidosis. Moreover, deoxygenated blood may shunt right-to-left through the foramen ovale and ductus arteriosus and into the systemic circulation. Preterm neonates with respiratory distress syndrome are at greater risk of having persistently high systolic pulmonary artery pressures without closure of the ductus than are term or premature neonates without respiratory distress syndrome.[2] The high pulmonary pressures may approach systemic pressure and cause bidirectional flow across the ductus arteriosus and cyanosis. Persistent pulmonary hypertension of the newborn often occurs with congenital diaphragmatic hernia, meconium aspiration, sepsis, pneumonia, birth asphyxia, and respiratory distress syndrome.

Safely anesthetizing a neonate with a patent ductus arteriosus and foramen ovale requires balancing pulmonary and systemic pressures in a way that will promote blood flow through the lungs to prevent cyanosis, as well as to the aorta to prevent hypotension. Hypovolemia must be avoided because it decreases pulmonary blood flow, but excess volume will worsen lung disease and risk congestive heart failure. Pulmonary vasoconstrictors include hypoxia, hypothermia, acidosis, and pain. High oxygen supply may increase pulmonary blood flow and

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oxygenation but will increase risk for systemic hypoperfusion if too much blood is shunted away from the aorta and into the pulmonary arteries across the ductus. Additional methods to reduce pulmonary vascular resistance and increase pulmonary flow include hyperventilation, treatment of metabolic acidosis, deepening the anesthetic, opiates, neuromuscular blockade, and inhaled nitric oxide (iNO). Hypothermia must be strictly avoided, as it will worsen pulmonary hypertension. The systemic blood pressure can also be cautiously increased with infusions or small boluses of vasopressor to drive blood flow into the pulmonary circulation.

The balance of ductal blood flow and oxygenation can be monitored during surgery with preductal and postductal pulse oximetry. The right hand is classically considered the preductal saturation, but both the right and left hands may reflect preductal saturations in some infants.[3] Thus, the postductal saturation is most accurately monitored on the foot. Because the brain receives a considerable portion of preductal blood supply, preductal hypoxia must be avoided.

Multiple factors contribute to the high risk of low cardiac output in neonates with pulmonary hypertension. These include capillary leak, poor venous return due to high intrathoracic pressure from mechanical ventilation, systemic vasodilation from anesthesia or other medications, ventricular dysfunction, and right ventricle overload with septal deviation into the left ventricle. In addition, high pulmonary vascular resistance will reduce venous return to the heart and compound hypotension.[4] Increasing concentrations of iNO up to 20 ppm will improve the oxygenation index. Improvements are marginal with delivery of higher concentrations of iNO.[5] Improvements in oxygenation from iNO are variable, however, in neonates with bronchopulmonary dysplasia. Some infants will exhibit marked improvement in oxygenation with iNO administration, whereas others will show no improvement.[6]

Perioperative considerations

All neonates should be considered high risk for postoperative apnea. In healthy adults, the relationship between CO_2 and minute ventilation is linear. That is, higher CO_2 levels cause greater minute ventilation.[7] However, this linear relationship is not consistently present in neonates because hypercarbia may not proportionately increase ventilation, particularly after anesthesia. Neonates born to mothers who smoked tobacco or had substance abuse issues during pregnancy are at very high risk of having a blunted ventilatory response to hypercarbia.[8]

Neonates are also at high risk of hypothermia. Multiple interventions may be required to ensure that the infant stays normothermic during transport to the operating room, surgery, and transport back to the neonatal intensive care unit. Some interventions include ensuring that the neonate has a minimum core temperature of 36°C before transport to the operating room, using a battery-operated incubator or a transport warmer, and placing heating gel packs under the baby.[9] All clinicians in the operating room must work to keep the baby warm by raising the room temperature, using a convection warmer, and keeping the baby covered with warm blankets. Hyperthermia must also be avoided, and the risk of overheating increases once the core temperature reaches 37.0°C.[10] Rectal or esophageal temperatures should be monitored, as skin temperature monitoring alone is not sufficient.

Hypocarbia must be strictly avoided because it induces cerebral vasoconstriction with decreased cerebral blood flow. Lower arterial CO_2 levels were associated with greater brain injury in infants with neonatal encephalopathy from birth asphyxia.[11] A goal $PaCO_2$ of $\geq$35 mmHg is appropriate, especially in neonates with preexisting brain injuries.

Regional anesthesia techniques are becoming increasingly common in neonates because they reduce the risk of postoperative apnea from opiates and improve postoperative recovery. Amide local anesthetics, which are easily identified by names with an “i” prior to “-caine,” are bound by alpha-1-acid glycoprotein and albumin. Neonates have lower alpha-1-acid glycoprotein levels than do older children and therefore are at increased risk of local anesthetic toxicity. Though surgery may increase alpha-1-acid glycoprotein levels during the first 2 postoperative days,[12] caution should still be used when dosing local anesthetics; it should be assumed that the neonate is at high risk of local anesthetic toxicity.

Specific surgical procedures

Necrotizing enterocolitis is most common among extremely low birth weight neonates. Ventilation and oxygenation may be difficult owing to an enlarged abdomen and respiratory distress syndrome. The high risk of cardiopulmonary failure is compounded by acidosis from bowel injury, renal failure, and coagulopathy with bleeding and high transfusion requirement. Good communication between the anesthesiologist, surgeon, and intensivist is essential. Some neonates are best served with a peritoneal drain to allow them to stabilize before more

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invasive surgery, whereas those with gangrenous bowel require laparotomy and bowel resection. Surgery at the bedside reduces the risk of hypothermia, cardiopulmonary collapse from changes in ventilation mode, and cardiovascular collapse from changes to the baby's position. Multiple IV lines for fluid and blood product resuscitation are essential, and an arterial blood pressure catheter is helpful when available. Preoperative preparation in the intensive care unit includes correcting coagulopathy, acidosis, and electrolyte abnormalities; initiating vasopressors and inotropes; and volume resuscitation with fluid and blood products. This resuscitation continues in the operating room. The anesthesiologist should be prepared to manage sudden hypotension when the abdomen is surgically opened.[13]

Tracheoesophageal fistulas are equally challenging to manage perioperatively. During intubation, the tip of the endotracheal tube ideally should be positioned past the fistula to reduce the amount of air that enters the stomach. Such positioning is difficult if the fistula is located at the tracheal carina, and single lung ventilation may be necessary. Positive-pressure ventatilation should be minimized to reduce the amount of air that passes through the fistula into the stomach. The surgeon should be present in the operating room during induction in case the stomach requires decompression, which is fortunately a rare event.

Many neonatal lesions, including tracheoesophageal fistulas, esophageal atresias, and congenital diaphragmatic hernias, are managed by **laparoscopic surgery**. Thoracoscopy in neonates can cause significant hypoxia and hemodynamic instability as a result of direct compression of intrathoracic structures. CO_2 absorption from thoracic laparoscopy exceeds that of abdominal laparoscopy in neonates.[14] The hypercapnia may cause cerebral vasodilation,[15] raise the intracranial pressure, and shift the blood pressure lower limit of autoregulation to a higher blood pressure.[16] Very high thoracic pressures from the laparoscopy or from ventilation may impede cephalic drainage and also affect intracranial pressure.[17] Abdominal laparoscopy, such as for pyloromyotomy, may cause hypotension[18] from insufflation, reduced venous return, and inadequate fluid resuscitation.

Surgery for **hydrocephalus** is common in premature neonates with intraventricular hemorrhage. The fragile vascular anatomy and vascular overgrowth in premature brain increases the risk of hemorrhage.[19] Hypotension must be avoided, as elevated intracranial pressure shifts the blood pressure lower limit of autoregulation to a higher blood pressure.[20] It is nearly impossible to identify a neonate's optimal blood pressure goals because definitions for neonatal "hypotension" and "hypertension" remain unclear. In the absence of better hemodynamic guidelines and without neurologic monitors, the anesthesiologist is left with targeting the baby's preoperative blood pressure range during periods of normal neurologic activity.

Pyloric stenosis is a medical emergency, not a surgical emergency. The infant must be fully rehydrated and have normal electrolytes before surgical repair. Opinions vary on the best perioperative and surgical management. Some institutions use preoperative oral or nasal gastric tubes whereas others do not. The infants should be assumed to have a full stomach upon presentation to the operating room, and stomach contents should be evacuated with a large (i.e., 10F) multi-orifice gastric tube. This procedure does not guarantee complete evacuation of all stomach contents, however, and the anesthesiologist should consider rapid sequence induction or a technique that minimizes high pressure ventilation before intubation. Pyloromyotomies are performed laparoscopically or by open surgery, and both spinal and general anesthetics have been used successfully. General anesthesia may increase the risk of lower intraoperative blood pressure more than spinal anesthesia.[21] These infants are also at high risk of postoperative apnea.

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Anesthesia for Non-obstetric Surgery During Pregnancy

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Introduction

The incidence of surgery for non-obstetric procedures during pregnancy is between 0.3%-2%.[1,2] As there are approximately 4,000,000 deliveries per year in the United States this translates to 80,000 anesthetics for non-obstetric procedures to pregnant women per year, and most likely more due to surgery performed prior to clinical recognition of the pregnancy. Studies have demonstrated that many women presenting for surgery are unaware that they are pregnant. Unknown pregnancies in women presenting for surgery occurs in roughly 0.3%-1.3%[3,4] of adults and 2.4% of adolescents between the age of 15 and 20.[5] For this reason a urinary pregnancy test should be strongly considered in women of child-bearing age prior to surgery, unless an emergency clinical situation precludes this.

Surgery may be required at any time during pregnancy, though a large Swedish study of 720,000 patients found it was most common during the first trimester (42%), followed by the second (35%) and third (24%).[2] Appendectomy is the most frequently performed non-obstetric operation during pregnancy.[6] However, almost every type of surgical procedure has been successfully performed on the pregnant patient, including open heart procedures with cardiopulmonary bypass,[7] neurosurgical procedures requiring hypotension and hypothermia,[8] and liver transplantation.[9]

Anesthesia for the pregnant woman is one of the rare situations where the anesthesiologists must be concerned about two patients, the mother and the unborn fetus. Provision of a safe anesthetic requires an understanding of the physiologic changes of pregnancy and the impact of anesthesia and surgery on the developing fetus. Maternal considerations result from the physiology of pregnancy that affects almost every organ system. Fetal concerns include the possible teratogenic effects of anesthetic agents, avoidance of intrauterine fetal asphyxia and prevention of premature labor.

Maternal Considerations - Physiologic changes of pregnancy (Table 1)

The pregnant woman undergoes significant physiologic changes to allow adaptation for the developing fetus.

Respiratory System

Due to increased progesterone levels during the first trimester, minute ventilation is increased by almost 50% and remains so for the remainder of the pregnancy. Because anatomic dead space does not change significantly during pregnancy, at term, alveolar ventilation is increased by 70%. From 20 weeks gestation, the functional residual capacity (FRC), expiratory reserve volume and residual volume begin to decrease as a result of upward displacement of the diaphragm by the gravid uterus; this reaches its maximum reduction of 20% by term Vital capacity is not appreciably changed from pre-pregnancy levels. The increase in minute ventilation leads to a decrease in $PaCO_2$ to approximately 30 mm Hg. Arterial pH remains unchanged because of a compensatory increase in renal excretion of bicarbonate ions. The increased alveolar ventilation and reduced FRC lead to a more rapid uptake and excretion of inhaled anesthetics. The decrease in FRC in conjunction with increases in cardiac output, metabolic rate, and oxygen consumption lead to a much greater risk of arterial hypoxemia during periods of apnea or airway obstruction.

Anatomic changes to the airway include laryngeal and pharyngeal edema that can make ventilation and laryngeal visualization and tracheal intubation more difficult. In addition, mucosal capillary engorgement can cause bleeding during airway manipulation. Mallampati scores have been found to increase during pregnancy - Pilkington et al.,[10] found the incidence of grade 4 airways increased by 38% from the 12th to the 38th week of pregnancy. Together with inherent weight gain and enlargement of breasts, these changes make tracheal intubation more difficult, as evidenced by failed intubation, a well-recognized cause of maternal mortality.[11]

Cardiovascular System

Cardiac output is increased by 30-40% during the first trimester and 50% at term. This is primarily due to an increase in stroke volume (30-40%), and secondarily to an increase in heart rate (15%).[12] Further rises in cardiac output occur during labor and immediately postpartum. Blood pressure normally decreases during pregnancy because of a fall

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in systemic vascular resistance due to the vasodilatory effects of estrogen and progesterone. Near term, 10-15% of patients have a dramatic reduction in blood pressure in the supine position, often associated with diaphoresis, nausea, vomiting, pallor and changes in cerebration. This is known as the supine hypotensive syndrome and is caused by compression of the inferior vena cava and aorta by the gravid uterus.[13] This can begin as early as the second trimester and may lead to a reduction in renal and uteroplacental blood flow. Symptoms can be alleviated by tilting the patient on her left side.

Compression of the inferior vena cava by the gravid uterus leads to dilatation of the azygos system and the epidural veins. Epidural venous engorgement decreases the volume of the epidural and intrathecal spaces - drugs used in neuraxial blockade should therefore be decreased.

Gastrointestinal System

Traditionally, gastric emptying was considered prolonged in the pregnant woman by the end of the first trimester.[14,15] This was thought to be related to progesterone and mechanical changes as the stomach is displaced upward by the enlarging uterus. However, recent studies using acetaminophen absorption have not found a difference in gastric emptying in pregnant women. Wong et al., found no difference in gastric emptying between term women who ingested 50 mL vs. 300 mL of water in both non-obese[16] and obese women.[17] This is in contrast to active labor when gastric emptying is delayed.[18] Although gastric emptying per se may not be delayed until the onset of labor, when the gravid uterus enters the abdominal cavity at 20 weeks' gestation bariatric pressure is increased. In addition there is an increase in the acidity of gastric secretions and a reduction in lower esophageal sphincter tone due to the influence of hormones.[19]

Hematologic system

Intravascular volume is increased by 45% during pregnancy due to an increase in plasma volume. Since this increases by a greater proportion than the red blood cell volume (55% and 30% respectively) there is a relative anemia during pregnancy. Nevertheless a hemoglobin concentration of less than 11 g/dL is considered abnormal. Most of the coagulation factors are elevated during pregnancy and consequently pregnancy is considered a hypercoagulable state, with an increased risk of thromboembolic events.[20] Platelet counts generally decrease by approximately 20% during a normal pregnancy; approximately 7% of all parturients will present with a platelet count < 150,000·mm-3, and 0.5-1% will present with a platelet count < $100{,}000 \cdot mm^{-3}$.[21]

Hepatic Changes

Laboratory tests of liver function are commonly abnormal during pregnancy, though this does not necessarily indicate abnormal liver function. Pseudocholinesterase activity declines by as much as 20% during the first trimester and remains at this level for the remainder of the pregnancy.[22] However, prolonged apnea is rarely a problem following a standard dose of succinylcholine and the duration of ester-linked local anesthetics are not prolonged.

Nervous System

The minimum alveolar concentration (MAC) for inhaled anesthetics is decreased by up to 40% during pregnancy due to progesterone and endorphins and begins in the 1st trimester. Additionally, progesterone may increase the sensitivity of nerves to local anesthetics since neuraxial drug requirements decrease prior to uterine enlargement.[23]

Fetal Considerations

Drug teratogenicity

A teratogen is a substance that produces an increase in the incidence of a particular defect during fetal development that cannot be attributed to chance. In order to produce a defect, the teratogen must be administered in a sufficient dose at a critical point in development. In humans this critical point is during organogenesis, which extends from 15 days to approximately 60 days gestational age. However, the central nervous system does not fully develop until after birth, hence the critical time for the central nervous system may extend beyond gestation.

Well controlled randomized human studies are essentially impossible to perform due to ethical limitations and the large number of patients required to study these rare defects.[24] Four approaches have been utilized to study the effects of anesthesia in the pregnant patient: 1) animal studies, 2) retrospective human studies, 3) studies of chronic exposure of operating room personnel to trace concentrations of inhaled anesthetics, and 4) outcome studies of women who underwent surgery while pregnant.

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Animal Studies

Almost all anesthetic agents have been found to be teratogenic in some animal model. However, the results of animal studies are of limited value because of species variation and the doses of anesthetic agents in animal studies were generally in greater concentrations than those used clinically. In addition other known teratogenic factors such as hypercarbia, hypothermia and hypoxemia were either not measured or not controlled. Species variation is particularly important. Thalidomide has no known teratogenic effects on rats and was approved by the United States FDA for use in humans. However it later became apparent that thalidomide is teratogenic in humans.[25]

The United States FDA has established a risk classification system to assist physicians as they weigh the risks and benefits when choosing therapeutic agents for the pregnant woman (Table 2).[26] To date there are only five drugs known to be teratogens and none of them are anesthetic agents; Category X: thalidomide, isotrentinoin, coumarin (Warfarin), valproic acid, and folate antagonists,.[27] Most anesthetic agents have been assigned a Category B or C classification (Table 3). Only the benzodiazepines have been assigned as category D (Positive evidence of risk. Investigational or post-marketing data show risk to the fetus.) Nevertheless, potential benefits may outweigh the potential risk.

Nitrous Oxide

Nitrous oxide is a known teratogen in mammals and rapidly crosses the human placenta.[28,29] It had been presumed that the teratogenicity of nitrous oxide in animals is related to its oxidation of vitamin B_{12}, which then cannot function as a cofactor for the enzyme methionine synthetase - essential for the formation of thymidine, a subunit of DNA. There is some evidence that the effects in animals of nitrous oxide are not related to these proposed effects on DNA synthesis. Pretreatment of rats exposed to nitrous oxide with folinic acid, which bypasses the methionine synthetase step in DNA synthesis, does not prevent congenital abnormalities,[30] or suppression of methionine synthetase occurs at low concentrations of nitrous oxide[31] - concentrations found safe in animal studies.[32] Despite these theoretical concerns, nitrous oxide has not been found to be associated with congenital abnormalities in humans.[1, 2, 33, 34]

Benzodiazepines

The use of sedatives, in particular benzodiazepines, in the first trimester of pregnancy is controversial. Benzodiazepines exert their action through the inhibition of gamma-aminobutyric acid (GABA) receptors in the central nervous system. GABA inhibition has been shown to inhibit palate shelf reorientation leading to cleft palate formation.[35] Some investigators in human retrospective studies noted an association between diazepam ingestion in the first six weeks of pregnancy and cleft palate.[36,37] These findings have been questioned by the results of two prospective studies that did not demonstrate an association.[38,39] It is important to note that in the studies that found an association, the assessment was in women chronically exposed to benzodiazepines and not in women with a one-time low dose exposure as typically occurs during surgery. The FDA has assigned benzodiazepines a Class D designation and although controversial,[40] this author prefers not to use benzodiazepines during nonobstetric surgery unless there is a compelling reason to do so.

Human studies:

There have been two approaches to assess the effects of anesthetic agents on pregnancy outcome: large retrospective epidemiologic surveys of women chronically exposed to anesthetic gases, and retrospective database studies comparing women who underwent surgery while pregnant to those who were not.

Epidemiologic studies

A number of epidemiologic studies were performed in the 1970's to determine the health hazards of chronic exposure to anesthetic gases including birth defects and spontaneous abortions.[4142] All the studies found similar results and the most consistent finding was that the rate of miscarriage among exposed women is approximately 25-30% greater than non-exposed women. However, all these studies were later criticized for their lack of a control group, low response rate to questionnaires, recall bias, and statistical inaccuracies.[43,44]

Outcome studies of women who had surgery while pregnant

There have also been a number of retrospective studies of pregnant women who had undergone surgery to seek an association between anesthesia and surgery and congenital defects, spontaneous abortions or fetal demise. The largest study to date was performed by Mazze and Kallen.[2] They linked the data from three Swedish health registries - the

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Medical Birth Registry, the Registry of Congenital malformations, and the Hospital Discharge registry for the 9 year period 1973-1981. They examined the data for four adverse outcomes; congenital defects, stillborn infants, infants born alive but who died within 7 days, and infants with a birth weight < 1,500 grams and < 2,500 grams. They found 5,405 women had undergone surgery during their pregnancy from a total of 720,000 pregnancies. In their data set, most procedures were performed during the first trimester (41.6%), and the incidence decreased during the second (34.8%) and third (23.5%) trimesters. Most of the cases (54%) were done with general anesthesia, almost all of them (>98%) with nitrous oxide. They were not able to find an increase in congenital abnormalities or stillborn births among those who underwent surgery while pregnant during any trimester. However, the number of babies born with a birth weight < 1,500 and 2,500 grams, and the number of babies who died within 7 days of the operation was greater in those who underwent surgery while pregnant (Figure 1). This was true during all three trimesters. These risks could not be linked to either the specific anesthetic agents or the anesthetic technique. The increased risk to the fetus may be due to the condition that necessitated surgery in the first place, with the highest rate in gynecologic procedures. These data are important because they clearly demonstrate that anesthetic agents are not teratogenic and that the greatest risk is premature labor with the delivery of a low birth weight baby.

Behavioral teratology and Apoptosis in the newborn brain

In 1963 Werboff and Kesner[45] used the term behavioral teratology to describe the adverse action of a drug on the behavior of the offspring to its environment. It is well known that the halogenated agents particularly halothane and enflurane cause learning deficits in rodents.[46,47] Most anesthetic agents act by either blocking N-methyl-d-aspartate (NMDA) receptors or by enhancing GABA. Studies have demonstrated that when agents that act by either of these mechanisms (e.g., ketamine, nitrous oxide, midazolam, barbiturates and volatile agents) are administered to the rodent during the period of synaptogenesis, they induce widespread neuronal apoptosis in the developing brain.[48,49] Learning deficits have been described in the offspring of female rats exposed to commonly used anesthetic agents and widespread neurodegeneration was seen on histological examination.[50] The concern in the animal model extends beyond directly anesthetizing the animal but also anesthetizing the mother while she is pregnant. There are animal studies that demonstrate widespread apoptosis in the developing fetus and behavioral issues once born.[51,52] There are no human studies evaluating the developing fetus during non-obstetric surgery.

Although an association between anesthetic agents and neuronal apoptosis has been demonstrated in the animal model, extrapolation from animal studies to humans is problematic at best.[53] While most organ systems have completed development by the end of the first trimester or earlier, the brain continues to develop until after delivery. The time of greatest concern is during synaptogenesis or rapid growth spurt which is from the third trimester until three years of age. Randomized trials to confirm apoptosis in the human brain obviously cannot be done and evaluating effect of anesthesia on the brain is complicated. Recently, two separate authors assessed the effect of anesthesia and surgery on human behavior later in life. One looked at learning disabilities[54] and the other deviant behavior.[55] Both found an association between surgery and anesthesia and their outcome measures. The studies are far from conclusive as they were not randomized, and one was only a survey,[55] but they certainly highlight the need for well controlled studies.

The FDA has had multiple advisory meetings since 2007 to discuss the possible association between exposure to anesthetic agents and sedatives on human brain development. In December 2016 the FDA distributed an advisory that cautioned health care providers that repeated or lengthy exposure to general anesthetics and sedative agents may affect the development of children's brains and updated the package insert to reflect these concerns.[1]

The American College of Obstetrics and Gynecology responded to the advisory by emphasizing that all the studies on the effects of the fetal brain have been in the animal model and concluded that "no women should be denied a medically indicated surgery or procedure which may involve the use of these agents.[2] It is unclear if or how this advisory will affect anesthetic practice.

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1 http://www.fda.gov/Drugs/DrugSafety/ucm532356.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

2 http://www.acog.org/About-ACOG/News-Room/Statements/2016/ACOG-Statement-on-the-FDA-Warning-Regarding-Use-of-General-Anesthetics-Pregnancy

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Avoidance of intrauterine fetal asphyxia

The most important consideration for the fetus during non-obstetric surgery is the maintenance of a normal intrauterine physiologic milieu and avoidance of intrauterine fetal asphyxia. Fetal oxygenation is directly dependent on maternal arterial oxygen tension, oxygen carrying capacity, oxygen affinity, and uteroplacental perfusion. It is therefore critical to maintain a normal maternal PaO_2, $PaCO_2$ and uterine blood flow.

General anesthesia is a particular risk to the pregnant woman because management of the airway can be difficult, and the rate of hemoglobin oxygen desaturation is increased due to the decreased functional residual capacity and increased oxygen consumption. Care must also be taken during a neuraxial anesthetic because a high dermatomal level of anesthesia, a toxic local anesthetic reaction, or oversedation can also lead to a hypoxic event. Elevated maternal oxygen tension commonly occurs during general anesthesia. Some have expressed concern that increasing the inspired oxygen level to the mother could be detrimental to the fetus by causing premature closure of the ductus arteriosus or retrolental fibroplasias. However, due to placental shunting of blood, fetal PaO_2 never rises above 60 mmHg even if maternal PaO_2 is 600 mmHg. Therefore, maternal inspired oxygen concentration should not be limited.

Both maternal hypercapnia and hypocapnia can be detrimental to the fetus. Severe hypocapnia produced by excessive positive pressure ventilation may increase mean intrathoracic pressure, decrease venous return and lead to a decrease in uterine blood flow. In addition, maternal alkalosis, as produced by hyperventilation, will decrease uterine blood flow by direct vasoconstriction, and it will decrease oxygen delivery by shifting the maternal oxyhemoglobin dissociation curve to the left. Severe hypercapnia is detrimental because carbon dioxide readily crosses the placenta and is associated with fetal acidosis and myocardial depression.

Uterine blood flow is affected by both drugs and anesthetic procedures. Placental blood flow is directly proportional to the net perfusion pressure across the intervillous space and inversely proportional to the resistance. Perfusion pressure will be decreased by hypotension which may be due to the sympathectomy from local anesthetics administered as part of an epidural or spinal anesthetic, from aorto-caval compression in the supine position, or from hemorrhage.

Prevention of premature Labor

Spontaneous abortions, premature labor and preterm delivery are the most significant risks to the fetus during maternal surgery,[1,2,36,37] It is unclear if this is due to the surgery, anesthetic or underlying medical condition, but the greatest risk is during gynecologic or pelvic procedures when there is uterine manipulation and the lowest risk occurs during the second trimester. The potent inhaled anesthetic agents decrease uterine tone and inhibit uterine contractions so from this perspective they may be beneficial. Also, medications that increase uterine tone such as ketamine at doses > 2 mg/kg should theoretically be avoided. No study, however, has ever documented that any particular anesthetic agent or technique is associated with a greater or smaller incidence of abortion or preterm labor.

Laparoscopic surgery

Once considered an absolute contraindication during pregnancy, laparoscopic surgery is now routinely performed.[56,57] Reedy et al.[58] compared five fetal outcome variables among pregnant women who had a laparotomy (n=2,181) versus those who had laparoscopy (n=1,522) between the fourth and twentieth week gestation, and the general pregnant population who did not undergo surgery. They found that there was an increased risk of preterm delivery and low birth weight (<2,500 grams) in both surgical groups as compared to the general population. But there was no difference in any of the other outcome variables between the two surgical groups.

Specific anesthetic considerations during laparoscopy include maintaining normocapnia because carbon dioxide is commonly used to maintain a pneumoperitoneum. Adjusting maternal ventilation to maintain end tidal carbon dioxide between 30 and 35 mmHg should avoid hypercapnia and fetal acidosis. The Society of American Gastrointestinal and endoscopic surgeons proposed guidelines for laparoscopic surgery during pregnancy (Table 4). Surgical concerns include caution during placement of the trochars which can be accomplished as an open technique and maintaining low pneumoperitoneum pressures (< 15 mm Hg) to maintain uterine perfusion.[59]

Fetal heart rate monitoring

Fetal heart rate (FHR) monitoring becomes feasible around 16-18 weeks with an external tocodynamometer, but the indication for its use intraoperatively is less well defined, and it obviously cannot be used in every case such as abdominal procedures. One issue is how to act on the information? If the fetus is not viable and the FHR tracing is concerning, all that can be done is normalize the physiologic milieu. Is this sufficient reason to use the monitor when

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this should be done anyway? Katz et al.[60] reported a case in which they were able to correct an abnormal fetal heart rate in a woman who was undergoing eye surgery, by increasing the percentage of inspired oxygen given to the mother.

Another issue is who should interpret the tracing. Anesthetic agents will change the FHR baseline and decrease variability and these changes need to be distinguished from fetal compromise. Furthermore, if a change is noted and the fetus is viable will the obstetrician intervene with immediate delivery?

The American College of Obstetricians and Gynecologists issued a joint statement with the American Society of Anesthesiologists on this issue.[61] General guidelines from the statement include:

1. A qualified individual should be readily available to interpret the FHR.
2. If the fetus is below a viable gestation, it is generally sufficient to ascertain the FHR before and after the procedure, but that in "select circumstances" intraoperative monitoring may be considered to facilitate positioning or oxygenation interventions"
3. If the fetus is viable then simultaneous FHR and contraction monitoring should be considered intraoperatively and an obstetric provider should be available and willing to intervene for fetal indications

The statement concludes by stating, "the decision to use fetal monitoring should be individualized"… and "ultimately, each case warrants a team approach for optimal safety of the woman and fetus".

General Recommendations for anesthetic management

Whenever possible, anesthesia and surgery should be avoided during the first trimester. Although no anesthetic drug has been proven teratogenic in humans it is prudent to minimize or eliminate fetal exposure during this period of organogenesis if at all possible.

Prior to initiating any anesthetic an obstetrician should be consulted and fetal heart rate tones should be documented. Precautions against pulmonary aspiration by the mother should be taken from as early as the 12th week and a clear non-particulate oral antacid administered and H_2 receptor blocker and metoclopramide considered.

Apprehension should be allayed by reassurance from the anesthesiologist rather than with premedication, if possible. The patient should be informed that there is no known risk to the baby regarding congenital malformations but that there is an increased risk of abortion or premature labor. This is a good opportunity to educate the patient as to the signs of premature labor, e.g., back pain in someone prior to term, which can occur up to one week after the procedure. The patient should be transported to the operating room with left uterine displacement to avoid aorto-caval compression after 16-18 weeks gestation.

In addition to the standard ASA intraoperative monitors, the fetal heart rate and uterine tone should be monitored, if at all possible. It is the best way to assure maintenance of a normal physiologic milieu for the baby. Monitoring and interpretation should be performed by an obstetrician or someone other than the anesthesiologist with expertise in FHR interpretation. Regardless of the decision to perform intraoperative FHR monitoring, the FHR and uterine contractions should be monitored before and after the surgery.

The type of anesthesia should be based on maternal indications, the site and nature of the surgery, and the anesthesiologist's experience. Because MAC is decreased, the dose of all anesthetic agents for regional or general anesthesia should be reduced. Although no study has found any difference in neonatal outcome in terms of congenital defects or preterm delivery, regional anesthesia may be preferable to general anesthesia to avoid the risk of pulmonary aspiration and decrease fetal drug exposure.

The largest risk of neuraxial anesthesia is hypotension, which may reduce uteroplacental perfusion. Prevention is difficult since prehydration does not reliably reduce the incidence of hypotension. If hypotension occurs, ephedrine or phenylephrine can be used. The key is not which drug is chosen but that hypotension should be recognized and treated quickly.

General anesthesia should be preceded by careful evaluation of the airway, denitrogenation, and a rapid sequence induction with the application of cricoid pressure. Edema, weight gain and increase in breast size may make laryngeal visualization and tracheal intubation technically difficult. An array of laryngoscope blades and handles, and other emergency airway management equipment should be available. Capillary engorgement of the mucosal lining of the upper airway accompanies pregnancy. This mandates extreme care during manipulation of the airway and the use of a smaller-than-usual endotracheal tube. The use of a nasal airway and naso-tracheal intubation should be avoided to eliminate the risk of nasal hemorrhage. A high inspired concentration of oxygen should be used (at-least 50%) and arterial pCO_2 should be maintained at normal pregnancy levels (30-35 mmHg). End-tidal CO2 is an excellent

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approximation of paCO2 in the pregnant patient because the arterial-to-end-tidal CO2 gradient decreases during pregnancy.

Fetal heart rate and uterine activity monitoring should continue postoperatively. Epidural or subarachnoid opioids are an excellent choice for pain management because they cause minimal sedation and smaller doses can be utilized compared to the intramuscular or intravenous routes. Non-steroidal anti-inflammatory drugs should be avoided because they may cause premature closure of the ductus arteriosus.

Conclusion

Non-obstetric surgery during pregnancy is common and can be provided safely as long as certain principles are adhered to. The greatest risk to the mother centers around the airway and avoidance of hypoxia. The greatest risk fetus is preterm labor and delivery and not congenital defects. Regardless of the technique, attention to detail and maintenance of a normal intra-uterine physiologic milieu throughout the perioperative period, including the avoidance of hypotension, hypoxemia, hypercapnia, hypocapnia, hypothermia and acidosis, is the key to a successful outcome.

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LVADs 101:
What to Do When They Come to Your OR for Noncardiac Surgery

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Introduction

A left ventricular assist device (LVAD) is implanted in patients with end stage heart failure to improve their quantity and quality of life until cardiac transplantation ("bright to transplantation"), death in patients ineligible for transplantation ("destination therapy") or recovery ("bright to recovery") occurs. In the last decade, over 20,000 mechanical circulatory support devices, primarily LVADs, have been implanted in the United States. Survival following LVAD implantation continues to improve, with a one-year survival exceeding 80% and a median survival of approximately 5 years. It follows that more of these patients will continue to require and present for noncardiac surgery (NCS).

LVAD Physiology

LVADs most commonly pump blood from the left ventricular apex to the ascending aorta, but alternative anastomoses are possible. Modern generation LVADs are "continuous flow" in nature. With an LVAD, blood is continuously pumped from inflow to outflow cannulas by a rotor or impeller that spins at several thousand revolutions per minute. It follows that patients physiologically may either have pulses or be pulseless depending on a variety of factors including preload, afterload, left ventricular function, right ventricular function, etc.

LVAD Parameters

Slight differences exist in LVAD parameters and their normal ranges between LVAD manufacturers and models. However, the physiologic basis for these parameters is overall the same.

- LVAD speed represents the revolutions per minute at which the device is functioning. Speed is directly proportional to flow, and as LVAD speed increases, so does the amount of blood flow through the pump.
- LVAD power is the number of Watts that the LVAD is requiring to function at the set speed. In the presence of LVAD pump thrombus, LVAD power increases, as the LVAD accordingly requires more power to overcome the increases resistance of the thrombus.
- Pump flow is *calculated* from speed, power, and (in some LVAD models) hematocrit. This calculated value *estimates* the blood flow through the LVAD. In the case of pump thrombus and resultant elevation in LVAD power, the calculated pump flow is falsely elevated compared to actual blood flow in the LVAD.
- Some LVAD models determine pulsatility index, which is the variability in calculated pump flow throughout the cardiac cycle.

LVAD Anticoagulation Management

Continuous flow LVAD device manufacturers typically recommend antiplatelet therapy with at least aspirin and anticoagulation with warfarin for an international normalized ratio (INR) of 2-3. Not surprisingly, LVADs are associated with bleeding, particularly gastrointestinal bleeding. This is likely a result of multiple factors including their need for anticoagulation, acquired von Willebrand's disease, and continuous flow physiology. It follows that a given patient's anticoagulation and antiplatelet regimen must often be individualized to their history of bleeding and/or thrombophilia. In the NCS perioperative period, multidisciplinary collaboration between the anesthesiologist, surgeon, LVAD cardiologist, and potentially other experts in anticoagulation and LVADs such as hematologists and intensivists is recommended to formulate a management plan specific to both the patient and the NCS for anticoagulation and antiplatelet agents. With a rise in LVAD thromboses, full anticoagulation reversal may not be prudent in elective NCS without high bleeding risk. However, in NCS with life-threatening bleeding (e.g. cerebral hemorrhage), full reversal of anticoagulation is recommended.

