



CRITICAL CARE CLINICS



theclinics.com

Preface



Mark D. Siegel, MD
Guest Editor

In the developed world, routine ICU monitoring includes daily chest radiographs, laboratory tests, continuous telemetry and oxymetry, real-time hemodynamic and respiratory measurements, and on-demand CT and echocardiography. The relationship between close monitoring and better outcomes is, perhaps surprisingly, taken as a matter of faith. Careful surveillance may reveal unsuspected abnormalities that lead to timely therapy. Alternatively, monitoring may ensure that interventions achieve desired goals. Monitoring is a key component of several treatments that improve survival, such as low tidal volume ventilation and early goal-directed therapy for ARDS and sepsis, respectively [1–4].

Monitoring is not universally beneficial, however. It can potentially be useless or harmful, particularly if the resulting therapy is ineffective. Sometimes insufficient skills preclude benefit [5]. More often, an ill-considered instinct to correct physiologic or laboratory abnormalities can be harmful. In the past, before permissive hypercapnia was routine, intensivists undoubtedly contributed to the deaths of many intubated asthmatics while attempting to correct respiratory acidosis [6]. More recently, mounting evidence suggests harm when low transfusion triggers are used for anemia [7,8]. In dramatic fashion, Swan Ganz catheters, once the definitive ICU monitoring tool, are approaching obsolescence, with multiple trials failing to show benefit [9].

When it comes to ICU monitoring, neither naïve faith nor nihilism is appropriate. Intensivists should judge monitoring tools by the insight they provide and the outcomes that accrue. To do this, clinicians should understand

technical and physiologic underpinnings and consider the evidence supporting a link between monitoring and outcome. To this end, we have devoted this issue of the *Critical Care Clinics*. The range of topics covered by our all-star panel should interest all intensivists. We begin with a novel review by Friedman and colleagues that provides practical advice on choosing, designing, and implementing an electronic medical record. Next, Marik and Baram offer a comprehensive overview of noninvasive hemodynamic monitoring, after which Magder provides an elegant discussion of invasive techniques. Lui and colleagues follow with a timely piece devoted to intra-abdominal pressure monitoring, and Ezzie and colleagues present a provocative critique of routine laboratory testing. Next, Sakharova and Inzucchi thoughtfully review the benefits and sometimes unexpected pitfalls of metabolic monitoring. Two masterful reviews devoted to the central nervous system follow. The first, by Gunther and colleagues, addresses screening and assessment of cognitive dysfunction, while the second, by Wartenberg and colleagues, describes multimodality techniques used in neurocritical care. Next, Rubinowitz and colleagues provide a comprehensive overview of diagnostic imaging, replete with instructive images, advice on choosing appropriate tests, and a guide to interpretation. Two pulmonary reviews follow. The first is a state-of-the-art manuscript by Bekos and Marini devoted to monitoring mechanical ventilation. The second, by Siner and Manthous, offers a novel critique of methods used to assess readiness for liberation from the ventilator. Finally, we round out this issue with a contemporary overview of severity of illness and organ failure assessment by Afessa and colleagues and a compelling discussion by Berenholtz and Pronovost devoted to monitoring patient safety.

I would like to thank the contributing authors, whose exquisitely written manuscripts were a pleasure to read. I am indebted to Lisa Richman at Elsevier, whose editorial support ensured this issue of the *Critical Care Clinics* would be a “must-read” for the critical care community. Finally, I want to thank the four wonderful women in my life—Heide, Gabrielle, Isabella, and Francesca—who monitored me closely throughout the project and ensured that laughter, great food, and reality checks were always abundant. Their steady support assured there would be no doubt about this collection’s outcome. Guest Editor photograph by Gabrielle O. Siegel.

Mark D. Siegel, MD
Pulmonary & Critical Care Section
Department of Internal Medicine
Yale University School of Medicine
PO Box 208057
333 Cedar Street
New Haven, CT 06520-8057, USA

E-mail address: mark.siegel@yale.edu

References

- [1] Dombrovskiy VY, Martin AA, Sunderram J, et al. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med* 2007;35:1244–50.
- [2] Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–77.
- [3] Stapleton RD, Wang BM, Hudson LD, et al. Causes and timing of death in patients with ARDS. *Chest* 2005;128:525–32.
- [4] Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301–8.
- [5] Iberti TJ, Fischer EP, Leibowitz AB, et al. A multicenter study of physicians' knowledge of the pulmonary artery catheter. Pulmonary Artery Catheter Study Group. *JAMA* 1990;264:2928–32.
- [6] Darioli R, Perret C. Mechanical controlled hypoventilation in status asthmaticus. *Am Rev Respir Dis* 1984;129:385–7.
- [7] Gong MN, Thompson BT, Williams P, et al. Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. *Crit Care Med* 2005;33:1191–8.
- [8] Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999;340:409–17.
- [9] Rubenfeld GD, McNamara-Aslin E, Rubinson L. The pulmonary artery catheter, 1967–2007: rest in peace? *JAMA* 2007;298:458–61.

Implementing an Electronic Medical Record

Lloyd N. Friedman, MD^{a,b,*}, Neil A. Halpern, MD^{c,d},
James C. Fackler, MD^e

^a*Pulmonary and Critical Care Section, Department of Internal Medicine,
Yale University School of Medicine, New Haven, CT, USA*

^b*Intensive Care and Respiratory Therapy, Milford Hospital,
300 Seaside Avenue, Milford, CT 06460, USA*

^c*Departments of Anesthesiology and Medicine, Weill Medical College
of Cornell University, 525 East 68th Street, New York, NY 10021, USA*

^d*Critical Care Medicine, Respiratory Therapy, Department of Anesthesiology and Critical
Care Medicine, Memorial Sloan-Kettering Cancer Center,
1275 York Avenue, New York, NY 10021, USA*

^e*Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School
of Medicine, Blalock 901, 600 N. Wolfe Street, Baltimore, MD 21287, USA*

Having endured the difficult challenge of selecting and implementing an electronic medical record (EMR), we felt it important to share our experience. We will consider the practical aspects of justifying, planning, implementing, and budgeting for an EMR. The acceptance of such systems has become possible as a result of the increased operating speed of computers and networks, the ability to connect wirelessly to a hospital network, the growing facility of health care workers with computers, and increased pressures from the public and from regulatory agencies to drive efficiencies [1–5]. We will summarize the process for physicians, nurses, information technology experts, and administrators who are considering implementing a system

Lloyd N. Friedman, MD: Scientific Advisory Board, Stock, Cardiopulmonary Corp., Milford, CT.

Neil A. Halpern, MD: Medical Advisory Board, Instrumentation Laboratory, Lexington, MA; Global Care Quest, Beverly Hills, CA; Scientific Advisory Board, Cardiopulmonary Corp., Milford, CT.

James C. Fackler, MD: Consultant, Stock Options, Cerner Corporation, Kansas City, MO; Medical Advisory Board, Stock Options, Global Care Quest, Beverly Hills, CA; Scientific Advisory Board, Cardiopulmonary Corp., Milford, CT.

* Corresponding author. Intensive Care and Respiratory Therapy, Milford Hospital, 300 Seaside Avenue, Milford, CT 06460.

E-mail address: lloyd.friedman@milfordhospital.org (L.N. Friedman).

in their intensive care unit (ICU) and/or hospital, or have a partial system that they would like to enhance. It has been stated that “the introduction of an EMR system in a ≥ 200 -bed institution should be considered to take the same order of magnitude in time as the completion of construction of a new hospital building” [4]. There cannot be enough planning and preparation.

The goal of such a system is to allow the critical care physician the ability to review, thoroughly and within minutes, all of the information required to care for a critically ill patient, including reference material, without ever having to leave the mobile computer at the point of care, except to examine the patient.

An entirely paperless system would be most desirable, but if that is not immediately attainable, a secondary objective would be to get as close as possible and then scan any remaining documents into the EMR.

Designing an EMR for an ICU cannot be accomplished in a vacuum. An ICU must receive information from many parts of the hospital, eg, laboratory, radiology, pharmacy, medical records, admitting, and so forth. Likewise, an ICU must send information, often in the form of orders, to various departments, eg, laboratory, pharmacy, billing, central supply. Representatives from each of these areas must be intimately involved in the planning process. A physician champion must ensure that each discipline is designing its part so that staff physicians receive **ALL** pertinent information. Important data from a clinical area, eg, a comment on a specimen from the microbiology lab or a comment from a nurse in the operating room, may not necessarily flow to the EMR unless, during the development process, a physician ensures that it does. If there is minimal physician involvement, and the installed EMR is found to be cumbersome to use, it may be too late for corrective action. Thus, a competent, computer-literate physician champion must oversee the entire process, including the selection of the system, and must be accountable to the medical staff with frequent exchanges concerning the strengths and weaknesses of the system.

The features of an EMR that are desirable for the efficient functioning of an ICU may be found in [Box 1](#). A list of terms and abbreviations used in this chapter may be found in [Box 2](#).

Efficiency, safety, and regulatory issues

Leapfrog Group, Institute of Medicine, Institute for Healthcare Improvement, and HCIT

Organizations such as the Leapfrog Group [6], the Institute of Medicine (IOM) [7], and the Institute for Healthcare Improvement (IHI) are pushing the health care system toward health care information technology (HCIT) implementation. In the setting of critical care, Leapfrog is well known for its support of the intensivist-led model of critical care. Leapfrog also has

Box 1. Desirable features of an EMR in the ICU

- access to all vital signs, vascular monitoring, pulse oximetry, and waveforms
- immediate access to laboratory values, pathology reports, microbiology reports, and radiology images and reports.
- immediate access to electrocardiograms and rhythm strips
- online medication administration record with documentation of changes and explanations, eg, glucose values for insulin drip changes, PTTs for heparin drip changes
- input and output records with intravenous drip documentation and cumulative shift totals (drips must be noted in cc per hour as well as dosage per unit time or dosage per kilogram per unit time, where indicated)
- computerized physician order entry
- progress notes and nursing notes
- access to online medical reference information
- clinical decision support
- access to face sheet information, eg, insurance, next of kin, contact phone numbers
- e-mail within the system between all users

articulated the demand for implementation of computerized physician order entry (CPOE). Some, but certainly not all, data suggest that CPOE can reduce medication errors with computer-based error checking (for duplicate and/or dose errors) and improved patient identification procedures (see section on CPOE). The federal government also is pushing for HCIT systems, as both houses of Congress have introduced HCIT legislation and the president has created the Office of the National Coordinator for Health Information Technology (ONC). It generally is believed that universal implementation of HCIT will save billions of health care dollars [8].

JCAHO

The Joint Commission also has had a heavy hand in encouraging hospitals to migrate toward HCIT implementation. The Joint Commission is one of the entities that, as part of its survey function, verifies that a hospital is compliant with the Medicare Conditions of Participation. There are survey standards that assess how hospitals have migrated toward electronic communication of information. As an example, a new standard for medication reconciliation throughout all levels of care went into effect on January 1, 2006 [9]. Medications must be reassessed and verified at each transfer of care (eg, ICU to floor) so that no important medications are omitted, and

Box 2. Terms and Abbreviations

- APC–ambulatory payment classifications—a system used by Medicare to categorize outpatients into disease/payment categories
- Closed unit—An ICU where intensivists become the primary attending once the patient is transferred. It is not closed with respect to consultants.
- Core Measures—a JCAHO quality requirement that monitors indicators for the management of various diseases. Results are sent to the federal government and are available to the public. Examples include the use of appropriate medications for myocardial infarctions, and the appropriate and timely use of antibiotics for pneumonia.
- COWs—computer on wheels—mobile carts with computers that are wirelessly connected to the network.
- CPOE—computerized physician order entry
- DRG—diagnosis-related groups—a system used by Medicare to categorize inpatients into disease/payment categories.
- eMAR—electronic medication administration record (an electronic version of the MAR)
- EMR—electronic medical record
- Failover—a process whereby a backup component is automatically and seamlessly exchanged for a component that has failed
- HCIT - health care information technology
- HIPAA—Health Insurance Portability and Accountability Act of 1996. Ensures the privacy and security of patient data.
- HL-7—Health Level 7—refers to the structure and definition of health care data that can be exchanged within and between organizations; uniform definitions help ensure the proper exchange of information between vendor software
- I/O—fluid input and output records
- IHI—Institute for Healthcare Improvement
- IOM—Institute of Medicine
- IT—information technology
- JCAHO—Joint Commission on Accreditation of Healthcare Organizations. This organization is the usual path to document compliance with the Medicare Conditions of Participation that allow hospitals to receive payments from Medicare.
- Leapfrog—group of large health care purchasers organized to initiate improvements in the safety and overall value of health care to American consumers

- MAR—the medication administration record that is kept by the nurses on paper. It documents all medications that have been administered, who administered it, what time it was administered, and whether a scheduled dose was held.
- MD PnP—medical device plug and play (see PnP below)
- ODBC—open database connectivity—a standard database access method that allows access of data by any ODBC-compliant software program
- ONC—Office of the National Coordinator for Health Information Technology (also called ONCHIT)
- PACS—Picture Archiving and Communication System—computerized storage system for digital radiographs
- PnP—plug and play—This refers to the ability to plug a module, eg, pulse oximetry, directly into a portal that recognizes the unit and begins communication with the EMR.
- RFID—radio frequency identification
- RFP—request for proposals—a formal list of specifications that vendors use to submit a detailed bid
- SAN—storage area network; can be used for backup
- Tablet—a personal computer with an interactive screen that can be used for touch screen operations, writing, and drawing, sometimes with an attached keyboard
- 24/7—24 hours a day, 7 days a week

any medications that no longer are necessary are discontinued. Medication reconciliation can be simplified if HCIT provides data across the continuum of ambulatory to critical care and back to ambulatory environments. Since this requirement is relatively new, many vendors currently are attempting to create a usable process. For those hospitals considering the purchase of a system, a written guarantee is advisable to ensure that a medication reconciliation process is available. JCAHO Core Measures compliance also is an essential part of the functioning of any hospital and can be facilitated and monitored through the use of order sets in the EMR [10].

FDA

The Food and Drug Administration (FDA) has taken the position that “computer systems used to create, modify, and maintain electronic records and to manage electronic signatures also are subject to the validation requirements. Such computer systems must be validated to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records” [11]. The issue is not at all trivial; an FDA analysis of 3140 medical device recalls conducted between 1992 and 1998 showed

that 242 (7.7%) were attributable to software failures [11]. As decision support systems become more prevalent, the need for FDA oversight will become more relevant. Those systems with clinical decision support most likely will require FDA approval in the future.

HIPAA

HIPAA compliance is mandatory for any EMR. The privacy and security of patient data must be ensured. In each hospital, there is a HIPAA compliance officer who should be involved in the selection and implementation of the system to verify adherence to the regulations. Examples of such compliance include a prohibition against loaning a password to others; automatic log out of terminals if inactive for a period of time; and audit trails to determine whether confidentiality has been breached. The security of all wired and wireless connections must be ensured.

Care standards, safety, and efficiency

There is no doubt that an EMR in the ICU has the capability of improving information access [12]. It also is clear that easy access to data with specific reporting tools in a computer-based system can facilitate compliance with important care standards [10]. In one study, compliance with simple regimens such as deep vein thrombosis prophylaxis, stress ulcer bleeding prophylaxis, and elevation of the head of the bed to 30 degrees increased from as low as 32% to greater than 95% [10]. However, deciding whether CPOE is helpful or harmful has been more problematic [13], and will be discussed in detail later.

Infection control

Infection control personnel must ensure that computers and monitors do not become reservoirs for infection. They must consider whether computers on wheels (COWs) are allowed into patient rooms, whether skins are used for keyboards, and how often they are cleaned or changed. They must ensure that computers in the operating room (OR) do not pose an infection risk. These considerations will be important in complying with state regulations for infection control.

Develop a team and a plan

Develop an interdisciplinary working group and an initial assessment

It is vital to develop an interdisciplinary team to help choose and implement a system. This team must include high-level, hands-on representatives from administration, IT, nursing managerial staff, medical staff, pharmacy, medical records, admitting, finance, laboratory, materials management,

outpatient centers, human resources, and other ancillary services such as rehab, dietary, respiratory, case management, social services, infection control, HIPAA committee, etc.

Initial decisions that must be addressed include cataloging all existing systems within the hospital, determining whether they will be replaced or integrated into a new system, developing rough estimates of budgets and manpower (include hardware and personnel costs), and developing an oversight team which, at a minimum, should comprise IT, nursing, administration, and a physician champion. Other considerations include such issues as whether the ICU is an open or closed unit (implementation will be easier in a closed unit where fewer attending physicians need to learn the intricacies of the system) and whether or not housestaff rotate through the ICU (housestaff will be more willing to work with an imperfect system).

Develop a list of vendors

The list of potential vendors should not include just those that are within budget. The very best products should be assessed to ascertain the state of the art, and whether it is reasonable to compromise in selecting a less-expensive alternative. Plan for presentations from up to 10 or more vendors. Ensure that the vendors are prepared to show you a working demo with real data. A system that is not easy to navigate for an untrained physician at a demo will not likely become easy once installed. Determine for each vendor the number of years in business, sales figures, the size of the company, the number of years the product has been in use, the number of installations, the client retention rate, the track record for “sunsetting” software products and forcing clients to upgrade, bankruptcy contingencies, and the availability of 24/7 support. Also consider whether the system can support multiple sites and whether it has an integrated physician office component, if that is something that the organization wishes to pursue. A list of potential vendors from Frost and Sullivan may be found in [Table 1 \[14\]](#). This list, from a 2006 publication, comprises the industry leaders, but by no means is all inclusive. When the list of vendors is narrowed, plan site visits with the entire interdisciplinary team. A checklist for evaluating vendors and developing a budget can be useful, and one has been provided as a starting point ([Box 3](#)).

Interfacing old systems versus replacing with a new system

Most hospitals already have computer systems in place to facilitate work in such areas as billing, admitting, medical records, laboratory, materials management, and payroll. Thus, the first question a hospital must ask is whether to integrate current systems into a new system, or whether to replace all existing systems with one all-encompassing integrated hospital system. The team should develop a list of all current hospital systems with their pros and cons. Determine what improvements would be desirable, and whether the potential vendor meets those needs. If the old system is much

Table 1
Intensive care information systems market: solutions by major market participants (United States), 2005 [14]

Company	IC IS product name	Connectivity	Core features and functions in a typical installation	Optional features
Cerner	Cerner Critical Care (part of the Cerner Millennium family of Unified IT Systems)	Integrated into Cerner's HIS, also interfaces with non-Cerner systems Interfaces with bedside devices Interfaces lab and radiology databases	Patient care planning and coordination task integration; Nurse documentation; e-Medication administration record; Physician documentation; Evaluation and management documentation coding; Clinical lab and radiology results; Computer physician order entry; Outcomes analysis; Decision support	Evidence-based critical care alerts
Eclipsys	Sunrise Clinical Manager	Integrated to Eclipsys enterprise EMR or HIS Physiologic monitoring interface Remote access over the Web Sequel server .NET coding	Patient flow sheet; Clinical documentation for nurse; Documentation for physician; Nursing assessment; e-Medication administration record; Clinical decision support; Clinical summary; Clinical data repository; Review of lab, radiology data; Charge-capture–auto-populated; Electronic signature inbox	Computer physician order entry; Bar coding at point of care for bedside medication

Epic	EpicCare	Vital signs and clinical hemodynamic parameters monitoring interface	Patient flow sheet; Nurse documentation; Physician documentation; e-Medication administration record; Clinical decision support and trending; Clinical summary; Clinical data repository; Review of lab, radiology data	Computer physician order entry; IV management module documentation
iMD Soft	MetaVision Suite	Interfaced to hospital information system and ADT; Connectivity with patient monitors and physical device monitors (ventilators and infusion pumps); Interfaced with clinical lab results; Includes a wave form module, allergy module, PACS imaging interface, care plan module and digital video cath module	Flowsheet—automates workflow and brings patient device monitoring measurements into the flowsheet; Computer physician order entry; Nurse documentation; Physician documentation; Documentation for all other care givers—respiratory, physical therapy, nutrition, etc; Event manager—automatically reviews patient parameters, event alerts, trending; ICD-9 or -10 coding—multidisciplinary procedural coding; Remote connectivity and remote patient monitoring for Tele-intensivist activities	Native order entry but can interface to a hospital's existing CPOE; Structured form builder in Microsoft Word; Event manager able to evaluate at the patient level, the department level and hospital-wide; Decision support—queries, data mining; Offers a scaled down version for the step-down units

(continued on next page)

Table 1 (continued)

Company	IC IS product name	Connectivity	Core features and functions in a typical installation	Optional features
McKesson Provider Technologies	Horizon Clinicals	Incorporated into its integrated inpatient documentation solution; Captures patient vital signs	Patient flow sheets; Nurse documentation; e-Medication administration record; Physician documentation; Physician evaluation and management coding; Clinical lab and radiology results; Outcomes analysis	Computer physician order entry (optional); Charge-capture (optional)
MediTech	MediTech Management	Integrated to enterprise EMR or HIS Remote access over the Web	Patient flow sheet and tracking; Nurse workflow and documentation; Physician documentation; Order entry; Bedside medication verification; Clinical decision support and trending; Review of lab, radiology data	Available in a Microsoft Windows-based client/server platform Available in its proprietary operating system, Magic

Misys Healthcare Systems	Misys Optimum	Integrated into its Computer Patient Record, computer physician order entry, lab and pharmacy solutions	Patient care planning and coordination task integration; Computer physician order entry; Clinical lab and radiology results viewing; Online outcomes data analysis Point of care and remote Web access	
Philips Medical Systems	Care View and Care View Chart	Interfaced with electronic medical record Interfaced with bedside devices and medical devices such as ventilators Lab and radiology available at point of care	Patient flow sheet, tracking, census; Incorporates controlled medical terminology (SNOWMED); Nurse documentation; Physician documentation; Evaluation & Management coding; e-Medication administration record; Clinical decision support and trending; Review of lab, radiology data; Patient care planning and coordination	Computer physician order entry (optional as stand-alone solution or able to tie into existing enterprise CPOE solution)

(continued on next page)

Table 1 (continued)

Company	IC IS product name	Connectivity	Core features and functions in a typical installation	Optional features
Picis	CareSuite Critical Care Manager	Integration with Enterprise Information Systems as needed; Automated collection of and connectivity with patient monitoring and medical devices; Integration with clinical results databases—labs, radiology; and with pharmaceuticals; Multi-facility support; Client/server-based with remote connectivity	Patient care planning and coordination; Patient flow sheet of charted care at point-of-care; Lab and radiology data available at point-of-care; Controlled medical terminology; Nurse workflow and documentation—including the medication administration record; Physician documentation; Documentation templates; Online notifications and patient-specific alerts; Evidence-based critical care alerts; Evaluation and management coding; e-Medication administration record; Standard and customized reports; Outcomes analysis and reporting; Clinical decision support and trending	Computer physician order entry (optional as stand-alone solution or able to tie into existing enterprise CPOE solution)

Siemens	INVISION Clinicals	Interfaced with electronic health record through its enterprise access directory Interfaced with bedside devices and medical devices Web-based interface for point of care and remote access	Patient flow sheet, tracking, census; Nurse workflow and documentation; Physician documentation; Online notifications and patient-specific alerts; Evaluation and management coding; e-Medication administration record; Clinical decision support and trending; Review of lab, radiology data; Patient care planning and coordination	Computer physician order entry (optional as stand alone solution or able to tie into existing enterprise CPOE solution)
---------	--------------------	--	--	---

Abbreviations: ADT, (admit/discharge/transfer); CPOE, computerized physician order entry; EMR, electronic medical record; HIS, health information systems; ICIS, intensive care information systems; IT, information technology; PACS, picture archiving communication system; SNOWMED, Systematized Nomenclature of Medical Clinical Terms (also referred to as SNOWMED CT). Created by the College of American Pathologists, SNOWMED CT standardized medical terms used during diagnostic analysis, including laboratory results and other diagnostic procedures. (From Boone C, Sherry K. Intensive care information systems market: solutions by major market participants. U.S. high-acuity care information systems markets, N07D-48. Palo Alto (CA): Frost & Sullivan; 2006. p. 114–18; with permission.)

Box 3. Checklist for evaluating vendors and developing a budget (see text for more detail)

- Form an interdisciplinary team
- Keep medical and hospital staff informed about all progress
- Analyze current systems
- Develop a comprehensive written detailed specification of system expectations within each department
- Assemble a list of vendors and determine the capabilities of each
- Determine whether each vendor has a module for each clinical and nonclinical department (eg, lab, radiology, nursing, emergency department [ED], anesthesia, human resources, payroll, medical records)
- Determine for each vendor the number of years in business, sales figures, size of company, number of years the product has been in use, number of installations, client retention rate, track record for “sunsetting” software and forcing clients to upgrade, bankruptcy contingencies, and availability of 24/7 support
- Determine how each vendor handles routine maintenance (time of day and support staff); can they access the system remotely
- Decide on integration of old systems versus an entirely new system (discuss data conversion possibilities and costs with the vendors)
- Decide on full versus stepwise implementation
- Begin vendor presentations/demos
- Look carefully at all displays and give careful attention to laboratory data, dictations, intravenous medication drips in the fluid I/O display, eMAR, CPOE, nursing data and notes as they display in the EMR, physician note entry methods with electronic editing and signing, physician notifications
- Assess potential EKG modules and telemetry strip interfacing
- Identify all necessary subscription files (eg, pharmacy formulary lists, DRG/APC classification software, medical necessity software) and ensure that interfaces are possible
- Assess PACS vendors and discuss possibility of interfacing
- Look at all other modules that might be interfaced (eg, infusion pumps, bedside monitors, pulmonary function tests, fetal monitoring, automated medication cabinets, bar coding, sophisticated physician login methods) and ensure that interfaces are possible

- Check JCAHO compliance—ability to perform medication reconciliation, core measure data acquisition, etc.
- Check HIPAA compliance—audit trails, automatic log off
- Determine whether outside medical reference sites can be launched from the EMR
- Review discharge procedures—patient instructions, prescriptions, interfacility transfer forms
- Review the final paper printout of a hospital admission
- Assess hospital wired and wireless infrastructure
- Assess hardware and personnel requirements (adequate number of computers and COWs, adequate personnel for IT, increased hours required for installation and training)
- Assess methodology, equipment, and personnel needed for remote physician access
- Assess need for backup and redundant systems
- Narrow vendor list, make site visits and check all of the above in detail
- Create an RFP, based on the written detailed specification, that will be used to solicit bids from the vendors
- Choose one or more vendors and develop contracts—incorporate holdback, develop a time line, and price protect features that you are not sure you are buying
- Identify potential consultants
- Select a vendor, finalize a contract, and create an all-inclusive budget

better than the component in the new system, will interfacing with the old system be possible, and at what cost?

Cost and work of integrating old systems

The cost and time of integrating old systems into new ones are considerable, and are not always attainable. Bidirectional interfaces must be written by the vendors of the old system and the vendor of the new system so that information can be exchanged. These interfaces do not always work properly and do not always survive upgrades or fixes to the new or the old systems. They must be maintained continually to ensure that information is passing through correctly. The more old systems that are integrated, the more problems will occur in the future as changes, upgrades, and fixes are implemented in either system, and the higher the expense of maintaining the interfaces. Although it may be more disruptive initially, replacing all of the old systems with a single integrated system may save time and effort in the long run. In this way, one can ensure that one company is responsible

for integrating all of the information, and hopefully, upgrades will be seamless to the users and to the hospital support staff. It may not seem obvious at the time of purchase, but once an EMR problem arises in a multivendor system, each vendor may blame the other, and it may be very difficult to get the technical staff of either vendor to work on the problem. Furthermore, with multiple systems, multiple passwords to access various components can become roadblocks to efficient functioning.

Historical information conversion if a new system is chosen

If a single vendor is chosen, there still is the issue of conversion of historical information into the new system. The easiest way to deal with replacing old systems is to start fresh with a new system and leave the old systems running concurrently. This is cumbersome for the physicians who now have to access both systems, although after a period of a few weeks, there is less and less need to refer to the old system. Exceptions include old radiology and pathology reports, and dictations, where such information is needed often and should be converted. If much of the information is in the HL-7 format, data migration will be facilitated, but depending on the size of the files, such conversions can be costly and must be assessed up front. Often, the conversion is accomplished by a separate vendor. It never is as easy as the vendor claims, and sometimes cannot be accomplished at all. There must be assurances that conversions can be completed in a timely manner, as well as guarantees in writing with financial penalties if not delivered on time, since failure to perform can delay the overall project.

Full versus stepwise implementation

The implementation of a system can be accomplished all at once or in steps, depending on the size of the support staff. If it is accomplished in steps, the same number of consultants and staff can be deployed at each stage. Each step can include as many components as the staff can manage. However, if installation is accomplished all in one stage, there will be enormous personnel costs, and the hospital risks that the physicians will reject the system and ask that it be removed, as happened to the CPOE module at Cedars Sinai Medical System, in January 2003, after only 3 months of use [15].

Identify potential consultants

EMR vendors or other hospitals often can advise whether consultants are necessary for implementation. Often, this is related to the amount of support that the vendor supplies. Knowledgeable consultants who have had experience installing the chosen system can save enormous time and aggravation. These consultants should be identified as early as possible so that there is no delay in implementation. The scope of work and time line for

each consultant should be delineated. Often, separate consultants will be required for separate modules within the system. Consultants should be interviewed personally to determine the true extent of their knowledge of the system, as well as the number and success of previous installations. References must be checked carefully.

The request for proposals and the contract

Each hospital department must develop a written detailed specification of every clinical and technical item that the system must address. These written expectations will serve as a list that will help determine if the delivered system performs as promised. This comprehensive list will be modified to serve as the backbone for a request for proposals (RFP) that will allow the vendors to develop a bid that meets the scope of expectations. The implementation time line for a comprehensive EMR may take years. If components are installed or potentially installed along a time line, ensure that they are price-protected. A “holdback” must be part of the contract so that a percentage of the payment can be held back until the hospital is completely satisfied that the entire system is working as designed. Incorporate a vendor bankruptcy plan, which might include obtaining the source code. Ensure 24/7 support for the system.

The budget

Make rough estimates of budgetary needs early in the process. The purchase of the system may not be the largest expense. Be sure to include consultant costs, computer and server purchases, network costs, maintenance, personnel costs, and other software and interface costs. The IT staff must be enhanced to handle the tremendous increase in technology that will occur, as well as the need for 24/7 support for the system and the individuals using the system. Nursing and others must budget for many extra hours for training purposes.

Components of a full system

To promote physician acceptance, one should approach the development of the system in two broad categories, passive (eg, laboratory data, reports) and active (eg, writing progress notes, CPOE). Passive components should be installed first. The nursing module should be next, and may be disruptive for the first few weeks until nurses become familiar with the system. After the dust clears, one can consider proceeding sequentially with the active physician components (ie, daily progress and consultant follow-up notes, and CPOE). A test system must be in place where modules can be assessed fully before implementation; physicians should be able to navigate swiftly through the labs, radiographs, and reports.

Initial components: laboratory, microbiology, pathology, radiology, and dictated reports

The easiest, although by no means easy, part of the task of achieving a fully functional EMR is the implementation of the laboratory module. Laboratory analyzers can download results such as hematology and chemistry values directly and accurately into a patient's record in the EMR. Almost all hospitals have such systems, and are comfortable with them. To gain acceptance from physicians, the transition to a new system must be relatively seamless. The format of the new EMR lab data must be either very similar to, or must improve upon, the previous data display. Also, as mentioned earlier, it is an expensive and almost impossible task to convert old laboratory data into a new system. The best way to approach this is to start using the new system, keeping the old system running so that old labs will be available on a designated monitor on each ward. Within 1 to 2 weeks, no one will be dependent on the old system. However, for pathology and radiology, we recommend converting old reports into the new system. This can be extremely useful when faced with a returning patient.

As part of the lab implementation, microbiology and pathology sections also must be installed. In some cases, these may be in separate modules. Radiology reports also should be available. This can be accomplished with or without a Picture Archiving and Communication System (PACS). A discussion of PACS is beyond the scope of this chapter, except to say that one should see proof that the PACS integrates effectively with the EMR (visit a site where integration has occurred), and one should consider up to 10 or more PACS vendors before selecting a system. It is important to look at the speed of accessing a plain radiograph, a CT scan, or an MRI while in the EMR. The reports should be accessible while one is actually looking at a film. One also must budget for an adequate number of radiology workstations and viewing sites (includes two 3-megapixel monitors), which can be very costly. Radiologists often use voice recognition software to read the films, and this must integrate with the PACS and with the EMR. Finally, the team should visit a site that has been operational for a few years to see if there is a delay because of large volumes of stored data.

It also is advisable at this stage to develop access to all dictated reports. This is not a difficult task and can be accomplished within the medical records module either with transcribers within the department or with a transcription service. Ensuring easy electronic editing and signing by physicians is part of this process.

Pharmacy

It is desirable to engage the pharmacy at a relatively early date. This can be accomplished in parallel with or slightly after the laboratory implementation. We are not referring to physician order entry. We are referring to

medication management and charges, and recording ordered medication dosages and frequencies within a patient's EMR. Although physicians may be able to view the current medications, they still will have to refer to the handwritten medication administration record (MAR) for the documentation of the actual administration of medications, until the installation of an electronic medication administration record (eMAR) occurs.

When the pharmacy is online, a list of the medications that have been ordered may or may not be available to physicians, depending on the vendor. If it is available, it can be very useful, but may not always be accurate, eg, information about the initiation or discontinuation of a stock medication, such as dopamine, may not make its way to the pharmacy until later, if at all. Information about medications that have been held will be available on the paper MAR, but the only way to ensure an accurate medication list in the EMR is to install an eMAR, and one should try to accomplish this early in the process of component implementation. Furthermore, if automated dispensing cabinets are used, this may enhance the accuracy of the pharmacy data, but budgetary concerns must be addressed, and interfacing with the EMR must occur. As part of the overall process, the pharmacy may have to purchase and upload a comprehensive formulary list to address all inpatient and outpatient orders and prescriptions.

Order entry and order history

Order entry can be accomplished by CPOE, but often CPOE is installed later in the process. Until that time, nonmedication orders can be entered by the ward secretary after verification by the nurse. This information must flow accurately to the pertinent departments and must be transmitted to billing. Written medication orders can be verified and signed by nurses and can be faxed to the pharmacy where they are entered into the EMR.

The order history refers to the list of orders that have been written during a patient's hospitalization. The capability should exist to view these orders in chronological or reverse chronological order, by physician, by type of order (eg, pharmacy, lab, PT), or by status (eg, completed, active, pending).

Electronic medication administration record

The eMAR is a vital component of the EMR. Physicians constantly look at the paper MAR to determine if any medications were held, to find the time of administration, to see how much narcotic was administered in the preceding 24 hours, or to see how much acetaminophen a febrile patient received. A properly constructed eMAR will describe the time of every dose, whether a dose was held, will define why a prn dose was given or why a drip rate was changed, and will allow for a quick view of a complete history of the administration of that medication. The physician must ensure that these capabilities exist within the system, and that they are displayed properly in the EMR.

To ease the burden on the nurses, it is desirable to have medicines and patient identification bracelets that are bar coded, so that proper identification occurs and doses are entered correctly as medications are administered. This process potentially can reduce nursing errors.

Nursing

Nursing flow sheets

Nursing modules usually are assessed and implemented by the nursing department. However, the implementation decisions made by nursing may not always yield an output in the EMR that is physician friendly. It is important that vital signs, input and output, and other information entered by nurses are in an easily accessible format where 24 hours of important information can be viewed without too much scrolling or waiting. It is important to review a patient record with periods of frequent (eg, every 5 minutes) vital signs to make sure that vital data during a critical event can be viewed easily.

Nursing assessments

Nurses also must create care plans and record daily assessments. These can be typed in a narrative format or completed by using templates and “charting by exception.” Often the choice is to chart by exception where each assessment, such as the abdominal exam or cardiopulmonary exam, is evaluated and, if nothing is noted, a note is created with a list of normal symptoms and signs. There are drop-down menus to record positive findings. We cannot overemphasize the importance of ascertaining exactly where these assessments appear in the EMR, and determining the accessibility and readability of a shift’s worth of nursing documentation. The loss of the narrative discussion may be problematic for some physicians, and trying to follow the numerous assessments can become so cumbersome that the physician rarely ventures into them and simply asks the nurses about the events of the current and previous shifts. Furthermore, physicians from different specialties should ensure that appropriate inpatient information is accessible, eg, gastroenterologists need to see the number and quality of stools, heme testing, and nasogastric drainage amounts; surgeons need to see notes about wound care, and output from drains and pleural drainage devices; and oncologists need to see pain assessments and the amount of morphine administered to control a given level of pain.

I/O’s and drips

Fluid input and output (I/O’s) displays must be intuitive with the ability to view sequential 24-hour totals, sequential 8-hour totals, sequential 1-hour totals, and cumulative totals since admission, and must include medication drip rates and volumes. The output display must include line items for drains, dialysis, urine, nasogastric suction, and so forth. Medication drip

rates (eg, dopamine, heparin, insulin) must be displayed accurately in terms of volume as well as dosage (eg, $\mu\text{g}/\text{kg}/\text{min}$). This is extremely important in the ICU, and must be ascertained at a live site to ensure that the system can handle multiple drips and display the information accurately.

Notes and assessments from other services

There must be a designated method for entering and viewing notes from disciplines such as social services, case management, dietary, rehabilitation services, respiratory, and others. These notes must allow for viewing chronologically or in reverse chronological order, all together or by discipline. Most often, these notes are typed.

Styles of progress note entry

The method of entry of physician notes is an issue that requires much thought, planning, and discussion. It is second only to CPOE in terms of difficulty with physician acceptance. The problem usually is not with house staff or employed physicians. They can take the time to learn a system and all of its quirks because they are on-site all of the time. However, private MDs may be reluctant to spend extra time entering an electronic note. Several options exist and will be discussed below. Ideally, a note should be populated automatically with vital signs, laboratory data, and reports, and the physician should enter only subjective and objective findings, assessment, and plan. The Medicare Conditions of Participation and JCAHO now state that notes all be date and time stamped, and since compliance with this may be nearly impossible with handwritten notes, there may be an urgent need to transition to electronic notes. To facilitate acceptance, the system should accept multiple methods for entering a note, as noted below.

Dictation

Physicians often dictate their histories and physicals and initial consult notes and can continue to do so for the EMR. Usually, follow-up notes are handwritten; however, it is possible to dictate these notes using the same system. Certain vendors allow a voice file to be displayed in the EMR so that other health care professionals can listen to the dictation before the transcription actually appears. This is a relatively easy way to initiate the use of electronic notes, but there is a cost to the hospital, and a delay in the appearance of the typed note.

Typing and templating

EMRs allow physicians to type their notes directly into a note section. Some also allow sophisticated physician-specific templating with automatic display of labs and reports. However, even sophisticated templating requires some typing, and slow typists will be resistant to this method.

Voice recognition

Voice recognition has come a long way in recent years. Separate modules exist for different specialties and can be associated with templates. These modules require training, not only for the system to recognize the dictator's voice, but also for the dictator to understand how to use the system to correct errors and complete the document. Some physicians will never be trained adequately, sometimes because the system cannot accurately decipher their speech, or because they simply are reluctant to spend the time to learn the system. Some vendors might be willing to test a large sample of doctors to assess their ability to use the system, and determine the feasibility of attaining universal compliance. The cost of installation, training, and licenses for these systems can be high.

Handwriting recognition

Handwriting recognition on a PC tablet also is surprisingly good. Even very sloppy handwriting often can be ascertained by the programs. However, once the physician starts using more obscure terms and drug dosages, the system does not perform as well. If the physician writes slower and neater, results may improve. These systems may be tested on any tablet PC without having to incorporate them into an EMR, so that the planners can have some direction even before purchasing the EMR.

Handwriting into a picture file

If there are no other options, and the doctors cannot accept any of the options noted above, the record can never become truly electronic in real time. Handwriting by physicians onto a tablet is a simple solution, but is not offered routinely, although scanning a handwritten note in real time may be offered. Some vendors state that allowing a handwritten note defeats one of the purposes of an EMR, ie, to prevent illegible handwriting and improve documentation and coding as well as the flow of physician-derived information to other parts of the EMR. However, we assert that if physicians will not accept other alternatives, it is better to have an electronic medical record that can be accessed from any location, even one with sloppy notes, rather than one that is incomplete. The Medical Records Department no longer would have to collate paper charts and store records, and could downsize and reduce costs for the institution. This option could be offered to the few physicians who refuse or are incapable of mastering other techniques, or to those who use the hospital infrequently when they cover other physicians, but it would allow the hospital to develop a plan for full implementation of physician notes with gradual conversion over time for those who are unable to master the electronic note initially.

Furthermore, physicians, especially surgeons, occasionally need to draw a picture of their findings. If a photograph is taken (eg, during endoscopy or for a dermatologic lesion), it should be possible to incorporate it into a note. Thus, for several reasons, it is essential to allow picture files into notes.

EKG systems

The ability to read live EKGs online is an important part of an EMR in the ICU, and usually must be accomplished by interfacing with another vendor. It should be part of an overall system that allows storage and interpretation online. Rhythm strips from telemetry or the ICU also are an important feature, but are not necessarily included in the EKG systems that are on the market.

Other clinical areas

Emergency department

Often, vendors have separate ED modules within their system. If not, separate ED systems are purchased and must be interfaced with the EMR. ED systems often have a public “tracker” on a large LCD or plasma screen in the ED so that the staff can determine where a patient is, what tests have been ordered, what tests have been completed, and how long a patient has been in the ED from the time of triage or registration. It is a very effective method for managing patients and flow in the ED. Another part of the module is physician and nursing documentation. The format of a chart in the ED is not the same as the format of an inpatient chart, and thus, one should evaluate the ED module closely before purchasing the entire system to determine whether the module will serve the ED satisfactorily, and will integrate seamlessly (vital signs, I/O, medications, and so forth) with the inpatient electronic medical record if the patient is admitted.

Anesthesia/OR module

Similarly, a separate anesthesia module also is required that is specific to the needs of the anesthesiologist. Vital signs must be documented, and administered medications, fluid, blood, and anesthetic agents must be entered. An interactive tablet for graphic input might be desirable. Not all vendors have anesthesia modules, and it is important to note that an OR module does not necessarily contain an anesthesia module. The OR module handles scheduling, all of the day-to-day use of materials in the OR, the use of medications, specifics of room use and timing of surgery, sponge counts, and so on. Anesthesia modules are separate entities and stand-alone modules can be very expensive. It is possible to set up a process where the anesthesia record is scanned into the EMR in the hope that a chosen vendor will develop a reasonable module in the near future. However, even if the decision is made to scan the written record, it still is essential to enter the fluid input and output, blood, and medications directly into the EMR.

Other data

Each hospital has additional services that also must find their way into the EMR. They include pulmonary function tests, fetal monitoring, dialysis

services, and electroencephalography, among others. It is not always necessary to integrate each of these systems. It is possible to simply scan reports into the EMR, or allow a portal to access modules such as a fetal-monitoring system. For dialysis, fluid input and output and vital signs should be entered directly. One should ensure that the system has the capacity to store and retrieve these scanned reports expeditiously so that they do not clog the system after several years of input. Some vendors actually have modules that accept and organize these scanned documents.

Efficient documentation of material usage also is important. The use of bar-coded materials on the wards, associating their use with bar-coded patient bracelets, probably is the most practical method of documenting the use of materials such as IVs, dressing changes, and so forth. It probably is worth the extra expense so that all of the materials used can be attributed to a patient.

The system must be robust and allow the hospital to function in its usual way. If the system has no fields to satisfy certain functions, there should be methods for entering data in user-defined fields.

Computerized physician order entry

Although a consensus statement had been developed to help guide institutions through the process of CPOE implementation [16], only 9.6% of US hospitals in 2002 had CPOE completely available, and even in those hospitals, not all physicians used it [17]. The Leapfrog Group considers CPOE to be an important safety measure; however, it is not completely clear that CPOE truly saves lives or reduces medication errors [13]. Although there are studies that show a reduction in errors [18,19], a reduction in adverse drug reactions [20], and no increase in mortality [21], others have shown increased mortality [22], increased medication errors [23], an increase in physician documentation time of 238.4% [24], and numerous unintended adverse consequences [25]. It has been suggested that the increased mortality in the study by Han and colleagues [22] was attributable to inadequate preparation for CPOE implementation, inappropriate policy and process changes, insufficient infrastructure, and lack of critical care order sets [26]. Sittig and colleagues [27] published an important list of lessons to be learned from the Han study that should be reviewed by any team attempting to install CPOE. Although features such as medication interaction checking and dose range checking can improve safety, it still is possible to choose the wrong patient, the wrong drug, or the wrong dose [28]. "Well educated health informaticians are needed to manage and guide the implementation process"[29], and physicians must be intimately involved in every step.

One of the values of CPOE is the possibility of developing order sets that can be individualized for each physician. These order sets should be evidence-based; there are systems that can integrate with CPOE modules to provide such evidence-based order sets, or they can be developed de novo.

Order sets should be clear and self-explanatory. If a set of “cardiac enzymes” is ordered, for example, it should be possible to know the details of the order before selecting it.

Individual orders should be easy to select. The process should be similar to writing orders on paper. As each order is selected, it should populate a list that can be viewed *before* signing. Physicians should have a list of favorite orders, or mini-sets of orders that can be combined to complete a full set. Adjustments for renal failure should result from a prompt or from a semi-automatic adjustment feature. Before a list of orders is signed, it should be easy to change a dose or a frequency. Dosage selections should focus more on usual patient doses rather than on the strength of the pill. Drug interaction algorithms can help ensure that any potential harm can be averted, but the hospital should have the ability to set the level of severity that is checked since the module can slow to an unusable crawl if all interactions are checked. As the module is tested, try to imagine how the least computer-literate, most impatient, physician would navigate.

Consider what happens when a patient is transferred to another bed. Are all of the orders brought forward for review so that medication reconciliation can occur? If a doctor transfers a patient from the ICU to the floor with a revised set of medications, and the patient is not actually transferred that day, can the system accommodate this variation and implement the ordered medications even though the transfer hasn’t occurred physically? Try to envision as many scenarios as possible and test whether they are handled satisfactorily.

Discharge procedures

At the time of discharge, numerous functions must occur. The order to discharge must be written, outpatient medications and equipment must be ordered by electronic prescription, discharge and medication instructions must be printed, and facility transfer forms must be populated and printed. States often have standard forms for interfacility transfer, and the EMR should be able to populate most of the fields automatically. Some EMRs facilitate all of these processes and can even assist with the conversion of current medications to prescriptions for outpatient use.

Additional integration of ICU parameters into the system

There is a vast amount of data arising from physiologic monitors and bedside medical devices. Often referred to as “real-time” data, these are discrete data elements such as heart rate (from multiple sources such as EKG, pulse oximetry, and from intra-arterial catheters), respiratory rate, and arterial and venous blood pressures. There also are continuous waveform data (such as those from the arterial waveform, the EKG, the pulse oximeter, the end-tidal CO₂ monitor, and pressure volume loops from a mechanical ventilator). Further, there are data coming from devices such as

infusion pumps that currently are never tracked (eg, occlusion events). Ultimately, such data should be available in the EMR in real time. This will be possible in the near future.

Practically speaking, nurses cannot care effectively for critically ill patients if they must take the time to document vital signs every 5 minutes. Currently, vendors have written interfaces to incorporate static vital sign data directly from monitors into the EMR. It is important to know the protocol for downloading this information. Will the system incorporate an automatic noninvasive blood pressure measurement into the current vital signs even if it was taken more than 15 minutes earlier? A better option is to allow the nurse to evaluate the patient and decide to upload a set of data that he or she has reviewed. There are additional data that also are desirable, including ventilator data and infusion pump data. Interfaces are possible with these as well, but their development can be cumbersome. A more recent initiative, however, holds promise. Providers, academics, and industry are collaborating to develop plug and play (PnP) solutions for medical device connectivity. Medical devices should connect, communicate, and interact as easily as computer peripherals connected to a USB port, yet medical devices do not even have standard plugs. Some devices still are manufactured without data connection capabilities. For those devices that do communicate, the data elements are sent inconsistently and the data are transmitted in device idiosyncratic formats. One pulse oximeter will send the oxygen saturation and heart rate but not the signal strength, another will send the heart rate averaged over 8 seconds, whereas another averages the heart rate over a 20-second period and does not send the wave form. Even data labels are not standardized. The medical device (MD) PnP initiative [30], born within the Center for Integration of Medicine and Innovative Technology (CIMIT), is focused on delivering solutions to all of the problems described above. We believe that PnP will be successful because of the emergence of what Seiver called fourth-generation critical care information systems [31]. Fourth-generation systems are characterized by far more tightly integrated data with workflow tools and clinical decision support. If providers come to rely on a clinical decision support algorithm that monitors patients receiving patient-controlled analgesia (someday automatically manipulating the pump) using data from physiologic inputs, or if they are relying on pulse oximeter and/or end-tidal CO₂ data, and any of these devices become nonfunctional, providers must be able to unplug the bad device and plug in a new one, in real time, with minimal effort. MD PnP will make this happen, and although manufacturers may be reluctant to deliver at this moment, contracts for major purchases are beginning to include PnP demands.