Intraoperative Management

Several institutions have presented series of LVAD patients undergoing NCS. LVAD patients have presented for NCS involving nearly all surgical specialties. These patients are ideally cared for in centers with familiarity in caring for this patient population and readily available multidisciplinary support if required. However, the need for

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emergent NCS or other circumstances preventing patient transfer may necessitate perioperative management of LVAD patients in centers unaccustomed to caring for these patients. Select perioperative management considerations follow:

LVAD Power Source

Modern generation LVADs are able to be powered by portable batteries. Perioperatively and especially intraoperatively, LVADs should be connected to a definitive power source. This ensures they are not dependent on batteries that can be depleted for power. The LVAD should be additionally connected to the LVAD console so that the LVAD parameters are displayed and may be utilized to guide clinical management.

Blood Pressure Monitoring

There is controversy regarding the optimal modality to determine of blood pressure (BP) in continuous flow LVAD patients. With regard to noninvasive blood pressure (NIBP) modalities, the most reliable is Doppler determination of blood pressure. Doppler BP determination is performed by utilization of a Doppler probe and a manual BP cuff to determine at what BP Doppler signals become audible during manual BP cuff deflation. This typically is performed utilizing the brachial artery. With Doppler BP determination, a BP can typically be obtained in over 90% of attempts, compared automated BP cuffs producing a BP reading in approximately 50% of attempts. Manual auscultation or manual palpation BP determination is unreliable and not recommended intraoperatively in LVAD patients. Use of invasive arterial lines intraoperatively for BP determination in LVAD patients is highly variable, with their use reported in 0-72% of patients in recent series. The largest series to date of LVAD patients undergoing NCS to-date reported arterial line BP monitoring in 20% of anesthetics (Mathis et al.). However, the authors noted blood pressure monitoring gaps exceeding 20 min in 55% of anesthetics. Our recommendation is to favor invasive arterial line BP monitoring in LVAD patients undergoing general anesthesia, especially in cases where the anesthesiologist is inexperienced in caring for LVAD patients. For cases such as gastrointestinal endoscopy that typically involve monitored anesthesia care, noninvasive BP determination is typically adequate. However a plan to establish reliable BP readings must exist should NIBP modalities be unsuccessful. Finally, while hypotension may have adverse effects on end organ perfusion, hypertension can adversely affect LVAD performance, as these devices are afterload sensitive.

Defibrillation and Cardioversion

Modern generation LVAD manufacturers have advised that transcutaneous cardioversion and defibrillation are safe in patients with these devices. However, one must recognize that rhythms such as ventricular fibrillation that are traditionally lethal may be hemodynamically tolerated in LVAD patients provided that cardiac output from the right ventricle is maintained. Echocardiography is helpful in making this determination. Methods to assess end-organ perfusion such as capnography, cerebral oximetry, capillary refill, and BP determination may help clinicians to determine the need for defibrillation in LVAD patients with potentially life-threatening cardiac rhythms.

Chest Compressions

Controversy exists regarding the safety and timing of performing chest compressions in LVAD patients. American Heart Association guidelines recommend performance of chest compressions in LVAD patients in the event of cardiac arrest. When cardiac arrest is suspected, the LVAD hum should be immediately auscultated to verify function of the LVAD. Additionally, perfusion should rapidly be assessed by means such as patient responsiveness (if not under general anesthesia), end tidal CO_2, capillary refill, BP determination (invasively if an arterial line exists or noninvasively with Doppler BP determination), cerebral oximetry, etc. Given the potential rapid changes in hemodynamics intraoperatively in conjunction with the high level of monitoring in the operating room, we would recommend first line treatment modalities such as fluid or vasoactive medication administration, with chest compressions reserved for cases of true cardiac arrest. While not essential for all cases, anesthesiologists should have access to echocardiography to assess biventricular filling and function in cases of hemodynamic compromise.

Cardiac vs. Noncardiac Anesthesiologist

The majority (53-100%) of LVAD patients are safely being cared for by noncardiac anesthesiologists in recent series on LVAD patients undergoing NCS. We believe that a thorough comprehension of physiology and clinical considerations related to LVAD patients is more important than anesthesiologists' formal training when tasked with caring for this patient population. Given the continued upward trend in LVAD implantations worldwide, these

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devices will continue to become both more prevalent and mundane, making the necessity of providing perioperative care for this challenging patient population even more commonplace for all anesthesiologists.

Summary

With the number of LVAD implantations continuing to increase, the need for NCS in this patient population will accordingly rise. A thorough understanding of the physiology associated with these devices as well as important clinical considerations is paramount to anesthesiologists successfully delivering care perioperatively.

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Improving First-Case of the Day On-Time Starts CAN Increase Operating Room Efficiency

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Principles in Calculating Allocated OR Time for Use in Reducing Over-Utilized Time

Before I consider how improving first case of the day on-time starts can increase the efficiency of use of OR time, I need to address the question: what exactly is meant by "OR efficiency"? There are 3 simultaneous equations.

Suppose that the hours into which cases are scheduled in an OR have been calculated based on minimizing the expected inefficiency of use of OR time. Then, fewer than these allocated hours would be under-utilized OR time and greater than those allocated hours would be over-utilized OR time. For example, if the hours into which cases are scheduled in OR #1 are 7:15 AM to 3:30 PM, and the last case of the day ends at 1:30 PM, then there are 2 hours of under-utilized OR time from 1:30 PM to 3:30 PM.[1] Thus, there are 0 hours of over-utilized OR time. Conversely, suppose that the hours into which cases are scheduled in OR #2 are from 7:15 AM to 5:30 PM, and the last case of the day ends at 6:30 PM. Then, there is 1 hour of over-utilized OR time from 5:30 PM to 6:30 PM.[1] There are 0 hours of under-utilized OR time. These definitions for under-utilized and over-utilized OR time represent 2 of the 3 simultaneous equations.

The 3rd of the 3 equations is for the inefficiency of use of OR time itself. It equals the sum of two terms: (cost per hour of under-utilized OR time multiplied by the number of hours of under-utilized OR time) plus (cost per hour of over-utilized OR time multiplied by the number of hours of over-utilized OR time). Application of these 3 equations from operations research to OR management was figured out by Strum et al.[2]

These 3 equations have an implication. Suppose that the hours (above) into which cases were scheduled were chosen by committee decision (i.e., not by performing calculations to minimize the expected inefficiency of use of OR time). Then, there are not 2 hours of under-utilized OR time in OR #1 and 1 hour of over-utilized OR time in OR #2. For example, there is not, as far as I know, a name for the hours until 3:30 PM or past 5:30 PM, respectively. Be careful when you hear someone refer to "under-utilized" and "over-utilized" OR time. Hours are "under-utilized" and "over-utilized" only if compared to the allocated hours that minimize the inefficiency of use of OR time.

Continuing, OR workload for a service on a day of the week often follows a normal distribution.[2] Consequently, in principle (but, in practice, it is more involved mathematically), the inverse of the normal distribution function can be used to calculate the allocated OR time that maximizes OR efficiency.[2]

For example, suppose that, on Mondays, a hospital currently plans 3 ORs for orthopedics, each OR for 10 hours of cases (3 ORs x 10 hours = 30 hours). The total hours of orthopedic cases, including turnovers, follows a normal distribution with a mean of 30 hours. The relative cost of 1 hour of over-utilized OR time equals 2.0 multiplied by that of 1 hour of under-utilized OR time.[1,3] This is a typical value, being "time and a half" plus a bit extra for an intangible cost. With it being twice as expensive for finishing late rather than early, one wants to calculate the OR allocation that results in finishing early on 2/3rd of Mondays. That is the 66th percentile.

To apply the 66th percentile, consider a standard deviation of orthopedics' workload on Mondays, a typical value of 5 hours. In Microsoft Excel, use the following formula: "= NORMINV(2/3, 30, 5)". The answer that appears in the spreadsheet is 32.0 hours. Thus, the 66th percentile of the inverse of the cumulative normal distribution function with a mean of 30 hours and a standard deviation of 5 hours equals 32 hours. Using a mean of 30 hours, what OR allocation minimizes the inefficiency of use of OR time? 4 ORs with 8 hours of allocated time and 0 (zero) ORs with 10 hours of allocated time. The answer is not the mean of 30 hours.

{Note: this does **not** mean that the hospital "ought" to allocate 4 ORs for 8 hours. That depends on several factors such as the number of surgeons, whether there can be 4 ORs for 3 surgeons, etc.[1,3-5] Many papers and review articles have examined what to do in these more complicated but realistic situations. However, for understanding the principles of first case of the day starts, this simple approach is good enough.}

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Suppose that the standard deviation of orthopedics' workload on Mondays is 10 hours (a larger than typical value). Since workload is assumed to follow a normal distribution, we again use the inverse of a normal distribution, and again use a ratio of 2.0: 1.0 for the cost of over-utilized: under-utilized OR time. In Excel, this is the formula: "= NORMINV(2/3, 30, 10)". Notice that the formula only differs from the one above in that the last number is now 10 instead of 5. This formula gives an answer of 34 hours (i.e., the 66th percentile of the normal distribution function with a mean of 30 hours and a standard deviation of 10 hours equaling 34 hours). Thus, for a mean of 30 hours, what OR allocation minimizes the inefficiency of use of OR time? It would be 3 ORs with 8 hours of allocated time and 1 OR with 10 hours of allocated time, because that sums to 34 hours. Comparing this result to the preceding one with 32 hours, because the variability in the workload among Mondays is greater (10 hours instead of 5 hours), the anesthesia group, facility, etc. should allocate greater hours of OR time. Doing so reduces the expected hours of over-utilized OR time, and that reduces the hours that anesthesiologists, nurses, etc., work late.[6]

Reducing Tardiness of First Case Starts Can Increase Efficiency of Use of OR Time

The remainder of the material depends principally on reducing the hours of over-utilized OR time. The reason why the preceding principles matter is because, as already stated, the hours in an OR beyond the allocated hours (i.e., hours into which cases are scheduled) are "over-utilized OR time" only if those allocated hours are the hours that minimize the inefficiency of use of OR time.

At a facility, OR nurses, nurse anesthetists, and anesthesiologists are full-time employees. The allocated time is from 7:00 AM to 3:00 PM. {I'm going to say this for the 3rd time, so that there is no misunderstanding; this means that the hours of OR time that minimize the inefficiency of use of OR time are to 3 PM.} Today, there happens to be 9.0 hours of cases scheduled in one OR. The other 4 ORs are estimated to end earlier. The intravenous catheter and regional nerve block are placed in the holding area from 6:25 AM to 6:55 AM, rather than in the OR as typical. The OR finishes at 3:30 PM instead of at 4:00 PM. Has this resulted in an increase in the efficiency of use of OR time?

As we approach the day of surgery, the cost of an hour of under-utilized OR time becomes negligible, relative to the cost of an hour of over-utilized OR time.[7,8] The terms related to the cost per hour of under-utilized OR time are no longer relevant. The remaining terms are only those related to over-utilized OR time. Continuing, the cost per hour of over-utilized OR time will differ among anesthesiologists, OR nurses, nurse anesthetists, surgeons, surgical technologists, etc. However, for each, it is a constant. The consequence is that for all the stakeholders, OR efficiency is maximized on the day of surgery by minimizing the hours of over-utilized OR time.[7,8]

Returning to the scenario, the allocated time was from 7:00 AM to 3:00 PM. Having the existing personnel target the OR with the largest hours of cases resulted in the cases finishing in 8.5 hours instead of the expected 9.0 hours. What was sustained was 0.5 hours of over-utilized time instead of 1.0 hours of over-utilized time. Thus, reducing the time to incision of the first case of the day increased OR efficiency. Working faster early in the day definitely can increase OR efficiency.

Suppose, on the other hand, that the allocated OR time was from 7:00 AM to 4:30 PM. Then, even if the cases finished at 4:00 PM, there would not be over-utilized OR time. The same clinical intervention has not resulted in an increase in OR efficiency.

What this shows is that working quickly is <u>not</u> synonymous with being efficient. Rather, working quickly <u>can</u> increase efficiency, and whether efficiency is increased depends on the longer-term management decisions (i.e., those of the preceding section). That is why the preceding section matters. Good OR management operational decision-making on the working day before (and on) the day of surgery is highly sensitive to the OR allocations, which is why those values need to be calculated appropriately.[5,6]

Before investing financially in a lean initiative to improve on-time starts, I strongly recommend performing the full analysis.[1] That is what we published in our 2006 review article.[1] However, there is a simpler and usually suitable approach for screening for cost saving opportunities that result from improving on time starts. Suppose that the briefest period of staff scheduling is for 8.5 hours (i.e., a typical US value). Then, for ORs with less than or equal to 8 hours of cases, there would generally be no savings from reducing tardiness of first case starts.[9,10] The reason is that there will not be any over-utilized OR time, because the briefest allocated OR time would be 8 hours. {This is part of the real-world complexity I mentioned in the first section}. For ORs with greater than 8 hours of cases, each 1.0-minute reduction in tardiness reliably results in a savings of greater than 1 minute of regularly scheduled time.[9,10] One simulation method (study) showed 1.1 minutes while another showed 1.2 minutes.[9,10] This savings

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is principally achieved by reducing the allocated OR time.[9] That is a very important finding and principle. Often managers, clinicians, etc., think short term in relation to cost savings rather than to consider how staff scheduling can be adjusted long term. Reducing the tardiness of first case starts *can* increase OR efficiency and very often does so, but not by making a difference "today." Rather, it is by progressive, long-term changes in staff scheduling.

The full analysis of the cost savings realized by reducing tardiness of first cases of the day is the same as the analysis of turnover times.[1] Suppose that an OR has 3 cases and the first case of the day enters the OR 8 minutes late. This is the same as increasing the mean turnover time by 4 minutes.[1,9] The analysis is performed for each combination of service and day of the week. The review article shows that for multiple services and days of the week, at the Australian hospital studied, reducing tardiness of the first case of the day produced a large cost savings.[1]

Perceptions, biases, and physicians' roles

The preceding information essentially suggests targeting ORs with expected over-utilized time for reduction in tardiness of the first case of the starts. But, what about the other ORs? Do nurses, anesthesiologists, etc., in ORs with substantial under-utilized OR time slow down (e.g., to prevent add-on cases). No: Such behavior is not what is observed in practice.[4] There is a very slight but significant effect in the opposite direction ($P = 0.008$). The reason for this is that, on days with substantial under-utilized time, there are more providers available to help in other ORs.[4] Furthermore, only 1% of the variance in tardiness among first cases is attributable to anesthesiologists; there are generally not significant differences in tardiness among anesthesiologists when controlling for specialty.[9]

The most common cause of late first case of the day starts is tardiness of the surgeons.[11-15] Time series models of progressive changes over months in tardiness of first case starts show that anesthesiologists respond to greater on-time readiness of nurses and equipment, with a lag of 1 month ($P = 0.005$).[12] Surgeons respond to greater on-time readiness of anesthesiologists, nurses, and equipment, with a lag of 2 months ($P < 0.0001$).[12] This is, in my opinion, one of the classic studies in the application of operations research and management science to OR management. Quoting the authors: "These results contradict the Pareto principle: surgeons are the main cause of delay for first surgeries but one should not focus on them. It is the first source of the chain that needs to be closely controlled rather than the one which appears to cause the most delays."[12] The lesson is not just for handling first case starts,[12] but essentially all operational type problems in OR management.[16] Unless a facility has research-level accurate data and analysts who are going to perform the analyses as in the scientific papers, one should rely principally not on internal data and analysis, but on the results of those papers.[16] There is no additional effort required to do the literature search in order to find those papers because one cannot know if the facility has accurate data or has performed the appropriate analyses without having read the papers. Reference (16) reviews how to find OR management articles.

Why are these behavioral results counter-intuitive? Most anesthesiologists, OR nurses, surgeons, etc., lack scientific knowledge of over-utilized OR time ($P < 0.0001$).[17] When we studied why this was so, we found that the material in the first section could not be learned simply through the experience of working in ORs.[17] Also, most survey respondents falsely believed that 10 minutes of tardiness of the first case causes subsequent cases in the OR to start at least 10 minutes late ($P < 0.001$).[17] Most respondents did not know that most cases take less time than scheduled ($P = 0.008$).[17] Even among those respondents who did know that most cases take less time than scheduled, not a single one applied that knowledge to infer that 10 minutes of tardiness of the first case start time does not cause subsequent cases to start at least 10 minutes late ($P = 0.0002$).[17] This is an example of a "cognitive bias." The importance of this observation is that institutional fixation on first cases of the day is immutable to education.[17] Such cognitive biases are amplified by small groups (i.e., a surgical committee is less likely to make evidence-based decisions than a scientifically knowledgeable manager).[18,19] The route to achieving rational goals is to rely on a manager to make decisions autocratically while relying on the operations research (mathematical) type decisions.[19] Knowledgeable physician leadership matters.[20]

One way managers can improve on-time starts, and thus increase OR efficiency, is by providing electronic displays with evidence-based recommendations for use on the working day before surgery and the day of surgery.[21] As described in the 1st section, by definition, such displays need to incorporate OR allocations calculated based on maximizing efficiency of use of OR time.[21] The manager can insure that staff take courses (i.e., receive education), which increases trust in the manager's recommendations.[21,22] When monitoring a manager's performance, a good criterion for evaluating the manager's facility is whether the displays effectively provide recommendations and

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checklists for how to use the information.[23] The anesthesia group-facility agreement can be used to codify the performance criteria.[20,24]

Achieving the reductions in time for use to increase OR efficiency: Notifications on the day of surgery

When each patient's information was reviewed repeatedly, and an escalating notification system was used to contact each team member to attend to pending tasks, first case start delays were reduced significantly ($P < 0.001$).[14] Similarly, patient care assistants were notified 45 minutes before OR start time to go to the selected ICU bed and prepare the patient for transport.[25] The anesthesia provider was notified 15 to 20 minutes ahead of surgery for patient communication handoff with the ICU RN.[25] These notifications significantly reduced mean tardiness ($P < 0.0001$).[25]

Achieving reductions in time for use to increase OR efficiency: Planning the working day before surgery

At facilities where anesthesiologists medically direct multiple ORs, they must effectively use staggered starts (≅ 20 minutes to incision) during first cases of the day, since otherwise they cannot be present at all critical portions of the cases.[26] With 1:3 MD:CRNA, and medical direction, lapses would occur on greater than 96% of the days.[26] Therefore, as feasible, surgeons should be notified in advance which ORs will be the 3rd to start, so that those with later starts are not waiting in the ORs.[27] This can be done, because anesthesiologists are good at forecasting time from OR entrance until start of positioning.[28] Times differ depending primarily on anesthetic technique (e.g., general), the patient's American Society of Anesthesiologists' Physical Status, and the procedures to be done (e.g., arterial line placement).[29]

Teaching anesthesiology residents increases OR time before the start of surgery by a mean of 4 minutes.[30,31] Anesthesiologists are faster when not supervising multiple ORs.[32] Therefore, as appropriate and feasible, anesthesiologists practicing alone should be assigned to the ORs with over-utilized time, and 1st and 2nd year anesthesiology residents to ORs with substantial under-utilized OR time.[33]

Assigning sufficient numbers of anesthesiologists and support personnel to perform peripheral nerve blocks before OR entrance can reduce tardiness of first case starts.[34-36] As feasible, cases within surgeons' lists should be sequenced so that more cases with peripheral nerve blocks are performed later in the workday. Such sequencing does not increase the incidence of days with delayed PACU entrance.[37]

Surgical residents in specific specialties should have systems in place to assure no or small tardiness of starts, as relevant.[38] An example is having a mid-level resident leave team rounds early when rounds are taking sufficiently long as to influence first case start.[38] Another example is having surgical residents start morning rounds earlier, when needed, so that at least one resident can assure that site marking and surgical consent have been completed at least 30 minutes before the scheduled start time of each of the first cases of the day of their service.[39]

For an OR to be used for patients who were admitted preoperatively, the case most likely to start on time should be scheduled to be the first case start, changing it only if there is a new, emergency case.[40] This practice reduced the mean tardiness of first case starts of the trauma list by 26 minutes ($P < 0.001$).[40]

Disclosure

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Virtual Cadaver Lab – Anatomy Pearls in Regional Anesthesia to Improve Clinical Success

David B. Auyong, MD **Seattle, WA**

Learning objectives:

1) Compare highlighted anatomical structures in photos of fresh tissue dissections to anatomical structures on ultrasound images and videos;
2) Summarize the anatomical relationships of nerves to surrounding structures that facilitate placement of nerve blocks and improve clinical efficacy of regional anesthesia;
3) Examine, at a gross anatomy level, why some nerve blocks are more appropriate than others for specific surgeries of the upper and lower extremity;
4) Recognize anatomic variations in ultrasound images and cadaver dissections and correlate how these variations affect regional anesthesia

Description:

This lecture covers the anatomical relationships of nerves, vessels, muscle, bone, and skin that form the foundation of regional anesthesia. Images will be presented from multiple dissections in many different fresh tissue cadavers. Unique and clinically relevant correlations will be made between classic anatomical textbook images, the cadaver anatomy and ultrasound images. Anatomical pearls will be reviewed and highlighted for many nerve block approaches to the upper and lower extremity including cervical plexus, interscalene, supraclavicular, suprascapular, infraclavicular, axillary, femoral, fascia iliaca, adductor canal, and the sciatic nerve in the subgluteal and popliteal regions. The interplay of gross anatomy and ultrasound images will cement important anatomical relationships, improving clinical success in regional anesthesia. Many oft repeated teachings in regional anesthesia will be explored and then confirmed or refuted by revisiting the gross anatomy of the human body.

Learning Gap:

A valuable part of this lecture reviews current literature, using anatomical review to improve knowledge and retention. Clinical pearls should improve performance and efficacy with regional anesthesia.

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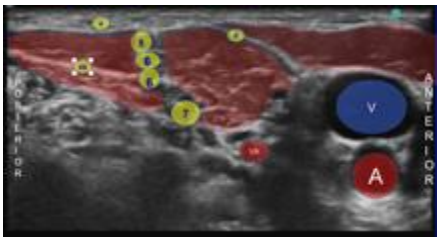
Summary:

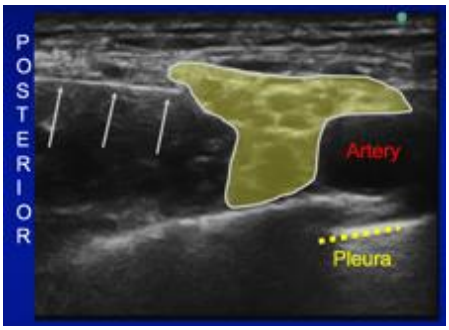
Interscalene Nerve Block

The interscalene nerve block is performed to supply analgesia to the shoulder and clavicle. Anatomical landmarks that can be identified are sternocleidomastoid muscle, anterior/middle scalene, pre-vertebral fascia, roots and trunks of the brachial plexus, vascular landmarks, and specific nerve roots (primarily C5 - monofasicular and C6 – bifasicular). C7 is much deeper. Ultrasound resolution is good enough allowing us to image some of the fascicles that make up the microscopic anatomy of these nerve roots and trunks. It is not good enough to image all fascicles. Other nerves that can be identified include dorsal scapular, long thoracic, suprascapular, and phrenic.



Supraclavicular Nerve Block

Evaluation of the classic image of the supraclavicular nerve block compared to cadaver dissections and microscopic anatomy results in most concluding that this block is usually performed at the level of the trunks. There are three trunks of the brachial with differing emphasis on injection depending on location of the surgery. At this level the suprascapular nerve is usually quite identifiable and presents a good location for local anesthetic deposition for shoulder surgery. The suprascapular nerve can often be located at the most lateral point of the supraclavicular ultrasound image. For more distal surgery (elbow or lower) the injection at the lower trunk is likely more appropriate.



Cervical Plexus Nerve Block

Although previously divided into a deep (muscular) and superficial (skin) nerve block without ultrasound guidance, a complete cervical plexus block can now be easily performed with an injection between the sternocleidomastoid (superficial) and scalene muscles (deep). In subjects that image well, small nerve roots of C2, C3, and C4 can be readily visualized traveling in this plane above the prevertebral fascia.

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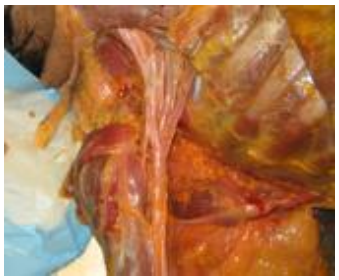
Infraclavicular Nerve Block

The infraclavicular nerve block is significantly facilitated by the Houdini Clavicle maneuver (abducting the arm). This moves the clavicle posterior and allows for a more posterior needle insertion. This posterior needle insertion allows a needle trajectory that is perpendicular to the ultrasound wave propagation and therefore results in a brighter needle image during advancement. This advancement also ensures injection deep to the clavipectoral fascia, a primary barrier to success. Dissections will show significant anatomic variation and the clinical correlate is to place local anesthetic deep to the artery for good success, peri-arterial for optimal success. For safety, needle trajectory should be aimed laterally. A variation is the RAPTIR approach behind the clavicle that can be useful when arm abduction is not possible.



Axillary Nerve Block

The axillary nerve block is similar to the infraclavicular block in that the nerves, though often described in a classic sense are almost randomly arranged around the axillary artery. In the same patient, nerves can be mobile and found in different places depending on arm, probe position, or probe compression. Most importantly, the "conjoint tendon" is not a tendon but rather a fascial covering. Tendons are terminations of muscles, not covering of muscles. Whatever you want to call it, the fascial covering of the teres major is the perfect anatomic structure to make axillary block reliable. Usually this blocks takes two or three injections: One below, one above, and the musculocutaneous.

Femoral Nerve Block:

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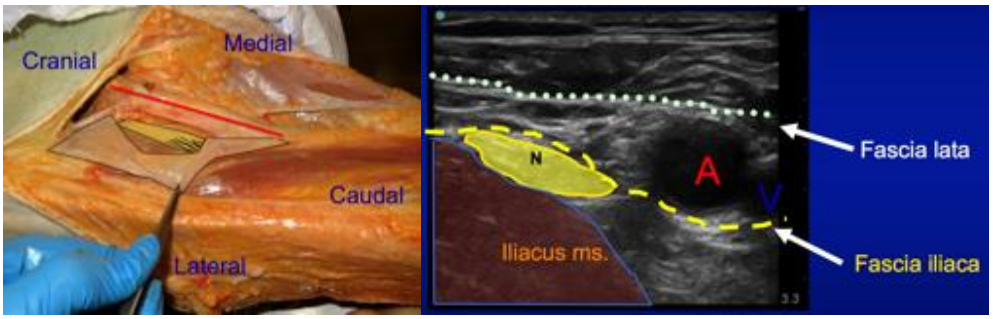
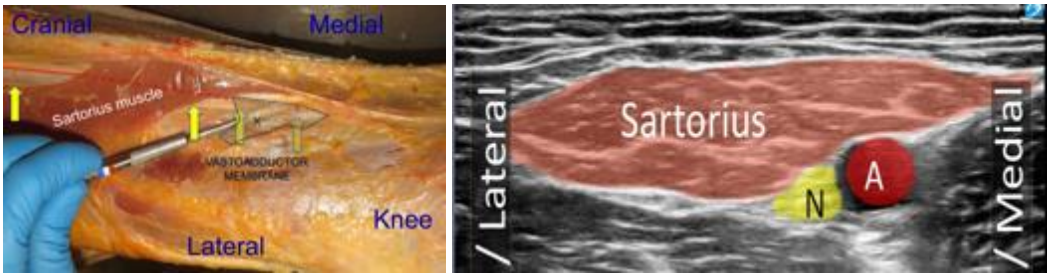
The femoral nerve block is dependent on placement of the local anesthetic under the fascia iliaca. The "triangle" next to the artery is not the femoral nerve. The branch of the femoral nerve that exits to innervate the sartorius muscle exits superficially and therefore is often stimulated with classic stimulator or out-of-plane femoral nerve block approaches. The "fascia iliaca" block is not much different than a properly executed femoral nerve block and likely provides the same clinical effect. A good ultrasound sign of proper injection deep to the fascia iliaca is the spread of local anesthetic underneath the artery. Innervation of the hip joint from the femoral nerve is significant and the branches to the hip capsule exit after the classic area a femoral nerve block is performed. The arteries of the femoral regional provide a perfect road map to identifying the femoral nerve.



Selective Femoral (Adductor Canal) Nerve Block [vs Femoral Triangle Block]:

The adductor canal nerve block is performed by identifying the superficial femoral artery in the medial mid-leg. At this level, the sartorius muscle presents an important landmark for placement of the adductor canal block. The sartorius muscle crosses over the artery so the placement of the artery directly under the sartorius muscle is a reliable landmark to ensure the block is not performed too proximal or too distal. The nerves of the adductor canal are reliably found with the artery at this level and are covered with a vasto-adductor membrane. This membrane must be traversed in order to place reliable nerve blocks at this level. Despite several publications, clinical differences of proximal adductor canal (Femoral Triangle) and distal adductor canal blocks have been minimal.



Sciatic, Popliteal

The anatomic relationship of the tibial nerve, artery, and vein at the crease of the knee (snowman) allows the tibial nerve to be easily identified. At this level, the nerves are surrounded in adipose tissue give two clinical correlates: a bayonet artifact may be present with in-plane needle approaches and prolonged nerve blocks may be possible. Clinically, the tibial component (medial and larger) of the sciatic nerve deserves the majority of the local anesthetic resulting in higher quality nerve blocks. Most of the innervation to the knee, leg and foot from the sciatic nerve can be blocked with this approach.

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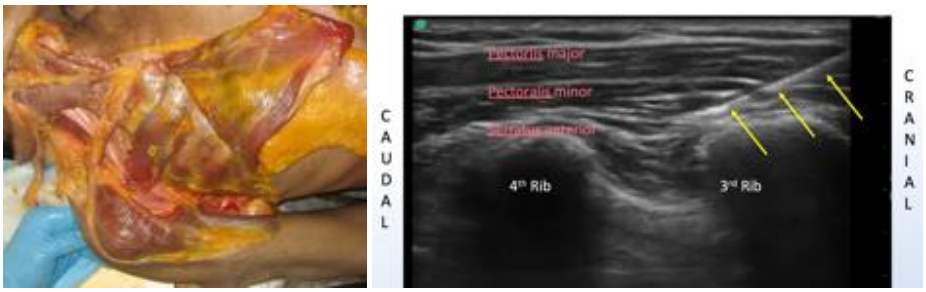
PECS / Serratus Plane

These relatively new nerve blocks have shown promise in providing analgesia for breast, thoracic, and upper abdominal wall surgery or trauma. The key is that these blocks provide nerve block of portions of the brachial plexus that may innervate these areas. There is also thought that local anesthetic deposited in these block locations may also traverse some of the fascial planes or anesthetize parts of the intercostal nerves. These blocks have been favored over paravertebral blocks as the approaches are usually shallower and further away from the lung, improving ease of placement with ultrasound. Solid evidence for these approaches is still required. Clinically, PECS I is placed between pectoralis major and minor. PECS 2 is placed under or on the lateral border of pectoralis minor. Serratus plane is placed on or underneath the serratus anterior muscle.



Disclosures

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Pediatric Trauma Update

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Introduction

Pediatric trauma accounts for more deaths in children in the United States than all other causes (sudden unexplained infant death, cancer, and infectious disease) combined. (1) It has been estimated that each year, 1 in 4 children will sustain an unintentional injury that requires medical care. (2) The annual cost of childhood injury has been estimated to be greater than $50 billion, as these patients may require long term care. (3, 4) The American Academy of Pediatrics notes that "improving outcomes for the injured child requires an approach that recognizes childhood injury as a significant public health problem." (5) Changes in hospital systems with respect to the care of children may address this need.

Trauma Systems

Trauma centers provide the necessary human and physical resources to properly administer acute care. Currently, the American College of Surgeons (ACS) designates four levels of care in designating facilities in the trauma system in providing optimal care to the injured patient and summarized below. (6)

Level I

The center provides comprehensive trauma care, serves as a regional resource, and provides leadership in education, research, and system planning. A level I center is required to have immediate availability of trauma surgeons, anesthesiologists, physician specialists, nurses, and resuscitation equipment. ACS volume performance criteria further stipulate that level I centers treat 1200 admissions a year or 240 major trauma patients per year or an average of 35 major trauma patients per surgeon.

Level II

The center provides comprehensive trauma care either as a supplement to a level I trauma center in a large urban area or as the lead hospital in a less populated area. Level II centers must meet essentially the same criteria as those for level I, but volume performance standards are not required and may depend on the geographic area served. Centers are not expected to provide leadership in teaching and research.

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Level III

The center provides prompt assessment, resuscitation, emergency surgery, and stabilization with transfer to a level I or II center as indicated. Level III facilities typically serve communities that do not have immediate access to a level I or II trauma center.

Level IV

Level IV facilities provide initial evaluation and assessment of injured patients, but most patients will require transfer to higher-level trauma centers. A Level IV facility must have 24-hour emergency coverage by a physician or midlevel provider. Specialty coverage may or may not be available, but a well-organized resuscitation team is important.

Anesthesiologists as collaborative clinical specialists

As noted above, anesthesia services are of critical importance in the care of trauma patients. The ACS further comments on the availability of anesthesia services as stated next. (6) Anesthesiology services are critical in the management of severely injured patients and must be available within 30 minutes for emergency operations and for managing airway problems.

In Level I and II Trauma Centers, anesthesia services in Level I and II trauma centers must be available in-house 24 hours a day. Anesthesia requirements may be fulfilled by anesthesiology senior residents or certified registered nurse anesthetists (CRNAs) who are capable of assessing emergency situations in trauma patients and of providing any indicated treatment, including initiation of surgical anesthesia. When anesthesiology senior residents or CRNAs are used to fulfill availability requirements, the attending anesthesiologist on call must be advised, available within 30 minutes at all times, and present for all operations.

In Level III hospitals, in-house anesthesia services are not required, but anesthesiologists or CRNAs must be available within 30 minutes. In Level III trauma centers without in-house anesthesia services, protocols must be in place to ensure the timely arrival at the bedside by the anesthesia provider within 30 minutes of notification and request. Under these circumstances, the presence of a physician skilled in emergency airway management must be documented. In Level III facilities, operative anesthesia may also be provided by a CRNA under on-site physician supervision.