Novel data displays, which coalesce the flood of data into meaningful patterns, also are on the near-term horizon. Because no human can effectively monitor all of these data streams, and because as much as 94% of threshold alarms may be clinically irrelevant [32,33], it is hoped that functional clinical decision support algorithms, such as multiparameter alarms

(eg, comparison of heart rate from multiple sources) and/or the use of control chart analysis of single or multiparameter signals, will be developed and propagated. Hopefully this will improve the current state of the art, where more than 25% of unintended adverse consequences in one survey were related to clinical decision support [25].

So called “dashboard technology” also is on the horizon where data are keyed to specific patients. The EMR efficiently links multiple systems and data together to the dashboard for simultaneous display in designated windows (most likely with some aspects in hidden windows), which might include laboratory, real-time vital signs, input and output, recent progress and consultant notes, nursing assessments, medication lists, EKGs, real-time rhythm strips, ventilator settings and waveforms, and radiology images. Filters can be programmed to prelaunch all images and data; for example, once a patient is selected, the dashboard already has launched the image system behind the scene, and every item of patient data either is on the screen or is accessible immediately by opening a window.

Wireless data acquisition

Wireless in critical care

To further facilitate the efficient acquisition of data from the bedside, and to free the patient from multiple connecting wires, one must consider “going wireless” [34]. The ultimate goal of hospital informatics managers and intensivists should be an EMR that is capable of accepting, assimilating, managing, storing, and displaying data generated through hospital systems and ICU bedside devices. Wireless technology allows a variety of bedside devices (ventilators and pumps) that are stand-alone and mobile to be “connected” to the patient, to network servers, and ultimately to the EMR. An added advantage of improved connectivity is the possibility of “virtual” grouping of like bedside devices to create a “community” of similar devices that can be viewed simultaneously. For example, respiratory therapy might concomitantly view all mechanical ventilators, or biomedical engineering might track the location, perform diagnostics, upload software, and download reports on all infusion pumps at one time. Thus, three conceptual wireless ICU constructs emerge, each of which can be introduced in phases. First, medical devices at the bedside can be networked wirelessly to device-specific servers or directly to the EMR. Second, the wireless devices throughout the ICU or hospital can be viewed remotely as their own independent wireless communities. Third, all bedside devices and personnel can be grouped with the patient to create a cohesive “bedside” patient-device-provider network.

Installing a wireless network

Creating a secure wireless ICU that prohibits intrusion should be addressed in the context of creating a secure wireless hospital. Wireless access

will be critical as nurses use medication COWs to document administered doses, and physicians use laptops or tablets to enter notes at the bedside. Adequate wireless communication to each bedside must be assured. The key element of wireless networking is the access point: a bidirectional “Wi-Fi” (802.11) transmitter/receiver that provides a zone of wireless coverage. The system must be capable of simultaneously handling multiple devices and adjusting to changes in wireless workload. It must be monitored continuously to ensure seamless and redundant wireless coverage, especially in the setting of physical renovations and occasional access point failure.

Once the ICU has installed sufficient wireless coverage, the transition to wireless operations can begin. The following are a few examples of common bedside devices available in wireless format:

Physiological monitors

Physiological monitors are present at every ICU bedside and typically are networked through wired connectivity to a central station. Monitoring companies now also support on-board wireless systems [35,36]. The wireless technology usually is available in smaller, portable units, although stationary bedside units also can be wireless. EKG leads are available in Bluetooth (short-range wireless) format [37]. Bluetooth also is available commercially for pulse oximeters and other devices [37]. Researchers currently are working to apply wireless connectivity to transducers for invasive blood pressure monitoring.

Mechanical ventilators

Unlike physiological monitors, mechanical ventilators typically are stand-alone devices. Ventilators commonly are not connected to bedside monitors. The wireless approach requires that a transmitter be attached externally to a ventilator since internal wireless connectivity is not available yet. A ventilator network management system may permit a centralized view of all ventilators. Through such a system, ventilator data can be seen through Web applications on a hospital intranet or via the Web externally. The ventilator management system can transmit alarm notifications of changes in a patient’s condition to remote paging devices. An added desirable feature would be real-time ventilator settings, monitoring values, and waveforms that all are available through the EMR.

Infusion pumps

Intravenous infusion pumps have been used largely as stand-alone devices and have had limited programming capabilities. Today, however, the newer generation of infusion pumps, referred to as “smart pumps,” incorporate multiple comprehensive drug libraries and infusion error reduction systems. Drip rates and medication infusions can be communicated to the EMR. All smart pumps today are available with on-board integrated wireless connectivity. With a wireless system, smart pumps can be tracked for

location, easily switched to a different patient, have their software updated, medication orders transmitted, and alarms forwarded. Using a pump network server, pumps are linked continuously to the patient, the pharmacy, and the EMR.

Bedside associations

A new paradigm of the ICU bedside features simultaneous association of patients with providers, bedside devices, and medications. This level of interconnection can be achieved through bar-coding and RFID (radio frequency identification). In the bar code approach, single- or 2-dimensional bar codes are placed on each person (patient and provider) or device or item to be linked together. A bar code scanner then is used to scan each bar code and virtually attaches them together. Alternatively, the bar code can be replaced with an RFID tag. In this scenario, an RFID reader (similar to EZ-Pass) associates all of the bedside elements together. Devices also may be accepted wirelessly into the bedside association through plug and play portals. Potentially, a pulse oximeter could be taken from one bedside to another where it could be associated dynamically with a new patient through a wireless plug and play portal, allowing it to begin transmitting the new patient's data to the EMR.

Other departments

It is beyond the scope of this chapter to discuss the details of the electronic versions of billing, admitting, medical records, human resources, payroll, materials management, and so on; however, some of these departments impact the physicians' work flow. For instance, if a patient is transferred within the EMR when a bed is available and not when the patient is actually in the room, then the physician will be searching for a new consult in the wrong room. In the medical records module, electronic editing and signing functions must be intuitive. Physician privilege lists must be available electronically in the OR and every other patient care area; time clocks must be interfaced with the payroll system; scheduling programs are needed for outpatient areas; electronic incident reports are important for risk management; and an electronic cancer registry can help to facilitate state reporting requirements.

To run effectively, some of the hospital departments may have to subscribe to software programs or data files. The pharmacy will need to purchase comprehensive formulary files, medical records will need DRG/APC classification software, lab and radiology may need medical necessity software to determine whether specific diagnostic tests in specific circumstances will be covered by insurance, and billing may need software to communicate bidirectionally with payers. All of these programs and files must be purchased and interfaced.

Data mining

It is important that a vendor is capable of producing reports that are useful for members of the organization. Administrators might wish to look at cost per patient per day, and administrative physicians might wish to review length of stay by physician for various DRGs. Nursing requires daily summaries of bed use and availability. It is important to have such reports readily available, with some ability to affect the way the breakdown occurs so that reports can be individualized. It also is important to have files that can be accessed for home-grown reports. This may be accomplished by downloading an ODBC-compliant set of data that can be accessed by other data-mining software. It also should be possible to download data into homegrown databases that are used to facilitate the functions of certain departments. If possible, some members of the IT staff can learn the programming language for the system so that custom reports and other tools can be developed.

Physician reminders notifications

When the physician signs on to the system, information relevant to the physician or group should be presented to help plan the day:

- all patients of the physician or group should be listed, including new admissions who have not been seen yet
- all patients on whom the physician or group is consulting, including new consults
- patients of the physician or group who currently are in the ED or in another outpatient area of the hospital
- lab, radiology, or other results that have not been reviewed yet
- abnormal and critical labs
- charts/orders that need to be signed/cosigned
- important messages generated by another user

Necessary computer hardware, networking, and backup

Computer hardware and networking

It is extremely important that computer terminals used by the physicians and nurses have adequate processor speed and memory, and that the hardwired and wireless networks have the proper bandwidths to accommodate the traffic. Many hospitals have networks and computer terminals in patient care areas that are perfectly adequate for current needs, but because of slower processing speeds, will limit the performance of a new system. Furthermore, there will be a marked increase in the use of computers by the staff, requiring an increased number of terminals in each patient care area. This can be accomplished through a combination of COWs, desktops, and other portable devices. To determine how many computers are necessary,

one can count the maximum number of doctors in each patient care area at peak times, and add the nurses, aides, and other personnel who also might need to use a computer. In the ICU and in other patient care areas, a choice must be made between the use of COWs or stationary in-room terminals. Furthermore, if the hospital has remote sites such as radiology or laboratory services, proper networking must be assured. Since hundreds of computers might be purchased or upgraded, and network connections created or upgraded, it is important to assess these costs early in the process.

Tablets

Whether or not the institution chooses to use interactive computer monitors, ie, tablets, will require research. If the system allows handwritten notes and/or drawings, this will be essential. Sometimes it is easier for nurses to select drop-down documentation with the use of an interactive monitor, but this must be assessed by the institution. We believe that tablets will become important in the future, although keyboard access will still be necessary.

Disaster planning, downtime procedures, maintenance, and backup

Considerable planning must occur to accommodate users during system maintenance periods or unplanned outages. There may be times when the entire system must be shut down for maintenance. Sometimes the vendor will provide sufficient support during working hours only, and this can be problematic for a hospital if maintenance can only be performed during peak hours. Ideally, maintenance should occur in the early hours just after midnight. This should be determined early in the vendor selection process. If the server is down, can some of the modules still continue to process and store data (eg, laboratory values) and download the data into the system once it is live again? What is the maximum number of hours that the module can function this way while waiting for the server to become operational?

Downtime procedures must be written so that the hospital will continue to function in the event of a disaster, or if a maintenance period is unexpectedly prolonged. There are those institutions, especially smaller ones, that have relied on a mixed electronic/paper system for many years and have had adequate downtime procedures to handle any contingencies. However, when the paper chart is no longer in use, it is more difficult for a hospital to convert from an EMR to a paper chart, and, thus, it is essential to determine that each department is equipped to print results, has adequate paper, has an adequate delivery system to get the paper results to the chart, and has sufficient binders so that the patient care areas can convert immediately to a paper chart system.

After installing a fully functional EMR, it soon will become apparent that the physicians are dependent on the system and will not tolerate any significant downtime. The vendor should know the available uptime for the system,

ie, at least “4 9’s” (99.99% operational time [downtime average less than 5 minutes per month, excluding scheduled downtimes]). Furthermore, system redundancy and failover systems will be essential so that operations will be seamless if a server fails or if the total system fails. The vendor should be able to access the system software remotely to apply fixes. The facility most likely will have on-site storage such as a storage area network (SAN), but also should have a completely redundant off-site system that can assume operations within a very short period of time, hopefully seamlessly. Even with redundant systems, a formalized backup system still is necessary. Although a backup system can be on site, the media should be stored off site. Redundant and backup systems can be developed by the hospital or purchased as a service through a vendor; the costs can run easily into the millions of dollars.

Remote access for physicians

Remote access for physicians is an important feature that must be implemented very early in the process. Physicians will demand access from their offices and often will need access from home or other locations. They should be able to review data and radiographs, as well as review dictations and sign them. There are numerous ways to accomplish this, and we will not list the vendors here, but we will emphasize that it must be a fast system. As long as a fast network connection exists, it is relatively easy to provide safe, fast, secure remote access. Currently, it also is possible to provide the same access through a broadband cellular connection. These links are so fast that even radiographs can be viewed, almost as fast as on a land line.

eICU—remote critical care

In 2000, Rosenfeld and colleagues [38] described a system where 24/7 intensivist coverage was provided with a video-link and computer-based communications to a 10-bed adult surgical ICU (SICU). Severity adjusted mortality in this otherwise “open” SICU decreased by 68% and 46% during the two study periods. Hospital mortality and costs also fell dramatically. Subsequently, another study showed a reduction in mortality from 12.9% to 9.4% (RR = 0.73), also with cost reductions [39]. It is possible that at least some of the benefit was related to the best-practice protocols that were instituted. Nonetheless, there is a place for remotely assisted critical care, sometimes referred to as telemedicine, largely because less than half of the approximately 55,000 adult, noncardiac, critically ill patients cared for every day in the United States have intensivist coverage, and only 4% meet the Leapfrog definition for high-intensity coverage [40].

Further advances include remote-presence wireless-enabled robots that allow remote ICU doctors to conduct rounds. Bidirectional images of the patient, the bedside devices, and the doctor can be transmitted simultaneously. Auscultation can even be achieved through electronic stethoscopes.

Paper record and legal record

When purchasing an integrated medical record, one often does not spend significant time learning about the “printout” options of a complete admission. This record can be either on paper or in an electronic file. This becomes important where the patient is transferred to another institution, or if the physician would like to review a complete record of an admission. At this point, he or she may be surprised to see that it is not structured in a way that is familiar. Sometimes, an audit trail of errors and changes have been included. Each vital sign may be listed separately with additional information that often seems unnecessary. There may not be a graphic representation or any format that allows one to follow the vital signs or the fluid input/output in a rational manner. Furthermore, an EMR paper printout of a 2-week admission can reach hundreds of pages. Therefore, it is extremely important to have each vendor present a paper copy of a discharge record, and to call other hospital medical record departments to gain their perspectives on a particular vendor.

The vendor must have the capability to print a legal record. This is not necessarily the same record that one would want to send to a receiving hospital. Remember that you cannot see changes to notes or orders in the usual view of the EMR, but the legal record must contain *all* of the information entered. It must contain the audit trail of notes and orders that have been changed, even if they were changed immediately. It can be a very long and cumbersome document, but if it is not generated automatically, it will create an enormous amount of work for the medical records department.

Online access to reference material

As physicians become comfortable with the EMR, it becomes important to give them easy access to reference information. When a diagnosis is entertained, it is essential to have the opportunity to review a differential, decide on an evidence-based treatment, and look up medications. The system should provide a portal to these references, which should include programs to facilitate disease diagnosis and treatment, online textbooks and journals, drug information, a Medline search, or anything else that might enhance patient care. This is done most efficiently through links within the EMR so that the doctor can view the information while in a patient’s record. Access to the reference sites through the EMR must be available from off-site locations as well.

Summary

We have tried to touch on the major issues involved in selecting an EMR. “Irrespective of the size of the organization, the implementation of an EMR takes vision, planning, and institutional perseverance” [4]. A fully electronic

medical record that is intuitive and acceptable to the medical staff is an enormous achievement for a hospital and its staff. While this functionality is desirable today, it will become a necessity in the near future. Early physician involvement, with at least one physician fully immersed in the process, is absolutely essential to accomplish this task.

References

- [1] Bates DW, Gawande AA. Improving safety with information technology. *N Engl J Med* 2003;348(25):2526–34.
- [2] Bria WF 2nd, Shabot MM. The electronic medical record, safety, and critical care. *Crit Care Clin* 2005;21(1):55–79.
- [3] Bria WF 2nd. Applied medical informatics for the chest physician: information you can use! *Chest* 2006;129(2):446–51.
- [4] Bria WF 2nd. Applied medical informatics for the chest physician: information you can use!—Part 2. *Chest* 2006;129(3):777–82.
- [5] Bria WF 2nd. Applied medical informatics for the chest physician: information you can use!—Part 3. *Chest* 2006;129(4):1057–60.
- [6] Birkmeyer JD, Dimick JB. The Leapfrog Group's Patient Safety Practices, 2003; The Potential Benefits of Universal Adoption. Available at: <http://www.leapfroggroup.org/media/file/Leapfrog-Birkmeyer.pdf>. Accessed April 12, 2007.
- [7] Kohn LT, Corrigan J, Donaldson MS, editors. *To err is human: building a safer health system*. Washington, DC: National Academies Press; 2000.
- [8] Hillestad R, Bigelow J, Bower A, et al. Can electronic medical record systems transform health care? Potential health benefits, savings, and costs. *Health Aff (Millwood)* 2005; 24(5):1103–17.
- [9] Joint Commission on Accreditation of Health Care Organizations. Hospital/Critical Access Hospital National Patient Safety Goals: goal 8. Available at: http://www.jointcommission.org/patientsafety/nationalpatientsafetygoals/07_hap_cah_npsgs.htm. Accessed April 12, 2007.
- [10] Wahl WL, Talsma A, Dawson C, et al. Use of computerized ICU documentation to capture ICU core measures. *Surgery* 2006;140(4):684–9.
- [11] General principles of software validation; final guidance for industry and FDA staff document issued on: January 11, 2002. Available at: <http://www.fda.gov/cdrh/comp/guidance/938.html>. Accessed April 12, 2007.
- [12] Sado AS. Electronic medical record in the intensive care unit. *Crit Care Clin* 1999;15(3): 499–522.
- [13] Berger RG, Kichak JP. Computerized physician order entry: helpful or harmful? *J Am Med Inform Assoc* 2004;11(2):100–3.
- [14] Boone C, Shariq K. Intensive care information systems market: solutions by major market participants. U.S. high acuity care information systems markets, N07D-48. Palo Alto (CA): Frost & Sullivan; 2006. p. 114–18.
- [15] Ornstein C. Hospital heeds doctors, suspends use of software. Cedar-Sinai physicians entered prescriptions and other orders in it, but called it unsafe. *Los Angeles Times*. January 22, 2003:B1.
- [16] Ash JS, Stavri PZ, Kuperman GJ. A consensus statement on consideration for a successful CPOE implementation. *J Am Med Inform Assoc* 2003;10:229–34.
- [17] Ash JS, Gorman PN, Seshadri V, et al. Computerized physician order entry in U.S. hospitals: results of a 2002 survey. *J Am Med Inform Assoc* 2004;11(2):95–9.
- [18] Mekhjian HS, Kumar RR, Kuehn L, et al. Immediate benefits realized following implementation of physician order entry at an academic medical center. *J Am Med Inform Assoc* 2002; 9(5):529–39.

- [19] Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *JAMA* 1998;280(15):1311–6.
- [20] Upperman JS, Staley P, Friend K, et al. The impact of hospitalwide computerized physician order entry on medical errors in a pediatric hospital. *J Pediatr Surg* 2005;40(1):57–9.
- [21] Del Beccaro MA, Jeffries HE, Eisenberg MA, et al. Computerized provider order entry implementation: no association with increased mortality rates in an intensive care unit. *Pediatrics* 2006;118(1):290–5.
- [22] Han YY, Carcillo JA, Venkataraman ST, et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. *Pediatrics* 2005;116(6):1506–12.
- [23] Koppel R, Metlay JP, Cohen A, et al. Role of computerized physician order entry systems in facilitating medication errors. *JAMA* 2005;293(10):1197–203.
- [24] Poissant L, Pereira J, Tamblyn R, et al. The impact of electronic health records on time efficiency of physicians and nurses: a systematic review. *J Am Med Inform Assoc* 2005;12(5):505–16.
- [25] Campbell EM, Sittig DF, Ash JS, et al. Types of unintended consequences related to computerized provider order entry. *J Am Med Inform Assoc* 2006;13(5):547–56.
- [26] Longhurst C, Sharek P, Hahn J, et al. Perceived increase in mortality after process and policy changes implemented with computerized physician order entry. *Pediatrics* 2006;117(4):1450–1.
- [27] Sittig DF, Ash JS, Zhang J, et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. *Pediatrics* 2006;118(2):797–801.
- [28] McDonald CJ. Computerization can create safety hazards: a bar-coding near miss. *Ann Intern Med* 2006;144(7):510–6.
- [29] Ammenwerth E, Talmon J, Ash JS, et al. Impact of CPOE on mortality rates—contradictory findings, important messages. *Methods Inf Med* 2006;45(6):586–93.
- [30] MD PnP. Available at: <http://mdpnp.org>. Accessed April 12, 2007.
- [31] Seiver A. Critical care computing. Past, present, and future. *Crit Care Clin* 2000;16(4):601–21.
- [32] Lawless ST. Crying wolf: false alarms in a pediatric intensive care unit. *Crit Care Med* 1994;22(6):981–5.
- [33] Tsien CL, Fackler JC. Poor prognosis for existing monitors in the intensive care unit. *Crit Care Med* 1997;25(4):614–9.
- [34] Halpern NA, Burnett G, Morgan S, et al. Remote communication from a mobile terminal: an adjunct for a computerized intensive care unit order management system. *Crit Care Med* 1995;23(12):2054–7.
- [35] Budinger TF. Biomonitoring with wireless communications. *Annu Rev Biomed Eng* 2003;5:383–412.
- [36] Paksuniemi M, Sorvoja H, Alasaarela E, et al. Wireless sensor and data transmission needs and technologies for patient monitoring in the operating room and intensive care unit. *Conf Proc IEEE Eng Med Biol Soc* 2005;5:5182–5.
- [37] Wallin MK, Wajntraub S. Evaluation of Bluetooth as a replacement for cables in intensive care and surgery. *Anesth Analg* 2004;98(3):763–7.
- [38] Rosenfeld BA, Dorman T, Breslow MJ, et al. Intensive care unit telemedicine: alternate paradigm for providing continuous intensivists care. *Crit Care Med* 2000;28(12):3925–31.
- [39] Breslow MJ, Rosenfeld BA, Doerfler M, et al. Effect of a multiple-site intensive care unit telemedicine program on clinical and economic outcomes: an alternative paradigm for intensivist staffing. *Crit Care Med* 2004;32(1):31–8.
- [40] Angus DC, Shorr AF, White A, et al. Critical care delivery in the United States: distribution of services and compliance with Leapfrog recommendations. *Crit Care Med* 2006;34(4):1016–24.

Noninvasive Hemodynamic Monitoring in the Intensive Care Unit

Paul E. Marik, MD, FCCM, FCCP^{a,*},
Michael Baram, MD^{a,b}

^a*Division of Pulmonary and Critical Care Medicine, Thomas Jefferson University,
834 Walnut Street, Suite 650, Philadelphia, PA 19107, USA*

^b*Department of Emergency Medicine, Thomas Jefferson University, 834 Walnut Street,
Suite 650, Philadelphia, PA 19107, USA*

Despite improvements in resuscitation and supportive care, progressive organ dysfunction occurs in a large proportion of patients with acute, life-threatening illnesses. It has been proposed that the multi-organ dysfunction syndrome (MODS) of the critically ill is a consequence of tissue dysoxia attributable to inadequate oxygen delivery, often exacerbated by a microcirculatory injury and increased tissue metabolic demands (distributive hypoxia) [1,2]. This may be further compounded by cytopathic hypoxia attributable to mitochondrial dysfunction [3,4]. Emerging data suggest that early aggressive resuscitation of critically ill patients may limit and/or reverse tissue dysoxia and progression to organ failure and improve outcome [5]. In a landmark study, Rivers and colleagues [6] demonstrated that a protocol of early goal-directed therapy reduces organ failure and improves survival in patients with severe sepsis and septic shock. Traditional goals of resuscitation have included blood pressure, pulse rate, central venous pressure (CVP), and arterial oxygen saturation. These variables change minimally in early shock and are poor indicators of the adequacy of resuscitation [7]. Furthermore, clinical assessment of cardiac output and intravascular volume status are notoriously inaccurate. Consequently, both invasive and noninvasive monitoring tools have been used in critically ill patients in an attempt to optimize resuscitation. Most of these technologies focus on “upstream” markers of resuscitation and provide information on cardiac output and fluid responsiveness. In this respect the pulmonary artery catheter (PAC) is regarded as the gold standard, as it provides an

* Corresponding author.

E-mail address: paul.marik@jefferson.edu (P.E. Marik).

accurate estimate of the cardiac output and can be used to determine fluid responsiveness [8]. However, the role of invasive hemodynamic monitoring in critically ill patients is controversial as the PAC has yet to be proven to improve patient outcome [9–14]. Furthermore, the PAC does not provide information as to the adequacy of tissue oxygenation, ie, “downstream” markers. Consequently, the current trend in critical care medicine is to use noninvasive hemodynamic monitoring devices in combination with “downstream” markers of tissue oxygenation. This article provides an overview of those devices currently available for noninvasive hemodynamic monitoring as well as those techniques for indirectly assessing the adequacy of organ perfusion and tissue oxygenation.

Definitions

Shock

Shock is best defined as end-organ dysfunction as a result of hemodynamic compromise [15]. While hypotension is an important marker of shock, it is clear that blood pressure alone cannot be used as the sole determinant of shock [16]. Shock models have demonstrated that the body can develop an “oxygen debt” in the setting of normal blood pressure [16]. This concept underscores the importance of evaluating organ function and microcirculatory perfusion in patients with hemodynamic compromise [17,18]. Rivers and colleagues [6] has coined the term “cryptic shock” to represent those patients who have normal vital signs despite inadequate organ perfusion.

Upstream and downstream markers

The concept of following tissue dysfunction as a guide to resuscitation has led to the concept of “upstream” and “downstream” indicators of organ perfusion (Fig. 1). Upstream markers assess flow and pressure in the heart, vena cava, pulmonary artery, and aorta. Upstream markers include systemic blood pressure, heart rate, central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and cardiac output. These are the traditional variables that have been used to assess the hemodynamic status of critically ill patients. However, shock with end-organ dysfunction occurs at the capillary and tissue levels [19]. Tools have therefore been developed that follow alterations in the microvasculature of critically ill patients [20]. These techniques are known as the “downstream” markers of resuscitation. Since patients’ oxygen and metabolic needs vary with different stressors and at different times, monitoring downstream variables can be helpful to determine the adequacy of cardiac output and perfusion pressure at a particular point in time. Currently available downstream markers include urine output, blood lactate, base excess, tissue carbon dioxide levels, and mixed venous oxygen and carbon dioxide levels.

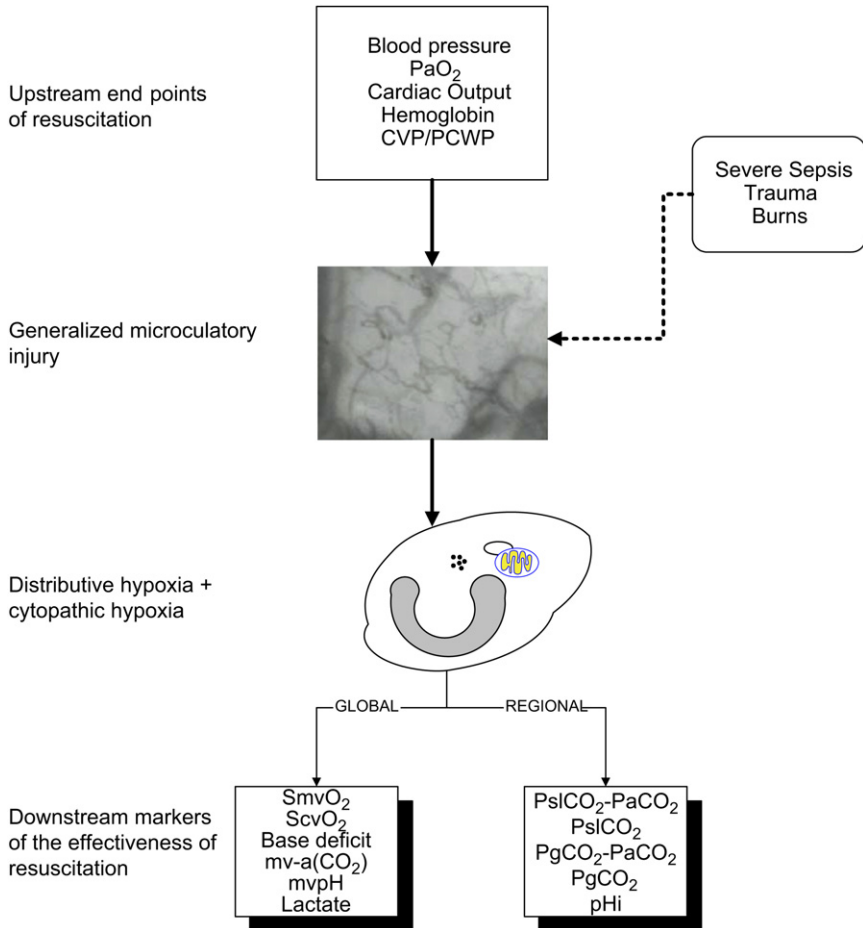


Fig. 1. The upstream end points of resuscitation do not reflect the severity of the microcirculatory injury nor the degree of tissue dysoxia. The downstream variables are markers of tissue perfusion and the adequacy of the resuscitation. The downstream "global" markers are less sensitive markers of tissue dysoxia and less responsive to change.

At the current time we have very few therapeutic interventions that can directly improve perfusion and oxygenation at the microcapillary level. The current concept is to use these downstream markers to ensure that interventions that alter upstream variables are improving tissue oxygenation. Downstream markers therefore provide a guide to upstream therapy. Traditionally, shock has been treated with vasopressor and inotropic agents. However, in the setting of normotensive shock, afterload reduction may be necessary. Furthermore, by understanding the interaction and independence of upstream and downstream markers, the use of vasodilator therapy may be appropriate in select circumstances [21].

Upstream hemodynamic monitoring: Measurement of cardiac output

The cardiac output is the most important upstream hemodynamic parameter. Adolph Fick [22] described the first method of cardiac output estimation in 1870. This method was the reference standard by which all other methods of determining cardiac output were evaluated until the introduction of the PAC in the 1970s [8]. Despite its limitations, cardiac output measurement with a PAC using the bolus thermodilution method has become the de facto gold standard for measurement of cardiac output and is the reference standard used to compare noninvasive technologies.

Echocardiography

In principle, echocardiography is a simple method of assessing cardiac function since it uses ultrasound waves to generate real-time images of the heart. It can assess chamber size, ventricular contractility, valve function, and with the aid of Doppler can assess flow [23,24]. However a high degree of skill is required in interpreting the images and there can be a large degree of interinterpreter variation. Additional consideration is the cost of the equipment, which can be considerable.

Newer portable ultrasound devices are making cardiac screening and dynamic evaluation of cardiac function more achievable. Assessment of global ventricular function is helpful in the management of critically ill patients [23,24]. Patients with tissue dysoxia and a hyper-contractile left ventricle may benefit from a vasopressor agent and/or fluid administration, whereas those with poor left ventricular function may benefit from an inotropic agent. Similarly, the presence of a dilated right ventricle will alert the intensivist to the presence of right ventricular dysfunction. With basic training this assessment can be learned by noncardiologists, but determining segmental wall motion abnormalities and valvular function remains a highly specialized skill requiring specialized training [25]. Ventricular chamber size can be directly measured allowing calculation of ejection fraction [23]. Flow through the valves (ie, forward flow and regurgitant flow) can be measured using Doppler imaging. This allows calculation of pulmonary artery pressures and cardiac output. However, the difficulty with these techniques is in the acquisition of adequate images in the correct plane, which requires significant experience.

Training tracks for noncardiologists exist; intraoperative transesophageal echocardiography is now commonly performed by anesthesiologists to evaluate cardiac function during open heart surgery and the “FAST” Protocol (Focused Abdominal Sonography in Trauma) is an integral part of the examination of trauma patients in the emergency room [26–29]. Bedside echocardiography as performed by the intensivist holds great promise for the future [23,24,30].

Cardiac output as measured by carbon dioxide rebreathing

Cardiac output can be calculated by the CO₂ partial rebreathing technique using the modified Fick equation [22]. NiCCO, a proprietary device (Respironics, Murrysville, Pennsylvania) measures cardiac output based on this principle. The CO₂ partial rebreathing technique compares end-tidal carbon dioxide partial pressure (etCO₂) obtained during a non-rebreathing period with that obtained during a subsequent rebreathing period. The ratio of the change in etCO₂ and CO₂ elimination after a brief period of partial rebreathing (usually 50 seconds) provides a noninvasive estimate of the cardiac output [31]. A limitation of the rebreathing CO₂ cardiac output method is that it only measures pulmonary capillary blood flow (ie, the nonshunted portion of the cardiac output). To calculate total cardiac output, intrapulmonary shunt and anatomic shunt fractions (Qs/Qt) must be added to the pulmonary capillary blood flow. The NiCCO system estimates Qs/Qt using a shunt correction algorithm, which uses oxygen saturation from pulse oximetry and the fractional concentration of inspired oxygen.

The CO₂ rebreathing technique has a number of significant limitations when used in an ICU setting. Almost all of the validation studies have been performed in patients undergoing anesthesia or in deeply sedated mechanically ventilated ICU patients, where the agreement with thermodilution cardiac output has varied from “poor” to “acceptable” [32–37]. In spontaneously breathing patients, the rebreathing period is associated with an increase in minute ventilation [38]. This reduces the accuracy of the cardiac output determinations [36,39]. Furthermore, a low minute ventilation, a high shunt fraction, and a high cardiac output result in inaccurate measurements [36,37,39]. Considering the limited data in ICU patients and the potential inaccuracies in this patient population, the routine use of the CO₂ rebreathing technique to estimate cardiac output cannot be recommended at this time.

Esophageal Doppler

The esophageal Doppler technique measures blood flow velocity in the descending aorta by means of a Doppler transducer (4 MHz continuous-wave, or 5 MHz pulsed wave, according to manufacturers) placed at the tip of a flexible probe. The probe is introduced into the esophagus of the sedated, mechanically ventilated patients and then rotated so that the transducer faces the descending aorta and a characteristic aortic velocity signal is obtained. The cardiac output is calculated based on the diameter of the aorta (measured or estimated), the distribution of the cardiac output to the descending aorta, and the measured flow velocity of blood in the aorta. As esophageal Doppler probes are inserted blindly, the resulting waveform is highly dependent on correct positioning. The clinician must adjust the depth, rotate the probe, and adjust the gain to obtain an optimal signal

[40]. Poor positioning of the esophageal probe tends to underestimate the true cardiac output. There is a significant learning curve in obtaining adequate Doppler signals and the correlations are better in studies where the investigator was not blinded to the results of the cardiac output obtained with a PAC [41].

A recent meta-analysis by Dark and Singer [42] demonstrated an 86% correlation between cardiac output as determined by esophageal Doppler and PAC. Although the correlation between the two methods was only modest, there was an excellent correlation between the change in cardiac output with therapeutic interventions. However, changes in cardiac output in response to a therapeutic intervention are probably more useful than the absolute cardiac output itself (see section on evaluating fluid responsiveness) [43].

While esophageal Doppler has some utility in aiding in the assessment of the hemodynamic status of critically ill patients, this technology has been slow to be adopted. This is likely the consequence of a number of factors including the less than ideal accuracy of the cardiac output measurements, the long learning curve, the inability to obtain continuous reliable measurements, and the practical problems related to presence of the probe in the patients' esophagus.

Pulse contour analysis

The origin of the pulse contour method of measuring cardiac output is derived from variations in the pulse pressure waveform. In general, the greater the stroke volume, the greater is the amount of blood that must be accommodated in the arterial tree with each heartbeat and, therefore, the greater the pressure rise and fall during systole and diastole, thus causing a greater pulse pressure. The pulse pressure is proportional to stroke volume and inversely related to vascular compliance. The pulse pressure waveform therefore changes predictably with changes in the compliance of arterial wall and stroke volume. As the compliance of the vasculature is difficult to measure directly, this is calculated based on age, sex, ethnicity and body mass index (BMI) [44]. Using complex proprietary formula (PulseCO, LiDCO, London, UK; PiCCO, Pulsion Medical Systems, Munich, Germany) the cardiac output is then calculated from analysis of the pulse contour [45]. Ideally the pulse contour analysis is calibrated to an injection dilution method. Stroke volume is calculated and compared with the stroke volume as determined by the dilution technique, and the cardiac output is then calculated. With beat-to-beat waveform analysis, cardiac output can be determined continuously [46]. External calibration every 6 to 12 hours confirms continued accuracy [45,47]. While the cardiac output as determined by pulse contour analysis shows good agreement with the cardiac output as measured by other techniques, the use of vasoactive agents (pure vasodilators/vasoconstrictors) may result in spurious changes in cardiac output [46,48]. Most

importantly, these devices also calculate the pulse pressure and stroke volume variation with positive pressure ventilation (see section on evaluating fluid responsiveness). A large pulse pressure/stroke volume variation ($> 10\%$ to 15%) is indicative of hypovolemia and predictive of volume responsiveness.

Lithium dilution and pulse contour analysis

Lithium is the contrast agent most commonly used with the injection dilution method for external calibration of pulse contour analysis devices (PulseCO, LiDCO). The lithium may be injected via a central or peripheral vein [49]. A lithium analyzer is connected to an arterial line, which then measures the wash out curve over time and generates a curve similar to the thermodilution curve of a PAC [45,50]. In an animal model, Kurita and colleagues [51] reported that the cardiac output as measured by the lithium dilution method correlated better with Doppler aortic flow than the cardiac output as determined by thermodilution. Reproducibility was also better with the lithium method as compared with the thermodilution method. In human studies a good correlation between thermodilution and lithium dilution has been reported [46,49,52].

Transpulmonary thermodilution and pulse contour analysis

PiCCO (Pulsion Medical Systems) uses the aortic transpulmonary thermodilution curve to calculate cardiac output (TP-TD). For this technique, a thermistor-tipped catheter is typically placed in the descending aorta via a femoral sheath. Iced saline (15 mL) is injected into a central vein and from the temperature change in the aorta, the cardiac output can be calculated and the pulse contour system calibrated [53–55].

Pulse contour without dilution calibration

As the concept of pulse contour analysis has become better understood, complex algorithms have been developed that can estimate cardiac output without the need for external calibration [56]. External calibration is replaced by correction factors that depend on the mean arterial pressure and the age, gender, weight, and height of the patient. There are limited published data on the accuracy of this methodology and while promising, additional studies are required before this technology can be used clinically [56–58].

Plethysmography

The use of thoracic electrical bioimpedance (TEB) to estimate cardiac output dates back to the early years of manned space exploration. Using low voltage, electrical impedance (or resistance) across the chest is measured. The higher the fluid content, the lower the impedance since fluid conducts electricity. As the heart cycles through systole and diastole the volume of blood in the thorax changes and this can be measured electrically [59].

Early studies demonstrated only a fair correlation between TEB and thermodilution cardiac output [60,61]. In addition, the accuracy of TEB worsened as the degree of volume overload increased. This incongruity occurs since heart failure results in increased pulmonary edema and pleural effusion, which effects conduction. Many of the problems associated with TEB have been overcome with newer generation devices using upgraded computer technology and refined algorithms to calculate cardiac output [62,63]. Van De Water and colleagues [63] demonstrated less variability and more accurate determination of cardiac output using a refined equation as compared with the predecessor equations of Kubicek, Sramek, and Sramek-Bernstein. Recently, a number of investigators have reported a good correlation between TEB and thermodilution in patients following cardiac surgery using these improved devices [63–67]. Similarly, Albert and colleagues [68] demonstrated that cardiac output as measured by TEB and thermodilution were significantly correlated in patients with decompensated chronic heart failure. There are limited data on the use of TEB in critically ill ICU patients; however, the improved TEB technology does hold promise in this group of patients.

Comparative studies

A number of studies have been performed comparing the accuracy of the various noninvasive devices reviewed in this paper [46,56,69]. Unfortunately, most of these studies suffer methodological problems in terms of the “gold” standard used and the sample size [70]. In general, no device stands out as being better than another and although not perfectly accurate, all the devices were able to detect changes in cardiac output and reflect appropriate trends.

Evaluating fluid responsiveness

Fundamentally the only reason to give a patient a fluid challenge is to increase stroke volume. This assumes that the patient is on the ascending portion of the Frank-Starling curve and has “recrutable” cardiac output. Once the left ventricle is functioning near the “flat” part of the Frank-Starling curve, fluid loading has little effect on cardiac output and only serves to increase tissue edema and to promote tissue dysoxia. In normal physiologic conditions, both ventricles operate on the ascending portion of the Frank-Starling curve [71]. This mechanism provides a functional reserve to the heart in situations of acute stress [71]. In healthy individuals, an increase in preload (with volume challenge) results in a significant increase in stroke volume [72,73]. In contrast, only about 50% of patients with circulatory failure will respond to a fluid challenge [74]. It is therefore crucial during the resuscitation phase of all critically ill patients to determine whether the patient is fluid responsive or not; this determines the optimal strategy of increasing cardiac output and tissue oxygen delivery.

Although cardiac filling pressures (central venous pressure and pulmonary capillary wedge pressure) as measured using a central venous catheter or PAC are widely used to predict fluid responsiveness, this approach is completely devoid of supportive scientific data. Indeed, multiple studies have confirmed that both the CVP and PCWP in healthy controls and in patients with various disease states are unable to predict the hemodynamic response to a fluid challenge [73–79]. It is therefore somewhat alarming that the CVP is still widely used as a guide to fluid resuscitation and is incorporated into protocols that are endorsed by professional societies [6,80,81]. Traditionally, the PAC has been used to determine fluid responsiveness; a patient is given a fluid challenge and the change in stroke volume and cardiac output is recorded. A number of noninvasive methods to determine fluid responsiveness have been investigated and are further reviewed.

Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation

In mechanically ventilated patients, the magnitude of the respiratory change in left ventricular stroke volume can be used to assess fluid responsiveness. Intermittent positive-pressure ventilation induces changes in the loading conditions of the left and right ventricles. Mechanical insufflation decreases preload and increases afterload of the right ventricle (RV). The decrease in RV preload is attributable to the decrease in the venous return pressure gradient that is related to the increase in pleural pressure. The decrease in RV preload and increase in RV afterload both lead to a decrease in RV stroke volume. The inspiratory reduction in RV ejection leads to a decrease in left ventricular (LV) filling after a phase lag of two or three heartbeats. Consequently, stroke volume, cardiac output, and systemic blood pressure all fall during each mechanical breath. Since venous return depends on the venous pressure gradient, the decrease in venous return with positive pressure ventilation is most marked in hypovolemic patients who have a low mean circulating filling pressure [82,83]. Furthermore, patients who are functioning on the ascending portion of the Frank-Starling curve have an exaggerated fall in stroke volume with decreased venous return during each positive pressure breath. Consequently cardiac output and blood pressure falls significantly in these patients with each mechanical insufflation. Multiple experimental and clinical studies have confirmed that large variations (greater than approximately 12%) in systolic pressure (SPV) and pulse pressure (PPV) as measured using an arterial catheter, predict an increase in cardiac output with fluid loading (ie, volume responsiveness) [77,78,84–86]. This dynamic test of “recruitable cardiac output” is highly reproducible and simply performed at the bedside.

Pulse pressure variation and stroke volume variation (SVV) with mechanical ventilation has logically been combined with pulse contour analysis to predict volume responsiveness [79,87–90]. In addition, ventilator-induced

changes in aortic blood flow velocity and stroke output as measured with esophageal Doppler [91–93] and changes in stroke volume by echocardiography have been demonstrated to predict fluid responsiveness [94]. Current evidence suggests that the dynamic changes in cardiac performance with positive pressure ventilation are more accurate in predicting volume responsiveness than the static filling pressures that have traditionally been used for this purpose [74,95]. In addition, cyclic changes in inferior vena-caval diameter as measured by echocardiography have been used to predict fluid responsiveness [96,97].

Downstream hemodynamic markers

Lactate

The concept that hypoxic tissues can generate a lactic acidosis has been understood since the 1970s [98]. To generate energy, the body must convert glucose into CO₂ via the Krebs cycle. In anaerobic environments, the Krebs cycle cannot completely metabolize glucose, so instead a partial metabolic pathway is followed, which generates lactate. The greater the oxygen deficit and with increased metabolic demands, the more lactate is produced. Lactic acidosis is, however, not limited to shock. Localized lactic acidosis can occur in muscles from repetitive use such as during exercise, or from a generalized tonic-clonic seizure.

Blood lactate concentration is commonly used as a global “downstream” marker of tissue perfusion and the adequacy of resuscitation [6]. Blood lactate, however, is an insensitive marker of tissue dysoxia [99–102]. If glycolysis occurs at a more rapid rate than is necessary for oxidative metabolism, some pyruvate may not be oxidatively metabolized in the Krebs cycle and will be converted to lactate. The result will be a concomitant increase in both pyruvate and lactate with an unchanged lactate/pyruvate ratio (L/P) [103,104]. James and colleagues [102] provide a compelling argument that a high blood lactate in critically ill patients may be a metabolic manifestation of high blood epinephrine levels (and glycolysis) and a poor indicator of tissue dysoxia. Similarly, Levy and colleagues [105] have elegantly demonstrated that skeletal muscle may be a major source of lactate production during sepsis as a consequence of increased aerobic glycolysis through Na⁺K⁺ ATPase stimulation. Lactate levels may therefore be a marker of illness severity rather than a measure of anaerobic metabolism. In addition, the blood lactate level depends on the rate of production as well as the rate of metabolism by the liver (Cori cycle). Because of decreased splanchnic blood flow and hepatocellular dysfunction, lactate removal may be impaired in critically ill patients.

A lactic acidosis must therefore be assessed in the proper clinical context before it can be used as a tool to assess downstream mitochondrial function. However, a blood lactate concentration in excess of 4 mEq/L is associated with a high risk of death [98,106]. Furthermore the rate of lactate clearance

has been demonstrated to be a good marker of outcome [107]. While an elevated lactate may be a marker of illness severity and a important prognostic marker, this variable has not been studied as an end point of resuscitation. Lactate clearance lags by many hours following therapeutic interventions and is therefore not suited for goal-directed resuscitation. Furthermore, lactate has never been proven to be a surrogate marker for cardiac output [108]. As a marker of index severity it may be appropriate to use an elevated lactate as a trigger to initiate aggressive care; however, that care should not be titrated to the lactate level.

Gastric tonometry and sublingual capnography

Because of the flow distribution away from the gastrointestinal tract the development of tissue dysoxia in the gastrointestinal tract appears to be a common and early finding in patients with deranged hemodynamics. Dantzker [109] has suggested that the gastrointestinal tract may be the “canary of the body,” with gastrointestinal dysoxia an “early warning of impending trouble.” It has been demonstrated that changes in gastrointestinal mucosal $p\text{CO}_2$ mirrors changes in gastrointestinal oxygen uptake during progressive flow stagnation [110,111]. Since the sublingual mucosa is embryologically derived from gut tissue, its perfusion and response to stress is similar to that of the splanchnic bed. The PCO_2 of the stomach wall (PgCO_2) and sublingual tissue (PsiCO_2) has been demonstrated to increase predictably during both hemorrhagic and septic shock [112–114]. Gutierrez and colleagues [115] randomized critically ill ICU patients to a standard treatment group or a protocol group in which treatment was titrated to maintain the gastric intramucosal pH (pHi) greater than 7.35. Survival was significantly improved in the protocol subgroup whose initial pHi was greater than 7.35. This study provides further support to the argument that the early detection and treatment of tissue dysoxia may improve the outcome of critically ill patients.

Gastric tonometry is logistically and practically difficult and this may be the main factor that has prevented the widespread use of this technology. The recent introduction of sublingual capnometry has resolved many of the difficulties associated with gastric tonometry. Sublingual capnometry is a technically simple, noninvasive, inexpensive technology that provides near instantaneous information as to the adequacy of tissue perfusion in critically ill and injured patients [112]. Sublingual capnometry may prove to be useful tool for both the risk stratification and as an end point for goal-directed resuscitation. The clinical experience with sublingual capnometry is, however, limited, and additional studies are needed that demonstrate the clinical utility of PsiCO_2 monitoring.

Mixed venous O_2 , mixed venous PCO_2 and base excess

Mixed venous oxygen saturation (SmvO_2) measured in either the pulmonary artery (with a PAC) or the right atrium (with a central venous catheter)

has been used to monitor critically ill patients and their response to therapeutic interventions [6,116–119]. A low SmvO_2 (in the absence of arterial hypoxemia) is usually an indicator of inadequate cardiac output. Mixed venous PCO_2 (PmvCO_2) represents the equilibration of systemic venous CO_2 that has returned to the right side of the heart and as such is a “global” indicator of tissue dysoxia. The major disadvantage of these global measurements is that they lack sensitivity; high tissue PCO_2 and/or low PO_2 draining vital organs will be diluted by blood draining organs with lower metabolic requirements with a lower PCO_2 and higher PO_2 . Silva and colleagues [120] measured global and regional indicators of tissue dysoxia in septic patients undergoing fluid challenge. While the gastric intramucosal PCO_2 gradient decreased significantly with volume resuscitation, the SmvO_2 and PmvCO_2 gradient remained unchanged. In addition, in patients with sepsis (and macrocirculatory shunting) the SmvO_2 may be a poor indicator of tissue dysoxia [121].

The base excess (BE) has become the standard end point of resuscitation in trauma patients. Remarkably, while the BE has been demonstrated to be of prognostic value in this patient population, it has never been assessed prospectively in trauma patients [122]. It is likely that tissue hypoperfusion may occur in the absence of a significant change in the BE. Furthermore, as it requires time for the liver and kidney to regenerate bicarbonate, it can be expected that there will be a long lag phase between the correction of intravascular volume deficit and normalization of the BE [123]. While the BE may indicate tissue acidosis, it is a crude indicator of tissue dysoxia that has not been well studied in critically ill patients and should therefore not be used as an end point of goal-directed therapy.

Summary

The quest for the holy grail of noninvasive cardiac output assessment methods continues. Although no tool is perfect, a number of noninvasive methods to determine the cardiac output of critically ill patients are now available. It is, however, important to stress that the cardiac output should be interpreted in conjunction with dynamic indices of volume responsiveness and downstream markers of tissue oxygenation. Furthermore, patients cannot be managed by simplistic algorithms or bundles but rather by thoughtful intensivists, who at the bedside can integrate a body of complex and interrelated information and chart a course based on the best available scientific evidence.

References

- [1] Ince C, Sinaasappel M. Microcirculatory oxygenation and shunting in sepsis and shock. *Crit Care Med* 1999;27:1369–77.
- [2] Beal AL, Cerra FB. Multiple organ failure syndrome in the 1990's: systemic inflammatory response and organ dysfunction. *JAMA* 1994;271:226–33.