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Pediatric Systems

Similarly in 2014, the American College of Surgeons released a statement advocating for verification of standards for institutions that care for the pediatric surgical patient. The (ACS) in collaboration with the Task Force for Children's Surgical Care have developed standards to improve surgical care for pediatric and children surgical patients. These standards have been supported by the American Pediatric Surgical Association and the Society of Pediatric Anesthesia, and set multispecialty standards for children's surgical care in the United States. The standards document, *Optimal Resources for Children's Surgical Care*, details the principles regarding resource standards, quality improvement and safety processes, data collection, and a verification process. The program evaluates three levels of care, aligned to the standards and expected scope of practice at the pediatric hospital as summarized below. (7)

Characteristic	Level I	Level II	Level III
Age of Patient	Any	Any	>6 months
ASA	1-5	1-3	1-2
Multidisciplinary management of comorbidities	Multiple medical and surgical specialties; pediatric anesthesiology	Typical, single surgical specialties; neonatology; pediatric anesthesiology	None
Operations	Procedures for major congenital anomalies and complex diseases, including those that are uncommon or require significant multidisciplinary coordination	Procedures for common anomalies and diseases that are typically treated by most children's surgical specialists and that do not require significant multispecialty coordination	Common, low-risk procedures typically performed by a single specialty
Ambulatory	ASA 1-3 Full-term and preterm infants may be cared for as ambulatory patients based on written guidelines established by the pediatric anesthesiologist in charge of perioperative care;	ASA 1-3 Full-term and preterm infants may be cared for as ambulatory patients based on written guidelines established by the pediatric anesthesiologist in charge of perioperative care;	Otherwise healthy (ASA 1-2) Age >6 months

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	institutional guidelines generally require full-term infants <4 weeks or preterm infants<50 weeks' PMA to be monitored for >12 hours postoperatively	institutional guidelines generally require full-term infants <4 weeks or preterm infants<50 weeks' PMA to be monitored for >12 hours postoperatively	

Note that requirements for At Level I children's surgical centers, two or more pediatric anesthesiologists must be on the medical staff, and one *must* serve as the primary anesthesiologist for all children 2 years or younger. One pediatric anesthesiologist *should* serve as the primary anesthesiologist for all children 5 years or younger or with an ASA of 3 or higher. A pediatric anesthesiologist's physical presence is required for procedures for which he or she is the primary anesthesiologist. At Level II facilities, children's surgical centers are required to have one or more pediatric surgeons available on a consultant basis to provide care within 60 minutes of such a request 24/7 and to provide relevant care for children 5 years or younger, as at a Level I center. A Level III children's surgical center must have continuous 24/7 availability within 60 minutes of anesthesiologists with pediatric expertise. One of these individuals *must* serve as the primary anesthesiologist for patients 2 years or younger, and one of them *should* serve in this capacity for all patients 5 years or younger. It is important to recognize that the definition of *pediatric anesthesiologist* is defined specifically in the standards document *Optimal Resources for Children's Surgical Care*. The definition includes American Board of Anesthesiology certified pediatric anesthesiologists, but extends additional criteria for anesthesiologist who may not have attained this certification.

Pediatric Trauma Systems

As of 2102, In the U.S., there were only 35 Level I, and 32 Level II Pediatric Trauma Centers verified by the American College of Surgeons. (8) Hospitals that pursue verification as pediatric trauma centers must meet the same resource requirements as adult trauma centers, in addition to pediatric resource requirements. Additionally, pediatric trauma centers should have sufficient volume of institutional experience with major pediatric injuries. A Level I pediatric trauma center must annually admit 200 or more injured children younger than 15 years. A Level II pediatric trauma center must annually admit 100 or more injured children younger than 15 years. These admissions may include inpatient or 23-hour observations but should exclude patients admitted for drowning, poisoning, foreign bodies, asphyxiation, or suffocation or patients who are dead on arrival to the facility. (6)

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Summary

The care for pediatric trauma patients continues to evolve with increased quality initiatives and multiple verification processes for the care of trauma patients and likewise the care of pediatric patients. Despite this, specialized pediatric trauma centers are still few and far between.

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Cesarean Delivery Pain Management for the Breastfeeding Mother

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Lecture Synopsis:
The lecture summarizes various multi-modal analgesic options to optimize pain management after cesarean delivery (CD), specifically the role of neuraxial opioids, non-steroidal anti-inflammatories (NSAIDs), acetaminophen, dexamethasone, gabapentin, ketamine, wound infiltration, transversus abdominis plane (TAP) block. Analgesic drug exposure in breastfeeding neonates, and techniques to minimize the transfer of analgesics into breast milk will be considered. Patient-centered pain management options will also be discussed.

Introduction:
Pain associated with CD is the most important concern for expectant mothers (Table 1),[1] and is often incompletely relieved by pain management protocols. Pain after CD is described as moderate to severe, and equivalent to that after abdominal hysterectomy.[2] Postoperative pain goals proposed by the Joint Commission (pain scores of consistently <3 out of 10),[3] are infrequently attained after CD.[4] Good post-CD analgesia improves maternal functional ability, enhances recovery, improves interaction with newborn infants, and decreases likelihood of persistent opioid use.[5,6]

Outcome	Rank†	Relative Value‡
Pain during cesarean	8.4 ± 2.2	27 ± 18
Pain after cesarean	8.3 ± 1.8	18 ± 10
Vomiting	7.8 ± 1.5	12 ± 7
Nausea	6.8 ± 1.7	11 ± 7
Cramping	6.0 ± 1.9	10 ± 8
Itching	5.6 ± 2.1	9 ± 8
Shivering	4.6 ± 1.7	6 ± 6
Anxiety	4.1 ± 1.9	5 ± 4
Somnolence	2.9 ± 1.4	3 ± 3

Table 1: Patient preferences for anesthesia outcomes prior to cesarean delivery[3]

Data are mean ± standard deviation; †Rank = 1 to 10 from most (1) to least desirable (10) outcome; ‡ Relative value = dollar value patients would pay to avoid outcome (e.g., pay $18 of a theoretical $100 to avoid postoperative pain).

Neuraxial Opioids:
In the United States, most CD are performed with neuraxial anesthesia (spinal, epidural, or combined spinal-epidural techniques),[7] with the vast majority performed with spinal anesthesia.[8] Neuraxial opioids provide superior postoperative pain relief compared to intravenous opioids,[9,10] and is recommended by the American Society of Anesthesiologist's Obstetric Anesthesia and American Pain Society's Clinical Practice Guidelines practice guidelines.[11,12]

Neuraxial morphine is currently the "gold-standard" single-dose neuraxial post-CD opioid and provides effective and prolonged analgesia. The duration of post-CD analgesia after intrathecal (IT) or epidural morphine is 14-36 hours,[10,13-15] and is dose dependent. Time to first request for additional analgesia of 9.7-26.6 hours for IT morphine doses of 50-100 mcg versus 13.8-39.5 hours for doses >100-250 mcg.[15]
Intrathecal vs. epidural morphine: Both IT and epidural administration provide similar efficacy and duration of post-CD analgesia.[16,17] However, IT morphine is considered the preferred route because of a faster onset of analgesia, and requires a smaller dose with potentially less neonatal effects.
Optimal neuraxial morphine dosing: Optimal dosing is difficult to determine because of variability in patient response to neuraxial opioids. Neuraxial morphine appears to have an analgesic ceiling (50-200 mcg intrathecally[18] and 2-4 mg epidurally[19]). Larger doses may increase side effects without providing significant additional analgesic benefit. Patients experience a lower incidence of nausea/vomiting (OR 0.44) and pruritus (OR 0.34) when receiving lower (50-100 mcg) versus higher (>100-250 mcg) IT morphine doses for CD.

Lipophilic opioids (e.g., IT fentanyl and sufentanil) improve intraoperative analgesia (especially during uterine exteriorization). Lipophilic opioids have a very quick onset, whereas neuraxial morphine requires 45-60 minutes to achieve peak effect. IT fentanyl or sufentanil reduce intraoperative nausea and vomiting, decrease local anesthetic

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requirements (less hypotension), and provide a better postoperative transition to other pain medications during recovery from neuraxial anesthesia.[20-22] However IT fentanyl 10-50 mcg provides limited post-CD analgesia, with a median analgesic duration of 2-4 hours.[13,14] A combination of a quick-acting lipophilic IT opioid (e.g., fentanyl 10-20 mcg) with a long-acting hydrophilic opioid (e.g., morphine 100-200 mcg) is commonly utilized,[8] with the aim of optimizing both intraoperative and postoperative analgesia.

Hydromorphone has an intermediate lipid solubility (between that of morphine and fentanyl). The analgesia and side effects with hydromorphone is similar to that observed with morphine;[23,24] although its onset is quicker and duration is slightly shorter.[25,26] The dose ratio of IT morphine to IT hydromorphone in the post-CD setting is 2:1.[24]

Continuous or patient-controlled epidural analgesia (PCEA) with neuraxial opioids such as fentanyl, sufentanil, hydromorphone, meperidine ± local analgesics has been used with some success after CD.[27,28] However, these catheter-based analgesic techniques decrease maternal mobility, increase nursing workload, may increase catheter-related complications (e.g., hematoma, infection) and add additional costs in comparison with single-dose neuraxial morphine.[29] PCEA may be worthwhile for patients with high postoperative analgesic requirements (e.g., chronic pain sufferers). No consensus currently exists regarding optimal continuous epidural or PCEA regimens.

Maternal and neonatal side effects: All opioids have the potential for placental transfer and therefore it is preferable to utilize small IT doses or to administer epidural opioids after cord clamping. Although neuraxial opioids provide superior post-operative analgesia compared to systemic opioids, certain maternal opioid-related side effects (such as pruritus) may be more frequent.[30,31] However, patients prior to CD rank pain relief above side effects such as nausea, vomiting or pruritus (Table 1).[1] Prophylactic metoclopramide and 5-HT_3 receptor antagonists reduce the incidence of postoperative nausea and vomiting and the need for rescue antiemetic treatment in women receiving IT opioids for CD.[32,33] Combination regimens may be more effective than individual antiemetic agents in treating nausea and vomiting. Opioid antagonists particularly nalbuphine 2.5 to 5 mg are considered first choice measure for managing opioid-related pruritus.[34] Antihistamines are less effective than the opioid antagonists.[35] 5-HT_3 receptor antagonists may be useful prophylaxis for neuraxial opioid-induced pruritus after CD.[36] The analgesic benefits derived from small doses of neuraxial opioids outweigh the rare risk of associated respiratory depression.[37,38]

Multimodal Analgesics:
There is over-reliance on opioids for the management of post-operative pain. Although neuraxial analgesia offers excellent postoperative analgesia, most women will require additional analgesics after CD. Multimodal analgesic approaches should be used to augment the analgesic effects of neuraxial opioids.[39,40]

NSAIDs: A number of studies have shown NSAIDs are very effective for post-CD pain, especially in relieving visceral cramping pain.[41] The pain relief numbers needed to treat (NNT) for NSAIDs range from 1.8-2.7. NSAIDs also reduce the need for opioid analgesics by 30-50%,[42,43] and decrease opioid-related side-effects (such as nausea, pruritus, sedation).[44] There are no comparative studies between various NSAIDs in the post-CD setting, and selection should be based on hospital availability and breast-feeding compatibility.
COX-2 inhibitors (e.g., celecoxib) have been shown to be effective perioperative analgesics with pain relief NNT of 4.2 (200 mg) and 2.5 (400 mg).[45,46] Although there are potential advantages in using COX-2 inhibitors in this setting (no effect on platelet function, less risk of bleeding), the routine use of these drugs is not currently recommended because studies evaluating the drug's use for CD showed limited analgesic benefit.[47-49] In patients that are intolerant of NSAIDs, celecoxib can be considered.[49]

Acetaminophen is an effective analgesic with a 20% opioid-sparing effect.[50] Around-the-clock scheduled acetaminophen rather than combination opioid/acetaminophen pills is preferable to minimize opioid use and avoid exceeding recommended maximum daily acetaminophen doses of 3,250 mg.[51] Intravenous acetaminophen preparations are useful in women unable to take oral medications, but should not replace oral formulations given the higher cost and lack of clear evidence for improved analgesia.[52] Acetaminophen and NSAIDs have an additive effect when used together for post-CD analgesia. [53,54] and therefore scheduled acetaminophen *and* NSAIDs for 2-3 days after CD is recommended.

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Gabapentin and pregabalin have been shown to be useful perioperative analgesics and to have an opioid-sparing effect in the acute postoperative period.[55,56] In the CD setting, gabapentin (single dose 300 or 600 mg after delivery or a 2-3 day course) has shown limited analgesic efficacy.[57-59] The high umbilical vein to maternal vein ratio (0.86), potential breast milk transfer and sedation limits routine gabapentin use as a pre-emptive and post-operative drug in the CD setting.[57,60] In selected patients with pain that is difficult to manage, gabapentin may be a suitable analgesic.

Ketamine: Sub-anesthetic doses (10-15 mg) of IV ketamine have been shown to reduce opioid use for 24 hours after general surgery.[61] Analgesic benefit has been demonstrated after CD under general anesthesia, however limited analgesic efficacy was reported with ketamine 10 mg IV after CD with neuraxial opioids and multimodal postoperative analgesia.[62] Ketamine may be better suited in selected patients with increased pain management needs.

Dexamethasone in a single perioperative doses ranging from 1.25 to 20 mg has been shown to decrease post-operative pain, reduce opioid consumption and decrease postoperative nausea and vomiting without increasing wound infection or healing.[63-65]

Intrathecal and epidural adjuncts (e.g., clonidine, neostigmine) do not appear to offer substantial improvement in acute postoperative pain over that of neuraxial opioids. Many of these neuraxial adjuvants are also associated with side-effects that has limited the routine use of these drugs.[66] However, these drugs may decrease pain sensitization and therefore may have a role in reducing persistent post-operative pain.[67]

Local anesthetics:
Wound infiltration: Studies investigating the analgesic benefit of local anesthetic wound infiltration in the obstetric populations have shown mixed results, and the analgesic effect is generally limited to the early post-operative period following general anesthesia.[68] Single-dose wound infiltration at the time of surgery is not usually effective following spinal anesthesia since the local anesthetic effect may not last beyond the duration of the neuraxial anesthesia (especially if an IT opioid is added).
A continuous irrigation of local anesthetic into the wound can prolong analgesia and decrease opioid consumption for 48 hour post-CD.[68-70] If continuous irrigation of local anesthetic is utilized, sub-fascial insertion of the wound catheter appears more effective than subcutaneous placement.[71] Continuous irrigation of local analgesia into the wound has been proposed as an alternative to an epidural technique,[72] however analgesic efficacy is limited to incisional analgesia and reliability is variable.[68,69] Neuraxial opioids provide incisional and visceral analgesia, and are particularly effective after abdominal surgery.[73] Local anesthetic infiltration or irrigation techniques should be considered as adjuvants for and not as replacements for neuraxial opioids or NSAIDs.
Incisional wound administration of drugs other than local anesthetics such as diclofenac, ketorolac, dexamethasone and opioids, have been demonstrated analgesic benefits post-CD.[74,75] Once the biological implications of wound administration are better understood, wound administration of adjuvant drugs may become a valuable analgesic alternative to systemic administration but with less potential side effects.

Transversus abdominis plane (TAP) block decreases pain and analgesic consumption in women who undergo CD under general anesthesia, and spinal anesthesia without IT morphine, however minimal additional analgesic benefit has been found with TAP blocks in women already receiving IT morphine with multimodal analgesia.[76,77] TAP blocks in this setting are usually performed after skin closure prior to transfer to recovery. Another proposed indication for TAP blocks for CD is for rescue analgesia to manage breakthrough pain after offset of spinal anesthesia, and to reduce the need for escalating opioid doses (with its associated side effects) following cesarean delivery.[78] Differentiation between somatic incisional and visceral cramping pain is important before offering TAP blocks since this technique is likely only effective for incisional pain. The duration of analgesia after TAP blocks with a single dose of ropivacaine or bupivacaine is limited to 8-12 hours.[79] Studies comparing TAP blocks to IT morphine have found that IT morphine provides better analgesia but more opioid-related side effects. [76,77] High local anesthetic blood concentrations are reported after TAP blocks,[80] and several cases of local anesthetic toxicity have been reported in this setting.[81,82] A case series suggests a role for continuous TAP block following CD.[83] Adjuvants such a clonidine, sufentanil and fentanyl offer limited additional analgesic benefit beyond the local anesthetic used for TAP block.[84] Quadratus lumborum block after CD with spinal anesthesia (without IT morphine) has been found to reduce opioid requirements and pain scores.[85]

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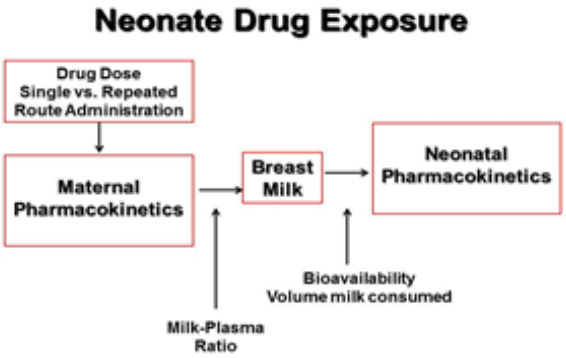
Breastfeeding Considerations:
The vast majority of women in the United States attempt breastfeeding in the early postpartum period.[86] Neonatal drug exposure depends on a number of maternal, drug and neonatal factors (Figure 1). A relative infant dose (RID) >10% is generally considered a level of concern.[87,88] Most post-operative analgesics are fortunately well below this level (Table 2).

Table 2: Analgesics	Relative Infant Dose (RID, %)
Acetaminophen	1.3-6.4
Ibuprofen	0.1-0.7
Ketorolac	0.2-0.4
Celecoxib	0.3
Dexamethasone	No data
Gabapentin	1.3-6.5
Hydrocodone	1.6-3.7
Oxycodone	1.5-8
Tramadol	2.4-2.9
Fentanyl	0.9-3
Morphine	5.8-10.7



Neonatal drug exposure can be minimized by: utilizing the lowest effective maternal drug dose; using the most effective route of administration (IT vs. IV or oral opioids); understanding breastfeeding physiology and drug transfer (avoiding breastfeeding at peak drug concentrations or breastfeeding before drug administration); selecting drugs with low breast milk transfer, short half-life, inactive metabolites and a long safety record in this setting.
All opioids enter the breast milk, transfer to the feeding infant, and may cause neonatal sedation and opioid-related side-effects. Fentanyl exhibits low breast milk transfer (RID 0.9-1.7%), has a short half-life and is rapidly redistributed, and is a preferred IV opioid in the breastfeeding setting.[89,90] Morphine has a low oral bioavailability that limits neonatal exposure.[91] Meperidine is metabolized to active normeperidine with a very long half-life (t ½±70 h) and is associated with neurobehavioral effects. Meperidine is best limited to small doses (e.g., 10-25 mg for shivering) in this setting.[89] Oxycodone and hydrocodone have been used extensively in nursing women with no reports of significant adverse effects to breastfed neonates, and are a better oral opioid than codeine after CD.[89,92] Due to their large molecular size and high degree of protein binding, there is minimal transfer of NSAIDs to breastfed neonates compared to opioids. The American Academy of Pediatrics and Academy of Breastfeeding Medicine considers most NSAIDs compatible with nursing mothers.[89,90] NSAIDs with short half-lives, long history of safe use, and minimal breast milk transfer such as ibuprofen (RID 0.1-0.7%, half-life of 2 hours) and ketorolac (RID 0.2-0.4%) are well-suited for breastfeeding women.[88,91,93] Celecoxib (a COX-2 inhibitor) also has minimal transfer to breast milk (RID 0.3%) and is considered safe if breastfeeding.[94] Acetaminophen is a drug with an excellent side-effect profile, a RID 1.3-6.4%, and no reported cases of neonatal harm. Acetaminophen is considered compatible with breastfeeding, although caution should be exercised in preterm neonates or neonates with liver dysfunction.[89,90] Gabapentin has a RID 1.3-6.5% and may result in sedation,[57,60] therefore caution should be exercised with the routine use of high-dose gabapentin. Local anesthetics result in very limited breast milk transfer; Ropivacaine (highly protein bound and very low breast milk transfer) is probably the best suited long-acting local anesthetic.[95]

Conclusions:
There is currently no analgesic "wonder drug" and post-CD pain must be managed using a multimodal analgesic approach as outlined by a suggested analgesic protocol (Table 3). Multimodal analgesia should include neuraxial morphine in conjunction with scheduled NSAIDs and acetaminophen should be administered in all appropriate women undergoing CD. The majority of women will require additional analgesics, and breakthrough pain is best managed with oral opioids (e.g., oxycodone, hydrocodone) while reserving IV opioids for severe or refractory pain. Local anesthetic wound instillation, TAP blocks, dexamethasone, gabapentin and ketamine are additional analgesic options in select patients or as rescue analgesia following CD (Table 3). In the future, standardized treatment plans

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may be replaced with individual plans that utilize treatments tailored around specific patient needs.[96,97] Additional studies are needed to better understand the development of chronic pain after CD, and refine treatments that can reduce the occurrence of persistent incisional pain.[39]

Table 3:	**Drug**	**Dose and Route**	**Prescribing Information**
Routine care*	Neuraxial morphine	IT morphine 150 µg or Epidural morphine 3 mg	With IT hyperbaric bupivacaine 12 mg + fentanyl 15 µg
	NSAIDs	Ibuprofen 600 mg PO (or ketorolac 15 mg IV if NPO)	Every 6 h for 48–72 h
	Acetaminophen	Acetaminophen 650 mg PO (or IV if NPO/vomiting)	Every 6 h for 48–72 h
	Oral opioids	Oxycodone 5–10 mg PO	As needed for breakthrough pain
Ongoing or severe pain	IV opioids	IV morphine, fentanyl, or hydromorphone	Intermittent IV boluses or IV patient-controlled analgesia
	Regional anesthesia	Bilateral TAP block	0.25% ropivacaine 20–25 mL each side Single-shot ± catheter
	Oral adjuvants	Gabapentin	600 mg PO single dose (300 mg PO every 8 h for ongoing pain)
		Dexamethasone	4-8 mg IV single dose

*For women identified at risk for severe postoperative pain (e.g. chronic pain, opioid tolerant), consider postoperative patient-controlled epidural analgesia (with local anesthetic and opioid); or local anesthetic wound instillation (0.5% ropivacaine 5 mL/h subfascially for 48–72 h post-CD); dexamethasone 4-8 mg after delivery; or ketamine 10–15 mg IV after delivery of the baby.
Based on the analgesic protocol utilized at Lucile Packard Children's Hospital, Stanford University, California.

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Preoperative Anemia- Embedding an Anemia Clinic Into Your Preoperative Practice

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Background: Anemia is present in 5-7% of elective surgical patients, and in 30% of all surgical patients depending on associated comorbidities [1]. Preoperative anemia, even when mild, is associated with increased 30-day mortality [2]. A hemoglobin (Hgb) <8 g/dL is associated with a 16-fold increase in mortality. Morbidity is increased in patients even with mild-moderate anemia [3, 4]. Perioperative risk begins with hematocrits (Hct) below the definition of normal (Table 1) and increases as the Hct decreases. There is an increased risk of cardiac events, pneumonia and delirium in anemic patients. In patients with comorbid conditions such as cardiovascular disease, diabetes, or chronic kidney disease who have concomitant anemia, the perioperative mortality rate is typically twice that seen with the underlying disease alone without anemia. Anemia increases need for perioperative transfusions and transfusions are associated with increased morbidity and mortality. Surgical patients receive 40%-60% of all blood products. Orthopedic and cardiac surgeries account for the most blood utilization. A restrictive transfusion strategy (maintaining Hgb between 7 and 9 g/dL) is at least as effective, if not superior, to a more liberal approach (targeting Hgb of 10-12 g/dL) in critically ill patients, with the possible exception of those with unstable coronary syndromes [5]. Transfusion practices are costly. In the United States 21 million units of blood components are used every year and half is transfused perioperatively. Each unit of red blood cells (RBC) costs $522-$1183. An average hospital cost per year is $1.6-$6 million. Surprisingly, blood is poorly reimbursed. There are other financial burdens related to materials and personnel. Additionally, transfused patients are more likely to require intensive care services, have prolonged ventilator dependence and length of stays.

In the past the only effective method to treat anemia in the typically short time before surgery was with red blood cell transfusions. Increasingly, with the identification of substantial risks and costs associated with transfusions attention has focused on identifying other effective measures. With newer intravenous preparations of iron which are safer, better tolerated it has become cost-effective and clinically effective to treat patients before planned surgery (Figure 1)

Types and Etiologies of Anemia: Iron deficiency is responsible for 30% of anemias in elective surgical patients. The rate is likely much higher in non-elective patients with cancer and chronic diseases. By the time anemia is present the patient has completely depleted iron stores. The most common cause of iron deficiency is blood loss (e.g., gastrointestinal, gynecologic, urologic sources), and then from malabsorption (e.g., 45% of gastric bypass patients, those with celiac disease). . In non-pregnant, non-menstruating women blood loss is most commonly from the gastrointestinal (GI) tract. There is a strong association with GI, bladder, uterine and kidney cancer in patients with iron deficiency anemia (IDA).

Many surgical patients may have a component of anemia of chronic disease which is a common type of anemia in most chronically ill individuals. Common etiologies of anemia of chronic disease are cancer, infections, chronic kidney disease and inflammation. Anemia of chronic disease is secondary to cytokine-mediated immune responses and up regulation of hepcidin. Hepcidin regulates iron absorption, transport and utilization. Elevated hepicidin levels lead to disruption of iron homeostasis.

A determination of etiology and correction of anemia are needed before proceeding with elective procedures.

Diagnosis: Patients may complain of fatigue or dyspnea, but typically are unaware until preoperative testing is performed. Ironically, most patients will have had chronic anemia which has never been adequately addressed by primary care providers. RBCs are typically microcytic (small) and hypochromic (pale). Extensive efforts must be undertaken to diagnose and correct anemia preoperatively, especially for elective surgeries, the elderly, or those

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anticipating surgeries with significant blood loss, those who refuse blood transfusions, if perioperative anticoagulation is planned, or patients with other diseases. Identifying IDA and providing intravenous (IV) iron infusions preoperatively to optimize hemoglobin and prevent transfusions are recommended [6]. Anemia of chronic disease is a diagnosis of exclusion. Patients with undiagnosed anemia should have measurements of iron, iron binding capacity, transferrin saturation (TSAT), ferritin, vitamin B_{12}, thyroid stimulating hormone (TSH), creatinine and a reticulocyte count. Ferritin is an acute phase reactant and can be elevated in conditions associated with inflammation even with iron deficiency. A TSAT <20% and/or a ferritin level <800 are seen in IDA (Figures 2 and 3).

Treatment: Pharmacological treatment of anemia plays an important role in preventing complications and avoiding blood transfusions in the surgical population. Treatment can be started in the preoperative setting and continued in the postoperative period if surgery cannot be postponed due to urgency. Iron supplementation is provided orally or IV. The most common IV preparations of iron include: iron dextran (low molecular weight), iron sucrose, ferric gluconate and ferric carboxymaltose. Iron sucrose is the preferred preparation for pregnant patients with a category B rating; ferric carboxymaltose has a category C rating. Total iron dose for iron replacement is calculated according to the Ganzoni formula:

Total iron dose (mg) = weight* (kg) x [(ideal Hb - actual Hb) g/dL] x 2.4 + 500 mg

- *Ideal body weight (IBW) in overweight patients. If underweight, use actual body weight.
- The final value can be rounded up to the nearest multiple of 100 mg.

Iron sucrose: 200 mg in 100 ml of 0.9% NaCl administered over 15-30 minutes every other day until total cumulative dose reached (may require up to 5 doses)

OR

Ferric carboxymaltose: at a dose of 15 mg/kg weekly, not to exceed 1500 mg total dose. Typically 750 mg in 100 ml of 0.9% NaCl administered over 30 minutes weekly until total cumulative dose reached (usually 1-2 doses)

Erythropoiesis-stimulating agents (ESA) (epoetin) has been recommended and used in patients with severe anemia as a means to increase oxygen carrying capacity and decrease allogenic blood transfusion [7, 8]. ESA use in patients undergoing elective surgery has been shown to reduce the rate of transfusion without increasing the incidence of perioperative venous thromboembolism (VTE). ESA is indicated in patients who have not adequately responded to iron replacement, if Hgb remains <10 g/dL or Hct < 30%. Target Hgb is 10-13 g/dL. ESA is indicated in patients who are expected to have potential blood loss of >1 liter who require time-sensitive surgery. ESA is an important option for patients who refuse blood products. Iron supplementation should continue throughout the course of ESA therapy. The starting dose of epoetin is based on ideal body weight (IBW). Epoetin 400 units/kg/week with rounding of doses to the nearest suitable vial size or combination of vial sizes needed is cost effective and acceptable. Alternatively, less intensive dosing regimens have been studied and the outcomes have been published: orthopedic patients have been randomized to receive epoetin doses from 225 to 2100 units/kg/week. Cardiac surgery patients have received dosing of 600-1500 units/kg/week without adverse side effects. The possible need for DVT prophylaxis during ESA treatment should be considered for patients at elevated risk. Precautions for ESA include uncontrolled hypertension (diastolic BP >100 mmHg), Hct >45%, seizure disorder, platelet count >450 x 10^9, history of cancer, acute infection, pregnancy (category C), lactation, or history of VTE, stroke or cerebrovascular disease.

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Monitoring and Follow Up: Patients should be monitored for proper response to iron and ESA therapies (target Hgb is 10-13 g/dL). Patients need to be identified who may require referrals to primary care physicians, hematologists, gastroenterologists, or nephrologists for further evaluation and long-term treatment of anemia beyond the perioperative period. Other tests may be necessary. Iron deficiency is common in menstruating and pregnant women, children, and others with a diet of excessive cow's milk or low iron-containing foods. In patients such as men or postmenopausal women additional testing to evaluate for blood loss is important. Cancers such as colorectal, gastric, bladder, uterine and renal cell carcinoma are common causes of IDA. Additional tests may include the following:

- Testing for blood in the stool (fecal occult blood test)
- Looking for abnormalities in the gastrointestinal tract - upper and lower endoscopy, enteroscopy (swallowing a tiny camera that takes images of the gastrointestinal tract), or small bowel biopsy
- Testing the urine for blood or hemoglobin
- In women with abnormal or increased menstrual blood losses, a gynecologic evaluation that may include a pelvic ultrasound or uterine biopsy

Sometimes it is difficult to diagnose the cause of iron deficiency, or we may be concerned that there is a problem other than iron deficiency causing the anemia. These may include inherited blood disorders called thalassemias in which RBCs also appear small and pale, hemoglobinopathies such as sickle cell disease (but not sickle cell trait alone), or other blood disorders. People with chronic infections or conditions such as kidney failure, autoimmune diseases, and inflammatory disorders may also have small RBCs. When the cause of the anemia is not clear, patients need to be referred to a hematologist for consultation and further evaluation.

Anemia Clinic Setup: The anemia clinic at Northwestern Memorial Hospital is staffed by registered nurses with an attending anesthesiologist on site. The physical space consists of rooms in the clinic with patient chairs, carts with materials for establishing IV access (e.g., gauze, dressings, angiocaths, IV tubing, chloropreps), emergency supplies with appropriate medications, portable suction, portable oxygen tank, nasal cannulas, monitors to measure vital signs, and computers for documentation. Upon check-in nurses “release” orders for iron infusions which are sent from the pharmacy within an average of 15-20 minutes. IV access is established by the nurses with assistance from the anesthesiologists if needed. Infusions occur over 15-30 minutes. Pre- and post-infusion vital signs are obtained and notes on infusions and patient status are documented in the patient’s electronic health record. Patients are monitored for 15 minutes post-infusion and discharged with an emergency contact phone number.

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Table 1. World Health Organization (WHO) Definition of Anemia

	Hematocrit (Hct)
Women	<36 g/dL
Men	<39 g/dL

Figure 1. Patients with Anemia Who Benefit from Iron Infusions

1. Iron Deficiency Anemia (IDA)

- Patients who will benefit from iron infusion
  - Ferritin level <30 ng/mL
  - Transferrin saturation level (TSAT) <20%.
  - Either one of these is sufficient to establish a diagnosis
  - Ferritin is an acute phase reactant and can be falsely elevated in IDA so do not rule out IDA if ferritin is elevated but TSAT is low

2. Functional Iron Deficiency Anemia (FIDA)

- Patients who MAY benefit from iron infusion
  - Ferritin level 31-800 ng/mL + TSAT <20%.
  - If the ferritin level is 31-800 ng/mL the TSAT should be <20% to warrant an iron infusion
- Patients who are UNLIKELY to benefit from iron infusion
  - Ferritin level <800 ng/mL + TSAT 21%-50%.
  - If an iron infusion is ordered one must document a response to the single infusion and re-measure the ferritin and TSAT levels before additional infusions

3. Iron Overload

- Patients with an absolute CONTRAINDICATION to iron infusion
  - Ferritin >800 ng/mL
  - TSAT >50%

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Figure 2. Clinical Process

Patient Identification

Primary care giver, surgeon or Preoperative Clinic can order a **Pre-procedure Anemia Evaluation Laboratory Test**

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Pre-procedure Anemia Evaluation Laboratory Test

-The testing centers or the preoperative clinic will draw 2 tubes (purple and light green) of blood from the patient.
-If the CBC (purple tube) results in a Hgb $\leq$12 g/dL then reflex orders will activate for the following tests (green tube):
-Iron, ferritin, total iron binding capacity (TIBC), transferrin saturation (TSAT), reticulocyte count, Vitamin B_{12}, creatinine, and thyroid stimulating hormone (TSH).

↓

Iron Infusions

-Patients who meet the criteria for Iron infusions (see "Anemias that may benefit from Iron Infusion) can have appointments made for the Anemia clinic by calling 312- 926-xxxx. Appointments are for 1 hour M-F, between 8-4.
-The amount of iron a patient will need can be calculated using a formula for Total Iron Deficit (TID)

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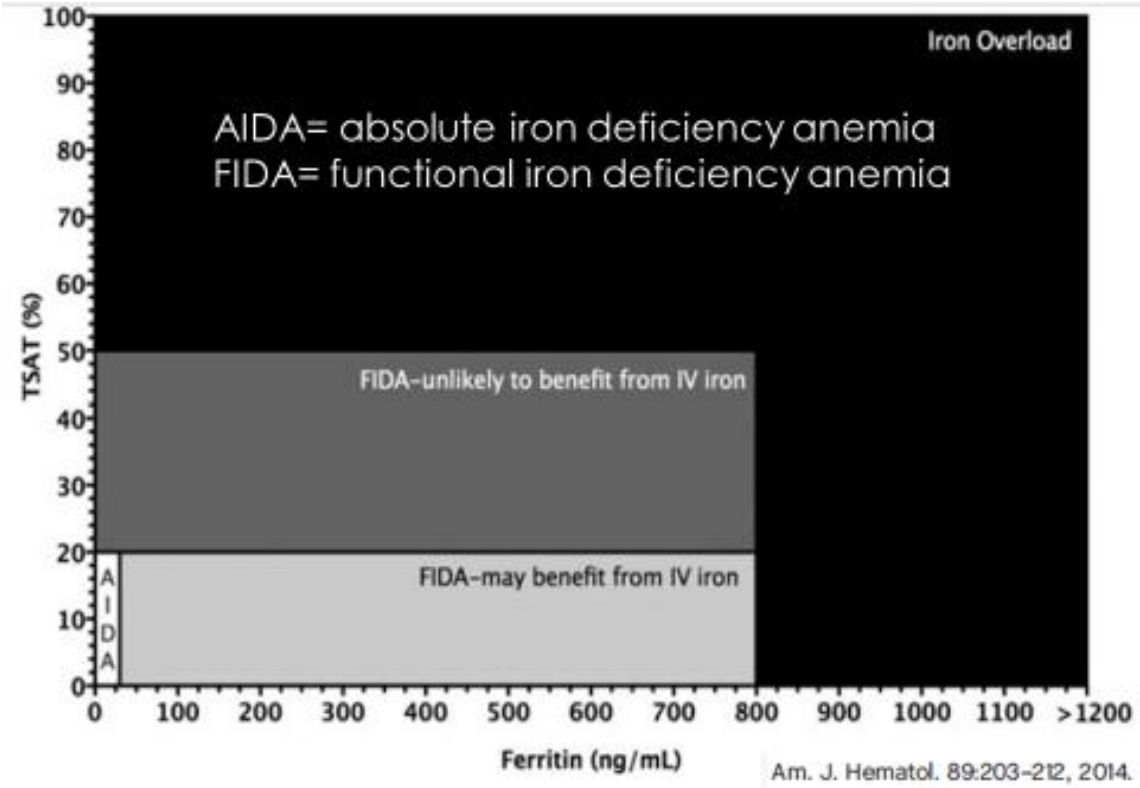

Figure 3. The relationship between TSAT, ferritin and iron stores.