- [3] Fink MP. Bench-to-bedside review: cytopathic hypoxia. *Crit Care* 2002;6:491–9.
- [4] Fink MP. Cytopathic hypoxia. Is oxygen use impaired in sepsis as a result of an acquired intrinsic derangement in cellular respiration? *Crit Care Clin* 2002;18:165–75.
- [5] Levy MM, Macias WL, Vincent JL, et al. Early changes in organ function predict eventual survival in severe sepsis. *Crit Care Med* 2005;33:2194–201.
- [6] Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–77.
- [7] Shock. Advanced trauma life support for doctors; student course manual. 6th edition. Chicago: American College of Surgeons; 1997. p. 87–112.
- [8] Ganz W, Donosco R, Marcus HS, et al. A new technique for measurement of cardiac output by thermodilution in man. *Am J Cardiol* 1971;27:392–6.
- [9] Connors AF, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. *JAMA* 1996;276:889–97.
- [10] Wheeler AP, Bernard GR, Thompson BT, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 2006;354:2213–24.
- [11] Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003;348:5–14.
- [12] Harvey S, Harrison DA, Singer M, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet* 2005;366:472–7.
- [13] Binanay C, Califf RM, Hasselblad V, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA* 2005;294:1625–33.
- [14] Richard C, Warszawski J, Anguel N, et al. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2003;290:2713–20.
- [15] Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;101:1644–55.
- [16] Wo CC, Shoemaker WC, Appel PL, et al. Unreliability of blood pressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness. *Crit Care Med* 1993; 21:218–23.
- [17] Sakr Y, Dubois MJ, De BD, et al. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med* 2004;32:1825–31.
- [18] Lam C, Tyml K, Martin C, et al. Microvascular perfusion is impaired in a rat model of normotensive sepsis. *J Clin Invest* 1994;94:2077–83.
- [19] De Backer D, Creteur J, Preiser JC, et al. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med* 2002;166:98–104.
- [20] Lindert J, Werner J, Redlin M, et al. OPS imaging of human microcirculation: a short technical report. *J Vasc Res* 2002;39:368–72.
- [21] Spronk PE, Ince C, Gardien MJ, et al. Nitroglycerin in septic shock after intravascular volume resuscitation. *Lancet* 2002;360:1395–6.
- [22] Fick A. Ueber die Messung des Blutquantums in den Herzventrikeln [German]. *Sitzungsberichte der Physiologisch-Medizinische Gesellschaft zu Wuerzburg* 1870;2:16.
- [23] Beaulieu Y, Marik PE. Bedside ultrasonography in the ICU, Part 1. *Chest* 2005;128:881–95.
- [24] Beaulieu Y, Marik PE. Bedside ultrasonography in the ICU, Part 2. *Chest* 2005;128: 1766–81.
- [25] Duvall WL, Croft LB, Goldman ME. Can hand-carried ultrasound devices be extended for use by the noncardiology medical community? *Echocardiography* 2003;20:471–6.
- [26] Cheung AT, Savino JS, Weiss SJ, et al. Echocardiographic and hemodynamic indexes of left ventricular preload in patients with normal and abnormal ventricular function. *Anesthesiology* 1994;81:376–87.

- [27] Reichert CL, Visser CA, Koolen JJ, et al. Transesophageal echocardiography in hypotensive patients after cardiac operations. Comparison with hemodynamic parameters. *J Cardiovasc Thorac Surg* 1992;104:321–6.
- [28] Porter RS, Nester BA, Dalsey WC, et al. Use of ultrasound to determine need for laparotomy in trauma patients. *Ann Emerg Med* 1997;29:323–30.
- [29] Tso P, Rodriguez A, Cooper C, et al. Sonography in blunt abdominal trauma: a preliminary progress report. *J Trauma* 1992;33:39–43.
- [30] Benjamin E, Griffin K, Leibowitz AB, et al. Goal-directed transesophageal echocardiography performed by intensivists to assess left ventricular function: comparison with pulmonary artery catheterization. *J Cardiothorac Vasc Anesth* 1998;12:10–5.
- [31] Jaffe MB. Partial CO₂ rebreathing cardiac output—operating principles of the NICO system. *J Clin Monit Comput* 1999;15:387–401.
- [32] Nilsson LB, Eldrup N, Berthelsen PG. Lack of agreement between thermodilution and carbon dioxide-rebreathing cardiac output. *Acta Anaesthesiol Scand* 2001;45:680–5.
- [33] Odenstedt H, Stenqvist O, Lundin S. Clinical evaluation of a partial CO₂ rebreathing technique for cardiac output monitoring in critically ill patients. *Acta Anaesthesiol Scand* 2002;46:152–9.
- [34] Kotake Y, Moriyama K, Innami Y, et al. Performance of noninvasive partial CO₂ rebreathing cardiac output and continuous thermodilution cardiac output in patients undergoing aortic reconstruction surgery. *Anesthesiology* 2003;99:283–8.
- [35] Binder JC, Parkin WG. Non-invasive cardiac output determination: comparison of a new partial-rebreathing technique with thermodilution. *Anaesth Intensive Care* 2001;29:19–23.
- [36] van Heerden PV, Baker S, Lim SI, et al. Clinical evaluation of the non-invasive cardiac output (NICO) monitor in the intensive care unit. *Anaesth Intensive Care* 2000;28:427–30.
- [37] Rocco M, Spadetta G, Morelli A, et al. A comparative evaluation of thermodilution and partial CO₂ rebreathing techniques for cardiac output assessment in critically ill patients during assisted ventilation. *Intensive Care Med* 2004;30:82–7.
- [38] Tachibana K, Imanaka H, Takeuchi M, et al. Effects of reduced rebreathing time, in spontaneously breathing patients, on respiratory effort and accuracy in cardiac output measurement when using a partial carbon dioxide rebreathing technique: a prospective observational study. *Crit Care* 2005;9:R569–74.
- [39] Tachibana K, Imanaka H, Takeuchi M, et al. Noninvasive cardiac output measurement using partial carbon dioxide rebreathing is less accurate at settings of reduced minute ventilation and when spontaneous breathing is present. *Anesthesiology* 2003;98:830–7.
- [40] Lefrant JY, Bruelle P, Aya AG, et al. Training is required to improve the reliability of esophageal Doppler to measure cardiac output in critically ill patients. *Intensive Care Med* 1998;24:347–52.
- [41] Valtier B, Cholley BP, Belot JP, et al. Noninvasive monitoring of cardiac output in critically ill patients using transesophageal doppler. *Am J Respir Crit Care Med* 1998;158:77–83.
- [42] Dark PM, Singer M. The validity of trans-esophageal Doppler ultrasonography as a measure of cardiac output in critically ill adults. *Intensive Care Med* 2004;30:2060–6.
- [43] Roeck M, Jakob SM, Boehlen T, et al. Change in stroke volume in response to fluid challenge: assessment using esophageal Doppler. *Intensive Care Med* 2003;29:1729–35.
- [44] Brumfield AM, Andrew ME. Digital pulse contour analysis: investigating age-dependent indices of arterial compliance. *Physiol Meas* 2005;26:599–608.
- [45] Pittman J, Bar-Yosef S, SumPing J, et al. Continuous cardiac output monitoring with pulse contour analysis: a comparison with lithium indicator dilution cardiac output measurement. *Crit Care Med* 2005;33:2015–21.
- [46] Bein B, Worthmann F, Tonner PH, et al. Comparison of esophageal Doppler, pulse contour analysis, and real-time pulmonary artery thermodilution for the continuous measurement of cardiac output. *J Cardiothorac Vasc Anesth* 2004;18:185–9.

- [47] Schuerholz T, Meyer MC, Friedrich L, et al. Reliability of continuous cardiac output determination by pulse-contour analysis in porcine septic shock. *Acta Anaesthesiol Scand* 2006;50:407–13.
- [48] Berberian G, Quinn TA, Vigilance DW, et al. Validation study of PulseCO system for continuous cardiac output measurement. *ASAIO J* 2005;51:37–40.
- [49] Garcia-Rodriguez C, Pittman J, Cassell CH, et al. Lithium dilution cardiac output measurement: a clinical assessment of central venous and peripheral venous indicator injection. *Crit Care Med* 2002;30:2199–204.
- [50] Jonas MM, Tanser SJ. Lithium dilution measurement of cardiac output and arterial pulse waveform analysis: an indicator dilution calibrated beat-by-beat system for continuous estimation of cardiac output. *Curr Opin Crit Care* 2002;8:257–61.
- [51] Kurita T, Morita K, Kato S, et al. Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for measurement of cardiac output. *Br J Anaesth* 1997;79:770–5.
- [52] Linton R, Band D, O'Brien T, et al. Lithium dilution cardiac output measurement: a comparison with thermodilution. *Crit Care Med* 1997;25:1796–800.
- [53] Ostergaard M, Nielsen J, Rasmussen JP, et al. Cardiac output—pulse contour analysis vs. pulmonary artery thermodilution. *Acta Anaesthesiol Scand* 2006;50:1044–9.
- [54] Halvorsen PS, Espinoza A, Lundblad R, et al. Agreement between PiCCO pulse-contour analysis, pulmonary artery thermodilution and transthoracic thermodilution during off-pump coronary artery by-pass surgery. *Acta Anaesthesiol Scand* 2006;50:1050–7.
- [55] Sakka SG, Reinhart K, Meier-Hellmann A. Comparison of pulmonary artery and arterial thermodilution cardiac output in critically ill patients. *Intensive Care Med* 1999;25:843–6.
- [56] Penttilä J, Snapir A, Kentala E, et al. Estimation of cardiac output in a pharmacological trial using a simple method based on arterial blood pressure signal waveform: a comparison with pulmonary thermodilution and echocardiographic methods. *Eur J Clin Pharmacol* 2006;62:401–7.
- [57] Horswell J, Worley T. Continuous cardiac output measured by arterial pulse pressure analysis in surgical patients. *Crit Care Med* 2005;33(Suppl):A67.
- [58] Manecke GR, Peterson M, Auger WR. Cardiac output determination using the arterial pulse wave: a comparison of a novel algorithm against continuous and intermittent thermodilution. *Crit Care Med* 2004;32(Suppl.):A43.
- [59] Shoemaker WC, Belzberg H, Wo CC, et al. Multicenter study of noninvasive monitoring systems as alternatives to invasive monitoring of acutely ill emergency patients. *Chest* 1998;114:1643–52.
- [60] Raaijmakers E, Faes TJ, Scholten RJ, et al. A meta-analysis of three decades of validating thoracic impedance cardiography. *Crit Care Med* 1999;27:1203–13.
- [61] Marik PE, Pendelton JE, Smith R. A comparison of hemodynamic parameters derived from transthoracic electrical bioimpedance with those parameters obtained by thermodilution and ventricular angiography. *Crit Care Med* 1997;25:1545–50.
- [62] Moshkovitz Y, Kaluski E, Milo O, et al. Recent developments in cardiac output determination by bioimpedance: comparison with invasive cardiac output and potential cardiovascular applications. *Curr Opin Cardiol* 2004;19:229–37.
- [63] Van De Water JM, Miller TW, Vogel RL, et al. Impedance cardiography: the next vital sign technology? *Chest* 2003;123:2028–33.
- [64] Suttner S, Schollhorn T, Boldt J, et al. Noninvasive assessment of cardiac output using thoracic electrical bioimpedance in hemodynamically stable and unstable patients after cardiac surgery: a comparison with pulmonary artery thermodilution. *Intensive Care Med* 2006;32:2053–8.
- [65] Sageman WS, Riffenburgh RH, Spiess BD. Equivalence of bioimpedance and thermodilution in measuring cardiac index after cardiac surgery. *J Cardiothorac Vasc Anesth* 2002;16:8–14.

- [66] Koobi T, Kaukinen S, Turjanmaa VM. Cardiac output can be reliably measured noninvasively after coronary artery bypass grafting operation. *Crit Care Med* 1999;27:2206–11.
- [67] Kaukinen S, Koobi T, Bi Y, et al. Cardiac output measurement after coronary artery bypass grafting using bolus thermodilution, continuous thermodilution, and whole-body impedance cardiography. *J Cardiothorac Vasc Anesth* 2003;17:199–203.
- [68] Albert NN, Hail MD, Li J, et al. Equivalence of the bioimpedance and thermodilution methods in measuring cardiac output in hospitalized patients with advanced, decompensated chronic heart failure. *Am J Crit Care* 2004;13:469–79.
- [69] van den BG, Tonino S, de FC, et al. Bench-to-bedside review: preventive measures for contrast-induced nephropathy in critically ill patients. *Crit Care* 2005;9:361–70.
- [70] Fontes ML, Bellows W, Ngo L, et al. Assessment of ventricular function in critically ill patients: limitations of pulmonary artery catheterization. Institutions of the McSPI Research Group. *J Cardiothorac Vasc Anesth* 1999;13:521–7.
- [71] Braunwald E, Sonnenblick EH, Ross J. Mechanisms of cardiac contraction and relaxation. In: Braunwald E, editor. *Heart disease*. Philadelphia: W.B.Saunders Company; 1988. p. 383–425.
- [72] Nixon JV, Murray RG, Leonard PD, et al. Effect of large variations in preload on left ventricular characteristics in normal subjects. *Circulation* 1982;65:698–703.
- [73] Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med* 2004;32:691–9.
- [74] Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest* 2002;121:2000–8.
- [75] Osman D, Ridel C, Ray P, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med* 2007;35:64–8.
- [76] Calvin JE, Driedger AA, Sibbald WJ. The hemodynamic effect of rapid fluid infusion in critically ill patients. *Surgery* 1981;90:61–76.
- [77] Kramer A, Zygun D, Hawes H, et al. Pulse pressure variation predicts fluid responsiveness following coronary artery bypass surgery. *Chest* 2004;126:1563–8.
- [78] Michard F, Boussat S, Chemla D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med* 2000;162:134–8.
- [79] Wiesenack C, Fiegl C, Keyser A, et al. Assessment of fluid responsiveness in mechanically ventilated cardiac surgical patients. *Eur J Anaesthesiol* 2005;22:658–65.
- [80] Boldt J, Lenz M, Kumle B, et al. Volume replacement strategies on intensive care units: results from a postal survey. *Intensive Care Med* 1998;24:147–51.
- [81] Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32:858–73.
- [82] Guyton AC. Physics of blood, blood flow and pressure hemodynamics. In: Guyton AC, editor. *Textbook of medical physiology*. 7th edition. Philadelphia: W.B.Saunders; 1986. p. 206–17.
- [83] Guyton AC. The systemic circulation. In: Guyton AC, editor. *Textbook of medical physiology*. 7th edition. Philadelphia: W.B.Saunders; 1986. p. 218–29.
- [84] Berkenstadt H, Friedman Z, Preisman S, et al. Pulse pressure and stroke volume variations during severe haemorrhage in ventilated dogs. *Br J Anaesth* 2005;94:721–6.
- [85] Preisman S, Kogan S, Berkenstadt H, et al. Predicting fluid responsiveness in patients undergoing cardiac surgery: functional haemodynamic parameters including the Respiratory Systolic Variation Test and static preload indicators. *Br J Anaesth* 2005;95:746–55.
- [86] De Backer D, Heenen S, Piagnerelli M, et al. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* 2005;31:517–23.
- [87] Reuter DA, Kirchner A, Felbinger TW, et al. Usefulness of left ventricular stroke volume variation to assess fluid responsiveness in patients with reduced cardiac function. *Crit Care Med* 2003;31:1399–404.

- [88] Reuter DA, Felbinger TW, Schmidt C, et al. Stroke volume variations for assessment of cardiac responsiveness to volume loading in mechanically ventilated patients after cardiac surgery. *Intensive Care Med* 2002;28:392–8.
- [89] Felbinger TW, Reuter DA, Eltzschig HK, et al. Cardiac index measurements during rapid preload changes: a comparison of pulmonary artery thermodilution with arterial pulse contour analysis. *J Clin Anesth* 2005;17:241–8.
- [90] Rex S, Brose S, Metzelder S, et al. Prediction of fluid responsiveness in patients during cardiac surgery. *Br J Anaesth* 2004;93:782–8.
- [91] Feissel M, Michard F, Mangin I, et al. Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. *Chest* 2001;119: 867–73.
- [92] Monnet X, Rienzo M, Osman D, et al. Esophageal Doppler monitoring predicts fluid responsiveness in critically ill ventilated patients. *Intensive Care Med* 2005;31:1195–201.
- [93] Vallee F, Fourcade O, De SO, et al. Stroke output variations calculated by esophageal Doppler is a reliable predictor of fluid response. *Intensive Care Med* 2005;31:1388–93.
- [94] Charron C, Caille V, Jardin F, et al. Echocardiographic measurement of fluid responsiveness. *Curr Opin Crit Care* 2006;12:249–54.
- [95] Bendjelid K, Romand JA. Fluid responsiveness in mechanically ventilated patients: a review of indices used in intensive care. *Intensive Care Med* 2003;29:352–60.
- [96] Feissel M, Michard F, Faller JP, et al. The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. *Intensive Care Med* 2004;30:1834–7.
- [97] Barbier C, Loubieres Y, Schmit C, et al. Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. *Intensive Care Med* 2004;30:1740–6.
- [98] Weil MH, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). *Circulation* 1970;41:989–1001.
- [99] Hotchkiss RS, Karl IE. Reevaluation of the role of cellular hypoxia and bioenergetics failure in sepsis. *JAMA* 1992;267:1503–10.
- [100] Marik PE, Varon J. The hemodynamic derangements in sepsis: Implications for treatment strategies. *Chest* 1998;114:854–60.
- [101] Marik PE. Gastric intramucosal pH. A better predictor of multiorgan dysfunction syndrome and death than oxygen-derived variables in patients with sepsis. *Chest* 1993;104:225–9.
- [102] James JH, Luchette FA, McCarter FD, et al. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. *Lancet* 1999;354:505–8.
- [103] Levy B, Bollaert PE, Charpentier C, et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized, study. *Intensive Care Med* 1997;23:282–7.
- [104] Gore DC, Jahoor F, Hibbert JM, et al. Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. *Ann Surg* 1996;224:97–102.
- [105] Levy B, Gibot S, Franck P, et al. Relation between muscle Na⁺K⁺ ATPase activity and raised lactate concentrations in septic shock: a prospective study [erratum appears in *Lancet*. 2005 Jul 9-15;366(9480):122]. *Lancet* 2005;365:871–5.
- [106] Moomey CB Jr, Melton SM, Croce MA, et al. Prognostic value of blood lactate, base deficit, and oxygen-derived variables in an LD50 model of penetrating trauma. *Crit Care Med* 1999;27:154–61.
- [107] Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med* 2004;32:1637–42.
- [108] Park M, Azevedo LC, Maciel AT, et al. Evolutionary standard base excess and serum lactate level in severe sepsis and septic shock patients resuscitated with early goal-directed therapy: still outcome markers? *Clinics* 2006;61:47–52.
- [109] Dantzker DR. The gastrointestinal tract. The canary of the body? *JAMA* 1993;270:1247–8.
- [110] Grum CM, Fiddian-Green RG, Pittenger GL, et al. Adequacy of tissue oxygenation in intact dog intestine. *J Appl Physiol* 1984;56:1065–9.

- [111] Schlichtig R, Bowles SA. Distinguishing between aerobic and anaerobic appearance of dissolved CO₂ in intestine during low flow. *J Appl Physiol* 1994;76:2443–51.
- [112] Marik PE. Sublingual capnometry: a non-invasive measure of microcirculatory dysfunction and tissue dysoxia. *Physiol Meas* 2006;27:R37–47.
- [113] Marik PE. Regional carbon dioxide monitoring to assess the adequacy of tissue perfusion. *Curr Opin Crit Care* 2005;11:245–51.
- [114] Creteur J, De Backer D, Sakr Y, et al. Sublingual capnometry tracks microcirculatory changes in septic patients. *Intensive Care Med* 2006;32:516–23.
- [115] Gutierrez G, Palizas F, Doglio G, et al. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 1992;339:195–9.
- [116] Astiz ME, Rackow EC, Kaufman B, et al. Relationship of oxygen delivery and mixed venous oxygenation to lactic acidosis in patients with sepsis and acute myocardial infarction. *Crit Care Med* 1988;16:655–8.
- [117] Mahutte CK, Jaffe MB, Sasse SA, et al. Relationship of thermodilution cardiac output to metabolic measurements and mixed venous oxygen saturation. *Chest* 1993;104:1236–42.
- [118] Vaughn S, Puri VK. Cardiac output changes and continuous mixed venous oxygen saturation measurement in the critically ill. *Crit Care Med* 1988;16:495–8.
- [119] Reinhart K, Kuhn HJ, Hartog C, et al. Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. *Intensive Care Med* 2004;30:1572–8.
- [120] Silva E, De Backer D, Creteur J, et al. Effects of fluid challenge on gastric mucosal PCO₂ in septic patients. *Intensive Care Med* 2004;30:423–9.
- [121] Marik PE, Bankov A. Sublingual capnometry versus traditional markers of tissue oxygenation in critically ill patients. *Crit Care Med* 2003;31:818–22.
- [122] Marik PE. The optimal endpoint of resuscitation in trauma patients. *Crit Care* 2003;7:19–20.
- [123] Totapally BR, Fakioglu H, Torbati D, et al. Esophageal capnometry during hemorrhagic shock and after resuscitation in rats. *Crit Care* 2003;7:79–84.

Invasive Intravascular Hemodynamic Monitoring: Technical Issues

Sheldon Magder, MD, FRCP(C)

*McGill University Health Centre, Royal Victoria Hospital, 687 Pine Avenue West,
Montreal, Quebec, Canada H3A 1A1*

Hemodynamics measurements are a fundamental part of the management of critically ill patients. Many millions of dollars are spent on equipment to make these measurements, and many hours are spent arguing over the appropriate algorithms for their use at the bedside. Despite the obvious fact that these measurements can only be useful if they are valid and accurate, studies repeatedly show that there is a lack of knowledge of the basic principles behind these measurements and the important artifacts that can result in unreliable measurements [1,2]. This is especially a problem for measurements of central venous pressure (CVP) and pulmonary artery occlusion pressure (Ppao), because the range of normal clinical values is small and errors can become a large percentage of the true value. In this article, the author reviews the basic principles of making hemodynamic measurements as well as common artifacts and pitfalls.

What is pressure?

Pressure is force per cross-sectional area. As described in Newton's second law, force is the product of mass and acceleration, and the force is measured as a vector, that is, in a straight line in a given direction. In biologic systems, forces usually need to be assessed over the surfaces of curved structures, such as vessels and the heart. To deal with this problem, force is analyzed as pressure, which is force per cross-sectional area. Pressures are measured most often in units of millimeters of mercury (mm Hg) and centimeters of water (cm H₂O). When these units are used, the applied force is gravity and the acceleration is the gravitational constant. The force is then related to the mass of fluid used for the measurement, which, in turn, is

E-mail address: sheldon.magder@muhc.mcgill.ca

determined by the volume and density of the substance used for calibrating the measurement. In the case of water, the density is essentially 1, and in the case of mercury, the density is 13.6 times that of water. The height of a column is equal to the volume divided by cross-sectional area, such that the pressure at the bottom of any structure is directly related to the vertical height of fluid in the structure. To convert cm H₂O to mm Hg, multiply by 1.36 (remember, it is centimeters to millimeters), and to convert from mm Hg to cm H₂O, divide by 1.36. These units are “relative,” because the force attributable to gravity varies with the difference in distance from the center of the earth, although ever so slightly. Physicists who determine the standards for force measurements care about these slight differences however; thus, the standard measurements are based on absolute forces that do not depend on gravity; these units are called Pascal units, which are equal to Newton/m², wherein a Newton is the force required to accelerate 1 kg 1 m per second per second; 1 kilo-Pascal is 7.5 mm Hg.

Pressures were originally measured with columns of fluids. A column of water was used when the pressure was low, and a column of mercury was used when the pressure was high, such that an excessively large column would not be necessary. Because a column of blood has a density close to that of water, the height of a column of blood gives an indication of the pressure in a vessel in cm H₂O. If blood pressure were measured with a column of blood, the normal systolic pressure of 120 mm Hg would require a tube that be larger than 160 cm and would obviously be cumbersome.

Today, pressure is usually measured with a transducer, which is a device that has a current running through a conducting membrane that can be distorted by forces on its surface. Distortion of the membrane alters the resistance to electron flow through the membrane, which results in a change in current for a given voltage difference across the membrane. Three factors have to be considered when using a transducer: (1) calibration, (2) leveling, and (3) zero setting.