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Emergency Manual Implementations and Uses During OR Crises: Linking Research with Practice

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Defining the Problem

During critical events in the operating room (OR), clinician actions can significantly impact patient outcomes.[1] For many life-threatening events, such as cardiac arrest, malignant hyperthermia (MH), or local anesthetic systemic toxicity, there are stacks of published literature on optimal management details. Yet, for rare crises, even expert clinicians often omit or delay key actions, with detrimental impacts on patient morbidity and mortality.[2] In multiple simulation-based studies, correct performance of key actions dramatically increased when emergency manuals (EMs), crisis checklists, or cognitive aids were used.[3–5] While the dissemination, adoption, implementation, and clinical use of EMs are relatively recent, their use is spreading rapidly in many settings worldwide. The Emergency Manuals Implementation Collaborative (EMIC) provides a central location for implementation and training resources as well as links to cost-free downloadable tools and published literature on rationale from multiple industries.[6] This ASA Refresher Course (RCL) integrates the known evidence on EMs from simulation-based OR studies and from pertinent use in other safety-critical industries like aviation, a conceptual framework for clinical implementation, and emerging data from perioperative clinical implementations and uses.

Emergency Manuals as Enabling Tools

Emergency manuals, which are context-relevant sets of cognitive aids such as crisis checklists, provide professionals with key helpful information for managing rare critical events (see EMIC at www.emergencymanuals.org). EMs are intended as both educational and clinical tools. For simplicity, the term *emergency manual* (or EM) will be used throughout this RCL, though the overlapping terms *crisis checklists*, *emergency checklists*, or *cognitive aids* are often also used interchangeably in referring to such tools. EMs are intended to be symbiotic adjuncts with, rather than replacements for, good preparation, teamwork, and judgment. EM use should never precede necessary immediate actions such as chest compressions for a pulseless patient. Their intended use begins once resources allow—either sufficient help is available for synchronous use at the beginning of a crisis, or initial clinical actions are already underway. Figure 1 shows EMs being used during simulated critical events.

Figure 1. Emergency Manual use by anesthesiologists during simulated critical events. Photos ©D. Gaba left, S Goldhaber-Fiebert right, reprinted with permission

Learning from Other Industries

Safety-critical industries, such as aviation and nuclear power, routinely integrate emergency manuals into their training exercises, and professional teams are expected to have available and use EMs during real critical events, after "immediate actions" are begun. The human factors and psychology literatures repeatedly demonstrate that memory retrieval is impaired for rarely used information, particularly under stressful and time-sensitive conditions, which makes relying on memory alone a risky strategy. Even when expert professionals know the correct management decisions under standardized testing conditions, these same experts are often not able to deploy this

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detailed management knowledge under stress.[7,8] Common errors during management of simulated OR critical events include both diagnostic and therapeutic cognitive errors,[9] and also cognitively recalling but never completing the action. One of the reasons for the latter is prospective memory error—forgetting to do something you intended to do—common because prospective memory is vulnerable to interruptions, which are frequent during crises.[10] In early clinical experience, the use of EMs—combined with good training, teamwork, and judgment—is helping to bridge this gap, via multiple mechanisms, to help teams deliver optimal care during critical events.[11–14] However, rigorous larger studies using mixed quantitative and qualitative methods are needed to further understand clinical implementation and use of EMs.

Four-Element Framework

Our prior work provided a conceptual framework for clinical implementation of emergency manuals by analyzing their implementation and use in safety-critical industries along with early data from healthcare.[15] The framework is relevant for EMs, and similar patient safety tools, because having a tool to implement is a necessary start, but is vastly insufficient for enabling effective use.

The four elements for implementation of EMs, which overlap and interact nonlinearly, are (Figure 2):

1. *Create* (or locally customize an available manual): Provides the EM content and design of what to implement (*i.e.*, a tool)
2. *Familiarize*: Train clinicians including why, as well as how and when to use
3. *Use* clinically: Includes accessibility in all needed locations as well as team–EM interactions, *e.g.*, triggering EM use and "reader" role
4. *Integrate*: Local safety climate or culture strongly influences clinician behavior, as described in the field of implementation science.[16]

As with other improvement efforts in healthcare, early experiences show that addressing these vital elements is greatly enabled by leadership engagement, local champions, and inter-professional implementation teams.[17,18]

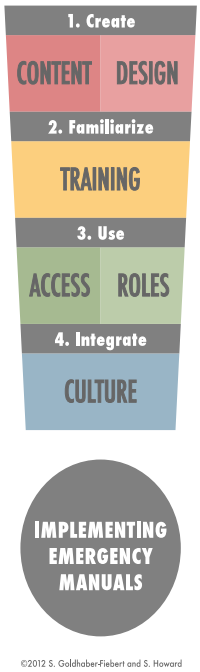

Figure 2. Four vital elements for implementing emergency manuals. ©S. Goldhaber-Fiebert & S. Howard, 2012, reprinted with permission

Figure 3. Crisis Resource Management (CRM) teamwork and dynamic decision-making interacting skills, including "Use cognitive aids." Reprinted with permission

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Why Now?

History
Emergency manual use builds synergistically upon prior patient safety and quality improvement developments in healthcare over the past few decades, and even century. The concept is not itself new, the first known mention being nine decades ago. In 1924, Anesthesia & Analgesia published a manuscript by Dr. Wayne Babcock (famous surgeon of the Babcock forceps) entitled "Resuscitation during Anesthesia."[19] In it he states, and I categorize here by concepts discussed above:
"If a response is not instantly obtained by simple measures (= immediate actions), a fixed emergency routine (= an EM or similar tool based upon best known data) posted on the walls of every operating room (= accessible where needed) and drilled into every member of the staff should be enforced" (= prior training along with a culture of expected use, albeit he emphasizes here top-down enforcement over other important cultural influences).

While a full history of simulation, teamwork training, cognitive aids, and checklists is beyond the scope of this module, some further background on each is provided in the Reference section.[10,20–24] In his 2014 ASA/APSF Ellison C. Pierce, Jr., MD, Patient Safety Memorial Lecture entitled "Competence and teamwork are not enough: the value of cognitive aids," Dr. David Gaba provides a detailed description of how EMs developed in anesthesiology and healthcare from a rich, broader history of cognitive aids and checklists.[25] Figure 3, on Crisis Resource Management, shows visually how all use of cognitive aids exists within the broader context of teamwork and dynamic decision-making skills.

Availability & Design
For many years, Advanced Cardiac Life Support cards and Malignant Hyperthermia posters were the only readily available cognitive aids for OR critical events. In the past few years, development work by multiple groups in parallel has provided cost-free access to several emergency manuals or crisis checklists designed for use in the OR during crises.[26] See Figures 4, 5, and 6 for examples of these tools, each of which had input from human factors design experts. A recent thorough exploration of cognitive aid development and design considerations was a collaboration between human factors design experts and anesthesiologists.[27]

Dissemination and Clinician Receptivity
Dr. Atul Gawande's popular book The Checklist Manifesto,[23] along with multiple healthcare implementations and studies regarding routine use of checklists,[28,29] all influenced the receptivity of clinicians and healthcare institutions to the concept and potential benefit of emergency manuals.When Dr. Babcock initially proposed the concept, at least for cardiac arrest, more than ninety years ago, the healthcare community was not yet ready. In contrast, the message of potential EM utility is now spreading quickly. The November 2013 issue of Anesthesia & Analgesia focused on the topic with three articles and two editorials on EMs, cognitive aids, or crisis checklists. Numerous articles in the American Society of Anesthesiologists (ASA) and Anesthesia Patient Safety Foundation (APSF) newsletters, as well as conference presentations, spread the word efficiently and, along with multiple research studies, piqued interest in a healthcare community now ready to effectively use these tools clinically. In September 2015, APSF held an experts' conference focusing on EM evidence, implementation, and use.18Since the Emergency Manuals Implementation Collaborative was founded in 2012, the combined downloads of EM resources from Stanford University, Harvard's Ariadne Labs, and the Society for Pediatric Anesthesia total more than eighty thousand in English, and hundreds of thousands including translated versions globally. (EMIC Steering Committee, personal communications, August 2018). Many users stated they then shared the content with numerous colleagues at their local institutions, implying much broader dissemination. Clebone et al. recently described the development, simulation testing, and broad dissemination of the Society for Pediatric Anesthesia Critical Events Checklists.[30]

Summary of Simulation-Based Data
There is now over a decade of studies examining whether the use of emergency manuals during realistic mannequin-based simulation scenarios helps clinicians perform better during these crises. The preponderance of the data points to yes, although there are clearly important nuances involved in how to best use these tools. Some of the most relevant studies are described here. In a 2006 observational study of anesthesia residents managing simulated MH cases, Harrison et al. found a positive correlation between the frequency of MH cognitive aid use and appropriate treatment of MH.[3] Burden et al. found that a majority of anesthesia and obstetrics residents did not use easily

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accessible cognitive aids, and proceeded to omit key actions during management of MH and obstetric cardiac arrest simulated scenarios. When a medical student "reader" was explicitly charged with reading to the team from the cognitive aid, key actions were then performed and the help appreciated—raising the question of how teams can trigger appropriate use and reader roles themselves.[31] Neal et al. found that anesthesia residents performed significantly better in managing a surprise scenario of local anesthetic systemic toxicity (LAST) when randomized to have access to a previously introduced, and therefore familiar, LAST checklist versus not having access to the checklist. Moreover, within the intervention group, the residents who used the LAST checklist more frequently performed even better.[4]

Arriaga et al. studied interprofessional OR teams managing eight different OR crises. Each team was randomly assigned to half of the events with, and half without, crisis checklists, serving as their own controls. The teams were familiarized with the crisis checklist concept and format, though not the specific events. When crisis checklists were available, 6% of key management steps were missed versus 23% when they were not, signifying a large improvement in event management.[5] Marshall broadly reviewed the cognitive aid literature and also discussed the impact of design factors for cognitive aids in healthcare.[32] Following this review, Marshall's group conducted multiple simulation studies to delve into the impacts of cognitive aid designs and use on team functioning and nontechnical teamwork skills.[33,34] Watkins et al. studied paper versus electronic versions in simulated settings at an institution without clinical implementation, but with a brief familiarization just prior to use. They found about a third did not use the tool at all, and that neither version had a major impact on performance, though pointing out that effective use of cognitive aids is greatly impacted by training and implementation as well as design of the specific tool.[35,36] Goldhaber-Fiebert and Howard put the healthcare literature into context with findings from other safety-critical industries and decades of iterative simulation-based development and testing, proposing the four-element implementation framework described above.[15]

Bould et al. found no difference in the management of neonatal resuscitation with or without a cognitive aid poster, though importantly, subjects were not familiar with the poster before the scenario and most in the "intention to treat" intervention group did not use it frequently, i.e., if it is not used, it cannot help.[37] Two studies by Nelson et al. highlight concerns: while many used a cognitive aid early, a large proportion of pediatric residents chose the wrong algorithm, and potentially as a result of this judgment error and/or fixation on the incorrect algorithm, vital actions such as CPR were delayed.[38,39] In their 2018 study, 54% of pediatric residents were not performing CPR when cognitive aid use started and only 3.4% then started CPR, prompting calls for better design. Hunt et al., with overlapping authors at same institution, showed that 'rapid cycle deliberate practice' simulation training helped correct conceptual confusions between unstable tachycardias and pulseless states, highlighting also that cognitive aids do not replace training for clinical judgment.[40]

Early Clinical Implementations: Data and Resources

Neily et al. surveyed Veterans Health Administration (VHA) anesthesia professionals six months after national VHA implementation of a 14-event clinical cognitive aid for OR critical events, which was initiated at the VA Palo Alto Health Care System, drew on prior work from the book Crisis Management in Anesthesia, and was a precursor of the Stanford Emergency Manual.[10,41,42] Of the respondents, six months after clinical launch 87% knew the tool existed, half had used it as a reference, and 7% had used it during a crisis. Among crisis users, all had used the aid previously as a reference, which likely improved familiarity with and awareness of the tool, and all felt it was helpful. Training varied across VHA sites, and crisis users were more likely to have received prior formal training.[41] While 7% may not sound like much, the relevant denominator of applicable critical events in the six months since implementation is not known and likely is itself small, with only a subset of respondents encountering an applicable opportunity.

Following recent widespread cost-free dissemination of the Ariadne Labs' crisis checklists,[43] Stanford Emergency Manual for Perioperative Critical Events,[42] and the Society for Pediatric Anesthesia's critical events checklists,[44] there have been case reports,[12,13] as well as many personal emails and stories told about effective clinical uses of EMs during clinical critical events. Most recently, a case-study of successful intraoperative use harnessed qualitative interviews with all team members to understand and categorize the perceived impacts of EM use.[14]

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The common emerging themes from this work combined include:

- Importance of EM accessibility and familiarity
- The need for someone on the team to suggest or trigger use
- Helpfulness of a reader role, separate from event leader, when resources allow
- The potential for EMs to catch omissions, decrease individual clinicians' stress, enable a calm setting, promote improved team communication, and thereby improve delivery of patient care

Many potential biases exist when single case uses are described individually. However, the multiple early reports do suggest that these tools are being used clinically and that at least some clinicians have found them to be helpful for patient care, underscoring the need for more formal mixed-methods research on clinical implementation and use of EMs.

Our team studied early clinical implementation and use, with mixed-methods survey data from Stanford anesthesia residents before and 15 months after clinical launch.[11] Residents reported that OR safety culture supporting appropriate use of cognitive aids improved meaningfully since clinical launch, and that the most impactful training exposures were mannequin-based simulations of critical events coupled with self-review. Of surveyed residents, 19 (45%) had used an EM during a clinical critical event, which—if conservatively presuming zero use by non-responders—still translates to at least a quarter of all residents. The vast majority of users felt the EM helped their teams deliver better care to their patient, and none felt it hurt or distracted from care. A figure in that article shows the wide variety of events for which EMs were used.

When our team assessed the impact on OR staff trainings for EMs and teamwork skills of in situ, low-tech simulation, we found increased awareness of, familiarity with, and intention to use EMs in the future.[45] The full curriculum, instructor's guide, and handouts are available through MedEdPORTAL.[46] Multiple groups have published or shared other online video-based training materials for why, how, and when to use EMs effectively.[6,47]

As more institutions pursue EM implementation locally, discussions reveal that common important factors include: leadership engagement, local champions, inter-professional implementation teams, training including rationale along with use details, and local customization, at least for key telephone numbers and conformity with local policies.[18]

Recently, a Harvard-led US national implementation study, with 368 respondents, showed that there is a dose-response relationship between number of implementation steps taken and implementation success, with both leadership support and time for training also correlating with implementation success.[48] Size of facility also was relevant, with small facilities having a four-fold increase in the odds of reporting implementation success. Implementation success was measured as reported regular cognitive aid use during applicable clinical events. A cost-free implementation toolkit was made available after this study at www.emergencymanuals.org, combining an implementation roadmap and useful resources for training, customization, and practical launch. Increasingly, in parallel these concepts are spreading in other acute-care fields, with multiple studies in fields such as labor and delivery.[49,50]

Conclusion and Next Steps

Perioperative medicine has reached a tipping point for enabling effective use of emergency manuals to help teams deliver better patient care during critical events. The evidence base from other safety-critical industries and from simulation-based studies has shown that there is a need, and that EMs can fill this need when used effectively during crises. Multiple cost-free tools are now widely available for clinical settings, along with implementation and training resources. As research on clinical implementation expands, among the next priorities are to:

- Understand dissemination, adoption, and implementation
- Study the impacts of clinical uses
- Assess barriers and facilitators for EM implementation and use
- Share effective implementation, training, and use strategies
- Actively seek out and mitigate any potential harms

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These goals will require rigorous mixed qualitative and quantitative methods from implementation science combined with well-planned local quality improvement efforts. The data described here suggest a promising role for EMs in helping teams deliver optimal care to patients during critical events, which is worthy of further exploration.

Acknowledgments
Many individuals, teams, and institutions have contributed to the development, testing, clinical implementation, use, and study of emergency manuals. In particular, I'd like to thank: the Stanford Emergency Manual team (Stanford Anesthesia Cognitive Aid Group), Ariadne Labs' Project Check, and the Society for Pediatric Anesthesia's Quality and Safety Committee for sharing the cost-free tools they each developed along with resources for using them well; the EMIC Steering Committee for gathering EM tools, implementation, and training resources in one location—links to the free tools discussed here and much more are all available at www.emergencymanuals.org; the many clinicians who have given feedback to improve design, training, and use of EMs; all those who have shared their experiences using EMs during critical events; the Stanford implementation team; Dr. Sylvia Bereknyei Merrell, Dr. Amanda Burden, and Dr. Alan Schwartz for their proofreading and manuscript edits. The Foundation for Anesthesia Education and Research (FAER) enabled our ongoing work in this area with a Research in Education Grant, though the views in this RCL are my own, and do not necessarily reflect those of FAER.

<u>Examples of Free Tools</u> (all linked from EMIC website www.emergencymanuals.org)

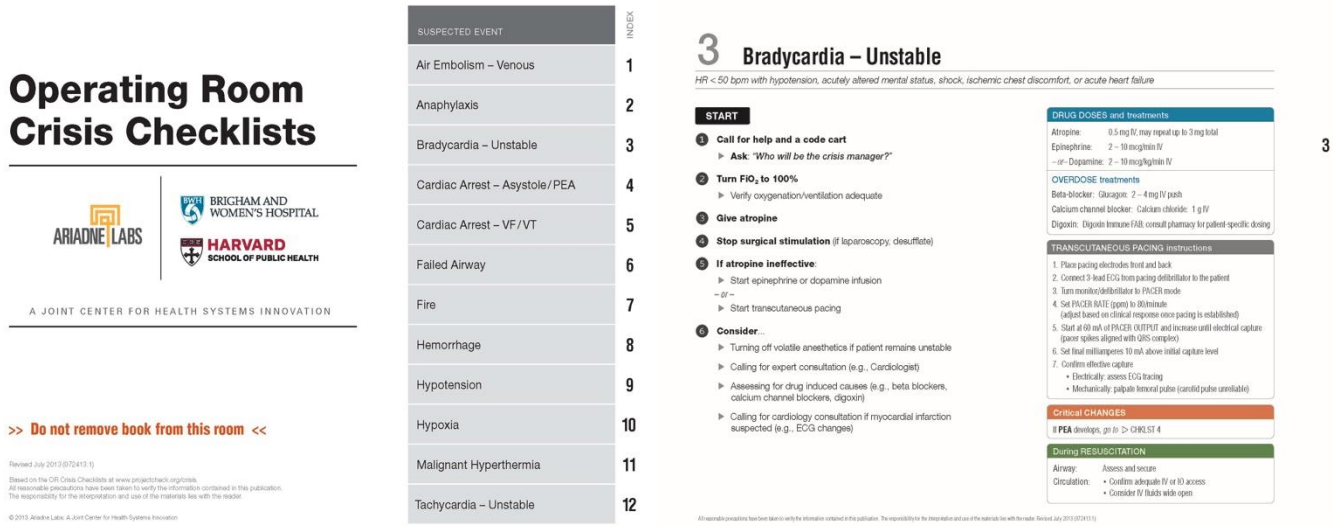

Figure 4. Table of contents and sample page from the Operating Room Crisis Checklists, from Ariadne Labs. For latest version see: http://www.projectcheck.org/crisis.html.

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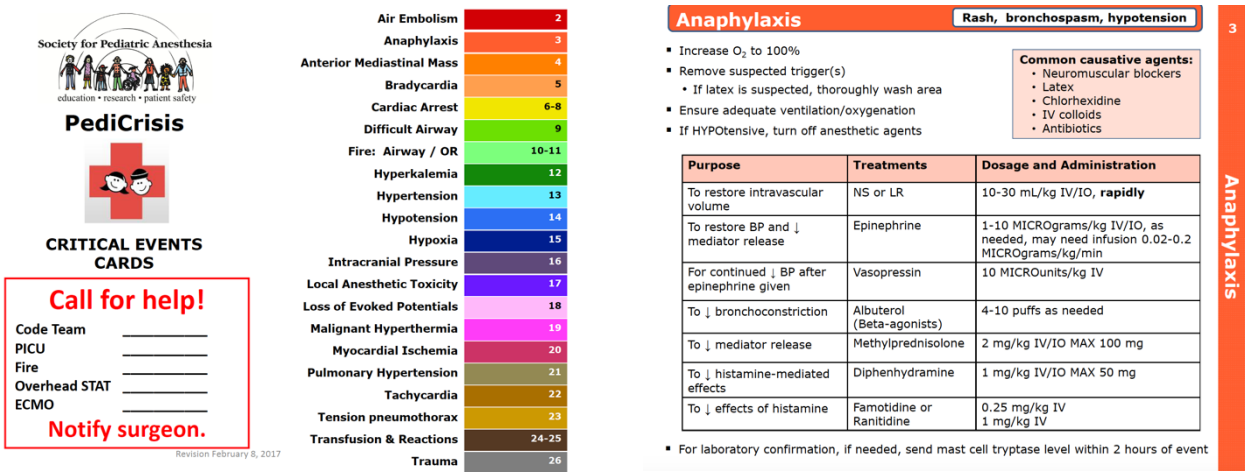


Figure 5. Table of contents and sample page from the PediCrisis Critical Events Checklist, from the Society for Pediatric Anesthesia's (SPA) Quality and Safety Committee. For latest version see: pedsanesthesia.org, Quality and Safety Committee, Critical Events Checklists.

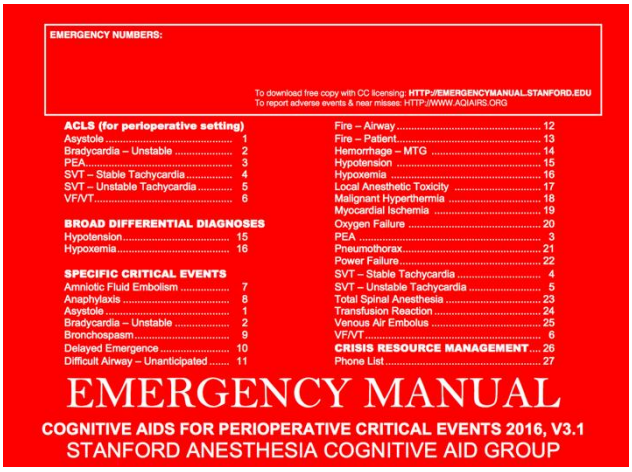
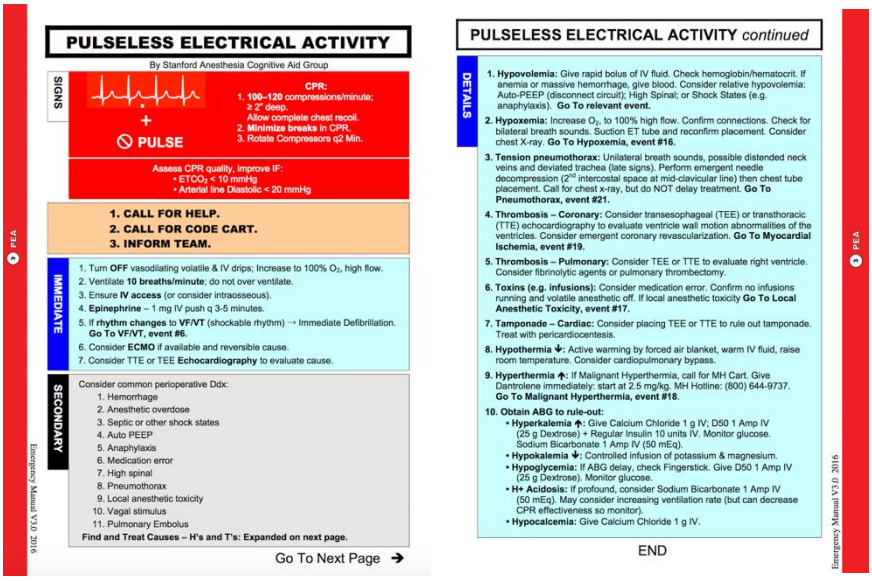


Figure 6. Table of contents and sample page from the Stanford Emergency Manual for Perioperative Critical Events by Stanford Anesthesia Cognitive Aid Group (SACAG).

For latest version see: http://emergencymanual.stanford.edu.



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Hemorrhagic and Infectious Complications of Neuraxial Anesthesia

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Spinal Hematoma

The actual incidence of neurologic dysfunction resulting from hemorrhagic complications associated with neuraxial blockade is unknown; however, recent epidemiologic studies suggest the incidence is increasing (1). In a review of the literature between 1906 and 1994, Vandermeulen et al. (2) reported 61 cases of spinal hematoma associated with epidural or spinal anesthesia. In 87% of patients, a hemostatic abnormality or traumatic/difficult needle placement was present. More than one risk factor was present in 20 of 61 cases. Importantly, although only 38% of patients had partial or good neurologic recovery, spinal cord ischemia tended to be reversible in patients who underwent laminectomy within eight hours of onset of neurologic dysfunction.

It is impossible to conclusively determine risk factors for the development of spinal hematoma in patients undergoing neuraxial blockade solely through review of the case series. However, large inclusive surveys that evaluate the frequencies of complications (including spinal hematoma), as well as identify subgroups of patients with higher or lower risk, enhance risk stratification. In the series by Moen et al. (3) involving nearly 2 million neuraxial blocks, there were 33 spinal hematomas. The methodology allowed for calculation of frequency of spinal hematoma among patient populations. For example, the risk associated with epidural analgesia in women undergoing childbirth was significantly less (1 in 200,000) than that in elderly women undergoing knee arthroplasty (1 in 3600, $p<0.0001$). Likewise, women undergoing hip fracture surgery under spinal anesthesia had an increased risk of spinal hematoma (1 in 22,000) compared to all patients undergoing spinal anesthesia (1 in 480,000).

Overall, these series suggest that the risk of clinically significant bleeding varies with age (and associated abnormalities of the spinal cord or vertebral column), the presence of an underlying coagulopathy, difficulty during needle placement, and an indwelling neuraxial catheter during sustained anticoagulation. They also consistently demonstrate the need for prompt diagnosis and intervention. Practice guidelines or recommendations summarize evidence-based reviews. However, the rarity of spinal hematoma defies a prospective-randomized study, and there is no current laboratory model. As a result, the *consensus statements* developed by the American Society of Regional Anesthesia and Pain Medicine represent the collective experience of recognized experts in the field of neuraxial anesthesia and anticoagulation(4). They are based on case reports, clinical series, pharmacology, hematology, and risk factors for surgical bleeding. An understanding of the complexity of this issue is essential to patient management.

Oral Anticoagulants

Clinical experience with patients who, congenitally, are deficient in factors II, IX, or X suggests that a factor activity level of 40% for each factor is adequate for normal or near-normal hemostasis. Bleeding may occur if the level of any clotting factor is decreased to 20% to 40% of baseline. The PT is most sensitive to the activities of factors VII and X and is relatively insensitive to factor II. During the first few days of therapy, the PT reflects primarily a reduction of factor VII, the half-life of which is approximately 6 hrs. After a single dose, marked prolongation of the INR may occur, although adequate factor levels are still present. However, with additional doses, an INR greater than 1.4 is typically associated with factor VII activity less that 40% (and the potential for inadequate clotting) (5).

Few data exist regarding the risk of spinal hematoma in patients with indwelling epidural catheters who are anticoagulated with warfarin. Odoom and Sih (6) performed 1000 continuous lumbar epidural anesthetics in vascular surgical patients who were receiving oral anticoagulants *preoperatively*. Epidural catheters remained in place for 48 hours postoperatively. There were no neurologic complications. While these results are reassuring, the obsolescence of the thrombotest as a measure of anticoagulation combined with the unknown coagulation status of the patients at the time of catheter removal limit the usefulness of these results. Therefore, except in extraordinary circumstances, spinal or epidural needle/catheter placement and removal should not be performed in fully anticoagulated patients.

There were no symptomatic spinal hematomas in two smaller series with a total of nearly 700 patients undergoing neuraxial block in combination with warfarin anticoagulation perioperatively (6-8). In both studies, epidural catheters were left indwelling approximately two days. The mean international normalized ratio (INR) at the time of catheter removal was 1.4, although in a small number of patients the INR was therapeutic (2.0-3.0). A large variability in patient response to warfarin was also noted, demonstrating the need for close monitoring of the coagulation status. There were no spinal hematomas in a series of 11,235 patients receiving epidural analgesia after total knee replacement (9). Patients received warfarin (5-10 mg) starting the night of surgery. Epidural catheters were removed within 48 hrs. The mean INR in a subset of 1030 patients at the time of catheter removal was 1.5 (range, 0.9-4.3); the INR was less than 1.5 in nearly 40% of patients. These series suggest that not only the INR but also the duration of warfarin therapy must be considered and that prolongation within the first 48 hrs may represent an increased risk.

Intravenous and Subcutaneous Standard Heparin

The safety of neuraxial techniques in combination with intraoperative heparinization is well documented, providing no other coagulopathy is present. In a study involving over 4000 patients, Rao and El-Etr (10) demonstrated the safety of indwelling spinal and epidural catheters during systemic heparinization during vascular surgery. However, the heparin was administered at least 60 minutes

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after catheter placement, level of anticoagulation was closely monitored, and the indwelling catheters were removed at a time when circulating heparin levels were relatively low. A subsequent study in the neurologic literature by Ruff and Dougherty (11) reported spinal hematomas in 7 of 342 patients (2%) who underwent a diagnostic lumbar puncture and subsequent heparinization. Traumatic needle placement, initiation of anticoagulation within one hour of lumbar puncture and concomitant aspirin therapy were identified as risk factors in the development of spinal hematoma in anticoagulated patients. Subsequent studies using similar methodology have verified the safety of this practice, provided the monitoring of anticoagulant effect and the time intervals between heparinization and catheter placement/removal are maintained.

Low-dose subcutaneous standard (unfractionated) heparin is administered for thromboprophylaxis in patients undergoing major thoracoabdominal surgery and in patients at increased risk of hemorrhage with oral anticoagulant or low molecular weight heparin (LMWH) therapy. There are nine published series totaling over 9,000 patients who have received this therapy without complications(12), as well as extensive experience in both Europe and United States without a significant frequency of complications. There are only five case reports of neuraxial hematomas, four epidural (2,13) and one subarachnoid,(14) during neuraxial block with the use of subcutaneous heparin.

The largest study of thrice daily unfractionated heparin involved 768 epidural catheter placements. Sixteen patients from this group had a positive match for hemorrhage codes on their discharge records, with none of the episodes being identified within a major hemorrhage category. Laboratory value analysis failed to reveal changes in the aPTT values of significance (15). The safety of neuraxial blockade in patients receiving doses greater than 10,000 U of UFH daily or more than twice-daily dosing of UFH has not been established. Although the use of thrice-daily UFH may lead to an increased risk of surgical-related bleeding, it is unclear whether there is an increased risk of spinal hematoma. If thrice-daily unfractionated heparin is administered, techniques to facilitate detection of new/progressive neurodeficits (eg, enhanced neurologic monitoring occur and neuraxial solutions to minimize sensory and motor block) should be applied.

Low Molecular Weight Heparin

Extensive clinical testing and utilization of LMWH in Europe over the last ten years suggested that there was not an increased risk of spinal hematoma in patients undergoing neuraxial anesthesia while receiving LMWH thromboprophylaxis perioperatively (2,16). However, in the five years since the release of LMWH for general use in the United States in May 1993, over 60 cases of spinal hematoma associated with neuraxial anesthesia administered in the presence of perioperative LMWH prophylaxis were reported to the manufacturer (17,18). Many of these events occurred when LMWH was administered intraoperatively or early postoperatively to patients undergoing continuous epidural anesthesia and analgesia. Concomitant antiplatelet therapy was present in several cases. The apparent difference in incidence in Europe compared to the United States may be a result of a difference in dose and dosage schedule. For example, in Europe the recommended dose of enoxaparin is 40 mg once daily (with LMWH therapy initiated 12 hours preoperatively), rather than 30 mg every twelve hours. However, timing of catheter removal may also have an impact. It is likely that the lack of a trough in anticoagulant activity associated with twice daily dosing resulted in catheter removal occurring during significant anticoagulant activity. Importantly, there are no data to suggest that the risk of spinal hematoma is increased with specific LMWH formulations (17). The incidence of spinal hematoma in patients undergoing neuraxial block in combination with LMWH has been estimated at 1 in 40,800 spinal anesthetics and 1 in 3100 continuous epidural anesthetics (19). It is interesting in that the frequency of spinal hematoma in this series is similar to that reported by Moen et al (3) for women undergoing total knee replacement with epidural analgesia.

Indications for thromboprophylaxis as well as treatment of thromboembolism or MI have been introduced. These new applications and corresponding regional anesthetic management warrant discussion (20). Several off-label applications of LMWH are of special interest to the anesthesiologist. LMWH has been demonstrated to be efficacious as a “bridge therapy” for patients chronically anticoagulated with warfarin, including parturients, patients with prosthetic cardiac valves, a history of atrial fibrillation, or preexisting hypercoagulable condition. The doses of LMWH are those associated with DVT treatment, not prophylaxis, and are much higher. An interval of at least 24 hours is required for the anticoagulant activity to resolve.

Dabigatran

Dabigatran etexilate is a prodrug that specifically and reversibly inhibits both free and clot-bound thrombin. Plasma levels peak at two hours. The half-life is eight hours after a single dose and up to 17 hours after multiple doses. It is likely that once daily dosing will be possible for some indications because of the prolonged half-life. Because 80% of the drug is excreted unchanged by the kidneys, it is contraindicated in patients with renal failure(21). Dabigatran prolongs the aPTT, but its effect is not linear and reaches a plateau at higher doses. However, the ecarin clotting time (ECT) and thrombin time (TT) are particularly sensitive and display a linear dose response at therapeutic concentrations. In October 2015 idarucizumab was approved by the U.S. Federal Drugs Agency (FDA) to be used in adult patients treated with dabigatran when rapid reversal of its anticoagulant effects is required in situations of emergency surgery/urgent procedures or life-threatening or uncontrolled bleeding. The recommended dose is 5 g via an intravenous (IV) infusion/injection.

A minimum of five days should elapse between discontinuation of rivaroxaban and neuraxial block. Indwelling neuraxial catheters are contraindicated. Likewise, indwelling neuraxial catheters should be removed six hours prior to initiation of dabigatran therapy postoperatively.

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Rivaroxaban

Rivaroxaban is a potent selective and reversible oral activated factor Xa inhibitor, with an oral bioavailability of 80%. After administration, the maximum inhibitory effect occurs one to four hours, however, inhibition is maintained for 12 hours. Rivaroxaban is cleared by the kidneys and gut. The terminal elimination half-life is nine hours in healthy volunteers and may be prolonged to 13 hours in the elderly due to a decline in renal function (hence a need for dose adjustment in patients with renal insufficiency and contraindicated in patients with severe liver disease).

Rivaroxaban was approved in the United States for thromboprophylaxis following total hip or knee replacement in 2011. While a "regional anesthetic" was performed in over half of the patients included in the clinical trials, no information regarding needle placement or catheter management was included. There are minimal clinical data on the use of neuraxial anesthesia in rivaroxaban-treated patients. Product labeling states: "Epidural or spinal hematomas have occurred in patients treated with rivaroxaban who received neuraxial anesthesia or underwent spinal puncture". However, no details regarding risk factors or frequency are reported. A review of the literature noted seven neuraxial hematomas associated with rivaroxaban.