The simplest of these three concepts is calibration. In this process, a known pressure is applied to the membrane and change in current is related to the applied pressure. For proper function, the response of the transducer must be linear in the range of measured pressures. This means that doubling the pressure doubles the voltage change in the range of the measured pressures. The applied force can be from a column of mercury or water; however, at the present time, it is usually supplied by the application of a standard electrical force to the system.

The next issue is the establishment of the “zero” value. A fundamental and often confused concept for making hydrostatic measurements with fluid-filled systems is that the measurement is relative to a reference value. The first reference value to consider is the surrounding pressure. Although we normally do not think about it or feel it, the pressure of normal atmosphere, which is approximately 760 mm Hg depending on the weather conditions, constantly pushes down on us and also pushes down on the

surface of the transducer, the column of fluid that is used to calibrate the transducer, and the containers that hold the fluids being assessed. Consider what this means for CVP. The usual clinical range of values for CVP is less than 10 mm Hg [3], whereas the background pressure is around 760 mm Hg. This means that when we say the CVP is 5 mm Hg, the actual pressure on the inner side of the wall of the veins is really around 765 mm Hg. For arterial pressure, the actual normal systolic pressure pushing on the wall of the arteries is not 120/80 mm Hg but rather 880/840 mm Hg. Because the measuring device and the systems we want to examine are all affected by the same atmospheric pressure, it makes sense just to examine changes from atmosphere for these as the changes that are attributable to changes in the physiologic system and to describe the pressure across the walls of the structures of interest. If this were not done, the measured value would fluctuate with changes in atmospheric pressure and it would be necessary to keep a barometer in the unit to interpret physiologic pressure changes. The process of subtracting the atmospheric pressure is called “zeroing,” and what is essentially being done is opening the fluid column on the measuring device to atmosphere and adjusting the electronics so that atmospheric pressure is the starting value or zero. If one were using a fluid-filled manometer, the equivalent would be letting out sufficient volume from the measuring column until it reaches the zero value inscribed on the manometer. Of importance, when stress is calculated on the wall of any vessel that does not have an extremely thin wall, the actual pressure needs to be used instead of the simplified Laplace relation to the pressure relative to atmosphere. When the actual pressures are used, the stress in the wall is negative (ie, the vessels are tending to explode), whereas if the pressure relative to atmosphere is used as in the simplified Laplace relation, the vessel seems to be collapsing [4–6].

The most confusing factor, and the one that leads to the greatest errors in hemodynamic measurements with fluid-filled catheters, is the concept of leveling. Before reading this section, try answering the questions in Fig. 1. The figure shows four cylinders that are filled with water to a level of 40 cm. A transducer is leveled at 20 cm below the surface of the water in Fig. 1A and B, at the level of the surface in Fig. 1C, and at the level of the bottom of the cylinder in Fig. 1D. A fluid-filled catheter is inserted to a level 20 cm below the surface in Fig. 1A, C, and D and the bottom of the cylinder in Fig. 1B. The question is what would be the value shown on the digital monitor in each case.

As already discussed, pressure measurements in a fluid-filled system are relative to a reference point that is arbitrarily picked, because the measurement is simply that of the force created by a column of fluid above the transducer. Thus, the level of the transducer relative to pressure being measured is the key determinant of the measured value, and the measured pressure is determined by the height of the fluid column above the transducer. The measured pressure is not affected by the location of the opening of the fluid-filled

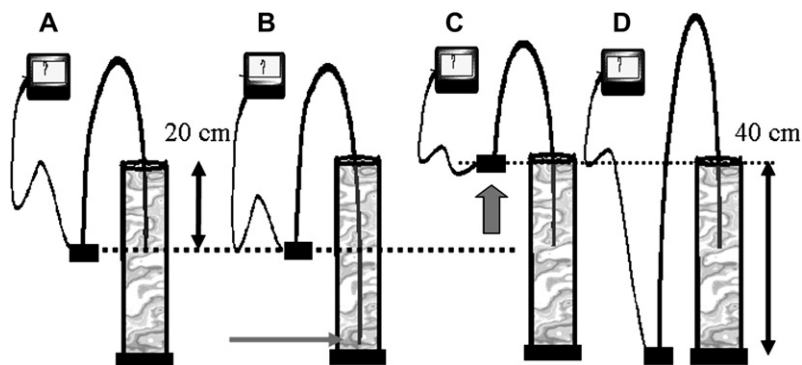


Fig. 1. Cylinder is filled with water to a height of 40 cm. In each case, a fluid-filled catheter is connected to a transducer and inserted in the fluid. (A, B) Transducer is placed 20 cm below the surface of the water. (C) Transducer is placed at the level of the water. (D) Transducer is placed at the bottom. What is the value on the monitor in each case? The answers are in the text.

catheter used to make the measurement if it is inside the fluid-filled system. Thus, in Fig. 1A and B, the measured pressure is 20 cm H₂O, even though the catheter has been advanced to the bottom of the container in Fig. 1B. This does not mean that the actual pressure is the same at 20 cm below the surface and at the bottom. The pressure is greater at the bottom of the tank. Think of the sensation you feel when you go to the bottom of a swimming pool compared with what you feel just below the surface. The measured value is not affected because it is based on the position of the catheter relative to the top of the tank. When the transducer is moved to the level of the surface of the water in Fig. 1C, the pressure is 0 cm H₂O because there is no fluid above the transducer. When the transducer is leveled to the bottom of the cylinder, the measured pressure is 40 cm H₂O. Thus, one must distinguish between the measured pressure and the actual pressure in the system.

Because leveling is so important, the choice of the reference level is critical. It is generally accepted that for physiologic measurements, an appropriate reference point is the midpoint of the right atrium, because this is where blood comes back to the heart and this is also the pressure that provides the preload for the heart as a whole. This is not to say that this has to be the reference level; rather, it is a consensus view, although others have been suggested (even though they may end up at the same position) [7]. A fortuitous anatomic feature is that the midpoint of the right atrium is, on average, a vertical distance of 5 cm under the sternal angle or angle of Louis, which is where the second rib meets the sternum and creates a bump on the sternum. This position is taught to all medical students as the reference value for measurement of jugular venous distension, a bedside measure of CVP [8]. An important advantage of this leveling value is that it remains at the level of the midpoint of the right atrium, even when a patient is sitting

at an angle of 60° . This is because the right atrium is a relatively round structure and is located just under the sternum. The radius of the atrium also does not vary by large amounts among individuals. This means that the transducer can be leveled to this position even when the patient is not supine, as is often the case when patients are being fed, when they have pulmonary edema, or when they are bleeding after cardiac surgery. Leveling is achieved by placing a carpenter's level on the sternal angle and setting the transducer 5 cm under this level (Fig. 2). As already noted, it does not matter whether the patient is supine or sitting at 60° as long as the transducer is 5 cm under this level. It is also important to consider the appropriate position on the transducer for leveling. The level representing the midpoint of the right atrium should be leveled to the top of the fluid column that is necessary to zero the transducer. This is situated at the level of the stopcock that is opened for zeroing the transducer. The difference between this value and the bottom of the transducer can be as much as 3 to 4 mm Hg, such that incorrect placement can have a considerable effect on the measured pressure.

A much more common leveling position in the intensive care unit (ICU) is the midthoracic position at the level of the fourth rib. It is argued that the advantage of this position is that it is easier to teach and does not require a leveling device. Measurements should only be made with this level in the supine position, however, because the middle right atrium does not maintain a constant relation to this position when the upper body is elevated. In the author's experience, the greater amount of teaching and care required for the sternal angle-based measurement is actually an advantage because it sensitizes the team to the importance of the level and means that the level is checked more often. As a useful conversion so that

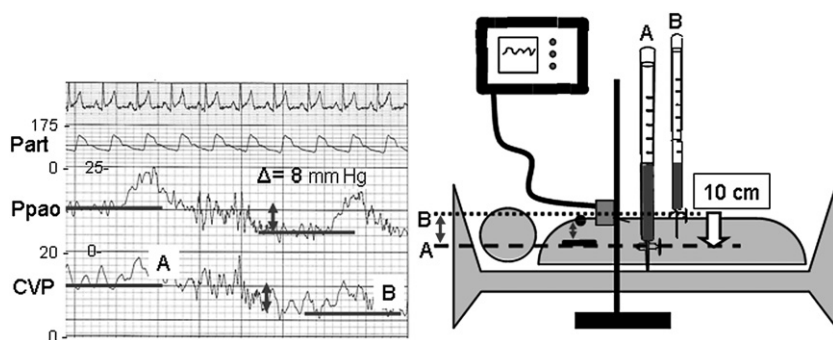


Fig. 2. Illustration of what happens when the bed is lowered but the transducer is not. The left side shows the change in pressures (*top*, arterial [Part]; *middle*, Ppao; *lower*, CVP), and on the right side, water monometers demonstrate how lowering the bed relative to the transducer lowers the measured pressure. In this case, the bed was lowered by 10 cm, which means that the proper level (A) is 10 cm lower than the current level (B), and this translates to a decrease in pressure of approximately 8 mm Hg.

measurements with the two methods can be compared, we found that, on average, the sternal angle–based measurement gives a value that is 3 mm Hg less than the midthoracic measurement [3]. Consider the consequences of changes in the level of the transducer relative to the midpoint of the right atrium. Most often, the transducer is not attached to the bed, such that changes in the bed relative to the mounting for the transducer change the value. For example, lowering the bed by 10 cm changes the recorded pressure by almost 8 mm Hg (see Fig. 2). This difference in the CVP measurement could mean the difference between a fluid challenge and an order for furosemide.

As discussed previously, the measured value is not the same as the actual pressure throughout the system. Thus, when the measured pressure for CVP is 10 mm Hg based on the sternal angle reference, it is actually around 17 mm Hg in veins along the patient's back because of the vertical distance between the level and the bottom of the patient [3]. This is the pressure in the capillaries that regulate filtration in this region. Of importance, leveling is not an issue when measuring gas pressures. This is because the mass of the gas is small, such that the weight of the gas is trivial over the heights we have to consider for the measurements. Thus, it is not necessary to level transducers for air-based measurements, such as airway pressure on a ventilator.

Transmural pressure

Another important concept is that of transmural pressure. The walls of elastic structures are stretched by the difference in pressure between the pressure inside the structure versus the pressure outside the structure, and the difference in these two pressures is called the transmural pressure (Fig. 3).

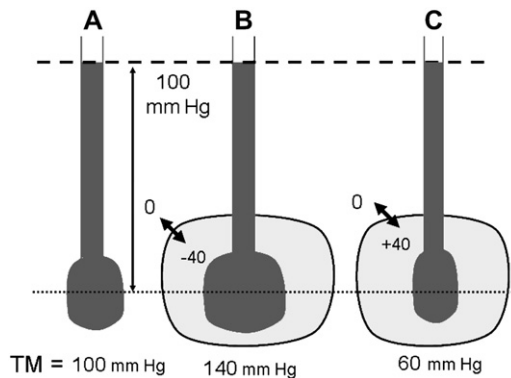


Fig. 3. Illustration of the concept of transmural pressure. (A) System is surrounded by atmospheric pressure, and the transmural pressure (TM) is $100 - 0 = 100$ mm Hg. (B) Pressure surrounding the elastic chamber is -40 mm Hg, such that the TM is $100 - (-40) = 140$ mm Hg. (C) Surrounding pressure is $+40$, such that the TM is $100 - 40 = 60$ mm Hg.

This concept is not a concern for vascular structures that are outside the chest, because the outside pressure is atmospheric pressure, which is used to zero the transducer. Thus, transmural arterial blood pressure is simply the arterial pressure as normally measured minus zero. The problem arises with elastic structures that are inside the chest or abdomen because they are not surrounded by atmospheric pressure but rather by pleural and intra-abdominal pressure, respectively, and these pressures vary throughout the ventilatory cycle. Unfortunately, pleural pressure is not easily measured in critically ill patients. Thus, the approach is to measure pressures of vascular structures in the chest at the phase of ventilation when pleural pressure is closest to zero. At end-expiration (functional residual capacity [FRC]), the lungs recoil inward and the chest wall outward, which gives a pressure around the heart of approximately -2 to -3 cm H₂O and not extremely different from atmosphere. Accordingly, vascular pressures should be measured at end-expiration (or preinspiration, which is the same) whether the person is ventilated with negative- (Fig. 4) or positive-pressure ventilation (Fig. 5). In a person breathing spontaneously, inspiration can be identified by the fall in pressure in vascular structures in the chest [9], and especially by an increase in the “y” descent (see Fig. 4) [10].

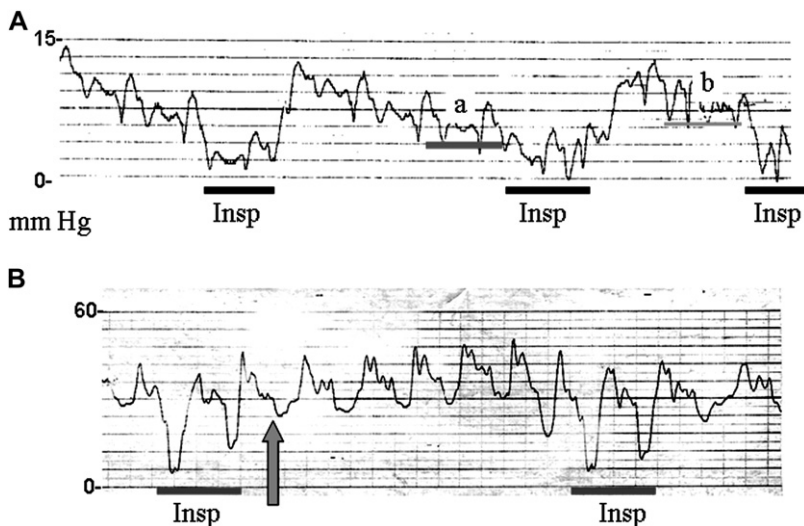


Fig. 4. Effect of forced or active expiration on CVP measurement in two subjects with spontaneous ventilatory efforts. Inspiration (Insp) is marked with the horizontal lines. (A) Progressive decrease in the pressure during expiration indicates abdominal recruitment and forced expiration. Note how the pressure is lower at a than at b. This is because expiration is longer in a than in b, and is therefore a better estimate of the CVP but still may be an overestimate. (B) Progressive increase in pressure during expiration. The measurement at end-expiration does not give a good estimate of the transmural pressure, and a better estimate is likely at the arrow, which indicates a period before the subject begins to push.

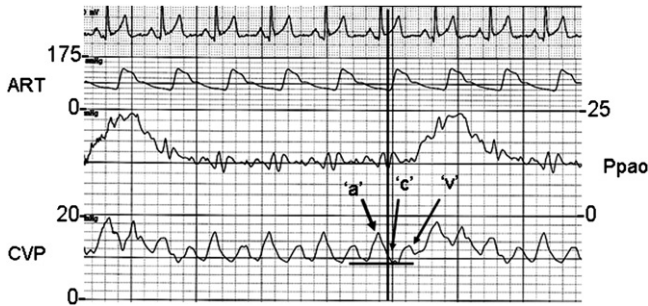


Fig. 5. Assessment of the atrial waveforms in a subject being ventilated with positive-pressure ventilation. The proper site for measuring the CVP (and Ppao) is at the base of the c wave, which can also be identified by a perpendicular line down from the QRS wave. ART, arterial pressure.

Furthermore, inspiration is usually approximately one third of the cycle. In a patient breathing with positive-pressure ventilation, inspiration produces a rise in pressure in vascular structures in the chest and a decrease in the y descent. Again, inspiration is usually shorter than expiration but can be longer when the ventilator is set to reverse the normal inspiratory/expiratory ratio.

Positive end-expiratory pressure

Positive end-expiratory pressure (PEEP) is an important problem for the measurement of vascular pressures in the chest because it creates a pressure around the heart that is always greater than atmospheric pressure; thus, the observed value always overestimates the transmural pressure. At low levels of PEEP, such as the standard 5 cm H₂O, there is only a minor error. In normal lungs, a little less than half the PEEP is transmitted to the pleural space, because energy is lost in overcoming the elastance of the alveoli. Thus, converting centimeters to mm Hg and reducing the standard PEEP value of 5 cm H₂O by half means that central measurements are only increased by 1 to 2 mm Hg, which is within the range of normal measurement error. When high values of PEEP are applied, or the patient has substantial auto-PEEP, the error can become large. High values of PEEP are usually used when lung compliance is decreased, however, and this substantially reduces the transmission of the PEEP to the pleural space. There is no simple solution to predicting the true transmural pressure of intrathoracic structures in patients with PEEP. Pinsky and coworkers [11] showed that rapidly withdrawing PEEP and observing the nadir of the Ppao could be used to assess the impact of the change in pleural pressure, Ppao. It is often not safe to lower high levels of PEEP transiently, however, because derecruitment and consequent hypoxemia can be rapid and recruitment can be slow. Furthermore, the technique cannot be used for assessing the effect

of PEEP on the pressure in the right heart, because CVP relative to atmosphere does not always change with PEEP (although the transmural pressure is changed) [12]. The author's own approach is to report in the medical record the measured hemodynamic values as obtained relative to atmosphere and have the clinician estimate the range of impact of the PEEP on the transmural pressure by considering the patient's lung compliance.

An important clinical point to consider with high levels of PEEP is that although the transmural pressures of vascular structures in the chest may be low when the measured value is high relative to atmosphere, the high value is not inconsequential because it directly affects fluid filtration and the back-pressure for venous flow in regions outside the chest. Furthermore, although values are recorded and charted at end-expiration, the systemic venous pressures are much higher during inspiration with positive-pressure ventilation. This is especially the case when the thoracic compliance is decreased, which includes patients with abdominal compartment syndrome.

Active expiration

Another important cause of errors in measurement of central pressures is active expiration. Normally, expiration is passive, such that pleural pressure does not increase during expiration. In a recent study, the author and his colleagues found that 30% to 40% of patients had active expiration [13]. This resulted in two major patterns (see Fig. 4). In the first type, the patient contracts expiratory muscles forcefully from the start of expiration so that there is a progressive fall in pressure throughout expiration. This results in lower pressures at end-expiration in breaths with longer periods of expiration. In the second type, the patient progressively increases the expiratory force, which results in a progressive rise in intrathoracic pressures. In these cases, the recommended end-expiratory value gives a completely erroneous measure of the true transmural pressure and values at the start of expiration are likely more valid. Because these patterns are so frequent, the author recommends that the actual tracings on the monitor always be examined before recording the values. When active expiration is present, many respiratory cycles need to be examined and the ones with minimal evidence of active expiration should be used for the measurement. These can be identified in spontaneously breathing patients by periods of relatively no change in the pressure during the end of expiration (immediately before inspiration). Forced expiration is harder to assess when a patient is receiving ventilatory assistance, because the positive pressure during inspiration produces a rise in vascular pressures and a gradual decline during expiration. When the inspiratory/expiratory ratio is small, there may never be a flat phase during expiration. One can also try to distract the patient for at least some breaths to obtain breaths with passive expiration. It needs to be appreciated that in some of these cases, it may not be possible to obtain a valid estimate of the

real values. In those situations, the author recommends putting a tracing in the medical record so that all users can at least see the basis of the estimate.

Where on the tracings of central venous pressure and pulmonary artery occlusion pressures do you make the measurements?

CVP and Ppao have important waves during the cardiac cycle that can be large, and the reported value varies significantly depending on the rule used to make the measurement. In the example shown in Fig. 5, the pressure difference from bottom of the tracings to the top is 10 mm Hg. The recommended position is the base of the “c” wave, because this is the final value in the atrium before the onset systole, and is thus the best estimate of the preload. The c wave is not always evident, however; in that case, the base of the “a” wave gives a good approximation. Alternatively, if there is a simultaneous electrocardiographic (ECG) tracing, one can draw a vertical line from the QRS to identify the expected position of the c wave. Although the base of the c wave is the recommended pressure to trend, this does not mean that the peaks of the a and “v” waves are without clinical significance. For example, in Fig. 6, the Ppao should be recorded at 18 mm Hg, but the large v wave has a direct effect on the pulmonary capillaries and results in pulmonary edema. In cases like this, the author would recommend charting the value as a Ppao of 18 mm Hg with a v wave of 23 mm Hg (which means that the pressure is $23 + 18 = 41$ mm Hg).

There are several technical factors that are specific for the Ppao [14]. It is important to identify the a and v waves to know that the pulmonary artery catheter is actually in the wedge position for the proper measurement of left atrial pressure. It is also important to make sure that the measured Ppao is less than the pulmonary artery pressure, because, otherwise, it is likely that the tracing represents a dampened pulmonary artery tracing rather than Ppao. An assumption in the use of the wedged pulmonary artery catheter for the measurement of Ppao is that there is a continuous column from the tip of the catheter to the left atrium. This is valid if the catheter is in

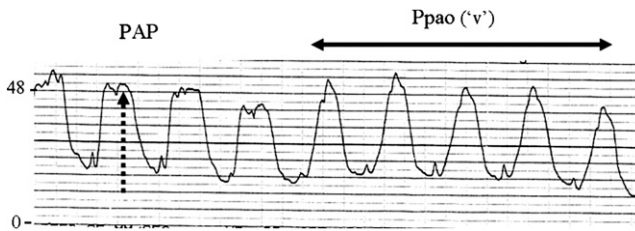


Fig. 6. Example of a tracing with giant v wave on the Ppao tracing. This could easily be confused with the pulmonary artery tracing, which occurs on the right of the figure. Note the notching of the pulmonary artery pressure (PAP) (dotted arrow), which is caused by the backward flow with the large v wave.

West zone III but not if it is in zone I or II, where there is a critical closing pressure [15]. The proportion of the lung in zone II increases with PEEP, which thus increases the risk of this problem. Keeping the catheter more central greatly reduces the likelihood of this happening, however, and also greatly reduces the risk of pulmonary hemorrhage. Because of this risk, and for proper placement, the chest radiograph should always be examined to make sure that the catheter is not beyond the lateral mediastinal border, and this is usually less than 55 cm from the entry site on the introducer. In cases in which a “wedge” measurement can only be made with the catheter more distal, the author recommends making the measurement and then withdrawing the catheter to a safer position.

Right ventricular dysfunction

The presence of right ventricular (RV) dysfunction and tricuspid regurgitation can make the identification of the pressures difficult; if not appreciated, this can result in failure to insert a flotation catheter in the pulmonary artery. Two examples are shown in Fig. 7. When placing a catheter in such a patient, it is important first to identify the pattern of tricuspid regurgitation on the CVP tracing, which is characterized by a broad v wave

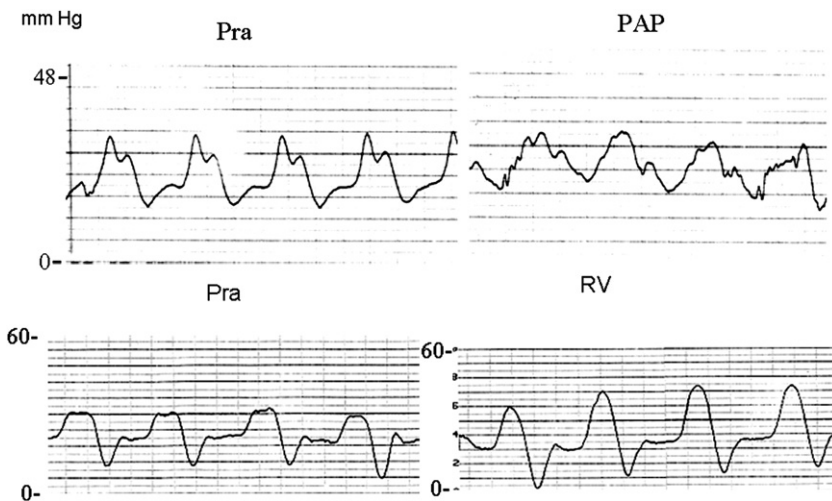


Fig. 7. Two examples of CVP tracings that could make placement of a right heart flotation catheter difficult. The top tracing shows a patient with an RV infarct. There is little change between the right atrium (Pra) and the pulmonary artery pressure (PAP) because of the high RV diastolic pressure and low systolic pressure generation. The shapes of the wave must be followed closely to identify the position of the catheter in such a patient. In the bottom tracing, the patient has marked tricuspid regurgitation and the shape of the Pra is similar to that of the RV tracing. This could make it difficult to recognize the crossing of the tricuspid valve.

that looks like a “ventriculization” of the atrial tracing. This can be identified by examining the CVP waveform in the initial 20 cm of the insertion and by then carefully noting the distance markers on the catheter while it is advanced. The tricuspid valve is almost always within 25 to 35 cm from insertion sites in the upper extremity, and when the tricuspid is not reached by these values, the catheter is likely curling or in the wrong place.