A minimum of three days should elapse between discontinuation of rivaroxaban and neuraxial block. Indwelling neuraxial catheters are contraindicated due to the "boxed warning". Likewise, indwelling neuraxial catheters should be removed six hours prior to initiation of rivaroxaban therapy postoperatively.

Apixaban

Apixaban inhibits platelet activation and fibrin clot formation via direct, selective and reversible inhibition of free and clot-bound factor Xa. , The oral bioavailability is 50%. After administration, the maximum inhibitory effect occurs in three to four hours, however, inhibition is maintained for 12 hours. Apixaban is cleared by the liver and kidneys. The terminal elimination half-life is 12 hours in healthy volunteers and may be prolonged in patients with renal impairment. There are no reports of epidural/spinal bleeding associated with a neuraxial anesthesia, although a single spontaneous hematoma has been reported.

A minimum of three days should elapse between discontinuation of apixaban and neuraxial block. Indwelling neuraxial catheters are contraindicated and should be removed six hours prior to initiation of apixaban therapy postoperatively.

Edoxaban

Edoxaban is also is an oral highly selective reversible fXa inhibitor. Following oral ingestion, maximum plasma levels are reached within 1-2 h. The elimination half-life after oral administration is 10-14 h in healthy patients. In the presence of mild, moderate and severe renal insufficiency, the total exposure to edoxaban is increased by 32%, 74%, and 72% resulting in an elimination half-life of 8.4, 9.45 and 16.9 h, respectively. There are no reports of epidural/spinal bleeding associated with a neuraxial anesthesia. There have been no reports of any neuraxial bleeding in association with neuraxial anesthesia, but the use of neuraxial anesthetic techniques in edoxaban-treated patients should be cautiously considered as there are no data.

A minimum of three days should elapse between discontinuation of apixaban and neuraxial block. Indwelling neuraxial catheters are contraindicated and should be removed six hours prior to initiation of edoxaban therapy postoperatively.

Table 1 Recommendations for Management of Patients Receiving Neuraxial Blockade and Anticoagulant Drugs

Warfarin	Discontinue chronic warfarin therapy 4–5 days before spinal procedure and evaluate INR. INR should be within the normal range at time of procedure to ensure adequate levels of all vitamin K-dependent factors. Postoperatively, daily INR assessment with catheter removal ideallyoccurring with INR< 1.5; monitor carefully for 1.5 < INR < 3.0
Antiplatelet medications	No contraindications with aspirin or other NSAIDs. Thienopyridine derivatives should be discontinued to allow complete recovery of platelet function (clopidogrel 5-7 days, ticlodipine 10 days, prasugrel 7-10 days, and ticagrelor 5-7 days) prior to procedure. GP IIb/IIIa inhibitors should be discontinued to allow recovery of platelet function prior to procedure (8 hours for tirofiban and eptifibatide, 24–48 hours for abciximab).
Thrombolytics/ fibrinolytics	There are no available data to suggest a safe interval between procedure and initiation or discontinuation of these medications. Follow fibrinogen level and observe for signs of neural compression.
LMWH	Delay procedure at least 12 hours from the last dose of thromboprophylaxis LMWH dose. For "treatment" dosing of LMWH, at least 24 hours should elapse prior to procedure. LMWH should not be administered within 24 hours after the procedure. Indwelling epidural catheters should be maintained only with once daily dosing of LMWH and strict avoidance of additional haemostasis altering medications, including NSAIDs. Post catheter removal, wait 4 hrs for subsequent LMWH dose.
Unfractionated SQ heparin	Delay needle/catheter placement 4-6 hours after last dose or document normal aPTT For higher dosing regimens, longer delays are needed. Also increase neurologic monitoring and cautiously co-administer antiplatelet medications.
Unfractionated IV heparin	Delay needle/catheter placement 2-4 hours after last dose, document normal aPTT. Heparin may be restarted 1 hour following procedure. Sustained heparinization with an indwelling neuraxial catheter associated with increased risk; monitor neurologic status aggressively.
Dabigatran	Discontinue 5 days prior to procedure; for shorter time periods, document normal TT. First postoperative dose 24 h after needle placement and 6 hours post catheter removal (whichever is later).
Rivaroxaban, Apixaban, and Edoxaban	Discontinue 3 days prior to procedure. First postoperative dose 24 h after needle placement and 6 hours post catheter removal (whichever is later).

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Antiplatelet Medications

Antiplatelet medications are seldom used as primary agents of thromboprophylaxis. However, many orthopedic patients report chronic use of one or more antiplatelet drugs. Although Vandermeulen et al (2) implicated antiplatelet therapy in 3 of the 61 cases of spinal hematoma occurring after spinal or epidural anesthesia, several large studies have demonstrated the relative safety of neuraxial blockade in both obstetric, surgical and pain clinic patients receiving these medications (22-24). In a prospective study involving 1000 patients, Horlocker et al (24) reported that preoperative antiplatelet therapy did not increase the incidence of blood present at the time of needle/catheter placement *or* removal, suggesting that trauma incurred during needle or catheter placement is neither increased nor sustained by these medications. The clinician should be aware of the possible increased risk of spinal hematoma in patients receiving antiplatelet medications who undergo subsequent heparinization (11). Ticlopidine and clopidogrel are also platelet aggregation inhibitors. These agents interfere with platelet-fibrinogen binding and subsequent platelet-platelet interactions. The effect is irreversible for the life of the platelet. Platelet dysfunction is present for 5-7 days after discontinuation of clopidogrel and 10-14 days with ticlopidine.

Prasugrel is a new thienopyridine that inhibits platelets more rapidly, more consistently, and to a greater extent than do standard and higher doses of clopidogrel. In the United States, the only labeled indication is for acute coronary syndrome in patients intended to undergo percutaneous coronary intervention. After a single oral dose, 50% of platelets are irreversibly inhibited, with maximum effect two hours after administration. Platelet aggregation normalizes in 7-9 days after discontinuation of therapy. The labeling recommends that the drug "be discontinued at least 7 days prior to any surgery". Platelet glycoprotein IIb/IIIa receptor antagonists, including abciximab (Reopro ®), eptifibatide (Integrilin ®) and tirofiban (Aggrastat ®), inhibit platelet aggregation by interfering with platelet-fibrinogen binding and subsequent platelet-platelet interactions. Time to normal platelet aggregation following discontinuation of therapy ranges from eight hours (eptifibatide, tirofiban) to 48 hours (abciximab). Increased perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving ticlopidine, clopidogrel and glycoprotein IIb/IIIa antagonists warrants concern regarding the risk of anesthesia-related hemorrhagic complications.

Anesthetic Management of the Anticoagulated Patient

The decision to perform spinal or epidural anesthesia/analgesia and the timing of catheter removal in a patient receiving thromboprophylaxis should be made on an individual basis, weighing the small, though definite risk of spinal hematoma with the benefits of regional anesthesia for a specific patient. Alternative anesthetic and analgesic techniques exist for patients considered to be at an unacceptable risk. The patient's coagulation status should be optimized at the time of spinal or epidural needle/catheter placement, and the level of anticoagulation must be carefully monitored during the period of epidural catheterization (Table 1). It is important to note that patients respond with variable sensitivities to anticoagulant medications. Indwelling catheters should not be removed in the presence of a significant coagulopathy, as this appears to significantly increase the risk of spinal hematoma (2,3). In addition, communication between clinicians involved in the perioperative management of patients receiving anticoagulants for thromboprophylaxis is essential in order to decrease the risk of serious hemorrhagic complications. The patient should be closely monitored in the perioperative period for signs of cord ischemia. If spinal hematoma is suspected, the treatment of choice is immediate decompressive laminectomy. Recovery is unlikely if surgery is postponed for more than 10-12 hours; less than 40% of the patients in the series by Vandermeulen et al. (2) had partial or good recovery of neurologic function.

Meningitis and Epidural Abscess

Bacterial infection of the central neuraxis may present as meningitis or cord compression secondary to abscess formation. Possible risk factors include underlying sepsis, diabetes, depressed immune status, steroid therapy, localized bacterial colonization or infection, and chronic catheter maintenance. Bacterial infection of the central neural axis may present as meningitis or cord compression secondary to abscess formation. The infectious source for meningitis and epidural abscess may result from distant colonization or localized infection with subsequent hematogenous spread and CNS invasion. The anesthetist may also transmit microorganisms *directly* into the CNS by needle/catheter contamination through a break in aseptic technique or passage through a contiguous infection. An indwelling neuraxial catheter, though aseptically sited, may be colonized with skin flora and consequently serve as a source for ascending infection to the epidural or intrathecal space.

Historically, the frequency of serious CNS infections such as arachnoiditis, meningitis, and abscess following spinal or epidural anesthesia was considered to be extremely low- cases were reported as individual cases or small series (25,26). However, recent epidemiologic series from Europe suggest that the frequency of infectious complications associated with neuraxial techniques is increasing (3,27). In a national study conducted from 1997 to 1998 in Denmark, Wang et al (28) reported the incidence of epidural abscess after epidural analgesia was 1:1930 catheters. Patients with epidural abscess had an extended duration of epidural catheterization (median 6 days, range 3-31 days). In addition, the majority of the patients with epidural abscess were immunocompromised. Often the diagnosis was delayed; the time to first symptom to confirmation of the diagnosis was a median of five days. *S. aureus* was isolated in 67% of patients. Patients without neurologic deficits were successfully treated with antibiotics, while those with deficits underwent surgical decompression, typically with only moderate neurologic recovery. It is difficult to determine why the frequency of symptomatic epidural abscess was so high in this series. Since perioperative antithrombotic therapy was involved in most cases, it is possible that the epidural abscesses were infected "micro" epidural hematomas, but this is not strongly supported by the diagnostic imaging studies and neurosurgical findings.

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In the series by Moen et al (3) there were 42 serious infectious complications. Epidural abscess occurred in 13 patients; nine (70%) were considered immunocompromised as a result of diabetes, steroid therapy, cancer or alcoholism. Six patients underwent epidural block for analgesia following trauma. The time from placement of the epidural catheter to first symptoms ranged from 2 days to 5 weeks (median 5 days). Although prevailing symptoms were fever and sever backache, five developed neurologic deficits. All seven positive cultures isolated *S. aureus*. Overall neurologic recovery was complete in 7 of 12 patients. However, four of the five patients with neurologic symptoms did not recover. Meningitis was reported in 29 patients for an overall incidence of 1:53,000. A documented perforation of the dura (intentional or accidental) occurred in 25 of 29 cases. In the 12 patients in whom positive cultures were obtained, alpha-hemolytic streptococci were isolated in 11 patients and *S. aureus* in one.

These large epidemiologic studies represent new and unexpected findings regarding the demographics, frequency, etiology and prognosis of infectious complications following neuraxial anesthesia. Epidural abscess is most likely to occur in immunocompromised patients with prolonged durations of epidural catheterization. The most common causative organism is *S. aureus*, which suggests the colonization and subsequent infection from normal skin flora as the pathogenesis. Delays in diagnosis and treatment result in poor neurologic recovery, despite surgical decompression. Conversely, patients who develop meningitis following neuraxial blockade typically are healthy and have undergone uneventful spinal anesthesia. Furthermore, the series by Moen et al (3) validates the findings of individual case reports of meningitis after spinal anesthesia- the source of the pathogen is mostly likely to be the upper airway of the proceduralist. While the frequency of serious infectious complications is much higher than reported previously, the results may be due to differences in reporting and/or clinical practice (asepsis, perioperative antibiotic therapy, duration of epidural catheterization)

Meningitis after Dural Puncture and Neuraxial Anesthesia

Dural puncture has long been considered a risk factor in the pathogenesis of meningitis. Exactly how bacteria cross from the blood stream into the spinal fluid is unknown. The presumed mechanisms include introduction of blood into the intrathecal space during needle placement and disruption of the the blood-brain barrier. Initial investigations were performed over 80 years ago (29). Subsequent clinical studies reported conflicting results regarding the causal relationship between dural puncture during bacteremia and meningitis However, the protective effect of antibiotic administration prior to lumbar puncture was suggested (30,31).

Epidural Abscess after Epidural Anesthesia

Several relevant studies have specifically examined the risk of epidural abscess in patients receiving epidural anesthesia and/or analgesia. Bader et al. (32) investigated the use of regional anesthesia in women with chorioamnionitis. Three hundred nineteen women were identified from a total of 10,047 deliveries. Of the 319 women, 100 had blood cultures taken on the day of delivery. Eight of these had blood cultures consistent with bacteremia. Two hundred ninety-three of the 319 patients received a regional anesthetic, in 43 patients antibiotics were administered prior to needle or catheter placement. No patient in the study, including those with documented bacteremias, had infectious complications. In addition, mean temperatures and leukocyte counts in patients who received blood cultures showed no significant differences between bacteremic and nonbacteremic groups. These authors continue to administer spinal and epidural anesthesia in patients with suspected chorioamnionitis because the potential benefits of regional anesthesia outweigh the theoretical risk of infectious complications.

The safety of epidural analgesia in 75 patients admitted to the intensive care unit was prospectively evaluated by Darchy et al (33). There were no epidural abscesses. However, five of nine patients with positive cultures of the catheter insertion site also had positive catheter tip cultures (epidural catheter infection); *Staphylococcus epidermidis* was the most commonly cultured microorganism. Local infection of the catheter site was treated with catheter removal. Concomitant infection at other sites, antibiotic prophylaxis, and duration of epidural analgesia were not risk factors for epidural-analgesia related infections. The authors noted that the presence of both erythema and local discharge is a strong predictor of local and epidural catheter infection.

Epidural anesthesia and analgesia in a patient with a known systemic or localized infection remains controversial. Jakobsen et al (34) retrospectively reviewed the records of 69 patients with abscesses or wound infections who underwent epidural catheter placement for surgical debridement over a seven year-period. Several patients had more than one catheter inserted. Catheters were left indwelling for a mean of nine days. On 12 occasions (eight patients) the catheter was removed because of local infection. None of the patients demonstrated signs or symptoms of neuraxial infection. The authors concluded that epidural anesthesia is relatively safe for patients requiring repeated surgical treatment of localized infection. In contrast, Bengtsson et al. (35) reported three epidural catheter-related infections in patients with cutaneous wounds over a four year-period. All patients were treated with antibiotic therapy; one patient underwent transcutaneous drainage of an epidural abscess. It is difficult to determine the actual risk of epidural abscess in patients with chronic localized infections who undergo epidural catheter placement due to the small number of patients studied and the rarity of this complication. Therefore, the clinician must maintain vigilance in neurologic monitoring to assure early recognition and treatment.

Neuraxial Blockade in the Immunocompromised Patient

Large series have demonstrated that patients with immunodeficiencies are at increased risk for infectious complications compared to those with intact immune function. However, there are few investigations which have evaluated the frequency of meningitis or epidural abscess within a specific immunodeficient population (3,27,36).

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Table 2. Infectious Complications following Neuraxial Anesthesia in the Immunocompromised Patient

- The attenuated inflammatory response within the immunocompromised patient may diminish the clinical signs and symptoms often associated with infection and result in a delay in diagnosis and treatment.
- The range of microorganisms causing invasive infection in the immunocompromised host is much broader than that affecting the general population and includes atypical and opportunistic pathogens.
- Early and effective therapy is paramount in optimizing neurologic outcome- consultation with an infectious disease specialist is advised.
- Prolonged antibiotic therapy (weeks-months) is often required because of persistent and immunologic deficiencies.
- Since eradication of infection is difficult once established, prevention of infection is paramount in caring for immunocompromised patients.

From: Horlocker, et al 2006, with permission

Herpes Simplex Virus

Herpes simplex virus type 2 (HSV-2) infection is an incurable, recurrent disease characterized by asymptomatic periods alternating with recrudescence of genital lesions. The primary infection is associated with viremia and can be accompanied by a variety of symptoms, including fever, headache, and rarely aseptic meningitis. In contrast, recurrent or secondary infections present as genital lesions without evidence of viremia. When obstetric patients present for delivery with evidence of active HSV-2 infection, cesarean section is recommended to avoid exposing the neonate to the virus during vaginal delivery. Neuraxial block in these patients is controversial because of the theoretical potential of introducing the virus into the CNS. However, there are little data to support these concerns.

Human Immunodeficiency Virus

The risk of performing neuraxial block in patients infected with human immunodeficiency virus (HIV) is largely undetermined. Approximately 40% of patients with the diagnosis of acquired immune deficiency syndrome (AIDS) have clinical signs of neuropathy, and 70% to 80% have neuropathic changes present at autopsy. Since the virus infects the CNS early in the disease, it is unlikely that neuraxial block would result in new CNS transmission. However, the neurologic symptoms associated with HIV infection such as aseptic meningitis, headache, and polyneuropathy would be indistinguishable from those related to regional technique. Hughes et al. (37) reported safe administration of neuraxial block to 18 HIV-infected parturients. The patients studied showed no postpartum change in immune, infectious or neurologic status. Avidan et al. (38) and Bremerich et al.(39) also reported a low complication rate for parturients with HIV infection on antiretroviral therapy who underwent spinal anesthesia. However, in all three series (with a combined total of 117 patients), the patients were relatively healthy and in the early stage of their disease. The effects of anesthesia on patients with more advanced disease are unreported.

Aseptic Technique

Although previous publications have repeatedly recommended meticulous aseptic technique, only recently have standards for asepsis during the performance of regional anesthetic procedures been defined (40) (Table 3). *Handwashing* remains the most crucial component of asepsis; gloves should be regarded as a supplement to- not a replacement of- handwashing (41). The use of an antimicrobial soap reduces bacterial growth and reduces the risk of bacteria being released into the operative field should gloves become torn or punctured during the procedure. An alcohol-based antiseptic provides the maximum degree of antimicrobial activity and duration. Prior to washing, all jewelry (rings, watches, etc) should be removed; higher microbial counts have been noted in health care workers who do not routinely remove these items before handwashing. *Sterile gloves* protect not only patients from contamination, but also health care workers from blood-borne pathogens and are required by the Occupational Safety and Health Administration (40). Glove leaks are more likely to occur with vinyl compared to latex gloves (24% vs. 2), with contamination of the health care workers' hands noted following the leaks in 23% of cases (42). Conversely, the use of *gowns* does not further reduce the likelihood of cross contamination in an intensive care unit setting compared to gloves alone. At this time, there are insufficient data to make recommendations regarding routine use for single injection or temporary neuraxial/peripheral catheter placement. However, placement of an *indwelling* permanent device, such as a spinal cord stimulator, warrants the same asepsis as a surgical procedure, including gowns, hats, and antibiotic pretreatment (40,43).

Surgical *masks*, initially considered a barrier to protect the proceduralist from patient secretions and blood, are now required by the Center for Disease Control due to the increasing number of cases of post spinal meningitis, many of which result from contamination of the epidural or intrathecal space with pathogens from the operator's buccal mucosa (3,44-47). A recent ASA Practice Advisory also recommends the wearing of masks (48).

Antiseptic Solutions

Controversy still exists regarding the most appropriate and safe antiseptic solution for patients undergoing neuraxial and peripheral techniques. Povidone iodine and chlorhexidine gluconate (with or without the addition of isopropyl alcohol) have been most extensively studied (49,50). In nearly all clinical investigations, the bactericidal effect of chlorhexidine was more rapid and more effective (extending its effect hours following its application) than povidone iodine. The addition of isopropyl alcohol accelerates these effects. Chlorhexidine is effective against nearly all nosocomial yeasts, and bacteria (gram-positive and gram-negative); resistance is extremely rare. It also remains effective in the presence of organic compounds, such as blood. It must be noted that chlorhexidine-alcohol labeling contains a warning against use as a skin preparation prior to lumbar puncture. The FDA

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has not formally approved chlorhexidine for skin preparation prior to lumbar puncture because of the lack of animal and clinical studies examining the neurotoxic potential of chlorhexidine, *not* due to a number of reported cases of nerve injury. Indeed, it is important to note that there are no cases of neurotoxicity with *either* chlorhexidine or alcohol (40). Therefore, as a result of its superior effect, alcohol-based chlorhexidine solutions are considered the antiseptic of choice for skin preparation before any regional anesthetic procedure (40).

Anesthetic Management of the Infected or Febrile Patient

In summary, several clinical and laboratory studies have suggested an association between dural puncture during bacteremia and meningitis. The data are not equivocal, however. The clinical studies are limited to pediatric patients who are historically at high-risk for meningitis. Many of the original animal studies utilized bacterial counts that were far in excess of those noted in humans in early sepsis, making CNS contamination more likely. Despite these conflicting results, it is generally recommended that except in the most extraordinary circumstances, central neuronal block should not be performed in patients with untreated bacteremia. Patients with evidence of systemic infection may safely undergo spinal anesthesia, if antibiotic therapy is initiated *prior* to dural puncture, and the patient has demonstrated a response to therapy, such as a decrease in fever. Placement of an indwelling epidural (or intrathecal) catheter in this group of patients remains controversial; patients should be carefully selected and monitored for evidence of epidural infection (51).

The attenuated inflammatory response within the immunocompromised patient, may diminish the clinical signs and symptoms often associated with infection. Likewise, the range of microorganisms causing invasive infection in the immunocompromised host is much broader than that affecting the general population and includes atypical and opportunistic pathogens. Consultation with an infectious disease specialist is advised to facilitate initiation of early and effective therapy (36). Meticulous aseptic technique, including hand-washing with chlorhexidine, wearing of mask and sterile gloves by the proceduralist, skin asepsis with chlorhexidine and antibiotic pretreatment for the placement of permanent devices, is critical to the prevention of infectious complications related to regional anesthesia (40).

Table 3. Variables That May Influence Infectious Complications
Site of catheter placement (thoracic vs. lumbar vs. caudal)
Choice of antiseptic and technique of application
Choice of barrier protection (masks, gloves, gowns)
Timing and selection of perioperative antibiotics
Duration of neuraxial or peripheral catheterization
Use of bacterial filters
Dressing type(s) (transparent vs. dry gauze dressing; use of antiseptic dressings)
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All patients with an established local or systemic infection should be considered at risk for developing infection of the CNS. A delay in diagnosis and treatment of even a few hours significantly worsens neurologic outcome. Bacterial meningitis is a medical emergency. Mortality is approximately 30%, even with antibiotic therapy. The clinical course of epidural abscess progresses from spinal ache and root pain, to weakness (including bowel and bladder symptoms) and eventually paralysis. The initial back pain and radicular symptoms may remain stable for hours to weeks. However, the onset of weakness often progresses to complete paralysis within 24 hours. Although the diagnosis was historically made with myelogram, radiologic examination such as CT scan, or more preferably MRI, is currently recommended. A combination of antibiotics and surgical drainage remains the treatment of choice. As with spinal hematoma, neurologic recovery is dependent on the duration of the deficit and the severity of neurologic impairment before treatment.

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Pollution and Patient Safety: Balancing Saving Lives With Protecting Public Health

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Introduction

Environmental health is critically linked to human health. The U.S. health care sector accounts for 18% of national GDP and is highly interconnected with industrial activities that significantly contribute to national emissions to air, water, and land. In a 2016, Eckelman and Sherman estimated that the U.S. health care sector contributed 9% of the nation's greenhouse gas (GHG) emissions, and 9% of criteria air pollutants.[1] These health sector emissions stem from the entire life cycle of products and services ("cradle to grave,") including direct care and purchases, as well as indirect supply chain activities. The pollution-related disease burden was estimated at 614,000 disability adjust life years (DALYs) lost per year due to health sector activities.[1,2] This is commensurate with preventable harm due to medical errors as first reported by the Institute of Medicine in *To Err is Human*—the landmark report that sparked the patient safety movement.[1] Health care pollution is a hidden patient safety issue that can no longer be ignored. If the current trajectory of modern medicine is left unmitigated, the costs of "business as usual" will contribute to the worsening of public health and increase the demand for health services. Anesthesiology is a resource intense specialty with great opportunity for, and obligation to, pollution prevention to make health care safer for patients and public health.

Climate change. The World Health Organization (WHO) named climate change the defining issue for health systems in the 21st century.[3] The United Nations Framework Convention on Climate Change recognizes six disease categories linked to climate change: cardiovascular disease, asthma and respiratory disease, infectious disease, compromised food and water security, increased weather disturbances, and threat to blood supply through changing vectors for blood borne illnesses.[4] The WHO calls upon physicians to use their authority to lead mitigation, and to protect public health.[3] While greenhouse gasses (GHGs) are a critical category of emissions and climate change may have severe, negative impacts on human health and society,[5] there are several other drivers of environmental and public harm important to consider.

Chemical pollution. Each day the U.S. produces or imports tens of billions of pounds of chemicals, and the health care sector is one of the largest chemical purchasers.[6] Pharmaceutical and industrial chemical pollutants have become widespread in the environment and food chains, and are also found in humans. Unlike pharmaceuticals, current regulation of industrial chemicals is covered under Toxic Substance Control Act of 1976 (TSCA) that does not require safety testing in humans prior to introduction into the marketplace. The Center for Disease Control (CDC) only recently began providing an ongoing assessment of the exposure of the U.S. population to environmental chemicals through biomonitoring. Of the 100,000 industrial chemicals in the marketplace, only a few hundred are currently looked for in humans.[7] Of those measured, hundreds of pollutants can be routinely found in any human being. Contamination by synthetic chemicals has been observed in amniotic fluid and humans as early as birth, with an average of 200 industrial chemicals identified (nearly all those looked for) in the umbilical cord blood of babies born in the U.S.[8] Many of these substances are known carcinogens, teratogens, neurodevelopmental toxicants, and endocrine disruptors.[8-10]

Quantifying environmental and human health impacts from pollution: Life Cycle Assessment (LCA)

To guide mitigation strategies in patient care, clinical pollution requires quantification. Life cycle assessment (LCA) is an internationally accepted scientific method to quantify emissions and multiple environmental and public health impacts of a product or process over its entire life span. The total life cycle ("cradle to grave") includes natural resource extraction, device manufacturing, transport, use/re-use, and disposal. In this way LCA accounts for direct and indirect emissions, including upstream and downstream impacts. Guidance documents have been promulgated by the US Environmental Protection Agency (EPA), Society for Environmental Toxicologists and Chemists (SETAC), and standards by the International Organization of Standardization (ISO) 14040 series.[11-14]

LCA illuminates particular processes or substances that contribute significantly to impacts, and enables comparison of related products along environmental dimensions. Several standard LCA impact categories exist, including carbon dioxide (CO_2) emissions, contributing to climate change; stratospheric ozone depletion, allowing higher levels of short-wave ultraviolet light through the atmosphere and increasing health risks of skin cancer; respiratory disease from inhalation of primary and secondary particulate matter (PM) and ground-level ozone (smog) stemming from emissions of criteria air pollutants; cancer and non-cancer disease through inhalation and ingestion routes of

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chemical exposure; environmental effects of acidification (from formation and deposition of acid rain) and eutrophication (algae blooms from excess nutrients) in soils and surface waters; and ecotoxicity that reflects the toxic burden of all emitted chemicals to aquatic organisms. Comparisons between items or processes may indicate relative advantages for one outcome that may be contrary to other outcomes, and prioritization of risks and benefits must be weighted.

LCA is commonly employed in sectors from chemicals to consumer products, to compare options and identify opportunities for design and utilization improvements that reduce pollution while maintaining or improving performance. Applications to health care are beginning to gain foothold to guide pollution prevention strategies. LCA applications to health care so far include hemodialysis practices[15] and non-surgical management approaches to acute myocardial infarction management.[16] LCA applications to anesthetic drugs and devices are also appearing, and can already begin to aid anesthesiologists in decision-making.[17-20] In 2012, the U.K. National Health Service launched the Greenhouse Gas Protocol Product Life Cycle Accounting and Reporting Standard project, to encompass the pharmaceutical and medical device sector.[21] The goal is for all drugs and devices to undergo LCA.

Inhaled anesthetics and atmospheric pollution

Greenhouse gases. Inhaled anesthetics are themselves potent greenhouse gases (GHGs). Inhaled anesthetics alone accounted for 5% of the U.K. hospital carbon footprint, and 2.5% of the entire health sector greenhouse gas emissions,[22] and thus they are an important target for mitigation efforts. These inhaled drugs undergo very little in vivo metabolism, and are exhaled virtually unconsumed and unchanged into anesthesia machines or the indoor atmosphere. Exhaled agents are "scavenged" by anesthesia machines (vacuumed out to protect against occupational exposure) and then vented directly into the atmosphere off of building rooftops as medical waste gases. All exhaled anesthetic gases remain for a long time in the troposphere—the lowest layer of the atmosphere in which the greenhouse effect occurs-- sevoflurane 1.1 years, isoflurane 3.2 years, desflurane 14 years, and nitrous oxide 114 years. Global Warming Potential (GWP) is a measure of ability to trap heat, and is determined by the atmospheric lifetime of a gas combined with its infrared absorption property. Carbon dioxide (CO_2) serves as the reference point, with a GWP = 1. Other substances are converted into CO_2 equivalents (CO_{2e}), enabling comparisons on a kilogram per kilogram basis over a given time period. A GWP 100-year (GWP_{100}) time frame is commonly reported in the international community. GWP_{100} for anesthetic gases include: sevoflurane 130, isoflurane 510, desflurane 2540, nitrous oxide 298.[23] Desflurane stands out with the highest global warming potential, followed by isoflurane, sevoflurane and nitrous oxide. However, these drugs must be contextualized to clinical practice for meaningful comparisons.

In addition to global warming potentials, differences in drug potency and fresh gas flow rates must be considered. When a steady state hourly amount of anesthetic necessary for 1 minimum alveolar concentration (MAC) at 2 LPM for sevoflurane, and 1 LPM for desflurane and isoflurane is weighted by the GWP, the clinically relevant quantities of each anesthetic can then be compared.[24] On a per-MAC-hour basis, the GHG impact of desflurane is more than 20 times higher than isoflurane and sevoflurane. Because of nitrous oxide's low potency and therefore high concentration requirements, and because of its long atmospheric lifetime, its GHG impacts are similar to desflurane on a per-MAC-hour basis.

Beyond the direct greenhouse gas effects of inhaled agents, life cycle assessment has been applied to look at the overall impacts of all of the inputs including manufacturing, transportation and use, as well as disposal of these drugs. LCA further permits conversion and comparison of impacts of inhaled and non-inhaled general anesthetic drugs such as propofol. **Total life cycle assessment demonstrated that desflurane (at 1 L/Min) accounts for the largest life cycle GHG impact among the common anesthetics: 15 times that of isoflurane (at 1 L/Min) and 20 times that of sevoflurane (at 2 L/Min) on a per MAC-hour basis when administered in an O2/air. Nitrous oxide GHG impacts are comparable to desflurane, and utilizing it as a carrier dramatically worsens all of the drug profiles. Because all of the inhaled drugs are potent GHGs in and of themselves, the waste phase dominated the life cycle impacts. By comparison, the total life cycle GHG effects of propofol are quite small, nearly 4 orders of magnitude lower than those of desflurane or nitrous oxide.** Unlike the inhaled drugs where the waste phase dominates, the GHG impacts of propofol primarily stem from the utilization phase from electricity requirements for pump delivery systems.[18]

Inhaled anesthetics and the OR footprint. Researchers at the University of Pittsburgh Medical Center (UPMC) evaluated the life cycle GHG emissions of 4 different surgical approaches to the hysterectomy at Magee-Womens

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Hospital.[25] The average GHG emissions of 62 hysterectomies varied based on surgery approach. Abdominal and vaginal hysterectomies showed similar trends, with average GHG emissions approximately half as much as the laparoscopic approach and one third as much as the robotic approach, predominantly owing to less disposable instruments and linens. The average impacts of anesthetic gases dominates these results, accounting for 67-73% of the GHG impacts for abdominal and vaginal approaches, and 30% of laparoscopic and robotic approaches. Inhaled anesthetics dominated the surgical footprint.

National contributions of inhaled anesthetics. The U.K. Sustainability Development Unit reported that their health sector is responsible for 3-4% of their national greenhouse gases.[26] Inhaled anesthetics accounted for 5% of their hospitals' carbon footprint, equivalent to half the emissions from gas used to heat buildings and water, and 2.5% of their entire health sector greenhouse gas emissions.[22] The U.S. health sector contributes an estimated 10% of national greenhouse gases.[1] In a very small study U.S. impacts from inhaled anesthetics were estimated at 5.6 MMT or 1% of national GHGs (excluding dental medicine)[27] All studies exclude laboratory and veterinary medicine.

Global contributions of inhaled anesthetics. Sulbaek-Anderson, at al., estimated total worldwide contribution of inhaled anesthetics to global warming at 0.01%.[28] This estimate is commonly cited as a reason to neglect pollution prevention by anesthesiologists, however this is problematic. This estimate is extrapolated from only one U.S. institution's anesthetic practices, and this institution uses virtually no desflurane. Researchers neglected to include nitrous oxide in their calculations, and reported an average of 17kg CO_{2e} per anesthetic. However, institutions that utilize some desflurane and account for nitrous oxide have reported an average of 175-220kg CO_{2e} per anesthetic.[25,27] Further still, Sulbaek-Anderson neglected to include dental, veterinary and laboratory medicine, and other life cycle phase inputs. They therefore likely underestimate the total worldwide contribution of inhaled anesthetics, possibly as much as an order of magnitude.[27]

Vollmer, et al., recently reported actual measures of atmospheric concentrations of volatile anesthetics.[29] Nitrous oxide was excluded due to its multiple sources in addition to health care. Researchers sampled different urban areas and the pristine Antarctic environment over the past decade, and detected "a rapid accumulation and ubiquitous presence of isoflurane, desflurane, and sevoflurane in the global atmosphere" to mean mole fractions in 2014 of 0.097 ppt, 0.30 ppt, and 0.13 ppt (parts per trillion,) respectively. The calculated global combined release to the atmosphere is 3.1 ± 0.6 MMT (million metric tons) CO_{2e} in 2014 of which ≈80% stemmed from desflurane. In all, emissions of those volatile anesthetic gases in 2014 amounted to an estimated 2.5 to 3.7 MMT of CO_{2e}. That's the same as the emissions of between 526,316 and 778,947 passenger vehicles.

Ozone depletion. Separate from greenhouse gas effects, nitrous oxide, and to a lesser extent halothane, are directly destructive to the ozone layer. The ozone layer exists in the stratospheric layer of the atmosphere and serves to protect the Earth and its inhabitants from ultraviolet radiation. National Oceanic and Atmospheric Administration scientists declared nitrous oxide emissions the single most important threat to the ozone layer. Anthropogenic N_2O emissions currently represent the largest contribution to ozone-depleting gas emissions.[30] Most N_2O emissions come from fertilizer for industrial agriculture. However, medical use appears to be gaining in popularity, particularly for routine analgesia for "natural" childbirth. In birthing suites, N_2O is likely to be delivered at high fresh gas flows and without consistent utilization of scavenging systems.