Factors related to kinetic energy

Although we generally deal with pressure differences as the determinants of flow, it is the actual energy differences that determine the movements of fluids. There are three types of energy in vascular systems: elastic, kinetic, and gravitational energy. The primary energy that is of importance for determining vascular pressures is the elastic energy. This is the force that distends the vascular walls. The gravitational component was already discussed in the section on the issue of leveling. The third component, kinetic energy, is the energy that is attributable to the flow of blood and only contributes a small component to the arterial pressure, although its contribution to the pressure in the vena cava and pulmonary circuit is larger. This is because the velocity of blood in the vena cava and main pulmonary artery is similar to that of the aorta but the elastic pressure is much smaller. The importance of kinetic energy for the measurement of pressures is that it results in differences in pressure when an end-hole catheter faces the flow or faces away from the flow. This occurs because when the flowing blood hits the hole at the end of the catheter, the blood stops, the kinetic energy is converted into elastic energy, and the recorded pressure is higher than what would be measured with a side-holed catheter. When the catheter hole faces away from the flow, the Bernoulli effect slightly lowers the pressure relative to a side-hole.

Dampening

Details on the physics of measuring devices are nicely reviewed elsewhere, and only a few key points are discussed here [16]. Pressure swings can be considered as waves and can be broken down into a series of sine waves with different frequencies. The measuring device must be able to respond to the frequencies of interest in the signal being measured; if it does not, the peaks and troughs of the signal are underestimated. When the pressure wave hits the transducer, it also induces reflected waves that amplify the signal. These gradually decrease because of friction in the tubing in a process called dampening. If the system is underdamped, the device exaggerates the pressure swings, and if the system is overdamped, the peaks and troughs are underestimated. The issue of dampening is especially a problem for recordings of arterial pressure. Systems have an optimal range for the relation of dampening, as measured by the relation of the amplitude of

the input-to-output signal, and the ratio of frequency of the system is stimulated relative to its natural frequency. Most monitoring devices permit the frequency response to be adjusted, which allows for changes in the dampening, but this may not be sufficient. Underdamping is sometimes attributable to microbubbles in the system, and flushing the system resolves problem. The attachment of a small needle open to air can be used to dampen signals that are underdamped because this increases the frictional energy loss and dampens the system; however, this leaves the system unsealed, and thus at risk of infection. It may also result in underdamping of the system. The adequacy of dampening can be assessed by flushing the system and observing the number of cycles needed for the signal to stabilize. This should occur in less than three waves.

Trouble-shooting

It is not possible to provide answers for all the technical problems that can occur. Many issues related to trouble-shooting have already been dealt with, but the author gives some others that he has found helpful. Perhaps the most important technical point is that one must gain experience with the measurements and always be on the alert for technical problems. As a first approach, one must consider that measured values should make sense with the overall clinical picture. It is true that invasive monitoring is used to obtain new insights, but the results should still conform to a believable hypothesis, and when the measurements are extremely different from the expected, potential technical errors must be looked for carefully. One should start by redoing the zeroing, leveling, and calibration. Sudden changes in values can be real but should raise the suspicion of a leveling problem or drift in the electronic signal. The key clue to a leveling problem is that all pressures change in the same direction and by a similar amount, because in most critical care units, pressure transducers are mounted on a common manifold. Conversely, changes in only one of the measures being followed suggest that there has been a "drift" in the zero value of the transducer. Sudden changes in the recorded CVP or Ppao should also raise the possibility of there being a respiratory effect, such as active expiration, that was not recognized by the person making the measurement. It could also indicate a pneumothorax or cardiac tamponade caused by bleeding into the pericardium, however. Examination of the tracing helps to give the answer. As a final point, it is not appropriate to dismiss a measurement because it is unreliable without some explanation for why the measurement is unreliable, such as a faulty amplifier, faulty cable, or blocked catheter. To do so runs the risk of ignoring important clinical information.

Summary

A careful and systematic approach to hemodynamic measurements can minimize error and result in more rational clinical choices. Proper

hemodynamic algorithms can only be effective when they are based on measurements that are valid and obtained in a consistent manner by clinicians who understand the basis of the measurements.

References

- [1] Iberti TJ, Fisher EP, Leibowitz AB, et al. A multicenter study of physicians' knowledge of the pulmonary artery catheter. Pulmonary Artery Catheter Study Group. *JAMA* 1990;264(22): 2928–32.
- [2] Iberti TJ, Daily EK, Leibowitz AB, et al. Assessment of critical care nurses' knowledge of the pulmonary artery catheter. The Pulmonary Artery Catheter Study Group. *Crit Care Med* 1994;10:1674–8.
- [3] Magder S, Bafaqeeh F. The clinical role of central venous pressure measurements. *J Intensive Care Med* 2007;22(1):44–51.
- [4] Azuma T, Oka S. Mechanical equilibrium of blood vessel walls. *Am J Physiol* 1971;221: 1310–8.
- [5] Oka S, Azuma T. Physical theory of tension in thick-walled blood vessels in equilibrium. *Biorheology* 1970;7:109–17.
- [6] Shrier I. Critical closing pressures, vascular waterfalls, and the control of blood flow to the hindlimb. Thesis; 1993.
- [7] Courtois M, Fattal PG, Kovacs SJ, et al. Anatomically and physiologically based reference level for measurement of intracardiac pressures. *Circulation* 1995;92:1994–2000.
- [8] Bickley LS, Hoekelman RA. Bates' guide to physical examination and history taking. 7th edition. Philadelphia: Lippincott; 1999.
- [9] Bellemare P, Goldberg P, Magder S. Do inspiratory changes in pulmonary artery occlusion pressure reflect changes in pleural pressure? *Am J Respir Crit Care Med* 2004;169(7):A343.
- [10] Magder S, Erice F, Lagonidis D. Determinants of the 'y' descent and its usefulness as a predictor of ventricular filling. *J Intensive Care Med* 2000;15:262–9.
- [11] Carter RS, Snyder JV, Pinsky MR. LV filling pressure during PEEP measured by nadir wedge pressure after airway disconnection. *Am J Physiol* 1985;249(4 Pt 2):H770–6.
- [12] Magder S, Lagonidis D, Erice F. The use of respiratory variations in right atrial pressure to predict the cardiac output response to PEEP. *J Crit Care* 2002;16(3):108–14.
- [13] Serri K, Chauvin R, Goldberg P, et al. The prevalence of forced expiration in critically ill patients. *Crit Care Med* 2007;34(12):A59 [Abstract].
- [14] Lodato RF. Use of the pulmonary artery catheter. *Semin Respir Crit Care Med* 1999;20(1): 29–42.
- [15] Permutt S, Riley S. Hemodynamics of collapsible vessels with tone: the vascular waterfall. *J Appl Physiol* 1963;18(5):924–32.
- [16] Fessler HE, Shade D. Measurement of vascular pressure. In: Tobin MJ, editor. *Principles and practice of intensive care monitoring*. New York: McGraw-Hill; 1997. p. 91–106.

Abdominal Compartment Syndrome: Clinical Aspects and Monitoring

Felix Lui, MD, Ayodele Sangosanya, MD,
Lewis J. Kaplan, MD, FACS, FCCM, FCCP*

*Yale University School of Medicine, Department of Surgery,
Section of Trauma, Surgical Critical Care and Surgical Emergencies,
330 Cedar Street, BB-310, New Haven, CT 06520, USA*

Critical care has undergone a quiet revolution in the past decade with regard to resuscitation and management of patient suffering from sepsis and its related syndromes. Previously, antibiotics and supportive care strategies dominated care paradigms for sepsis and focused on pulmonary management or antibiotic management strategies. To wit, a host of antibiotic guidelines with patients' severity stratification were published by the American Thoracic Society, the Infectious Disease Society of America, and others [1]. New scoring systems, including APACHE II and then III surfaced, as well as a host of organ dysfunction scoring systems, were proposed to aid in risk stratification and perhaps therapeutic intervention [2,3]. Perhaps most visibly, the supremacy of the ARDSNet guidelines for mechanical ventilation best exemplifies the public nature of change in critical care paradigms [4]. While all of these sweeping changes occurred in a highly visible fashion, changes in resuscitation occurred more quietly, which is all the more remarkable because the changes brought the medical and surgical worlds into proverbial alignment.

The study by Rivers and colleagues of Early Goal Directed Therapy (EGDT) represents the driving force for the resuscitation paradigm shift for patients presenting to an emergency department (ED) with sepsis [5]. Given its success, EGDT tenets have been broadly applied outside of the ED as well. It is this quiet revolution that provides the genesis for the rest of this article. The downstream effects of vigorous resuscitation include enhanced survival at the expense of increased early crystalloid fluid, red cell mass

* Corresponding author.

E-mail address: lewis.kaplan@yale.edu (L.J. Kaplan).

expansion, and pressor use. However, the sentinel study by Rivers and colleagues [5] did not examine any deleterious effects of that resuscitation. One untoward consequence of rapid resuscitation using crystalloid solutions is the abdominal compartment syndrome (ACS) [6]. The remainder of this article will address the physiology of the ACS, diagnostic criteria, monitoring techniques, and acute therapeutic interventions to relieve the syndrome. The corollary is that early identification and therapy for the ACS translates into a survival benefit for patients.

Definitions and classification

Since the ACS has surfaced in the past 2 decades in the trauma patient population in the context of damage control surgery for exsanguinating hemorrhage, a genre of medical literature and a dedicated society have sprung up around the syndrome [7]. In the consensus definitions and recommendations of the World Society of the Abdominal Compartment Syndrome (WSACS; www.wsacs.org), the range of normal intra-abdominal pressure (IAP) is less than 7 mm Hg. Increases above 12 mm Hg constitute intra-abdominal hypertension (IAH). Further increases in IAP may lead to the abdominal compartment syndrome as a consequence of organ compromise as a result of the increased intra-abdominal pressure. Accordingly, the ACS is defined by a sustained IAP of 20 mm Hg or higher associated with new, attributable organ dysfunction or failure [8]. Other objective measures may supplement these diagnostic criteria and will be later explored.

Before developing the ACS, IAP increases above normal to peaks of differing magnitudes and at differing rates depending on the driving force that generates the increased pressure. IAH can be by graded by the magnitude of IAP elevation, and may be further classified by the time course over which the IAH develops (Tables 1 and 2; www.wsacs.org) [9]. To determine which patient one must monitor, one must first define those patients who are at risk for IAH.

Intra-abdominal hypertension in at-risk populations

Patients at risk for IAH may be conveniently grouped into several categories, all of whom share a common element: appropriate, but vigorous

Table 1
Intra-abdominal hypertension grading

Grade	Intra-abdominal pressure
I	12–15 mm Hg
II	16–20 mm Hg
III	21–25 mm Hg
IV	> 25 mm Hg

Table 2
Timing designations of abdominal compartment syndrome

Type	Description	Example
Chronic	Associated with abdominal disease process of a progressive nature	Cirrhosis with massive ascites
Acute	Associated with injury or disease in the abdomen requiring intervention	Intestinal ischemia, abdominal trauma
Subacute	Usually associated with extra-abdominal disease processes, but may also involve intra-abdominal catastrophe resuscitation	Aggressive fluid resuscitation for sepsis regardless of locus
Hyperacute [9]	Development of abdominal compartment syndrome intraoperatively during repair of extra-abdominal injuries with massive concurrent resuscitation or during temporary abdominal wall closure with intra-abdominal injury	Massive resuscitation for shock during operative intervention for chest trauma (gunshot wounds) or major vascular injury; packing of abdominal injury while addressing acidosis, coagulopathy, and hypothermia

resuscitation for diminished effective circulating volume. The reader should understand that the vast majority of data derives from patients resuscitated with crystalloid fluids rather than colloids, reflecting the present US standard of care. The following list outlines the major risk factors present in most patients who are at risk for IAH and the subsequent ACS (*from* Betro and Kaplan [10]; with permission).

1. Massive volume resuscitation (> 10 L crystalloid or 5 L colloid over 24 hours)
2. Massive transfusion protocol use (> 10 U PRBC over 24 hours)
3. Management with an open body cavity (chest or abdomen)
4. Core hypothermia (temp < 33°C)
5. Coagulopathy requiring component therapy (aPTT > 2 times normal; INR > 1.5)
6. Sepsis, severe sepsis, or septic shock regardless of cause
7. Critical illness in the setting of cirrhosis or other liver failure accompanied by extant ascites
8. Mechanical ventilation
9. PEEP > 10 cm H₂O pressure (intrinsic or extrinsic)

As such, these risk factors will define a patient population for whom monitoring is appropriate to detect IAH and embark on corrective therapy to prevent the ACS, as syndrome development engenders significant morbidity and mortality.

Abdominal compartment syndrome

That IAH could derange physiology has been recognized since the beginning of this century [11]. It was proffered that IAH could lead to respiratory, cardiovascular, and renal compromise. Effective monitoring systems, however, were not available, and practitioners were limited to what are currently considered archaic and even barbaric methods when IAH was suspected (although this quite frankly did not occur very often). In a fashion much akin to venting of “evil humors,” venotomy for bleeding, leech therapy, purgatives, and fluid restriction were used to some effect in patients with IAH, likely stemming principally from ascites. As medical science developed, and the underlying physiology of increased abdominal pressure was better characterized in the crucible of exsanguinating hemorrhage from severe hepatic injury, attention turned to precisely defining the consequences of IAH [12]. This effort culminated in a published series by Kron and colleagues [13] in 1984 that used elevated IAP as a criterion for abdominal decompression. Their seminal work demonstrated that decompression improved organ function in patients with elevated IAP. The association of increased IAP with the constellation of clinical manifestations defined by Kron and others was dubbed the “abdominal compartment syndrome” (ACS) [14]. The ACS was further refined as a consequence of recurrent hemorrhage and organ edema in trauma patients who required damage control laparotomy for exsanguinating hemorrhage by Rotondo and colleagues [15] in 1993.

While best characterized in the injured patient population, ACS is clearly not limited to surgical patients; ACS is increasingly identified in the critically ill medical patient population [16]. The rise of the ACS in the nonsurgical patient relates to vigorous resuscitation leading to rapid and progressive ascites formation as well as visceral edema. As with many “newly appreciated” syndromes, ACS incidence has been documented at rates much higher than originally anticipated. In several multicenter studies of severely ill mixed medical and surgical patients, the incidence of increased IAP ranged from 32.0% to 41.0%, with an accompanying alarming mortality of 27.5% to 50.0% [17,18]. It is important to note that the ACS represents a final common pathway for IAH that stems from a diverse number of etiologies.

Accordingly, the ACS may be defined as primary, secondary, or recurrent depending on the etiology of the increased pressure that creates the syndrome. These different forms of the ACS are outlined below:

- **Primary ACS**

Associated with injury or disease (commonly infection or ischemia) in the peritoneal space, frequently requiring surgical or radiological intervention. Clinical entities include but are not limited to abdominal aortic aneurysms, solid organ hemorrhage, pancreatitis, and intestinal ischemia, as well as hepatic transplantation.

Previously known as “surgical” or “acute” ACS.

- **Secondary ACS**

Commonly associated with extra-abdominal pathology, such as those patients who receive large-volume crystalloid or colloid resuscitation for severe sepsis or septic shock from pneumonia, or fulminant hepatic failure.

Previously known as “medical” or “subacute” ACS.

- **Recurrent ACS**

ACS that recurs after previous surgical or medical treatment of primary or secondary ACS. This is most commonly associated with recurrent hemorrhage or visceral edema, but may reflect reaccumulation of ascites that has been externally drained without operative intervention. Formerly known as “tertiary” ACS (www.wsacs.org).

Understanding the pathophysiology of the ACS allows one to intelligently design interventions to either relieve the syndrome or temporize the patient until definitive therapy may be undertaken.

Pathophysiology of intra-abdominal hypertension

This section will artificially separate different organ systems to explore the effects that increased abdominal pressure exerts within that system. In reality, each of these systems acts in concert such that a perturbation or intervention in one will have objectively quantifiable consequences in another. Moreover, in practice, one establishes interventions in multiple systems simultaneously in an effort to improve the patient’s clinical circumstance as rapidly as possible and reduce morbidity and mortality as a result. Certain organ system effects such as hypotension (cardiovascular), oliguria (renal), and increased peak airway pressures (pulmonary) rapidly come under clinical scrutiny and drive rapid intervention.

Cardiovascular system

Extensive animal data identify that all instances of IAH compromise cardiovascular performance and do so in proportion to the increase in pressure above normal [19]. Intra-abdominal hypertension increases the external pressure placed on the inferior vena cava (IVC) leading to diminished venous return and thus, cardiac output [20]. Even in the absence of a prior effective circulating volume deficit, once IAH is established the patient will appear to be preload responsive. In the setting of hypovolemia, decreases in preload associated with increased abdominal compartment pressures can result in severe and rapidly fatal decreases in cardiac output that may not be responsive to circulating volume expansion alone; pressor therapy is usually indicated at this point as a temporizing measure in conjunction with plasma volume expansion. Pressor selection should avoid those that could induce vasodilatation (such as dobutamine) as this will only worsen

the preload responsive state; norepinephrine or epinephrine are much more ideal adjunctive agents while moving to definitive therapy. In this fashion, the therapy is similar to that for cardiac tamponade.

Pulmonary system

The landmark article that clearly defined the pulmonary pathophysiology of intra-abdominal hypertension was authored by Richardson and Trinkle [21] in 1976. Their data demonstrated that IAP exceeding 25 mm Hg significantly increased end-inspiratory pressure when delivering a fixed tidal volume of gas. As a result, early determinations of the need for therapy for the ACS hinged on an intra-abdominal pressure that exceeded 25 mm Hg. We now recognize that the syndrome may occur at lesser pressures. Nonetheless, this phenomenon was further investigated by Ridings and colleagues [22], illustrating decreased respiratory system compliance and CO₂ clearance, as well as distorted pulmonary flow characteristics, with a measured increased intra-thoracic pressure that was directly proportional to and paralleled the IAP. The pathophysiologic result was an anomalous elevation of the right atrial (Pra) and pulmonary artery occlusion pressure (Ppao) with a corresponding decrease in the cardiac output, resembling the pathophysiology of an extra-parenchymal restrictive lung disease process. It is important to note that the increase in Pra and Ppao do not represent increases in transmural pressure and may coexist with decreased ventricular preload.

In the United States, the most common mode of mechanical ventilation is volume cycled ventilation. Accordingly, increases in IAP augment the size of the peritoneal envelope by dislocating the hemi-diaphragms upward. While therapeutic pneumoperitoneum has been used as a preoperative adjunct for reconstruction of large herniae that have lost the right-of-domain [23], increased IAP in the critically ill is commonly deleterious. IAH is reflected in the mechanically ventilated as increased peak airway and plateau pressures for a given delivered tidal volume at a given peak flow rate on a given waveform for gas delivery.

One additional danger is that acute increases in IAP may so severely limit diaphragmatic excursion that the patient's mechanical breath may be pressure limited, terminate early, and deliver less than the prescribed tidal volume on volume-cycled ventilation or less than desired resultant tidal volumes on pressure-cycled ventilation. This unfortunate circumstance could result in compromised CO₂ clearance, and respiratory acidosis in a patient who already suffers from hypoperfusion-related metabolic acidosis. The unaware may interpret the increased peak airway pressure as an indication of acute lung injury or incipient acute respiratory distress syndrome (ARDS), and engage the ARDSNet pathway instead of addressing IAH and the ACS instead. Low tidal volumes are not indicated for the ACS if there is no evidence of lung injury, and in the setting of ACS, high pressures do not indicate overdistension. Eventually, even severely decreased tidal

volumes will fail to correct increased peak airway and plateau pressures, and usually force an alternate diagnosis to be entertained.

Renal system

Acute renal failure (ARF) in the setting of increased intra-abdominal pressure was initially documented both clinically and experimentally by Richards and colleagues [24]. Currently, we would classify Richards and colleagues' ARF as acute kidney injury (AKI) using the risk injury failure loss end-stage (RIFLE) classification scheme [25]. Regardless of term, renal impairment is typically detected as a combination of abnormal plasma creatinine coupled with oliguria. The pathophysiology underlying AKI is multifactorial with impairment of glomerular filtration rate by extrinsic renal vein compression, increased renal venous impedance from IVC compression, water conservation via an activated renin-angiotensin system coupled with up-regulation of antidiuretic hormone (ADH), decreased renal perfusion from low cardiac output, and potentially acute tubular necrosis [26]. Clearly some of these mechanisms are adaptive and compensatory (hormone regulation), and others are consequences of deranged physiology extrinsic to the kidney (venous compression). Moreover, renal oxygen delivery is compromised by reduced net flow on the basis of renal vein hypertension.

Although the ACS shares some pathophysiology with cardiac tamponade, the response to plasma volume expansion is quite different. The heart will initially respond to increased chamber volume with an increase in performance and reduced cardiac injury. The kidney, unfortunately, is not protected from AKI or subsequent ARF by plasma volume expansion [19]; therefore, intervention before developing the ACS serves as the key for renal preservation in patients with IAH. Current research into renal biomarkers will hopefully shed some light on incipient renal injury and allow one to intervene earlier in the progression from IAH to ACS to maximize renal salvage [27].

Central neuraxis

The effects of a developing ACS on the central neuraxis is predictable based on decreased cardiac output. As venous return is progressively compromised, aortic and atrial stretch receptors are activated, initiating vasoconstriction with an increase in catecholamine output, as well as activation of the renin-angiotensin-aldosterone system. These adaptive compensatory mechanisms serve to maintain cerebral blood flow, oxygen delivery, and consumption. As these mechanisms are overwhelmed by progressively decreased stroke volume and cardiac output, disordered mentation with agitation, restlessness, and disorientation may be observed in unsedated critically ill patients. As the ACS develops, frank obtundation may occur with severe functional hypovolemia and hypotension. These signs are commonly masked by concomitant sedation that forms part of the standard care for mechanically ventilated patients.

The difficulty in monitoring the level of sedation in the critically ill, especially those receiving sedation, analgesia, and neuromuscular blockade has prompted a number of corporations to develop objective sedation monitors, like the Bispectral monitor (Aspect Inc., Waltham, Massachusetts). Although there is significant experience with monitors such as this one in the anesthesia environment [28,29], no validated data exist in using the monitor for “sedation monitoring” as a result of cerebral hypoperfusion as would occur with the ACS. Quite commonly, this aspect of the physical examination is lost in the critically ill because of concomitant injury or medication therapy.

Hepatic system

In a fashion similar to other organs, the liver suffers from hypoperfusion with progressive decreases in venous return and cardiac performance. Although there are few clinically relevant acute hepatic derangements that may be ascribed to the ACS (likely due to lack of study), it is during the period of ACS relief that the liver suffers the majority of damage, likely as a result of reperfusion injury [30]. Restoration of oxygenated flow leads to release of oxygen free radicals such as singlet oxygen, hypochlorous acid, superoxide, and peroxide [31]. The hepatic response to reperfusion manifests as deranged coagulation cascade, serine protease production, acute phase reactant elaboration, increased hepatocellular enzyme elaboration, and organ swelling. These abnormalities (except for swelling) respond to infusion of clotting factors as fresh frozen plasma, and plasma volume restoration. It is important to note that the hepatic swelling will persist and may limit subsequent abdominal wall closure efforts.

Gastrointestinal system

In a fashion similar to that of the liver, the gastrointestinal viscera suffer hypoperfusion and reperfusion injury. It has been noted that the ACS also impairs mesenteric lymph flow and explains one mechanism of bowel wall edema formation [32]. Like the liver, small and large bowel swelling may also significantly limit the ability to subsequently close the anterior abdominal wall. Reperfusion may also derange the glycocalyx such that feeding attempts with nonelemental formulae may be met with feed intolerance [33,34]. Thus, the authors recommend initiating luminal nutrition with an elemental diet in patients who have had an ACS relieved.

The physical examination correlates of the ACS are listed in **Box 1**. The ability of the bedside clinician to diagnose the ACS without objective data is supported by physical examination characteristics but their sensitivity and specificity remains undefined. Furthermore, the plethora of objective data points available to the clinician warrant incorporating those data points into a synthesized diagnosis. Careful physical examination has been

Box 1. Physical findings in the abdominal compartment syndrome*Physical examination findings*

Abdominal distension
Firm abdominal wall
Tachypnea or hyperpnea
Diminished diaphragmatic excursion
Hypotension with narrowed pulse pressure
Tachycardia
Oliguria (concentrated urine with high specific gravity) or anuria
Cool extremities
Flat neck veins
Weak or thready pulses
Delayed capillary refill
Disordered mentation
Tube-feeding intolerance (high residuals); succussion splash

demonstrated to be a good indicator of hypoperfusion regardless of etiology and has compared favorably with data from invasive monitoring devices [35]. Once deranged physiology is understood, one must then determine how best to monitor the at-risk patients for IAH and progression to the abdominal compartment syndrome.

Measurement of intra-abdominal pressure

The reliable diagnosis of IAH or ACS is dependent upon the fidelity of the intra-abdominal pressure measurement technique. The intravesicular technique originally described by Kron and colleagues [13] has evolved as the gold standard for monitoring IAP because of its noninvasiveness, reproducibility, cost-effectiveness, and portability. There are a variety of techniques for IAP measurement that may be compared with the current gold standard. We will examine the potential advantages and disadvantages of each technique.