Solutions: Inhaled anesthetic pollution prevention

Lowest fresh gas flows (FGFs). **Conscious effort should be made to minimize fresh gas flows**.[31,32] After induction and before intubation, turning off FGFs as opposed to the vaporizer prevents waste and flushing of the system into the indoor environment. Avoiding unnecessary flushing of the circuit prevents excess occupational exposure, and also maintains drug concentration in the system. Attention should be made to turning FGFs down immediately after induction is complete. Lowest maintenance flows should be chosen: 1 LPM sevoflurane up to 2-MAC-hours, then 2 LPM in the U.S.; for desflurane and isoflurane, less than 1 LPM can be maintained so long as patient oxygen requirements are met, leaks in the system adjusted for, and bellows fill. Very low fresh gas flows serve well when entering the emergence phase, to permit dialing down of vaporizer concentration while creating a nearly closed circuit to finesse timing of wake up. High fresh gas flows for emergence are ideally reserved until the vaporizers are turned off and wake up is desired. **High FGFs ought to be conscientiously reserved for quick changes in anesthetic depth only.**

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Anesthetic choice. **Clinical circumstances dictate the indicated anesthetic. Where choices exist in how to safely administer care, pollution prevention ought to weigh into clinical decision-making to protect public health.**[33] Environmental research suggests that desflurane and nitrous oxide should be reserved for only those cases where they could reduce morbidity and mortality over other drug/drug combinations. These inhaled anesthetics have lower solubility and therefore faster emergence **for short cases** compared to drugs with greater solubility.[34] However, with a little practice, the timing of emergence for any drug--even those with greater solubility--can be mastered. Nitrous oxide should not be used simply to spare volatile anesthetics, such as during the emergence phase. N_2O for routine labor analgesia ought to be reconsidered where alternatives exist.[24,32] When clinically appropriate, IV anesthesia and regional anesthesia techniques may provide the most environmentally sound approach.[18]

Waste Anesthetic Gas (WAG) capture vs. destruction. Waste anesthetic gas capturing technologies are readily available, some at a modest cost. These systems prevent WAG release into the environment, and reclaim the drug for potential re-separation/re-use. One type of WAG capturing can be built or retrofitted into the OR exhaust systems. It is activated only when the patient exhales, as opposed to standard continuous scavenging systems, and thereby saves considerable energy use.[35] Another system requires installation of a canister into existing scavenging circuits and then adsorbs the volatile anesthetic drugs.[36] Neither system captures N_2O. The Food and Drug Administration is presently considering approval for reprocessed volatile drugs, which could also find applications in laboratory and veterinary medicine. Technologies using photochemical air purification for N2O destruction are becoming more common, e.g. in Sweden and Japan; however, they are not currently being used to destroy volatile waste anesthetic.

Pharmaceutical pollution

In the U.K., the National Health Service (NHS) reported 22% of its health sector greenhouse gas footprint stemmed from pharmaceuticals[26] (excluding waste anesthetic gas.[22]) Manufacturing contributed the greatest amount of all the life cycle phases, suggesting the importance of improved efficiency in both industry and clinic practices.

In addition to GHGs, chemical pollution is concerning. The majority of all non-inhaled medications are secreted in the urine, either unchanged or as metabolites. Medications are often adapted to resist biodegradation and can therefore remain in the environment for a long time. Municipal wastewater treatment currently does not process drugs. Pharmaceuticals leach into the environment with higher levels detected near sewage facilities, manufacturing plants, and hospitals. Many medications have been found in drinking water, which is a warning sign that current handling is inadequate. While these quantities typically are sub-therapeutic, small amounts and unknown synergies may result in developmental disorders where timing of exposure is critical. Ecosystem disruption has been documented.[37,38]

Solutions: pharmaceutical pollution prevention

Drug choices and manufacturing. Beyond the general anesthetic drugs noted above, there is currently no information available to health care providers that adequately compares or standardizes environmental harm of pharmaceuticals. The environmental department of Stockholm County Council[39] initiated an environmental hazard assessment in 2003, aimed at reducing pharmaceutical residues in the ground, water, and air. A hazard ‘‘PBT’’ Index for substances emerged that newly includes persistence (P) and bioaccumulation (B), in addition to traditional consideration for toxicity (T). The index rates pharmaceuticals on a 0 to 9 point scale based equally on these 3 factors. When choices exist, the PBT index is intended to aid clinicians in giving priority to pharmaceuticals that are least harmful to the environment. Anesthesia drugs have only been partially indexed at this time. In 2012, the U.K. National Health Service launched the Greenhouse Gas Protocol Product Life Cycle Accounting and Reporting Standard project, to encompass the pharmaceutical and medical device sector.[21] The NHS project in the near future will aid clinicians, and importantly will direct industry towards environmentally safer practices and innovation.

Reduce pharmaceutical waste. In addition to selecting and developing low-impact pharmaceuticals, it is critical to reduce pharmaceutical waste. The **use of prepackaged drug syringes** is gaining in popularity to increase shelf life, particularly to decrease waste during critical shortages. Prepackaged syringes are widely available for purchase or can be prepared in hospital pharmacies. It is essential for pharmacy to **purchase smallest available vials**. Single-use vials that are too large for a single patient entice drug splitting by anesthesia staff, despite regulations against such practice to prevent cross contamination**. It is therefore a patient safety issue to utilize pharmacy to divide doses.** Beyond pre-filled syringes, **clinicians ought to always select smallest vials possible.** Effort should be made to predict length of cases, level of stimulation, and patient tolerance to aid in estimating drug requirements and best

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vial size selection. **If the most appropriate size vial is not conveniently located, effort should be made to contact pharmacy management to address systems improvement.**

Proper pharmaceutical waste disposal. **Every effort should be made to avoid wasting drugs into wastewater, or into regular trash headed for landfill.** For narcotic waste, there is a critical goal is to render waste immediately un-reclaimable, to prevent diversion. This is achieved in many states through use of solidifiers in disposal containers and/or use sharps containers. Some states or facilities dictate opioid wasting down the drain, however it is possible to work with and educate regulators and come to agree to institute solidifiers and reduce wastewater pollution. Some facilities have begun to classify propofol as a controlled substance, and subsequently waste it down the sink. Safest disposal of propofol is through incineration, either after wasting into the sharps container and/or into a solidifier to achieve compliance with non-reclaimability. **Propofol is toxic to ecosystems and should not be discarded to wastewater or to regular trash.**

Reusable vs. Single-Use Disposable (SUD) medical devices

Criteria for the selection and purchase of medical devices typically include safety for patients and staff, efficacy and ease of use, and purchase and handling costs. On the basis of such criteria, single-use disposable (SUD) medical devices are increasingly supplanting reusable devices in the U.S. and elsewhere[7]. In the U.K., 8% of the national health sector greenhouse gas footprint stems from medical devices.[26] While a parallel study does not exist in the U.S., there appears to be a greater reliance upon and faster rate of adoption of single-use disposable (SUD) products than the U.K. The increase in disposables is largely attributed to infection prevention, however without much supporting evidence of superiority over proper cleaning of reusable devices.[17,40,41] **U.S. hospitals now throw away 5.9 million tons of hospital waste per year.[25]**

Problems with plastic. Plastic is highly resistant to degradation, and can last hundreds of years in the environment. Incinerated plastic produces many harmful chemicals such as heavy metals, air pollutants, and potent carcinogens including dioxin. In 1996, the US EPA declared medical waste incineration the number one source of dioxin contamination in the atmosphere. This declaration lead to a Memorandum of Understanding between the U.S. EPA and the American Hospitals Association (ASA) resulting in the closure of the majority of medical incinerators from 5000 in 1995 to less than 100 in 2008.[6] The majority of medical waste is now treated and sent to landfills, however this trend is now reversing as landfills are maxing out and "waste-to-energy" incineration is on the rise—a modest improvement over traditional incineration. Hazardous waste is still incinerated making it a prime target for waste reduction strategies. **Proper attention to correct waste segregation is essential to minimize unnecessary incineration, save money and prevent pollution.**

Polyvinyl chloride (PVC) is the most commonly used polymer in plastic hospital devices. The plasticizer di-ethyl-hexyl phthalate (DEHP) is routinely added to impart flexibility to PVC-based products, and many medical devices such as IV bags and tubing, and LMAs and ETTs contain up to 40% DEHP by weight. DEHP is lipid soluble and leaches out of PVC, and urinary metabolites are measurable. The EPA classifies DEHP as a probable carcinogen, and as a possible endocrine disrupter.[42,43] Evidence of reproductive and developmental toxicant effects from DEHP led the FDA to issue an advisory in 2002 and recommend alternatives for patients deemed at high risk, namely infants, toddlers, and pregnant and lactating women. The AMA urges hospitals and health systems to reduce their use of PVC products in general, and especially those containing DEHP.[44]

Solutions: solid waste stream diversion: reusing, reprocessing, and recycling

Reusables vs. disposables. Purchase and maintenance costs for disposable devices are typically perceived to be less than for reusables, yet in reality expenses are typically spread across multiple cost centers making comprehensive assessment challenging. Life cycle assessment includes manufacturing, materials, labor, and energy and water use on the front end and disposal labor, energy, landfill costs, and environmental and human health impact on the back end. Economic and environmental costs often favor reusable equipment.[21,41]

Laryngeal mask airways (LMAs) provide a good anesthesia example. Although reusable LMAs can be adequately cleaned and have not been noted to transmit disease, studies have shown that a biofilm can remains after cleaning which is concerning to some. Further, the purchase of disposable LMAs is believed less expensive. A recent LCA comparing reusable and disposable LMAs found that at Yale-New Haven Medical Center, reusables were environmentally preferable to disposables if at least 10 uses were achieved. Reusables were actually cheaper if the manufacturer recommended lifetime of 40 uses could be achieved. Certain practices would further reduce the

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environmental impacts of reusable LMAs, such as simply autoclaving full loads of devices as opposed to partial loads. For both environmental and economic considerations, management and operating procedures should be put in place to ensure that reusable LMAs are not accidentally discarded prematurely. These benefits must be weighed against concerns regarding transmission of infection, though routine use of disposables appears unwarranted.[17]

Third-party reprocessing of single-use devices. Another option that can lower environmental impact of disposable items is the reprocessing of single-use items through a third-party vendor. Many medical devices sold as ''single use,'' are designated as such only by the manufacturer, and not the FDA. This includes many surgical instruments, and anesthesia items such as pulse oximeter probes, blood pressure cuffs, and sequential compression devices. Several companies now reprocess these used equipment items (Renu, Ascent, and Nellcor for example). Equipment is collected, cleaned, tested to insure performance mandated by the FDA,[17,40,41,45] then resterilized and packaged. Unlike new items that are sample batch tested, every reprocessed device is tested, and device failure rate is no different between them.[46] In addition to waste stream diversion, reprocessed items may be sold back to hospitals with as much as a 40% discount. Surgical equipment such as laparoscopic trochars is routinely reprocessed, and anesthesia equipment such as pulse oximeter probes, blood pressure cuffs, and laryngoscope blades and handles can be as well. Reprocessing reduces environmental impacts and provides considerable cost savings on disposal and purchasing.[47]

Clinical recycling. Recycling is now making its way into the ORs. Without doubt, reduction of waste and reuse of devices are preferable. Where these are not possible, e.g., with packaging, significant cost and environmental savings can be achieved through waste stream diversion. OR recycling may be achieved through collecting items during case setup, where more than one third of OR waste is generated. Doing so prior to bringing patients into the OR reduces concern for infectious contamination. Single-source waste stream recycling is gaining in popularity, making collection simple by eliminating the need to separate types of recyclables.[48,49]

Environmental impact and anesthesia practice

The ecological footprint of healthcare is enormous. Noble concern and care for the individual patient often neglects the impact of such dedicated practice on community and planetary health. The specific ecological footprint of perioperative practice is one of the largest in all of healthcare, representing more than a third of hospital waste streams. Many strategies are available for reduction of waste and pollution from operating rooms and perioperative areas. These include environmentally preferable purchasing (EPP), shifting back to reusable devices, reprocessing equipment, recycling materials, avoiding DEPH-laden plastics, donating equipment to programs such as REMEDY,[50] and energy efficient OR re-design.[51] Additionally, clinicians can select least-impact drugs, use pre-packaged syringes, minimize lowest fresh gas flows, chose least impact volatile agents, and use IV anesthesia and regional anesthesia where safe and feasible. Some of these more basic strategies may be in place already, with education and awareness limiting factors of implementation.

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Patient Experince in the Perioperative Settings

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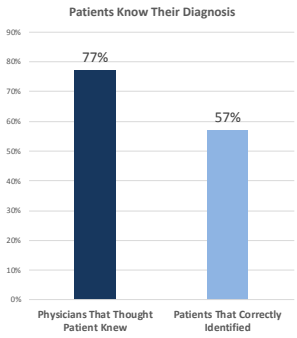
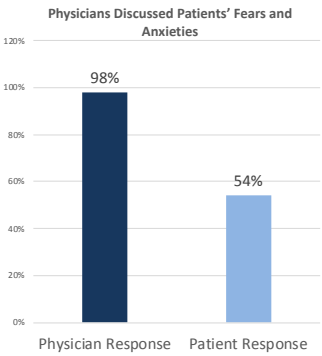
The American medical environment is currently experiencing a dramatic transformation and much of that relies on the Patient Protection and Affordable Care Act (ACA) and Triple Aim initiative. The Triple Aim was developed by Don Berwick of the Institute for Healthcare Improvement (IHI) in 2008 and focuses on revolutionizing US healthcare through three main tenets: (1) improving individuals' experience of healthcare, (2) improving the health of an aging US population and (3) reducing the ever-rising per capita costs of healthcare. The ACA of 2010 has significantly altered the American healthcare system, shifting priorities to emphasize the greater importance of patient-centered outcomes. In that context, the ACA mandated public reporting programs that incorporate information collected using the Consumer Assessments of Healthcare Providers and Systems (CAHPS®) surveys. Recently the CMS has introduced the OAS CAHPS (Outpatient and Ambulatory Surgery Survey), which aims to improve quality of healthcare in the perioperative space and to measure patient experiences with surgeries performed at hospital outpatient surgery departments or ambulatory surgery centers. In this refresher course, the speaker intends to address the basic fundamentals of patient experience within the perioperative settings. Once the basic communications skills have been reviewed, this speaker will cover the fundamentals of the methodology which CMS is using to assess our performance within the context of patient satisfaction and experience.

Clinician Patient Communication:

The first underlying fundamental question is why should an anesthesiologist care about patient experience? The paragraph above provides the first clue to answer. Today hospitals are getting by CMS partially based on the patient experience ratings (HCAHPS) score and the value-based purchase programs. Indeed, 2018 Value-Based Purchasing Domain Weighting consists of 25% of patient experience, 25% of clinical care outcomes, 25% of patient safety and 25% of efficacy and cost reduction. But let's try and look at some factors beyond those. Consumers define care quality through a series of proxies…these are often non-clinical and communication-linked. Indeed, multiple reports have indicated that global patient rating of the providers is not associated with the technical quality of their care but rather with the interactions they had with the providers. This concept, indeed, may provide some challenge to the practicing anesthesiologists who may pride themselves in their skills in echocardiography but not in their ability to communicate with their patient. Of interest is that there are communication discrepancies between physicians and hospitalized





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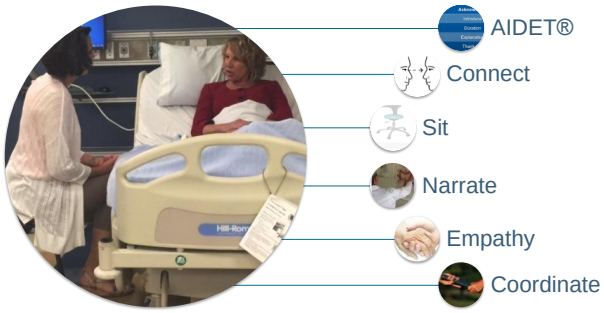
patients. In a 2010 article published in Archives of Internal Medicine Olson et al. reports that while 98% of the physicians thought that they have discussed patients fear anxiety only 54% of the patients felt that the physicians actually discussed this topic. Similarly, Olson et al. reports that 77% of the physicians thought the patient knew their diagnosis, only 57% of the patients actually were aware of their diagnosis. While the topic of the association between patient satisfaction scores and the clinical quality of care is somewhat controversial, recent reports clearly indicate that better clinical care is associated with higher patient experience scores and vice versa. For example, Doyle et al reported in 2013 in the BMJ on a systematic review, that included numerous healthcare settings and study designs. He concludes that preponderance of studies concludes positive association of patient experience and clinical safety/effectiveness. Indeed, 77% of the studies reviewed report positive associations, 22% of the studies reviewed report no association and less then 1% of the studies report negative association. Sacks et al. in a 2015 study published in JAMA Surgery found that in a large national sample of patients undergoing surgery that there is a significant association between hospital performance on a patient satisfaction survey and objective measures of surgical quality. Indeed, Sacks et al. demonstrated that patients treated in hospitals with the highest patient satisfaction scores experienced lower rates of postoperative mortality, failure to rescue and minor complications.

We hope that at this point we were able to answer the "why" question within the context of patient experience and to demonstrate that there is a significant discrepancy between how we all think we perform in our interactions with patients as compared to how we actually perform. Considering that patients don't know how technically good we are in the operating rooms and how knowledgeable we are, one can submit that excellent clinician patient communication skills are strongly needed for every practicing anesthesiologist. Typically, our interaction with our patients should consist of three part. 1) First impressions – we need to make sure that our tone and demeanor are appropriate to the patient within the context of the culture and ethnicity of the patient. It is always best to use a non-clinical opener and we should be aware about the "why" of the visit (individualized Patient Care) and information; 2) Middle - History and circumstances paraphrased, perform P.E and share P.E. findings, inform of test results and develop a shared plan; 3) End- Close the loop/summarize, answer Q's, teach-back and thank the patient for putting their care in our hand. Essentially, when the patient meets us preoperatively they want to know who are you? Are you any good? And do you care? Let's elaborate on this topic some more. When you see the family from about 10 feet, make eye contact and from about 5 feet you have to acknowledge them with some none clinical ice breaker. From this point on, it is great to follow a conceptual model such as AIDET (Acknowledge, Introduce, Duration, Explanation, Thank you). The introduction phase should consist not only of your name and the fact that you are an anesthesiologist, but also of your skill set, experience and certification. We should remember the patient does not know us and they are



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really anxious before their surgery. This is also a great opportunity for the anesthesiologist to "manage up" their team members. Manage up is an affirming statement which forecasts positivity of an upcoming experience, usually with an individual or a process. It sets a positive perception of the care team or care process. For example, "You are very fortunate to have Judy as your nurse. She is one of our finest and cares deeply for her patients…". Next, we need to discuss the "duration" of the procedure as well as the mechanism at which they will be updated with the time progress of the

surgical procedure. Next comes the explanation of what are we actually going to do. This should start with why are we doing this? What will happen and what should you expect? What questions do you have? Explain in a way that aligns with a patient's education and intellect. "Teach Back" is a tool to verify comprehension of key information. We should note that one of the HCAHPS Questions is: "How often during your stay did doctors explain in a way that you could understand?" Its always good to finish the explanation phase in a statement such as ""Now its my time to listen…What questions do you have?". Once this phase is concluded, we have to move to the thank you phase. Here, you can use a statement such as: ""Thank you for choosing us ….Thank you for waiting … Thank you for coming in today…What other questions do you have?"

CMS Based Patient Experience Surveys

The history of the CAHPS dates back to 1995 when the first survey that was created by the Agency for Healthcare Research and Quality (AHRQ) in conjunction with the Center for Medicare and Medicaid Services (CMS). According to the CMS and AHRQ, the CAHPS survey goals are: (1) "To develop standardized surveys that organizations can use to collect comparable information on patients' experience of care" and (2) "To generate tools and resources to support the dissemination and use of comparative survey results to inform the public and improve health care quality"[1]. While numerous studies have reported the high reliability and validity of the CHAPS surveys, many clinicians criticize these surveys and indicate that the questions presented in the surveys are not clear and attribution to individual specialty or physician is very difficult. That said, it is important to the reader of the *Monitor* to appreciate that these surveys are being used since 1995 and its highly unlikely that "they will go away".

The OAS-CAHPS survey is aimed to measure the experiences of care for patients who received care in a Medicare-certified hospital outpatient departments and ambulatory surgery center. Specifically, the aim of the survey is to measure patients' perspectives on constructs that are important (for patients) when choosing a facility for their care. The development of the OAS-CAHPS has been underway since 2012, and an initial test was conducted in 2014 (24 facilities) to assess validity, reliability and implementation procedures. Following the initial testing, OAS-CAHPS was revised and in 2015 a second process of testing was conducted. The survey received accreditation as a CAHPS® survey in February 2015. The second process of testing was particularly important as its aims were to assess data collection and develop models to adjust for patient characteristics prior to public reporting. This later aim is highly important since it is well known that certain social characteristics bias the responses to CAHPS surveys and as such a

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process of "statistical adjustment" has to be done prior to comparing and individual center to national bench marks. Many more details regarding the development and implementation can be found at the www.OASCAHPS.org site. It is important to note that currently there is not a specific timeline for linking OAS-CAHPS performance to reimbursement.

The OAS-CAHPS measures patient's perception of the quality of care in 5 Domains, comprised of 37 questions (13 of which are focused on demographics). As can be seen from Table 1, there are four questions that specifically mention the term anesthesia. These questions relate to information provision and nausea and vomiting. When examining the other questions, however, three more questions are related to "doctors in the facility". The OAS CAHPS survey will be given to adult patients who had specific procedures or surgeries (based on a list of CMS approved CPT codes and G codes). These procedures have to be performed in a Medicare certified Hospital Outpatient Department or a Medicare-certified freestanding ASC and overnight stay patients are included. Patients are only eligible to receive the OAS CAHPS survey once every six months. HOPDs or ASCs can apply for exemption from mandatory OAS CAHPS, if they have 59 or fewer OAS-CAHPS eligible patients annually. The OAS CAHPS survey must be administered by an independent CMS approved vendor and can be administered by mail, telephone or a combination of mail with a telephone follow-up.

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Advanced Teaching Skills for the OR: How to Teach Effectively when faced with High Clinical Workload and Lack of Time?

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Advanced Teaching Skills for the OR: How to Teach Effectively when faced with High Clinical Workload and Lack of Time?

Introduction

Teaching in the fast-paced, high-pressure environment of the operating room (OR) can be very demanding. High clinical workload and lack of protected time represent major obstacles to education and are unlikely to change in the near future;[1-7] thus, the educator-anesthesiologist must learn teaching strategies that are effective and time-efficient. The goal of this review is to provide an overview of the relevant teaching theories, highlight potential teaching obstacles, and provide effective techniques to improve teaching without compromising quality of care.[8]

I. CURRENT AND RELEVANT EDUCATIONAL MODELS

Multiple educational models have been described. The two outlined below are particularly relevant to the educator-anesthesiologist:[1, 2, 9-13]

Adult Learning Theory (ALT)[14] promotes self-direction in learning.[14, 15] The central idea of the ALT is that as the person matures, they develop a drive and desire to learn as well as assimilate responsibility for their own training. Therefore, the energy and motivation comes from the trainee. Consequently, the educator should:

- Promote *independent learning.* Example: Provide educational materials and encouragement to read independently.
- Focus on knowledge with practical relevance. Example: Concentrate on topics relevant to *current patient care,* thereby demonstrating the *practicality of such knowledge.*
- Promote a respectful learning environment and treat the learner as a colleague. Example: Solicit learner opinions when appropriate.

Dreyfus and Dreyfus model

The Dreyfus and Dreyfus model describes the progression from a novice learner to master across sequential stages of increasing complexity: *Novice, Advanced Beginner, Competent, Proficient, Expert, and Master.*[5, 16]
The tenets that drive this process are: *familiarity with recurrent clinical presentations, prioritization, and development of fast, intuitive, pattern-recognition approach to clinical situations.*[2, 5, 6, 9, 10, 16] The *novices* approach a skill with a primarily rule-based and context-free mindset. Exposure to clinical work facilitates (Table 1):[5, 6, 16]

1. Recognition that many clinical presentations are "copies" of prior patients allowing quick, efficient, and safe treatment by using a pattern-recognition approach without textbook consultation.
2. Developing "own" idiosyncratic anesthesia techniques ("illness scripts").
3. Developing the ability to prioritize and see the "big picture".

II. EFFECTIVE AND TIME-EFFICIENT TEACHING TECHNIQUES FOR THE OR

The key to productive and time-efficient teaching in the OR is to spend the limited time *effectively*. Research has shown that this can be best accomplished with a simple 3-step-approach:[17-19]

Step 1: Identify the learning needs of the particular resident
Step 2: Focus teaching on those resident specific requisites *only (e.g., limited and rapid teaching)*
Step 3: Finish strong with feedback to ensure that the learning needs have been met and reinforced

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This "*target an educational need, teach only that need, and then make sure you got your message across!"* reduces the time required for OR teaching by focusing only on what is lacking, and not what the learner already knows, or is not prepared for (increasing "teaching productivity").[17-19]

Step 1: Identify the learning needs of the particular resident.

A. Asking questions is a very quick and effective way to assess learning needs.

B. Observation is a simple yet effective tool that can be performed anytime and anywhere. It is an efficient tool to identify a wide range of requisites: interpersonal interactions, physical examination, technical skills (iv-placement, A-line or central line placement, intubation, etc.).

C. It is important to note that *most faculty are using both techniques already,* whether they realize it or not. The learner is often unaware that these moments are educational opportunities, running the risk of perceiving questions and observations in a negative manner.[2] For example,

- Observation by the attending could have a counter-productive effect by making the resident think *"Is my attending going to take the procedure away from me?!"* Similarly,
- Well-meant questions, like *"Did you give the patient the 2mg of midazolam?"* can be perceived negatively by the learner: "*Did I do something wrong?"*

What needs to happen instead is to purpose questions and observations as educational opportunities – they must be "disclosed" as an educational activity.

Step 2: Teach only the identified needs

Once the specific learner's needs have been identified, teaching should focus on addressing *only* those requisites:

A. One-Minute Preceptor Model (1-MP)[20-24]

The 1-MP model is a well-established teaching method in educational literature. It includes 4 steps:

- **Step 1:** Obtain a commitment from the learner regarding a clinical problem. For *example*: You are called to the OR because of bradycardia. On arrival, you ask the trainee "*What do you think is going on?" (*providing insight into the learner's reasoning).
- **Step 2:** Probe for supporting evidence focusing on the learner's clinical reasoning, e.g., "*What led you to that conclusion?" or What would you like to do now for this patient?"*
- **Step 3**: Teach a general principle, based on the identified learner's strengths/needs.
- **Step 4:** Brief feedback

B. The Think Aloud Approach[25, 26]

Here the expert reports aloud to the learner what s/he was thinking when making a particular clinical decision. This teaching method is considered by some clinicians as possibly the most powerful tool in clinical reasoning education. Typically, it only requires a few minutes of the attending's time to review step by step his/her decision making methodology.

C. "Activated" Demonstration Model[19]

This is an excellent method to address deficits in technical skills. In the "Activated" Demonstration Model the tables are turned and the learner observes the master clinician:

1. **Step 1:** "Disclose" as *an educational activity*; No procedure will be taken away from the learner
2. **Step 2:** Tell the learner *what to focus on*. - This is a key step!
3. **Step 3:** Following the demonstration, "*activate*" the learner by asking them to clearly describe what they observed to verify they "got the teaching point"
4. **Step 4:** Offer the resident an opportunity to repeat the just demonstrated activity to reinforce the teaching point.
5. **Step 5:** Provide brief feedback

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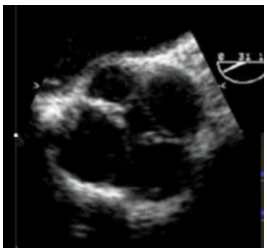
D. The Aunt Minnie Model[27]

This is a very effective technique to teach pattern recognition introduced in the 1940s by Dr. Ben Felson, a radiologist at the University of Cincinnati. The model is based on the observation that "*A case with radiologic findings so specific and compelling that no realistic differential diagnosis exists." - If someone walks like Aunt Minnie, talks like Aunt Minnie, and looks like Aunt Minnie, then it's Aunt Minnie!*[27-29] It can be a very powerful method in promoting rapid pattern recognition.

Example #1: - *Attending: What is this?*



E. Focused *"Teach General Principle"* Model

This old-fashioned model can be more time-efficient and effective, [2, 8] by dividing the deficits into urgent or non-urgent categories:

- Urgent needs refer to deficits that if not corrected ASAP could endanger a patient.
- On the other side, there are many non-urgent *knowledge needs*. For example, if the resident doesn't know the molecular effect of epinephrine it is unlikely that a patient will be endangered. Thus, this learning need can be covered at any time, especially, when acute demands have diminished in the case.

- Obtain the learner's undivided attention. One well-established approach is taking over the case (and saying this out loud) so that the learner can focus fully on just learning.
- Provide clinical pearls in context of the current patient
- Limit teaching to learner's requisites only and limit teaching time to 10-15 minutes per "episode". – *Less is more.*

Step 3: Finish strong with feedback to ensure that the identified learning needs have been resolved

Providing meaningful feedback is a critical, but challenging skill.[30-35] The old-fashioned "feedback sandwich" is so widespread that most learners are familiar with its methodology. So, while the teachers are pointing out the positive things they observed, the learners are not paying much attention. – They are waiting for the "meat" of the feedback. Thus, the interested reader might consider the new sandwich: "ask-tell-ask":[36, 37]

- ASK: General questions, for example *What do you think about today? How did you do?*
- TELL: Opportunity to be positive, agree with resident assessment, for example "*You are correct, this was not a great intubation*", and even build up the resident "*I think your intubation was better than you described. You did well.*"
- ASK: Focus on future aspects: *So, what are you going to do differently next time?*

Overall, the new Ask-Tell-Ask sandwich is more interactive and less confrontational.

III. SUMMARY: ADVANCED TEACHING SKILLS - HOW TO TEACH UNDER PRESSURE?

Let's conclude this review by providing a simple set of Guidelines for Practical Application: [1, 2, 9, 10]

- **Get buy-in from the resident**
  a. Establish educational context
  b. Ask about learner's past experiences & current rotational goals
  c. Identify learning needs
  d. Be aware of idiosyncrasies (resident vs. you)
- **Maintain buy-in**

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a. Be interested
    i. Pay attention to what they do and their approach to clinical thinking (talk about it)
b. Teach identified needs (no more than 1-3 points)
    i. Clinical context; clinical pearls
    ii. Get commitment - Probe for evidence
    iii. Wait for the right moment
c. Explain your decision-making process
d. Don't be defensive. Be the expert – and set the stage.

- **Finish strong**
    a. Solid feedback (Ask-Tell-Ask), so they remember you did it!
    b. Go over teaching points; Review what they learned; Ensure teaching-productivity
    c. Appreciate learner's efforts / work

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Anesthesia for Head and Neck Surgery: State-of-the-Art

Vladimir Nekhendzy, MD **Stanford, California, U.S.A.**

Learning Objectives:
The learner will be able to:
1. Define the specifics of preoperative assessment of patients presenting for head and neck (H&N) surgery.
2. Identify and summarize challenges of airway management for patients undergoing head and neck surgery.
3. Discuss and formulate the principles of anesthetic management for patients undergoing head and neck surgery.

Description:
This Refresher Course Lecture will outline and comprehensively discuss the principles of preoperative assessment and anesthetic care for patients undergoing H&N (ENT) surgery, and will review unique challenges and solutions of airway management for these patients.

1. INTRODUCTION AND GENERAL CONSIDERATIONS.

State-of-the-art anesthesia management for H&N surgery require the anesthesiologist to be adept with a variety of advanced airway management techniques, to competently execute different intraoperative ventilation strategies, to be proficient with inhalation induction and total intravenous anesthesia, and to devise the anesthetic plans suitable to variable or unpredictable duration of surgery. Successful management of H&N cases requires a high degree of cooperation with the surgeon, a reciprocal understanding of the potential problems, and adequate preparation on both sides to meet the anticipated challenges that may arise.
The core anesthesia objectives for H&N surgery and strategies are listed in **Table 1** and will be discussed in the lecture in detail.

2. EXPERT AIRWAY MANAGEMENT.

Difficult and emergency airway is observed more frequently in H&N patients than in general surgical population. In the Fourth National Audit Project (NAP4) H&N patients comprised nearly 40% of cases with airway management related complications, and almost 75% of cases where emergency surgical airway was required for "cannot intubate-cannot ventilate" (CICV) situation **[1,2]**. Several large studies have demonstrated that difficult tracheal intubation (TI), defined as ≥ 3 attempts on direct laryngoscopy (DL) may be encountered in up to 7-9% of H&N cases **[3-5]**, which is at least 2-4 times higher than in mixed surgical population **[6-9]**. The H&N cancer patients, predominantly males are at highest risk: difficult DL and TI can be observed in over 12% of these patients. **[1-3]**.
Patients with H&N cancer, especially those with supraglottic and glottic tumors or the history of radiation therapy require the longest intubation times and represent the highest risk for adverse TI outcomes **[1,2,4]**. In NAP4, airway management was considered poor in nearly 30% of these cases **[1,2]**.

Prediction of difficulty
A systematic and comprehensive preoperative airway assessment based on the 11-point ASA bedside airway assessment tool **[10]** is essential. However, standard airway assessment tests are poorly predictive **[9,11]** do not account for aspiration risk and lower airway problems, and fail to assess the severity of upper airway disease and base of the tongue pathology, (e.g. lingual tonsillar hypertrophy).
The history of difficult TI is one of the most important predictors of anticipated airway management difficulties **[12-14]**, yet it is still taken lightly in anesthesia practice and leads to a lack of preparation on the part of the anesthesiologist **[15]**.
The history of prior H&N radiation therapy must be elucidated, as exposure to radiation therapy frequently makes TI difficult. The radiation-induced tissue fibrosis results in loss of tissue compliance, frequently leads to long standing

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glottic and epiglottic edema due to impaired lymphatic drainage, and may also restrict patient's mouth opening and neck extension **[16]**.
Postradiation changes in the neck and decreased mandibular protrusion are important factors predicting the risk of difficult and impossible mask ventilation, and associated difficult DL **[17-20]**. The predictors of difficult video laryngoscopy (VL) and difficult supraglottic airway placement (see below) should also be carefully elucidated.

Preoperative endoscopic airway examination and Imaging studies
In patients with H&N cancer airway imaging and nasal endoscopy are considered a minimum necessary level of investigation for assessing airway management options, especially if symptoms of airway obstruction are present **[2,21]**. For high-risk patients, these results should be reviewed and discussed jointly with the surgeon **[21]**.
Preoperative nasal endoscopy is routinely performed by H&N surgeon, but with sufficient practice can be quickly and effectively executed by the anesthesiologist (preoperative endoscopic airway examination, **PEAE**) **[22]** as part of the preoperative assessment. The PEAE provides precise information about the upper airway and laryngeal anatomy, helping to formulate appropriate airway management strategies.
The illustrative examples of PEAE impact on airway management decision making will be provided at the lecture.

Tracheal extubation and early recovery period present increased challenges for the anesthesiologist **[1,23]**. A preformulated extubation strategy **[10]** is required for H&N patients that are at high risk for extubation failure **[1,23]**. According to NAP4, 1/3 of adverse airway events occurred during emergence and recovery from anesthesia, with airway obstruction being the most common cause **[24]**. The detailed approach to extubation of the difficult airway in general, and H&N difficult airway in particular is outlined in the Difficult Airway Society (DAS) Extubation Guidelines and other review publications **[23,25]**. The difficulty of the intubation procedure, the extent and duration of the surgery, the degree of postoperative swelling and anticipated airway obstruction, the possibility of postoperative bleeding, the patient's state of consciousness on emergence, as well as the patient's preoperative status - all should play a role in the anesthesiologist's decision making **[23,26,27]**. Every extubation of at risk H&N patient should be considered a possible reintubation, and all the necessary airway equipment and manpower should be available before the extubation trial starts.

Team centered approach to an anticipated difficult airway in H&N surgery is essential. The recurring theme in NAP4 is the need for maintaining close lines of communication with the surgical team before and during the intubation procedure **[28,29]**. Failure to anticipate and plan for problems, and to develop safe airway strategies will contribute to failures and increase patient's morbidity **[30,31]**. An airway strategy can be defined as the predetermined set of sequential plans for managing failure of the previous attempts, and for achieving and maintaining adequate ventilation, oxygenation, and protection against aspiration **[30]**.
Determining the optimal airway management approach depends on the surgery being performed, location of the lesion, patient's symptoms, acuity of the situation, and patient's tolerance of the procedure. It may also be dictated by the anesthesiologist's skills set and equipment availability, with a large room for improvement in both these areas **[30]**.
The pertinent preoperative imaging and PEAE findings must be reviewed and discussed with the surgeon to accurately estimate the degree of pathology and facilitate decision making. Special expertise in H&N anesthesia and complex airway management should be encouraged among the anesthesiologists, as it may improve TI outcomes, result in quicker intubation times, better patient oxygenation, and fewer failures **[4]**.

Versatility with difficult airway devices and techniques

a) Awake vs Asleep approach to tracheal intubation.

An awake approach to TI is indicated when significant anatomical distortion is present or the patient's mouth opening is severely limited. For patients with undefined risk the decision should follow the framework suggested in the American Society of Anesthesiologists (ASA) difficult airway algorithm **[10]**, with the special attention directed to true predictors of difficult mask ventilation, impossible mask ventilation, and their association with difficult DL and TI (see above).
The likelihood of difficult supraglottic airway (SGA) ventilation and difficult surgical airway access must also be considered and evaluated **[10]**. However, if the surgical airway is contemplated as part of the overall strategy, success should not be assumed **[21]** and it is best to secure the patient's airway awake.

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If the patient's airway is marginal, but an awake approach is not feasible, the "airway double set up" is warranted: the CTM should be marked, the patient's neck should be prepped, and the surgical team must be present for induction, ready to perform an emergency cricothyroidotomy or tracheostomy.

b) Role of conventional and video laryngoscopy.

A consistent NAP4 finding in patients with H&N pathology was the deterioration of the airway following a single or repeated attempts at DL **[1]**. The H&N tumors can cause considerable airway distortion, and can be friable, leading to bleeding, defragmentation, airway soiling, and rapid edema formation **[1]**. If DL is chosen as a primary approach to TI, multiple attempts should be avoided, to avert total airway obstruction and CICV situation **[1,2,~~26~~21]**.
Given a high incidence of anticipated difficult airway in H&N patients, it is prudent to reach for video laryngoscopy (VL) as a primary TI technique in many cases. Such approach capitalizes on extensive body of evidence and is supported by the ASA Difficult Airway Task Force recommendations **[~~12~~10]** for different VL techniques. We, therefore, advocate expanding airway evaluation beyond the ASA recommendations, to determine the likelihood of difficult VL **[32-39]**.

c) Role of operative laryngoscopy and rigid bronchoscopy.

Should DL or VL fail, the airway rescue using operative laryngoscopy or rigid bronchoscopy performed by the surgeon may be successful **[10,40-44]**. The surgical anterior commissure scopes are very effective in handling poor laryngeal exposure or glottic obstruction, and can be used as a conduit for TI when the bougie introducer or ETT are passed directly down the lumen **[44]**.
Rigid bronchoscopy can rescue failed TI and CICV situation, and also serves as an indispensable tool for managing acute airway obstruction resulting from foreign bodies, hemoptysis, or tumors **[45,46]**.

d) Role of inhalation induction.

Inhalation induction has limited value in complex H&N pathology, especially in patients with advanced upper airway obstruction. In NAP4 study, inhalation induction failed in 12/16 (75%) of H&N patients with the compromised airway, and in nearly all these patients (11/12) spontaneous ventilation became impossible **[1]**.
Inhalation induction may be best reserved for the non-collapsing lesions, with anticipated failure rate in these settings of approximately 5% **[4]**. Its use should be considered highly problematic if mask ventilation difficulty is anticipated **[4]**.

e) Role of flexible fiberoptic intubation and optical stylets.

Both awake and asleep **flexible fiberoptic intubation** (FFOI) can fail frequently in H&N patients: in NAP4, such failure was observed in nearly 61% of these cases **[1]**. When performed by designated H&N anesthesiologists, a much lower, yet still sufficiently high failure rate of 8.8% may be expected **[4]**.
The most common reasons for awake FFOI failure in H&N patients appear to be the inability to either identify the glottis or to pass the flexible fiberoptic bronchoscope (FFB) or ETT **[1]**. Additional reasons for the failure of asleep FFOI include repeated TI attempts, bleeding, and airway obstruction **[1]**.
The **optical intubation stylets**, such as Bonfils, Shikani, SensaScope, Clarus Video System, etc. can effectively lead within ETT to help bypass a mobile supraglottic and glottic masses. The FFB may fail in this situation, either because of the inability to displace the tumor, or because ETT simply would not pass.

f) Role of the supraglottic airways (SGAs) and the SGA-ETT exchange.

The reliable SGA ventilation in many H&N patients can be problematic due to difficulties associated with SGA insertion (e.g., restricted mouth opening), difficulties with achieving SGA proper positioning (e.g. space occupying lesions, previous radiation therapy), and/or difficulties with maintaining an adequate airway seal pressure (ASP) and SGA ventilatory capability (e.g. obstructing pathology either at, or below the vocal cords).
The NAP4 study has demonstrated high failure rate of the **first-generation SGAs** and numerous cases of aspiration of gastric contents associated with their use **[24]**. Should placement of SGA be required for H&N patient, it is prudent to reach for the **second-generation SGAs** with greater ventilation capability and gastric access, e.g. the LMA Proseal or LMA Supreme. A 3.8-5.2% failure rate with the second-generation SGAs may be anticipated **[47]**. To minimize these failures, we recommend adopting the bougie introducer-assisted insertion technique **[48]**, to maximize the first pass success rate, and to assure optimal esophageal and laryngeal seals **[49]**.
The **LMA Fastrach** (intubating laryngeal mask airway, iLMA) possesses excellent ventilatory capability and provides a 92-94% success rate of blind TI in patients with anticipated difficult airways **[50,51]**. In patients

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with glottic or infraglottic pathology, blind TI intubation should be avoided, and superseded by the flexible fiberoptic bronchoscope (FFB)-guided iLMA-ETT exchange, which can be performed with or without the use of the Aintree intubation catheter (AIC).

The **tubular SGAs,** such the Combitube and the laryngeal tubes (LT) are especially beneficial in patients with limited access to the airway and massive upper airway bleeding or regurgitation, when rapid control of the airway is necessary. The ventilation through the Combitube can be effective when other SGAs (e.g. LMA) had failed **[52]**, and Winterhalter et al. **[53]** have documented successful LT ventilation in 95% of patients with oropharyngeal cancer.

g) The use of the supraglottic airways as the primary ventilatory devices in elective H&N surgery

Not all H&N patients need to be tracheally intubated. The use of the SGAs as a dedicated airway for elective H&N surgery may be strongly preferred over ETT when smooth emergence from anesthesia is essential, e.g. otologic surgery, functional endoscopic sinus surgery, and facial cosmetic surgery.

Selection of the **second-generation SGAs** with greater ventilating capability and gastric access (e.g. the LMA Proseal, the LMA Supreme) will increase the margin of safety, and we prefer their use for otologic surgical procedures, where the patient's head is turned to one side and not manipulated until the completion of surgery. However, for the procedures such as facial cosmetic or intranasal surgery, where the LMA shaft must be moved away from the surgical field, the use of the **flexible laryngeal mask airway** (FLMA) is preferred. The properly placed FLMA adequately protects the lower airway from blood, secretions, and surgical debris, thus eliminating the need for the use of the throat pack by the surgeon **[54-60]**.

Both retrospective and prospective studies on the use of LMA or FLMA as a primary ventilatory device in H&N surgery demonstrate decreased incidence of upper airway trauma and adverse respiratory events, absent need for neuromuscular blocking (NMB) agents, improved maintenance of a stable plane of anesthesia and controlled hypotension, and smoother and faster emergence from anesthesia **[60-63]**.

We recommend the use of the positive pressure ventilation (PPV) through the SGAs for elective H&N surgery, in order to preserve normocapnia. Continuous monitoring of the pressure-volume and flow-volume loops, the shape of the $EtCO_2$ waveform, and total compliance on the newer anesthesia machines will help to immediately detect the decreased tidal volume (V_t) and increased leak fraction associated with the lighter planes of anesthesia **[64]**.

h) Combined intubation techniques.

A combined use of VL with FFB or optical stylet is gaining popularity in complex airway management. The VL provides an enlarged view of the glottis and facilitates FFB/optical stylet maneuvering when the anatomy is severely distorted or supraglottic/glottic tumors are present. This technique allows for continuous observation of the intubation procedure, with diminished risk of tumor disturbance.

i) Surgical airway as a primary approach to tracheal intubation & airway rescue.

An awake tracheostomy is usually undertaken in patients with significant airway compromise, where postoperatively the caliber of the airway is not expected to improve. The procedure should be performed under local anesthesia, without sedation. An awake dilator cricothyroidotomy also can be safely performed, and may serve as a viable alternative to tracheostomy for many H&N patients with the difficult airway **[4,65]**.

However, the majority of H&N surgeons prefer to perform a tracheostomy under controlled conditions, after induction of anesthesia, to avoid airway trauma, tumor disturbance, and tracheostomy tube displacement or obstruction **[4]**.

For emergency airway management, surgical cricothyroidotomy is strongly preferred over the transcutaneous CTM access: in NAP4 study, the emergency transcutaneous cannula cricothyroidotomy had failed in 60% of H&N patients **[1,2]**.

Advanced oxygenation techniques.

The oxygenation centered airway management is critical for H&N patients, who present with the higher incidence of failed TI and CICV situation. For anticipated difficult airway, advanced oxygenation techniques, such as high flow nasal oxygen (transnasal humidified rapid insufflation ventilatory exchange, THRIVE) should be strongly considered for prolonging apnea time during intubation attempts **[66-69]**.

Other strategies may include placement of the transtracheal jet ventilation (TTJV) catheter or cannula before induction of anesthesia for providing tracheal oxygen insufflation or high-frequency TTJV **[70]**. Substituting TTJV catheter for Arndt cricothyroidotomy cannula offers the advantage of using its 3 mm ID lumen with the low-pressure gas source, thus allowing for manual ventilation using the anesthesia circuit or an Ambu bag **[71]**.

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Shared airway precautions and **Surgery-specific airway management requirements** will be reviewed during lecture.

3. ANESTHESIA MANAGEMENT FOR H&N SURGERY.

Provision of a stable plane of anesthesia and a clear surgical field

The density and complexity of H&N anatomy dictate the delicate nature of many of the surgical procedures. The anesthesiologist must effectively block the nociceptive responses from the highly reflexogenic areas to assure a stable plane of anesthesia at all times, and provide a clear, dry surgical field.
These objectives are readily achieved with the stratified use of IV opioid analgesics, TIVA, and maintenance of moderate controlled hypotension.

Opioid based techniques

The opioid based anesthetic techniques provide many advantages for H&N surgery (**Table 2**). Continuous IV infusions of opioids result in decreased total opioid dose, greater hemodynamic stability, more rapid recovery of consciousness, less pain in the immediate postoperative period, and decreased discharge times from the recovery room compared to the opioid IV bolus technique **[72-75]**. The anesthesiologist should be familiar with the context-sensitive half-lives of different opioid infusions to facilitate patient's prompt awakening. Proper stratification of the opioid infusions for improving perioperative course and facilitating patient's discharge from the recovery room will be discussed at the lecture.

Total intravenous anesthesia (TIVA) and Hypnotic monitoring

Inhalational anesthesia, balanced inhalational anesthesia, TIVA, and even a "sandwich" propofol-inhalational anesthetic have all been successfully used for maintenance during H&N surgery **[76-79]**.
TIVA with propofol 80-180 μg/kg/min (TCI 3-5 μg/ml) and an opioid that best suits for the profile of surgical stimulation and immediate postoperative recovery, facilitated by intraoperative hypnotic monitoring represents our anesthetic technique of choice. The use of hypnotic monitoring (e.g. processed electroencephalogram activity) helps to maintain adequate anesthetic depth at all times, adds extra vigilance to management of cases where NMB is avoided, and facilitates decision making for treating intraoperative hypertensive responses, therefore promoting the maintenance of controlled hypotension.
The full synergistic effect of propofol with rapidly-acting opioids, such as remifentanil, allows quick titration of anesthetic to the desired clinical effect **[72,77,80-84]**. TIVA produces profound depression of pharyngeal and laryngeal musculature and reflexes, suppresses hormonal stress response to H&N surgical procedures, and effectively blocks the catecholamine release and associated hyperdynamic cardiovascular responses, thereby facilitating maintenance of induced hypotension **[76,80,85-92]**. Postoperatively, TIVA results in quicker recovery times, faster return of cognitive function, decreased incidence of postoperative nausea and vomiting (PONV), and improved patient satisfaction, thus allowing to fast-track patients for discharge **[77-81,86-90,93-99]**.

Moderate controlled hypotension

Maintenance of moderate controlled hypotension (systolic blood pressure, SBP, below 100 mmHg; mean arterial pressure, MAP, 60-70 mmHg) is essential for maintaining optimal operating conditions. A variety of pharmacological approaches, such as the use of IV sodium nitroprusside, IV beta blockers (esmolol, labetalol, metoprolol), IV calcium channel blockers (nicardipine), IV α_2-adrenoreceptor agonists (dexmedetomidine), IV magnesium sulfate, and the use of potent inhalational agents and IV opioids have been successfully employed for this purpose, all producing comparable improvement in the quality of surgical field **[100-106]**.
Our experience, as that of others **[81,102,104]**, has shown that the use of remifentanil seems to be particularly effective due to its superior potency and titratability.

Immobility of the surgical field

Absence of patient's movement

Avoidance of any active patient movement intraoperatively constitutes a challenging task if NMB agents are not used or contraindicated, e.g. for monitoring and preservation of the facial/cranial nerve function, neck dissection, thyroid surgery, etc. Absent NMB, deeper planes of anesthesia may be required to avoid sudden patient motor responses, which creates a potential for hemodynamic instability in the elderly patients or patients with cardiovascular disease.

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The use of remifentanil as part of the anesthetic technique (see above) greatly facilitates maintenance of a stable plane of anesthesia and patient immobility, without affecting the quality of neural monitoring **[94]**.

Avoidance of iatrogenic motion interference

Any accidental movement of the surgical field during precision surgery, e.g. otologic and neurotologic surgery, laser otolaryngologic surgery, functional endoscopic and cranial base surgery, TORS may have disastrous consequences. The surgeon must be informed of any plans that may provoke patient motion – even those that would otherwise seem insignificant **[107]**. Situational awareness is required on the part of the anesthesiologist at all times to avoid any inadvertent action that may result in movement of OR table.

For the otologic, neurotologic, functional endoscopic and cranial base surgery the non-invasive blood pressure (NIBP) cuff should be positioned on the patient's arm opposite to the surgeon, to eliminate the possibility of triggering sudden surgical tremor during cuff inflation **[107]**.

4. ADVANCED VENTILATION TECHNIQUES FOR LARYNGOLOGIC SURGERY

Jet ventilation

A "tubeless" JV technique is commonly used for elective laryngoscopic surgery, providing the enlarged, minimally obstructed surgical field. Modern automated jet ventilators incorporate multiple safety features, including automatic ventilator shutdown, if the user preset pressure limits are exceeded.

A high-frequency JV (HFJV) is most commonly employed, and is usually initially set at 150 cpm (100-300 cpm). Higher frequencies significantly reduce laryngeal motion and afford a quiet surgical field without the need for interrupting ventilation; however, dead space ventilation is increased with possible reduction of CO_2 elimination **[108-110]**.

With ***supraglottic JV***, the jet nozzle is positioned above the glottic opening, resulting in a very low risk of barotrauma. However, proper positioning of the suspension laryngoscope against the glottis is essential for safety and effectiveness of the technique. ***Infraglottic JV*** is most commonly used, and is established by bypassing the

larynx from above with a small (3-4 mm OD) laser-resistant double-lumen JV catheters or a metal jet cannula. The rigid bronchoscope can also be used, and is most commonly employed for bypassing the obstructing lesions of the airway. With HFJV catheter, strategies for minimizing the risk of barotrauma on initiation of infraglottic HFJV may include starting ventilation with low driving pressures at or below 1.0 bar (1.0 bar is approximately 15 psi); promoting sufficient exhalation time by using LFJV first; and maintaining the patient's airway patency with the assistance of an oral airway or providing a jaw lift **[110-114]**. Alternatively, initiation of the infraglottic HFJV can be held off until the suspension laryngoscope is deployed, and ventilation is supported conventionally through a face mask or SGA. With ***transtracheal JV***, the larynx is bypassed from below by a long catheter or Ravussin-type cannula placed through CTM **[111,113,115]**. The higher ASA physical status correlates with the higher incidence of complications with infraglottic and TTJV techniques **[112]** and these patients should be given special attention. Patients with previous neck radiation therapy are at higher risk for multiple attempts at TTJV catheter placement and subsequent risk of developing intraoperative barotrauma **[113]**. The barotrauma complications also are most frequently observed during TTJV, although the incidence is small (1%) **[112,113]**.

Clinical monitoring of the patient to prevent barotrauma should remain the standard of care for all JV techniques **[112,113]**. Ensuring an adequate level of anesthesia, analgesia, and muscle relaxation; painstaking attention to maintaining unobstructed exhalation; and diligent monitoring of vital signs and chest excursions are essential for the patient's safety **[112,113,116,117]**.

Apneic intermittent ventilation.

Apneic intermittent ventilation (AIV) remains a relatively popular technique for microlaryngeal surgical procedures of short duration in some surgical centers **[118]**. Compared with spontaneous ventilation, it affords more stable and controlled anesthetic conditions, as well as full muscle relaxation. With patient in suspension, patient's trachea is intubated by the surgeon with a small diameter ETT that is placed through the lumen of the laryngoscope **[118]** and the patient's lungs are hyperventilated with an FiO_2 of 1.0. The ETT is then removed to provide a fully unobstructed and still surgical view of the larynx. We prefer to use a cuffed 5.0 mm ID microlaryngeal tube (MLT) to facilitate its passage down the lumen of the surgical laryngoscope, and to minimize laryngeal trauma.

High flow nasal oxygen.

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There have been some small feasibility studies on the use of THRIVE as the sole means of providing oxygenation and ventilation for short, elective laryngologic surgical cases **[119-122]**.
The use of THRIVE for laryngologic surgery will be discussed in detail during the lecture.

5. SMOOTH AND RAPID EMERGENCE FROM ANESTHESIA.
Smooth emergence from anesthesia, devoid of patient straining, bucking, and coughing is essential for avoiding the formation of hematoma, disrupting delicate surgical repairs (e.g. facial nerve repair, closure of cranial base/dural defects), or dislodging surgical grafts (e.g. tympanoplasty, ossicular chain reconstruction). Avoidance of protracted straining or retching associated with PONV is equally critical in that regard, and adequate pharmacological PONV prophylaxis should be routine **[78,101,107,123,124].**
Smooth extubation strategies include **the use of SGA in lieu of ETT**, the ETT-SGA exchange at the end of the case (the **Bailey maneuver**), and a pharmacological approach involving the use of opioids, particularly **remifentanil** to blunt the tracheal responses. These strategies will be discussed in detail during the lecture.

6. FAST-TRACKING PATIENTS FOR DISCHARGE.
Provision of anesthesia care aimed at fast-tracking patients for discharge is dictated by the outpatient nature of many of H&N surgical procedures, increased focus on improved patient outcomes, and by economics of modern perioperative care.

Stratified opioid use, Multimodal analgesia, and Adjuvant techniques
A ***rationale choice of an opioid*** and administration of **TIVA** will greatly facilitate patient's discharge from the recovery room. Remifentanil-induced hyperalgesia has not been an issue in our experience, possibly because of the relatively low remifentanil IV infusion rates typically required intraoperatively (0.1-0.3 μg/kg/min).
A ***multimodal analgesia***, incorporating the perioperative use of steroids (e.g. dexamethasone 4-8 mg), and either IV acetaminophen or selective and non-selective oral NSAIDs (e.g. celecoxib, ibuprofen) can further decrease postoperative pain, reduce postoperative opioid requirements, and improve the quality of recovery and patient satisfaction after outpatient H&N surgery **[125-133]**.
The ***adjuvant techniques***, such as intraoperative IV infusion of esmolol can be tried for outpatient H&N surgery. Esmolol IV infusion results in decreased opioid administration intraoperatively and in the immediate postoperative period, and may also reduce the incidence of PONV **[134]**. Targeting opioid sparing effect with significantly smaller IV esmolol infusion rates, e.g. 5-15 μg/kg/min may be equally effective **[134]** compared to larger doses of IV esmolol required for maintenance of controlled hypotension.

Prophylaxis of postoperative and postdischarge nausea and vomiting
Shortening of the discharge time can be further improved by ***aggressive prevention of PONV***, usually with IV 5-HT3 antagonist (e.g., ondansetron 4-8 mg). A combination of a 5HT-3 receptor blocker with IV dexamethasone (8-10 mg) appears to be safe and highly effective **[135,136]**, and may lead to improved patient outcome **[190,192]**.
Multimodal PONV prophylaxis (e.g. the addition of transdermal scopolamine patch) is warranted in high-risk patients **[135,137]**, and may also include intraoperative IV administration of acetaminophen **[138]** PONV can be further reduced with TIVA, when the emetogenic effect of inhalational anesthetics is avoided **[135]**. However, the lower incidence of PONV associated with TIVA appears to be limited to the early postoperative period only **[135,137]**.

7. SUMMARY.
Close cooperation and good working relationship with the surgeon are essential for patient safety and favorable patient outcomes. The anesthesiologist should understand the disease process and steps of the surgical procedure, be familiar with comprehensive preoperative airway assessment that involves PEAE and imaging studies, and thoroughly appreciate the unique anesthesia management requirements for different types of H&N surgery.
Core surgical and anesthesia objectives include expert airway management, provision of a stable plane of anesthesia, maintenance of a clear, immobile surgical field, smooth and rapid emergence from anesthesia, and fast-tracking patients for discharge, where appropriate.
Management of complex H&N cases will progressively benefit from perioperative involvement of a dedicated H&N anesthesia team, especially when the patient's airway is compromised or proficiency with special ventilation techniques (e.g. JV or THRIVE) is required.

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Table 1. Core anesthesia objectives and strategies for head and neck surgery

Expert airway management

1. Increased level of difficulty
   - Increased need for difficult and emergency airway management
   - Increased risk of airway management failure
   - Extubation challenges
2. Prediction of airway management difficulty
   - Predictors of difficult and impossible mask ventilation and their association with difficult direct laryngoscopy
   - Predictors of difficult video laryngoscopy
   - Predictors of difficult supraglottic airway placement
   - Preoperative endoscopic airway examination
   - Imaging studies
3. Team centered approach
4. Versatility with difficult airway devices and techniques
5. Advanced oxygenation techniques
6. Shared airway precautions
7. Surgery-specific airway management requirements

Provision of a stable plane of anesthesia and a clear surgical field

1. Opioid based techniques
2. Total intravenous anesthesia (TIVA)
3. Moderate controlled hypotension
4. Hypnotic monitoring

Immobility of the surgical field

1. Absence of patient's movement
2. Avoidance of iatrogenic motion interference

Advanced ventilation techniques for laryngologic surgery

1. Jet ventilation
2. Apneic intermittent ventilation
3. High-flow nasal oxygen

Smooth and rapid emergence from anesthesia

1. Remifentanil
2. Bailey maneuver
3. SGAs as the primary ventilatory device

Fast-tracking patients for discharge

1. Stratified opioid use
2. Multimodal analgesia
3. Adjuvant techniques
4. Prophylaxis of postoperative nausea and vomiting

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Table 2. The advantages of the opioid based anesthesia for head and neck surgery.

Powerful intraoperative analgesia
Excellent postoperative pain control
Superior maintenance of controlled hypotension
Decreased general anesthetic requirements
Promotion of patient's immobility
Improved hypnotic monitoring
Improved intraoperative neurophysiological monitoring
Potent suppression of upper airway reflexes
Promotion of smooth and rapid emergence from anesthesia

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Perioperative Management of Pulmonary Arterial Hypertnsion and RV Dysfunction.

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Key points:

- The physiology of patients with PAH involves complex cardiopulmonary interactions.
- PAH patients are at high risk for complications and ideally should be managed in specialty centers. If it is a "have-to-do" scenario, summon help from someone versed in managing perioperative PAH.
- Complications can often be prevented by understanding the conditions causing perioperative deterioration.
- Many monitoring modalities are important in at risk patients. The choice is patient/ situation specific. The CVP is a very useful monitor, as a low CVP generally means that the RV is "coping", while a high CVP (>20) likely portends trouble. In high risk patients, continuous monitoring of RV function with echocardiography and PA pressures with a PA catheter may be helpful. Continuous RV pressure monitoring from the RV port of the PAC is a simple and invaluable beat-to-beat RV function.
- Systemic hypotension, from any cause, is disastrous in patients with PH. It causes further displacement of the intraventricular septum towards LV, globular dilation of RV, further RV dysfunction of the already compromised RV, and reduced coronary artery perfusion. This leads to a rapid and lethal spiral.
- Emergency vasopressors must be must be in-line and "ready to go" when caring for these patients, and should start while searching for the cause of the hypotension. Use incremental boluses of vasopressin, starting with boluses of 0.2 to 0.4 U (20U vasopressin in 100ml diluent = 0.2U/ml), rapidly escalating if needed, and start an infusion of 2.4U/hr. (12ml/hr. of aforementioned solution). Also start a norepinephrine infusion at 0.05mcg/kg/min, and titrate as required.
- The cause of acute RV failure in the setting of PH is often multifactorial and includes: factors that exacerbate the existing PAH (increased PVR), change in RV function due to changes in volume, rate, rhythm, septal position, and contractility. The causes must be immediately treated.
- PVR is dependent on many factors that can be manipulated in the perioperative period. Most acute increases in PVR can be remedied by the non-pharmacological methods, especially those factors that affecting functional residual capacity and PVR. An inhaled pulmonary vasodilator must be immediately available if these measures are not successful.
- Delay in treating acute RV failure causes rapid organ system failure due to "the double hit" phenomenon.
- Institution of acute mechanical circulatory assist (peripheral VA ECMO) must be available in very high risk cases. It must be started early in the cycle of RV deterioration, before the onset of organ injury.

Introduction

Pulmonary hypertension (PH) and the associated right ventricular (RV) dysfunction are increasingly being encountered in the perioperative period. Managing these patients is challenging as they have a high morbidity and high mortality. Understanding of the pathophysiology of PH and the related RV dysfunction allows the practitioner to anticipate, prevent, and manage these patients. Normal systolic, diastolic, and mean PA pressures are 25, 10, and 15 mmHg, respectively; normal range for pulmonary vascular resistance (PVR) is 0.9–1.4 Wood units or 90–120 dynes • s • cm–5. PVR = (ΔP)/flow, where ΔP represents the mean pulmonary artery pressure (mPAP) minus the left atrial pressure (LAP), and flow is the cardiac output (CO). The gradient between mPAP and LAP is the transpulmonary gradient (TPG). If the TPG is elevated, there is an increase in PVR; on the contrary, if the TPG is not elevated, the increase in mPAP is caused by an elevation in LAP resulting from left heart pathology. Therefore, only three physiological factors cause a rise in mPAP: (1) ↑ LAP, (2) ↑pulmonary flow (congenital heart disease with L to R shunt), and (3)↑ PVR (caused by pulmonary parenchymal/airway disease, hypoxia, interstitial lung disease, thromboembolic disease, or idiopathic pulmonary artery hypertension (PAH).[1] Because of pulmonary vascular remodeling in the long run, even factors 1 and 2 could eventually lead to an ↑ PVR, and the associated rise in mPAP will reflect both an ↑ in LAP as well as an eventual elevation in PVR. For example, patients with mitral stenosis who have an ↑ mPAP solely because of elevated LAP (without increased PVR, i.e., early or "reversible" PH) usually have an uncomplicated mitral valve replacement with little risk of RV failure after surgery. In comparison, patients with

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mitral valve stenosis associated with a preoperative ↑ in LAP, mPAP, and PVR (secondary to pulmonary vascular remodeling, i.e., "fixed" PH) may have severe RV failure after mitral valve replacement, which could lead to difficulty in weaning from bypass. Acute-on-chronic ↑in PVR are common in the perioperative period and can lead to acute decompensation in RV function. Some of the factors responsible for acute exacerbations in PVR are hypoxia, hypercapnia, acidosis, hypothermia (shivering), ↑ sympathetic tone (pain, anxiety), and exogenous or endogenous pulmonary vasoconstrictors such as catecholamines, serotonin, thromboxane, and endothelin. Early recognition and reversal of these causes of acute deterioration can be lifesaving. This educational session will be focus on the periop management of those patients with PAH/RV failure, and not that related to left heart disease.

The definition and classification of pulmonary hypertension The diagnosis patients with PAH is largely based on guidelines developed during the World Symposia on PH (WSPH). Normal resting mPAP is 14 ± 3 mmHg, with an upper limit of 20 mmHg. The significance of mPAP between 21–24 mmHg is unclear. The European Society of Cardiology and Respiratory Society define precapillary PH as a persistent increase in mPAP ≥ 25 mmHg at rest as assessed by right heart catheterization in the setting of a normal pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg, PVR ≥3 Wood units, and normal or reduced cardiac output. They define postcapillary PH as a persistent increase in mPAP ≥25 mmHg at rest as assessed by right heart catheterization (RHC) in the setting of an increased PCWP ≥15 mmHg, PVR ≥3 Wood units, and normal or reduced CO.[2]

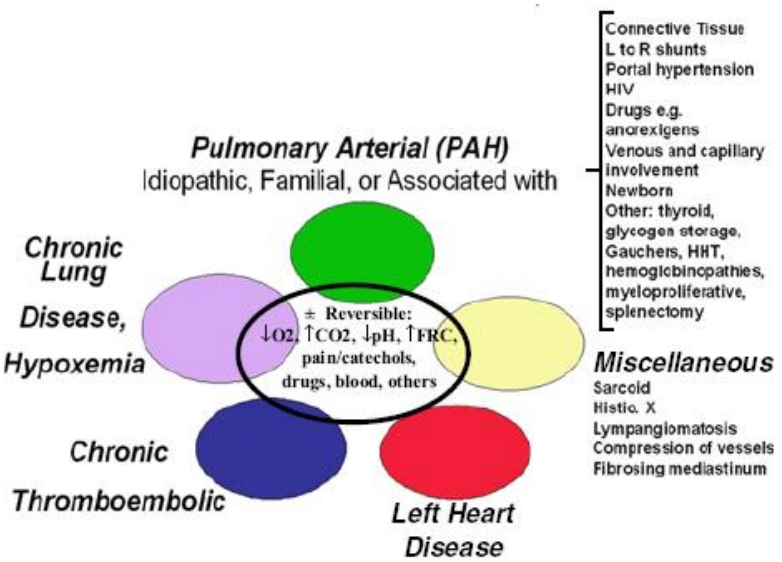

Figure 1: WHO classification of pulmonary hypertension. The definition of PH according to the American College of Cardiology/American Heart Association 2009 Expert Consensus Document on Pulmonary Hypertension is a measurement, by RHC, of a resting mPAP ≥25 mmHg, PCWP/LAP ≤15 mmHg, and PVR ≥3 Wood units.3 PH has undergone several reclassifications over the past 20 years (**Figure 1**).[4] There are 5 major categories: (1) pulmonary arterial disease (PAH), (2) left heart disease, (3) lung disease with hypoxemia (4) chronic thromboembolic PH (CTEPH), (5) unclear and/or multifactorial causes. Because this classification is not based on a physiological approach, classification into *precapillary, postcapillary*, and *mixed* PH may more useful in the perioperative period **(Figure 2).**

Precapillary PAH
Persistent ↑mPAP ≥25 mmHg at rest with PCWP <15 mmHg, PVR >3 Wood units, and normal or ↓ cardiac output

Postcapillary PAH
MPAP ≥25 mmHg at rest with PAWP ≥15 mmHg, PVR ≤3 Wood units, and normal or ↓ cardiac output

Mixed (PAH out of proportion to ↑ LAP)
Postcapillary PAH causing 2° changes in PVR

Figure 2: Physiological classification of pulmonary hypertension. (PAH = pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; LAP = left atrial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance)

Pathogenesis

PH is a syndrome resulting from a pathological increase in PVR that leads to restricted flow through the PA circulation and, ultimately, RV failure. The loss of vascular cross-section due to remodeling is the predominant reason for the rise in PVR;

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however, excessive vasoconstriction may be a significant contributing factor in about 20% of patients.[5] The vasculopathy, which predominantly affects small pulmonary arteries, consists of intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombus in situ, and inflammation. The causes are shown in **Figure 1.**

Diagnosis and investigations

Many of the patients presenting in the periop will have had a full workup and will be on the therapy. The most common presenting symptoms are related to cardiopulmonary limitation: fatigue, dyspnea, chest pain, syncope, palpitations, and lower extremity edema. Syncope is ominous and a poor prognosis. Signs of PH and RV are: tachypnea, tachycardia, distended neck veins, RV lift, TR murmur, RV S3 gallop, hepatomegaly, ascites, and lower extremity edema. ECG, chest x-ray, and transthoracic echocardiogram (TTE) display signs suggestive of PH. A TTE is essential to assess severity of PH/Rv dysfunction, as well as excluding heart disease. CTEPH must be excluded; 50% of these patients have no history of PEs. A right heart cath will delineate the hemodynamic profile and assess response to vasodilators. Targeted serology is done to delineate possible systemic disease. Liver and kidney functions assess the severity of chronic RV failure. Polysomnography is done when sleep apnea when suspected.

Long-term therapy

Treatment goals include efforts to improve functionality (6-minute walk test), lowering mPAP, normalizing CO, slowing progression, and improvement in survival.[3] Low-level aerobic exercise is encouraged. Oxygen therapy is indicated if resting saturation is < 90%. Ideally, pregnancy should be avoided. Judicious use of diuretics and a sodium-restricted diet are indicated in RV dysfunction. Calcium channel blockers are indicated in only a small group of patients with idiopathic PAH patients. BIPAP may improve PVR and RV function in patients with OSA. There are 5 classes of drugs: prostanoids (IV, SC, inhaled, and oral), phosphodiesterase inhibitors (PO), endothelin antagonists (PO), guanylate cyclase stimulants (PO), and calcium channel blockers (PO) **(Figure 3**).

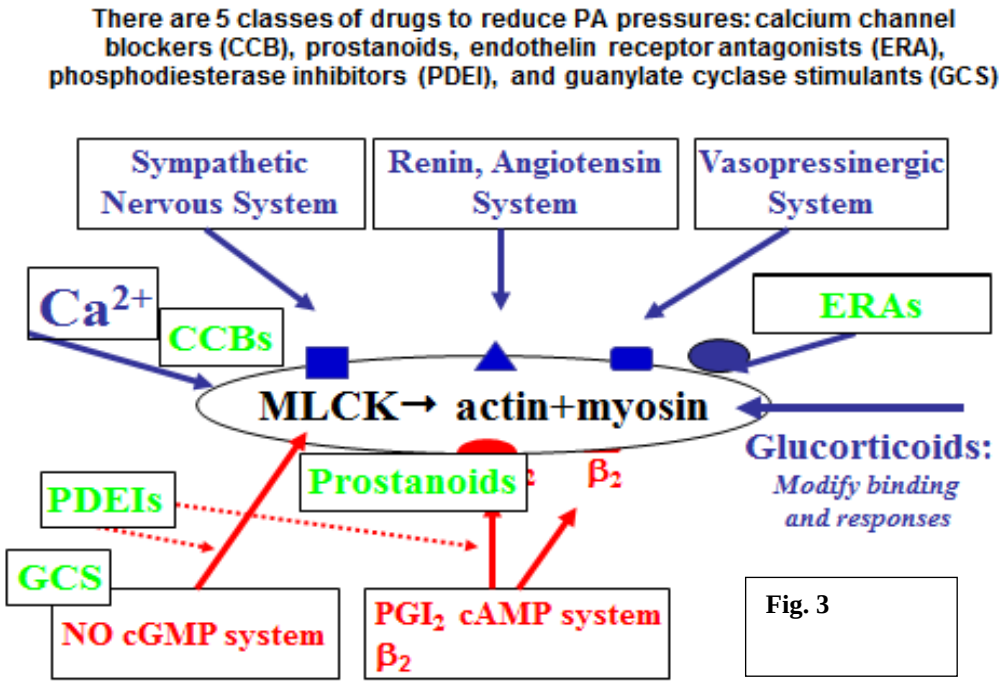

Figure 3: Classes of drugs for treating PHT. (PDEI = phosphodiesterase inhibitors; ERA = endothelin receptor antagonists; MLCK = myosin light chain kinase; GCS = guanylate cyclase stimulantors; PGI2 = prostacyclin; cAMP = cyclic AMP; cGMP = cyclic GMP; CCB = calcium channel blocker)

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The agent chosen is dependent of the disease severity, availability, cost, medical support in a particular community (ability to deliver home IV infusions), patient preference, etc. Functional class IV were often stabilized with IV prostanoid therapy (prostacyclin, treprostinil), but less invasive therapies have rapidly evolved. Treprostinil can be given subcutaneously, and iloprost can be given by inhalation. Oral prostanoid therapy is now a reality. Many patients eligible for prostanoid therapy do not receive it due to the high cost. Although tachyphylaxis occurs, the beneficial effects of prostanoids are sustained for years and many patients have been removed from heart-lung transplantation lists. Activation of endothelin receptors causes pulmonary vasoconstriction; the oral endothelin receptor antagonists (bosentan, ambrisentan, macitentan) are also used as first-line oral therapy in less severely symptomatic patients. Oral phosphodiesterases(PDE) inhibitors (sildenafil, tadalafil) are also first line agents in less severely symptomatic patients. PDE-3 and -5 are the enzymes that metabolize cAMP and cGMP respectively, the second messengers of prostacyclins and NO. PDE augment cAMP- and cGMP levels, causing vasodilation and decreased PVR. A new class of oral agent called the soluble guanylate cyclase stimulators (riocuguat) increases the production of and sensitivity to cGMP. Combinations of the various agents are also used in severe cases.

Patients whose PH is associated with Eisenmenger syndrome (R to L shunt) generally have superior survival rates compared to patients with idiopathic PAH, mainly because of decompression of a pressure-overloaded RV, improved LV filling, and a resulting increase in CO.[8] Atrial septostomy is considered a palliative procedure and may be a bridge to lung or heart-lung transplantation.[8] The shunt causes a decrease in systemic arterial oxygen saturation that is compensated for by increases in CO and systemic oxygen delivery. Pulmonary endarterectomy is an important therapy for some patients with CTEPH. Identification of these patients is important, since CTEPH is underdiagnosed has a poor prognosis if untreated.[9] Bilateral lung transplantation (and occasionally heart-lung transplantation) is the final option for a minority of patients in whom medical therapy has failed or present in an advanced stage. Only approximately 4% of lung and combined heart/lung transplants performed annually worldwide are for patients with PH.[10] Extracorporeal support is an important rescue option for acute RV failure caused by reversible causes e.g. massive PE and others. VA ECMO has also been used as a bridge to lung transplantation, support after lung transplant, treatment of severe reperfusion pulmonary edema after pulmonary endarterectomy, and for RV failure unresponsive to medical therapy.[11,12] Patients with end-stage RV failure due to idiopathic PAH have generally done poorly with RV assist devices, as the increased flow in a high resistance circuit damages the pulmonary microcirculation, causing hemorrhage.

Long term prognosis

Predictors of poor prognosis include advanced NYHA Functional Class 3 or 4, rapid symptom progression, poor exercise capacity, significant RV dysfunction, low CO, elevated brain natriuretic peptide, and an associated diagnosis of scleroderma. The best survival rates are seen in patients with congenital heart disease associated with PH. The natural history of idiopathic PAH reveals a median survival of 2.8 years with 1-, 3-, and 5-year survival rates of 68%, 48%, and 34% respectively.[13]

Perioperative RV failure in patients with PAH

Although often preventable, acute decompensation of patients with PAH during the periop period is common, may be fatal, and results in acute RV cardiogenic shock. As recent as 2002, patients with Eisenmenger syndrome undergoing cesarean section had a mortality of 70%.[14] In 2005, patients with PAH undergoing liver transplantation had a reported mortality of 80%.[15] The perioperative risks associated with PAH have improved substantially, likely as a result of better medical management, risk stratification and periop management **(Figures 4 and 5)**.

Emergency procedures, ASA class >2, intermediate- or high-risk surgery, longer duration of surgery (>3 hours), CAD, chronic renal insufficiency, history of PE poor functional class have been identified as predictors of morbidity and mortality after non-cardiac surgery. High-risk surgical procedures are: significant systemic inflammatory response, blood loss, high possibility of CO2 (laparoscopic), fat or cement emboli, and lung resection. Surgery should be delayed, if possible, if the PVR is largely fixed during vasodilator testing, or if there is moderate to severe PAH with significant RV dysfunction. Important factors that impact decisions are also shown in **figure 4**. Attempts must be made to optimize PVR before surgery, including maximizing medical therapy and preventing conditions that may cause acute deterioration. Patients on chronic PAH therapy should continue their regimen throughout

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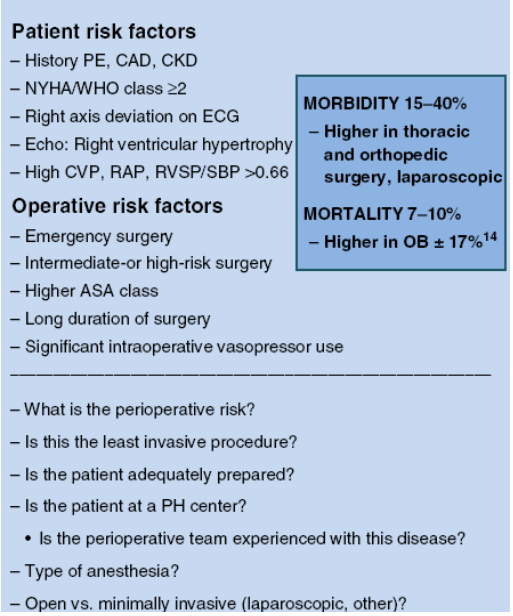
the perioperative period, as discontinuation can precipitate an acute PAH hypertensive crisis. Intravenous prostacyclin has potent antiplatelet properties and changing to inhaled therapy preoperatively should be considered, especially if increased blood loss is anticipated. In patients not on PAH-specific therapies, a preoperative RHC, vasodilator trial and PAH-specific therapy should be started. Acute perioperative decompensation and the subsequent potentially lethal RV failure are often under-recognized or misdiagnosed.



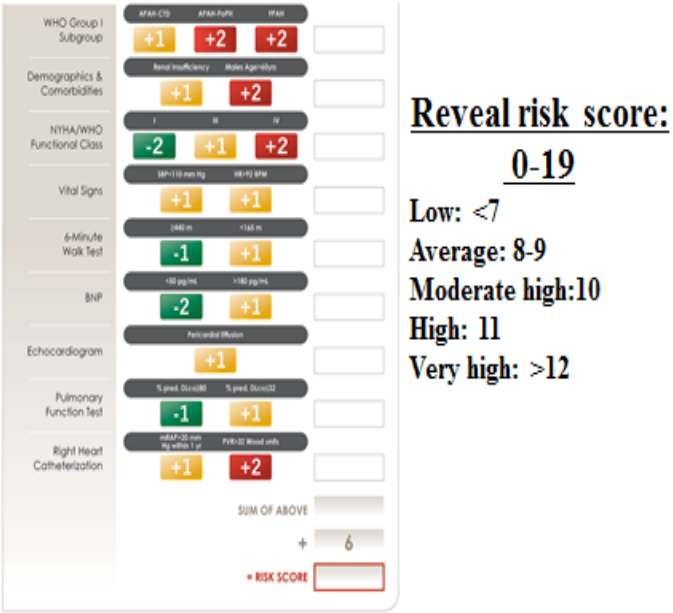


Figure 4: Perioperative risk factors.
Figure 5: REVEAL risk score.[6]

Shock caused by acute RV failure is schematically presented in **Figure 6 and 7;** it has a poorer prognosis as compared to LV. RV failure (low end-organ inflow pressure due to reduced LV stroke volume and high end-organ outflow pressure due to elevated RA pressure) has a worse prognosis than shock due to acute LV failure (only low end-organ inflow pressure) because of the *"double-hit"* on end-organs, leading to rapid multiorgan system failure. In addition, elevation in RA may cause hypoxemia by R to L shunting across a PFO. It is important to note that TR is common in acute and chronic RV failure; hence, thermodilution CO are not reliable at all. However, PA pressure measurements are useful to monitor in selected patients to assess response to vasodilators, inotropes, vasopressors and to assess the very helpful RV pressure curves (see below). Many issues in the perioperative period, some of them "minor" by themselves, can critically affect the outcome of these patients. These include, among others, the timing of extubation, meticulous management of mechanical ventilation, the surgical acumen, fluid and electrolyte shifts, balancing the positive vs. negative effects of transfusion, intravascular volume optimization, acid-base optimization (pH >7.4, PaCO2 30–35 mmHg, PaO2 >100 mmHg), avoiding hyperchloremia, temperature control, optimized analgesia, and early restarting of noninvasive ventilation.

Prevention and treatment of perioperative complications

1. *Optimize heart rate, rhythm*

Restoring and maintaining SR is critical for optimal filling of a hypertrophied/dilated RV. Because of the association of RV failure with TR, higher heart rates (80–100 bpm) may be desirable to reduce end-diastolic volume. Because an increase in RV stroke volume is limited by the increase in RV afterload, it is best to avoid bradycardia (RV CO is rate dependent). Early cardioversion should be considered; the loss of SR may lead to acute RV shock. If pacing is possible, atrial or AV pacing may improve RV cardiac output. RV pacing is usually poorly tolerated. Electrolytes

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must be optimized to prevent arrhythmias. Efforts made to mitigate mechanical irritation of the cardiac chambers by central lines (e.g. make certain the distal end of the central venous catheter does not enter the RA).

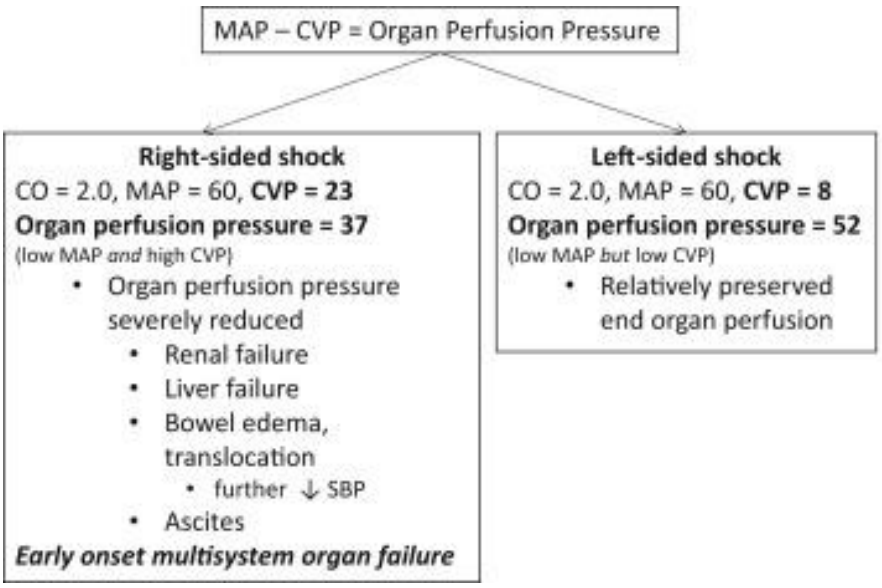

Figure 6: Comparison of left and right-sided cardiogenic shock.[1]

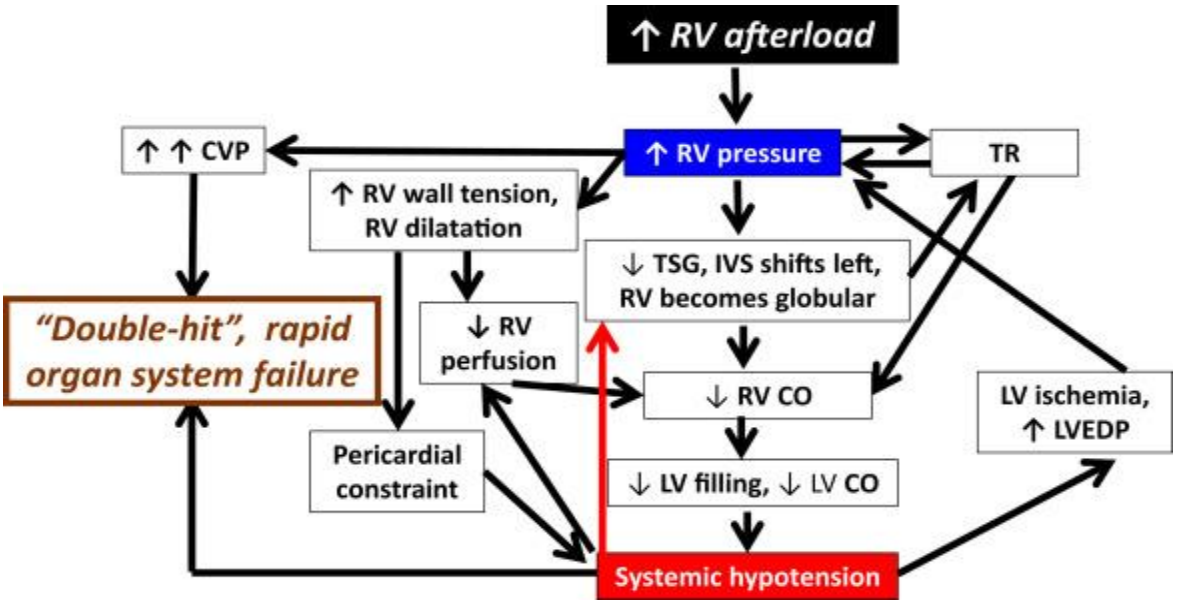

Figure 7: The rapid and lethal cycle of RV cardiogenic shock.[1] The "double-hit" consists of systemic hypotension and elevated central venous pressure (CVP) resulting in organ system failure. An increase in RV afterload or volume causes increased wall tension, septal shift due to a reduced trans-septal gradient (TSG). Tricuspid regurgitation (TR) occurs, exacerbating RV volume overload. The increased wall tension decreases right coronary artery (RCA) perfusion, resulting in ischemia. The TSG reduction reduces LV compliance, decreases preload, and results in hypotension)

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2. *Optimize RV filling*

Periop CVP monitoring is crucial. In general, if the CVP is low, the RV is "coping", even if the PA pressure and PVR are elevated i.e. the RV is "primed" (hypertrophied) as a result of being exposed to high PAP/PVR over time, or it is truly underfilled. On the other hand, an elevated CVP may imply a failing RV, especially when accompanied by ↑ size of V waves (worsening TR) and ↓ in PA pressure and CO (by clinical signs, pulse pressure, but no thermo-dilution). The compromised RV will tolerate neither hypovolemia nor overfilling; therefore, an optimal position has to be determined and maintained on the (compromised) RV Frank-Starling curve. Because the RV is mainly a "volume chamber," it is less dependent on preload than the LV. Thus, for a given ↑ in preload, a smaller ↑ in SV is expected. However, because the normal RV it is thin walled, the RV is much more afterload dependent than the LV, and RV cardiac output↓significantly with an acute↑in mPAP. Past teachings have often suggested that the RV be filled aggressively to passively increase pulmonary blood flow and CO. This may hold true when the PVR is normal (Fontan physiology), but not when it is high i.e. the case of patients with PH. Excess volume loading in these circumstances will result in acute RV distention, ↑ TR, further R to L shift of the interventricular septum, and impaired LV filling, leading to a ↓ in LV SV and CO . The resultant drop in systemic blood pressure causes decreased RCA perfusion as well as a decline in the transeptal gradient (TSG), and eventually hemodynamic collapse. This is especially true once the CVP reaches 15–20 mmHg. Assessment of optimal RV filling can be very difficult. Options include a fluid bolus (500 mL of Lactated Ringer's solution) or autotransfusion (by elevation of legs). Ongoing fluid boluses are indicated if leg elevation causes a modest (2–5 mmHg) ↑ in CVP and corresponding ↑ in PCWP, CO, and/or MAP; an ↑in only the CVP (with minimal or no change in PCWP, CO, or MAP) likely indicates RV distention and precludes further fluid boluses. A relatively underfilled RV is likely the lesser of the two evils. Bedside TTE is invaluable. If TTE is not possible, TEE should be considered if intubation was to be part of the periop plan. In patients with a PAC, monitoring RV filling pressures through continuous transducing of the RV pressure tracing is an underused but invaluable (see below). The assessment of volume status is therefore a multimodal approach; no one approach is superior.

3. *Maintain RV myocardial performance* (**Figure 8**)

This includes maintenance of RV coronary perfusion pressure and RV inotropy. Normally, RV coronary perfusion occurs during systole and diastole. However, as the PVR and RV systolic pressure ↑, flow through the R coronary artery occurs mainly in diastole, similar to left. RV subendocardial ischemia caused by myocardial oxygen supply-demand imbalance is common in PAH.

	RV Inotropy	PVR (with sPsA vasodilator)	SVR	TSG	TSG + sPA vasodilator
PDE_3I	++	↓↓	↓↓↓	↓↓	
β-agonists	++	↓	↓	↓	
Ca^{2+} sensitizers	++	↓↓	↓↓↓	↓↓	
α-agonists	--	(↓↓)	↑↑	±	↑
AVP	-	(↓)	↑↑	↔ or ↑	↑
Inotrope + AVP	++	(↓↓)	↑	↔	↑
Inotrope + NE	++	(↓)	↑↑	↔ or ↑	↑

Figure 8: The effect of vasoactive agents in RV cardiogenic shock. (TSG = trans-septal gradient; sPA – selective PA vasodilator; NE = norepinephrine; AVP = arginine vasopressin)

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Therefore, systemic hypotension and excessive ↑ in RV systolic pressure, contractility, and HR must be avoided. When acute RV failure is suspected, the systemic blood pressure must be increased immediately to ensure adequate RCA perfusion and restoration of TSG. This is achieved by optimizing volume status and with early use of norepinephrine and vasopressin. Accumulating clinical experience, as well as animal data, suggests that vasopressin causes little or no ↑in PVR, whereas norepinephrine its alpha agonism, does ↑ PVR. Vasopressin binds to peripheral V1 receptors and causes systemic vasoconstriction, while stimulating NO release and vasodilation in the pulmonary circulation. The choice of anesthetic technique (GA vs. regional) and the anesthetic agents used are much less important than understanding the physiological perturbations. All anesthetic agents and techniques cause varying degrees of myocardial and autonomic nervous system depression. In this regard, volatile agents, propofol, thiopental, narcotics, ketamine, and etomidate can all be used in the appropriate manner. Contractility may need to be enhanced in the acutely failing RV with either a β-adrenoreceptor agonist (dobutamine) or PDE-3 inhibitor (milrinone). If the ↑ in RV CO not offset the ↓ in SVR, blood pressure will decrease, resulting in ↓ RCA perfusion and a ↓ TSG. The combination of low-dose dobutamine and low-dose milrinone is synergistic in inotropy and has fewer negative effects on SVR.

Invasive and non-invasive monitoring is helpful to guide management **(Figure 9)**. CVP is crucial monitor. If CVP is low, RV cardiogenic shock is unlikely. However, excessively high CVP (venous congestion) contributes to decreased vital organ perfusion. Temporal trends and response of CVP to fluids and inotropes is a seminal part of managing RV shock. Efforts should be made to decrease CVP to < 20 mm Hg. The PA catheter is very useful in patients with RV shock. PAP response to therapy can be monitored; both an increasing or decreasing PAP can be signs of worsening problems. An increasing PAP and decreasing CVP might indicate an improved CO flowing through the high PVR system. A decreasing PAP and increasing CVP is indicative of a very low CO.

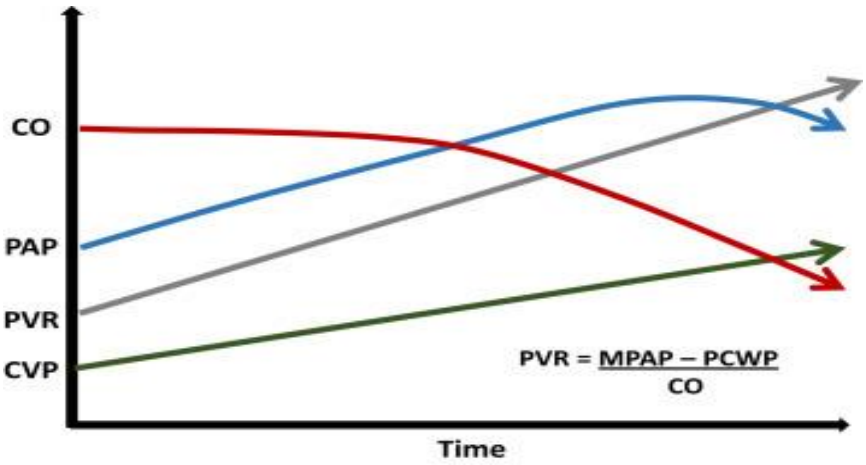

Figure 9: Invasive and non-invasive monitoring in RV shock.[1] Relationship between cardiac output (CO), pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), and central venous pressure (CVP). As pulmonary pressures increase, CO will decrease. MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure)

Mixed venous saturation is a valuable surrogate for CO, but will be misleading in presence of intra-cardiac shunting. PH and RV distention are invariably associated with TR. Acute TR underestimates thermodilution CO (tdCO) when the CO is high, and overestimates when CO is low. Mild TR has minimal effect, but severe TR underestimates tdCO. Consequently, tdCO should not be used in RV cardiogenic shock. Monitoring overall RV function with continuous RV pressure transduction through the RV port of the PAC is invaluable **(Figure 10)**, which shows progression form a flat (A) diastolic pressure relationship (i.e. a normal, compliant RV), to the non-compliant square-root type waveform in the failing, pressure-overloaded RV.

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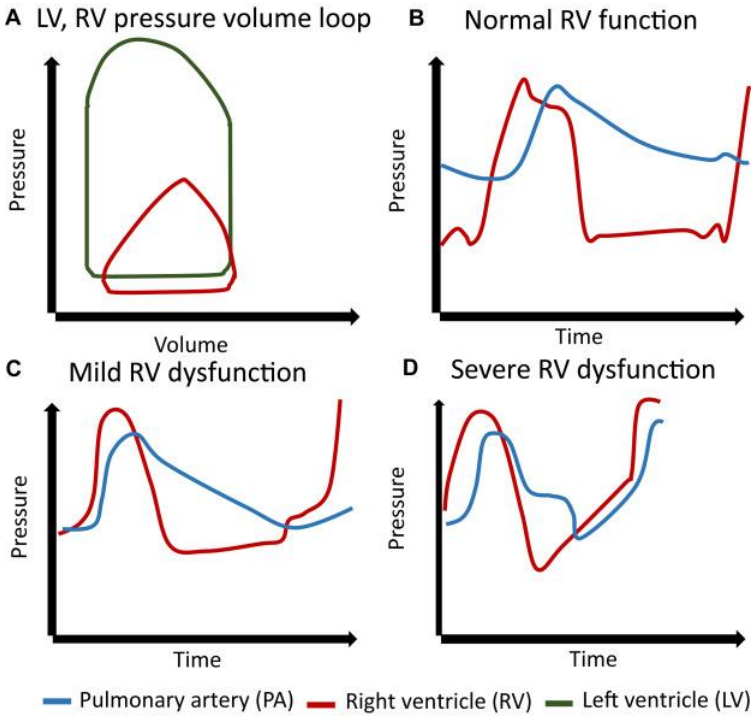

Figure 10: Monitoring the RV port of the PA catheter.[1]

3. *Maintain the TSG and RV geometry*

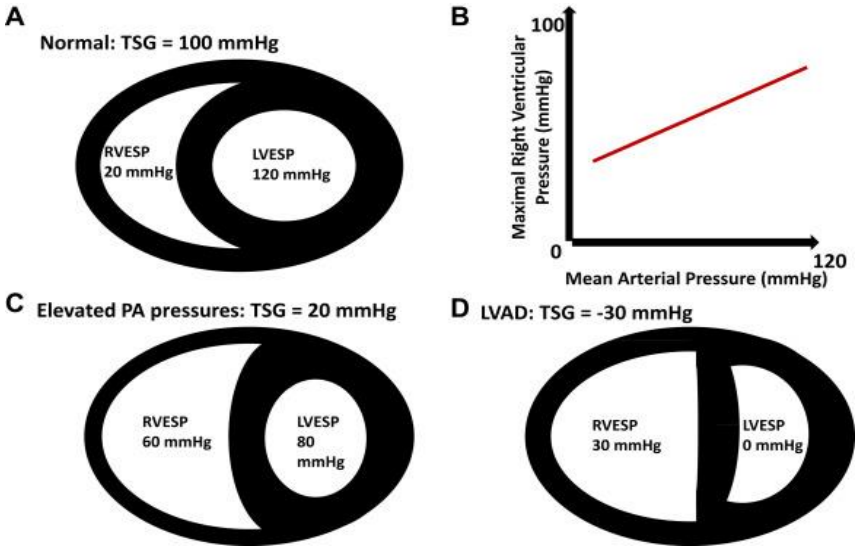

Figure 11: The critical concept of trans-septal gradient.[1] (RVESP = right ventricular end systolic pressure; TSG = trans-septal gradient; LVESP = = left ventricular end systolic pressure; LVAD = left ventricular assist device)

At normal systolic pressure (RV 20 mmHg, LV 120 mmHg, **Fig 11A**), there is a large TSG (TSG = 100 mmHg) which is responsible for bulging of septum towards the RV (i.e. the normal configuration of the IV septum); this provides a "base: for the free wall to contract against. The septal component accounts for more than 50% of RV systolic function. It is important to note that the peak pressure that an RV can develop is proportional to systolic blood pressure (**Fig 11B**), and hence maintaining a high systolic pressure is a crucial aspect of managing a failing RV. Therefore, conditions that reduce LV systolic pressure (systemic hypotension) or increase RV systolic pressure will reverse the TSG and severely compromise RV function. In patients with PHT, the RV pressure in increased, the

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systemic pressure is often reduced because of reduced CO, and hence the TSG is very reduced **(Fig 11C)**. This situation is very important when patients are implanted with an left ventricular assist device (LVAD, **Fig 11D**), when the LV pressure becomes very low (close to zero) and hence the TSG become negative; this is an important reason why there is such a high incidence of RV failure after LVAD placement. This reduction in the TSG causes a change in the orientation of cardiac myofibrils. The normal helical nature of myocardial fibres and bands will unfold and lead to a globular, dysfunctional RV **(Figure 12).** Septal function be compromised because of misalignment of the obliquely oriented septal myofibrils to a transverse configuration, resulting in less contractile force, but the free wall loses its sturdy "base" as the distance between the free wall and the septum increases (the result of leftward septal bowing). In order to restore the TSG, the PVR needs to be reduced and LV systolic pressure needs to be aggressively maintained or increased. This is critical!

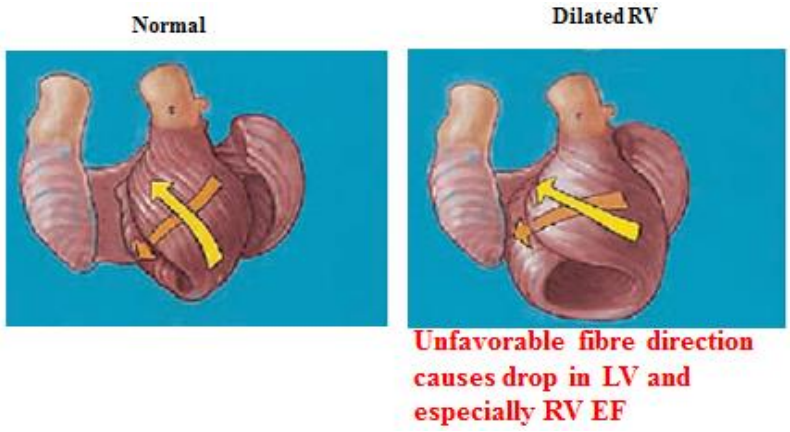

Figure 12: The normal helical orientation of cardiac fibers (A), and the unfolding of the helical orientation of the fibers as a result of RV dilatation (B), and reduced RV ejection fraction.[5]

4. *Reduce the PVR*

Perioperative hypoxemia, hypercapnia, atelectasis, pleural effusions, hypothermia, fluid overload, pain, and anxiety all cause acute rises in PVR with resultant RV decompensation. Patients on chronic therapy for PAH should continue established treatment. Functional residual capacity (FRC) must be carefully maintained, as both hyperinflation and atelectasis cause an increase in PVR. The important relationship between lung volume and FRC during mechanical ventilation is U - shaped with PVR the lowest at FRC **(Figure 13).** At low lung volumes, hypoxia and hypercapnia cause hypoxic pulmonary vasoconstriction; on the other hand, hyperinflation causes compression of intraalveolar vessels with a resultant increase in PVR in both circumstances. PEEP >15 mmHg also leads to an increase in PVR. In contrast to systemic arteries, PAs constrict with hypoxia (Euler-Liljestrand reflex) and dilate with hyperoxia. Therefore, perioperative ventilation strategies for patients with PH should incorporate high concentrations of oxygen, low TV (6 mL/kg of predicted weight), a respiratory rate sufficient to achieve mild hypocapnia, and optimum PEEP (5–10 cmH2O). Early drainage of pleural effusions and recruitment maneuvers should be considered. Intravenous air or particulate material (precipitated drugs) should be meticulously avoided as R to L embolization through an open PFO may occur. In addition to the aforementioned physiological considerations, the PVR can be reduced by selective PA vasodilators. Unfortunately, none of common the IV vasodilators (NTG, SNP, CCB) are selective to not cause accompanying catastrophic systemic vasodilation; these agents could also potentially worsen hypoxia by inhibiting HPV. They should not be used. Similarly, IV prostacyclin should not be started during a crisis. Inhaled PA vasodilators are a crucial part of the management of the PAH/RV failure crisis when non-pharmacological methods have not corrected the increased PVR. Inhaled PA vasodilators improve V/Q matching and arterial saturation, which in itself decreases PVR and reduce PVR with much less systemic effects. Unfortunately, there are few outcome studies and most of their use is based on case reports, institutional experience and protocols. It is advisable that all centers that that deal with perioperative PH develop a plan for what inhaled pulmonary vasodilator they will use. One such proposed algorithm for their use is shown in **Figure 14**. Unlike the IV PA vasodilators, these agents have little effect on SVR. Inhaled nitric oxide (iNO) is a selective PA vasodilator (increases cGMP production) that is almost immediately inactivated by binding to Hb and is easy to use. Other agents that have been given by inhalation include sodium nitroprusside, nitroglycerine, prostacyclin, milrinone, iloprost, sildenafil, treprostinil and others. Rapid weaning of any inhaled agent can lead to rebound PAH. The

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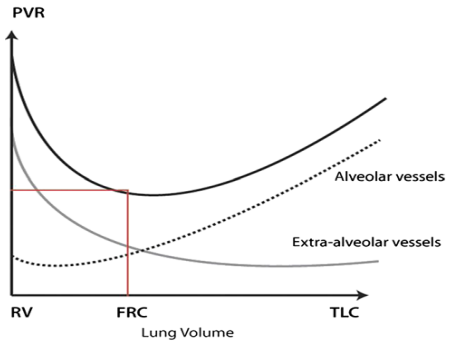
powerful inhaled prostanoids treprostinil and iloprost are ideally suited to use in the perioperative period, although there is little published.



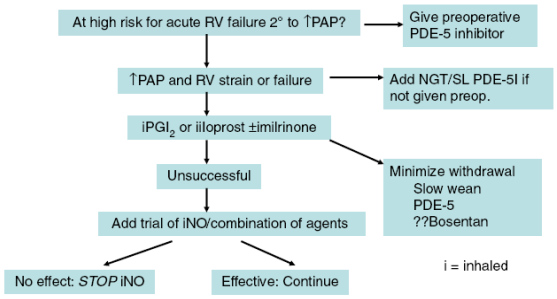


Figure 13: The relationship between lung volume and pulmonary vascular resistance.[4] (RV = residual volume; FRC = functional residual capacity; TLC = total lung capacity)

Figure 14: An algorithm for use of inhaled pulmonary artery vasodilator therapy in perioperative RV failure.[4] (PDE5I = phosphodiesterase 5 inhibitor e.g. sildenafil; NGT = nasogastric tube; SL = sublingual; NO = nitric oxide; iPGI2 = inhaled prostacyclin)

No one inhaled agent has been shown to have better outcomes. A combination of these agents, working at different receptor sites, may give have added benefit on PVR reduction. What is crucial is that the medical center has an algorithm for inhaled PA vasodilator use, that the practioners are familiar with it, and that the inhaled agents are immediately accessible. The PDE-5 inhibitor sildenafil has been used to manage acute RV dysfunction in heart transplant recipients, wean patients from iNO, reduce the duration of mechanical ventilation, and prevent pulmonary endothelial cell dysfunction after prolonged CPB. It also extends and potentiates the effects of iNO. Sildenafil has a significant first-pass metabolism, so the sublingual route (25-50 mg dissolves readily 1ml of sterile water) is an easy way to augment the inhaled agent.

5. *Mechanical circulatory assist*:

Peripheral VA ECMO is an option for acute RV failure that is not responsive to medical therapy and if the overall patient condition is conducive to this intervention. In the appropriate patient this should not be a “late” event but should rather be instituted before the onset of multiple organ system dysfunction. VA ECMO will serve as a bridge to recovery of RV function due to reversing the precipitating event and optimizing medical therapy, and some situations, as a bridge to a heart-lung transplantation. Pure RV assist devices have little or no role in acute RV cardiogenic shock due to a PH crisis as the high flows through a high resistance lung causes pulmonary bleeding. RV assist devices may of course have a significant role in RV cardiogenic shock due to mainly RV contractile dysfunction in the absence of severely abnormal pulmonary vascular resistance.

Conclusions

The periop management of patients with PAH and associated RV dysfunction is complex and requires a thorough understanding of the pathophysiology. Failure to make an early diagnosis of RV shock and institute the correct therapy will lead to high perioperative morbidity/mortality. The anesthesiologist must be aware of the potential treatment strategies including optimizing physiological parameters, use of selective PA vasodilators, inotropic support, and systemic blood pressure maintenance. Wherever possible, these patients should be cared for in specialty centers.

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