Intravesicular

This technique as originally described by Kron and colleagues [13] disrupts a normally sterile system for each measurement of IAP. Newer techniques allow monitoring to proceed without compromising the sterility of the bladder drainage system and have been described by Iberti and colleagues [36,37] and Cheatham and Safcsak [38]. This technique demonstrates the best fidelity relative to IAP measured by any other method. The technique relies on an indwelling bladder catheter coupled to a partially

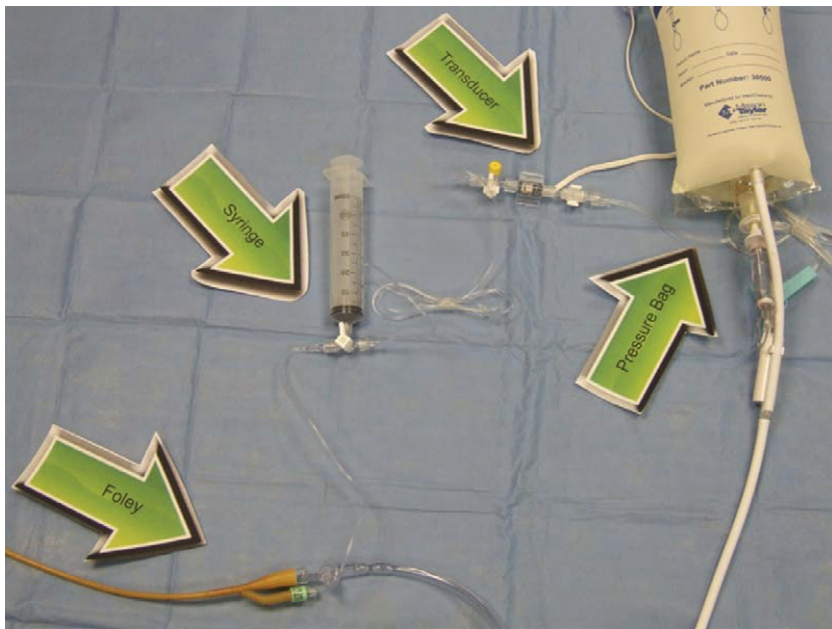


Fig. 1. A standard fluid-coupled bladder pressure transduction system.

fluid-filled bladder with pressure measured by a transducer proximal to the bladder catheter (Fig. 1). The symphysis pubis is used as the phlebostatic axis, and the IAP measurement is recorded at end-expiration with the patient in the supine position. It is important to note that the patient's anterior abdominal wall must be free of voluntary tension or the measured pressure will be artificially elevated.

A significant amount of controversy remains regarding the volume with which to distend the bladder to best garner the most accurate measurement of IAP. The World Congress on the Abdominal Compartment Syndrome recommends infusing 25 cc to 50 cc of 0.9% saline to eliminate bladder wall coaptation [8]. Volumes greater than 50 cc may overly distend a non-compliant bladder and provide falsely elevated values. Recent data suggest an increased false measurement rate with distending volumes that exceed 25 cc [39]. Regardless of the fluid-coupled measurement system used, each will minimally, but measurably increase the risks of urinary tract infection and urosepsis as a result of catheter manipulation and health care worker exposure to body fluids.

Gastric

IAP may also be measured by means of a naso- or oro-gastric or gastrostomy tube connected to a pressure transducer as originally described by Collee and colleagues [40]. The advantages of this technique included its

cost-effectiveness, decreased risk of sepsis, and noninterference with urine output measurements. The disadvantages of this technique are the issues of gastric wall coaptation (unlike the bladder, there is an easy means of fluid egress via the pylorus), the intermittent nature of abdominal pressure measurements, interference of the gastric pressures with the gastric migrating motor complex, and interference with administration of intragastric nutrition. Also, this technique has not been validated in patients who are being cared for with a transgastric jejunal feeding catheter as this catheter stents open the pylorus; increasing numbers of patients are managed with nasojejunal catheters, or surgically or interventional radiology–placed transgastric jejunal catheters. While gastric pressure transduction compares favorably with bladder pressure measurements in the noncritically ill, certain clinical conditions render this technique less useful. These conditions include but are not limited to gastric laceration repair, ileus or bowel obstruction with large volume gastric aspirate, as well as surgical conditions requiring partial or total gastric resection.

Recognizing that a pressure measurement describes only one aspect of IAH, gastric tonometry, and its ability to measure intramucosal CO₂, has been proposed as an adjunctive technique that complements recording only intragastric pressure. While its proponents believe that the tonometer data provide a sensitive marker for early intestinal ischemia as a result of IAH [41], studies are contradictory and confusing. In fact, one study demonstrated tonometer insensitivity to reduction of mesenteric blood flow of 50% before an increase in mucosal CO₂ readings and documented a poor correlation of pH to the level of intestinal ischemia, raising considerable doubt of the use of this modality in clinically assessing the impact of IAP on perfusion [42].

Inferior vena cava

IVC pressure has been explored as a reasonable surrogate for IAP measurement [43]. A standard 30-cm central venous catheter is inserted into the inferior vena cava via the left or right common femoral vein. The intra-abdominal position of the catheter is confirmed by portable lower abdominal radiography, and by noting a rise in IAP following application of external abdominal pressure. A three-way stopcock is connected to the distal lumen, one end of which is connected to a pressure transducer via arterial tubing while the other end is connected to a pressurized bag of 0.9% saline. The transducer is zeroed at the midaxillary line with the patient in the supine position and the IAP is measured at end-expiration. The use of IVC pressures to approximate IAP provides a high degree of correlation between the two values when the catheter is in a subhepatic position.

Major advantages of this technique include a continuous trend of IAP measurements much like that for usual central venous pressure (CVP) measurement. However, the main pitfall of this technique is the invasive nature of the method that engender risks of IVC thrombus, bacteremia, catheter

related infection, and sepsis. Given the recent recommendations for central venous pressure monitoring catheter position to favor the internal jugular and subclavian positions over femoral placement as a means of reducing catheter-related infection, this technique (femoral) is infrequently used [44]. Indeed, following injury, common femoral vein catheters are usually large-bore diameter sheath introducers that are not suitable to measure IAP because of their limited length that supports rapid flow.

Airway pressure

Increased IAP is transmitted to the thoracic space and leads to increased intrathoracic, intrapleural, and airway pressures. Respiratory system compliance decrements in the setting of IAH closely correlate with IAP increases [45]. By direct extrapolation, airway pressures may be used to indirectly assess IAPs. While initially attractive, the technique relies on a number of assumptions that must be true for the extrapolation to be valid. A major disadvantage of this technique of measurement is the requirement that the patient must be intubated and free from any progressing parenchymal process such as pneumonia or acute lung injury—a limiting condition indeed. By virtue of remaining intubated (if IAP measurement is the sole indication for intubation), patients incur an increased risk of hospital-acquired pneumonia [1], and there is no cost-effectiveness advantage to this technique.

Direct IAP transduction

In the interest of obtaining an accurate bladder pressure measurement that is not confounded by anatomic abnormalities, a number of investigators have created direct measurement systems [45–49]. Confounding variables that may impact the fidelity of all pressure measurement systems include pelvic fracture with bladder architecture distortion, large-volume pelvic clot, and abdominal wall asymmetry as a result of abdominal wall defects such that there is unequal pressure distribution within the abdomen. At present, the utility of these systems is unclear and they are limited to patients with an open abdominal wall. Thus, these systems are not applicable to the vast majority of patients who would be cared for in a medical, cardiac, cardiothoracic, or neurosurgical ICU. Moreover, the cost-effectiveness of such a system is similarly unclear, but is likely to compare unfavorably with a simple bladder pressure measurement system.

Related indices and monitoring frequency

While the IAP is important in assessing risk, it may be insensitive to changes in intra- or retroperitoneal volume since not all patients demonstrate the same degree of abdominal wall compliance. Moreover, the definitions fail to account for atherosclerotic disease and diminished organ blood flow on

that basis. A model for this manner of evaluation exists in patients with carotid arterial occlusive disease who require a higher perfusion pressure to support their cerebral parenchyma. In this fashion, the perfusion of the brain may parallel that of the intra-abdominal organs. This concept leads to the abdominal correlate of the cerebral perfusion pressure: the abdominal perfusion pressure [50]. The abdominal perfusion pressure (APP) is the difference between mean arterial pressure (MAP) and IAP such that $APP = MAP - IAP$; normal APP is 60 mm Hg or higher and uses IAP rather than Pra (right critical pressure) even when the IAP is lower than Pra. Thus, an attractive and physiologically based definition of the ACS, and one that would perhaps lead to earlier intervention is an IAP higher than 20 mm Hg and an APP less than 60 mm Hg. These two variables need to be coupled to accurately represent a patient's physiology as one would not credit that a patient with an IAP of 12 and an MAP of 65 ($APP = 65 - 12 = 53$ mm Hg) has an ACS.

Having identified (1) the physiologic parameters that define IAH and the ACS, (2) who to monitor, and (3) how best to accomplish that monitoring, one must now understand the available options for therapeutic intervention. The commonality among all of the treatment options is relief of IAH. Concomitant therapy is also required to treat the sequelae of the hypoperfusion that accompanied the compartment syndrome before its relief. Clinically, these sequelae are identified as organ failure and may be measured by any number of organ dysfunction scores (<http://www.sfar.org>).

It is presently unclear how frequently and for how long to monitor the at-risk patient population. However, it is clear that the major period of risk is during resuscitation both before and after the ACS is diagnosed. Thus, it makes physiologic sense to monitor all at-risk patients on arrival and through to completion of resuscitation. The frequency with which one monitors patients during that resuscitation period may be institution-specific, and many strategies have been suggested. A reasonable progression is every 2 hours for 8 hours, every 4 hours for 16 hours, and every 8 hours thereafter provided the pressure is stable. If the pressure has increased by more than 2 mm Hg between measurements, then monitoring should continue every 2 hours until stable. This sequence is used at the author's institution with success.

Treatment of abdominal compartment syndrome

The evolution of treatment of the ACS has mirrored compartment syndrome management in other body domains. Similar to the standard management of extremity or thoracic [51] compartment syndrome, definitive management depends on surgical decompression of the affected compartment, in this case the peritoneal cavity. Decompressive laparotomy is the current gold standard for management of the ACS and is coupled with an open abdomen management technique. Leaving the fascia and skin widely separated augments the size of the peritoneal envelope and diminishes the

pressure exerted by the peritoneal contents. The method of temporary abdominal wall closure varies (either commercial dressings or custom, “improvised” versions), but the essential features include a sterile barrier to prevent bowel wall adhesion to the posterior aspect of the anterior abdominal wall, packing to fill the soft-tissue defect, with or without a closed suction drainage system to aspirate peritoneal fluid and create a vacuum effect, covered with an adhesive and fluid-impermeable barrier to serve as a seal for the wound [52]. It is important to recognize that decompressive laparotomy arose as the gold standard out of the crucible of damage-control laparotomy where the primary etiology of the ACS was hemorrhage. Thus, the gold standard for primary ACS may not be directly applicable to secondary ACS as their etiologies may be quite distinct.

Nonsurgical management of abdominal compartment syndrome has been extensively studied and for selected patients, may be the therapy of choice. While the concept of avoiding the physiological stress of surgery, as well as the subsequent management inherent in the open abdomen approach are enticing, nonoperative management must be tailored to the etiology of the IAH. Patients with large-volume ascites may benefit from large-volume paracentesis [53], although the benefits are only transient if the underlying cause of ascites development is not addressed. In fact, these attempts may be unsuccessful if there is a significant component of organ swelling that has established the ACS. Thus, nonoperative approaches may drain or reduce ascites, but will likely not impact visceral swelling. Intestinal luminal decompression may be ideal for patients with IAH as a result of gastrointestinal luminal distension from gas, fluid, or enteric contents such as in distal small bowel obstruction. Gastric suctioning, rectal lavage, and suction decompression, as well as gastro- and colono-prokinetics may have some utility for patients with functional obstruction such as Ogilvie’s syndrome.

Other nonsurgical options also include diuresis (with or without concomitant colloid administration) [54], aggressive ultrafiltration [55], and continuous negative abdominal pressure [56], as well as heavy sedation or neuromuscular blockade to eliminate the contribution of muscular tension across the abdominal wall. In the authors’ experience, management of IAH with neuromuscular blockade (even when appropriately coupled with sedation and analgesia) serves only to delay an appropriate management strategy that targets the underlying physiology. In general, reduction in IAPs with these modalities are limited and temporary but may serve as a bridge to transport a patient to a facility capable of delivering definitive care, or providing time for a definitive care team to assemble.

Future investigations

The Vietnam War provided ample data regarding fluid resuscitation from hemorrhagic shock. Interestingly, with aggressive crystalloid resuscitation,

“Da Nang lung” surfaced as a consequence [57,58]. No similar entity was readily identified during the Korean conflict. The difference was attributed to early resuscitation as well as the primacy of crystalloid resuscitation compared with plasma that was used in Korea. Similar concerns are being raised within the surgical community regarding the exuberance of fluid resuscitation for trauma and emergency general surgery patients. Several recent studies document improved resource use and shorter ICU lengths of stay with appropriate fluid prescription practices that identify preload responsive patients as the target population for plasma volume expansion [59]. Indeed, the 2007 Society of Critical Care Medicine’s annual meeting showcased a parallel session addressing the untoward consequences of “over-resuscitation.”

Moreover, a European Union trial addressing bedside assessment of preload responsiveness using an algorithmic approach to functional hemodynamic monitoring is about to begin [60]. One must wonder if the incidence of IAH and the ACS will decrease as well. There is some suggestive data that the resuscitation with colloids solutions will decrease organ edema and diminish the incidence of IAH and the ACS as well [61]. While colloid resuscitation is common outside of the United States, the current US standard for plasma volume expansion remains crystalloid solutions, many of which are hyperchloremic with regard to plasma and will induce a hyperchloremic metabolic acidosis [62]. Active management of iatrogenic acidosis is an important management priority for patients who have been hypoperfused (like those with the ACS), especially those with preexisting conditions affecting organs intimately involved in acid-base homeostasis (ie, renal, hepatic, pulmonary). To date, an outcome advantage has yet to be demonstrated with commercially available colloids.

An unexplored aspect of compartment syndrome is pressure management at the organ level. Current thoughts evaluate pressure-volume dynamics within defined body compartments. To date, there are no studies addressing intraorgan dynamics. By way of example, consider the case of a patient with a contained intraparenchymal renal injury after a motor vehicle crash; there are no other intra-abdominal injuries. Current management principles support a nonoperative approach, leaving the intraparenchymal hematoma in place with an intact renal capsule [63]. The clinician has no current means by which to measure intraorgan pressure, nor any trigger by which to pursue a decompressive management strategy. It is unclear what the natural history of such injuries may be as one cannot select those with increased intraorgan pressures above a threshold value from those without. Nonetheless, it would seem logical that intraorgan hypertension would result in similar pathophysiological derangements and consequences to the larger entity of ACS. The ability to answer this question must await invasive or noninvasive techniques to be developed that allow one to reliably assess intraorgan dynamics.

Summary

Markedly elevated IAPs will result in predictable hemodynamic consequences related to compromised venous return. When the hemodynamic abnormalities are associated with organ dysfunction or failure, patients suffer from the ACS. At-risk patients should be routinely monitored for IAH, and a multidisciplinary care paradigm should be established. Vigorous resuscitation of both surgical and medical patients highly correlates with IAH and ACS risk. Vigilance, prompt diagnosis, and intervention for ACS will reduce the morbidity and mortality in critically ill individuals. Future challenges include altering resuscitation strategies to reduce ascites formation, earlier diagnosis of organ dysfunction, and intraorgan monitoring techniques.

References

- [1] American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388–416.
- [2] Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818–29.
- [3] Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic scoring system: risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991;100:1619–36.
- [4] Bernard GR. Acute respiratory distress syndrome: a historical perspective. *Am J Respir Crit Care Med* 2005;172(10):1241–5.
- [5] Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–77.
- [6] Biffi WL, Moore EE, Burch JM, et al. Secondary abdominal compartment syndrome is a highly lethal event. *Am J Surg* 2001;182(6):645–8.
- [7] Meldrum DR, Moore FA, Moore EE, et al. Prospective characterization and selective management of the abdominal compartment syndrome. *Am J Surg* 1997;174:667–73.
- [8] Sugrue M. Abdominal compartment syndrome. *Curr Opin Crit Care* 2005;11(4):333–8.
- [9] Rodas EB. Hyperacute abdominal compartment syndrome: an unrecognized complication of massive intraoperative resuscitation for extra-abdominal injuries. *Am Surg* 2005;71(11):977–81.
- [10] Betro G, Kaplan LJ. Abdominal compartment syndrome. In: Kellum JA, Ronco C, Bellomo R. *Critical care nephrology*. 2nd edition. Elsevier, in press.
- [11] Emerson H. Intra-abdominal pressures. *Arch Intern Med* 1911;7:754–84.
- [12] Shelly MP, Greatprex R, Calne RY, et al. The physiological effects of vasopressin when used to control intra-abdominal bleeding. *Intensive Care Med* 1988;14:526–31.
- [13] Kron IL, Harman PK, Nolan SP. The measurement of intra-abdominal pressure as a criterion for abdominal re-exploration. *Ann Surg* 1984;199:28–30.
- [14] Moore EE, Burch JM, Francoise RJ, et al. Staged physiologic restoration and damage control surgery. *World J Surg* 1998;22(12):1184–90.
- [15] Rotondo MF, Schwab CW, McGonigal MD, et al. “Damage control”: an approach for improved survival in exsanguinating penetrating abdominal injury. *J Trauma* 1993;35(3):375–82.
- [16] Malbrain ML, Chiumello D, Pelosi P, et al. Prevalence of intra-abdominal hypertension in critically ill patients: a multicenter epidemiological study. *Intensive Care Med* 2004;30(5):822–9.

- [17] Malbrain ML, Chiumello D, Pelosi P. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. *Crit Care Med* 2005;33(2):315–22.
- [18] Lonardo M. Incidence of intraabdominal hypertension in the intensive care unit. *Crit Care Med* 2005;33:2150–3.
- [19] Cullen DJ, Coyle JP, Teplick R, et al. Cardiovascular, pulmonary, and renal effects of massively increased intra-abdominal pressure in critically ill patients. *Crit Care Med* 1989;17(2): 118–21.
- [20] Lynch FP, Ochi T, Scully JM, et al. Cardiovascular effects of increased intra-abdominal pressure in newborn piglets. *J Pediatr Surg* 1974;9:621–6.
- [21] Richardson JD, Trinkle JK. Hemodynamic and respiratory alterations with increased intra-abdominal pressure. *J Surg Res* 1976;20:401–4.
- [22] Ridings PC, Bloomfield GL, Blocher CR, et al. Cardiopulmonary effects of raised intra-abdominal pressure before and after intravascular volume expansion. *J Trauma* 1995;39: 1071–5.
- [23] Moreno IG. Chronic eventration and large hernias: preoperative treatment by progressive pneumoeritoneum. *Surgery* 1947;22:945–53.
- [24] Richards WO, Scovill W, Shin B, et al. Acute renal failure associated with increased intra-abdominal pressure. *Ann Surg* 1983;197:183–7.
- [25] Bellomo R, Ronco C, Kellum JA, et al. Acute dialysis quality initiative workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. *Crit Care* 2004;8:204–12.
- [26] Harman PK, Kron IL, McLachlan HD, et al. Elevated intra-abdominal pressure and renal function. *Ann Surg* 1982;196:594–7.
- [27] Leblanc M, Kellum JA, Gibney RT, et al. Risk factors for acute renal failure: inherent and modifiable risks. *Curr Opin Crit Care* 2005;11(6):533–6.
- [28] Gan TJ, Glass PS, Windsor A, et al. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. *BIS utility study group*. *Anesthesiology* 1997;87:808–15.
- [29] Liu SS. Effects of bispectral index monitoring on ambulatory anesthesia: a meta-analysis of randomized controlled trials and a cost analysis. *Anesthesiology* 2004;101(2):311–5.
- [30] Diebel LN, Wilson RF, Dulchavsky SA, et al. Effect of increased intra-abdominal pressure on hepatic arterial, portal venous, and hepatic microcirculatory blood flow. *J Trauma* 1992; 33(2):279–82.
- [31] Marubayashi S, Dohi K, Kawasaki T. Role of free radicals in hepatic reperfusion injury. *Ann N Y Acad Sci* 1994;723:368–70.
- [32] Diebel LN, Dulchavsky SA, Wilson RF. Effect of increased intra-abdominal pressure on mesenteric arterial and intestinal mucosal blood flow. *J Trauma* 1992;33(1):45–8.
- [33] Mythen MG. Postoperative gastrointestinal tract dysfunction. *Anesth Analg* 2005;100(1): 196–204.
- [34] Boley SJ, Brandt LJ, Veith FJ, et al. A new provocative test for chronic mesenteric ischemia. *Am J Gastroenterol* 1991;86(7):888–91.
- [35] Kaplan LJ, McPartland K, Santora TA, et al. Start with a subjective assessment of skin temperature to identify hypoperfusion in intensive care unit patients. *J Trauma* 2001; 50(4):620–7.
- [36] Iberti TJ, Kelly KM, Gentil DR, et al. A simple technique to accurately determine intra-abdominal pressure. *Crit Care Med* 1987;15:1140–2.
- [37] Iberti TJ, Lieber CE, Benjamin E. Determination of intra-abdominal pressure using a transurethral bladder catheter: clinical validation of the technique. *Anesthesiology* 1989; 70:47–50.
- [38] Cheatham ML, Safcsak K. Intra-abdominal pressure: a revised method for measurement. *J Am Coll Surg* 1998;186:594–5.

- [39] Malbrain ML, Deeren DH. Effect of bladder volume on measured intravesical pressure: a prospective cohort study. *Crit Care* 2006;10(4):R98.
- [40] Collee GG, Lomax DM, Fergusson C, et al. Bedside measurement of intra-abdominal pressure (IAP) via an indwelling naso-gastric tube: clinical validation of the technique. *Intensive Care Med* 1993;19:478–80.
- [41] Arnold J, Hendriks J, Ince C, et al. Tonometry to assess the adequacy of splanchnic oxygenation in the critically ill patient. *Intensive Care Med* 1995;21(9):777.
- [42] Kellum JA, Rico P, Garuba AK, et al. Accuracy of mucosal pH and mucosal-arterial carbon dioxide tension for detecting mesenteric hypoperfusion in acute canine endotoxemia. *Crit Care Med* 2000;28(2):462–6.
- [43] Lacey SR, Bruce J, Brooks SP, et al. The relative merits of various methods of indirect measurement of intra-abdominal pressure as a guide to closure of abdominal wall defects. *J Pediatr Surg* 22:1207–11.
- [44] Joynt GM, Gomersall CD, Buckley TA, et al. Comparison of intrathoracic and intra-abdominal measurements of central venous pressure. *Lancet* 347:1155–7.
- [45] Engum SA, Kogon B, Jensen E, et al. Gastric tonometry and direct intra-abdominal pressure monitoring in abdominal compartment syndrome. *J Pediatr Surg* 2002;37:214–8.
- [46] Schachtrupp A. Evaluation of a modified piezoresistive technique and a water-capsule technique for direct and continuous measurement of intra-abdominal pressure in a porcine model. *Crit Care Med* 2006;34(3):745–50.
- [47] Risin E. A new technique of direct intra-abdominal pressure measurement: a preliminary study. *Am J Surg* 2006;191(2):235–7.
- [48] Gudmundsson FF, Viste A, Gislason H, et al. Comparison of different methods for measuring intraabdominal pressure. *Intensive Care Med* 2002;28:509–14.
- [49] Sugrue M, Buist MD, Lee A, et al. Intra-abdominal pressure measurement using a modified nasogastric tube: description and validation of a new technique. *Intensive Care Med* 1994;20: 588–90.
- [50] Cheatham ML, White MW, Sagraves SG, et al. Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. *J Trauma* 2000;49(4):621–7.
- [51] Kaplan LJ, Trooskin SZ, Santora TA. Thoracic compartment syndrome. *J Trauma* 1996; 40(2):291–3.
- [52] Barker DE, Kaufman HJ, Smith LA, et al. Vacuum pack technique of temporary abdominal closure: a 7-year experience with 112 patients. *J Trauma* 2000;48:201–6.
- [53] Parra MW, Al-Khayat H, Smith HG, et al. Paracentesis for resuscitation-induced abdominal compartment syndrome: an alternative to decompressive laparotomy in the burn patient. *J Trauma* 2006;60(5):1119–21.
- [54] Oda S, Hirasawa H, Shiga A, et al. Management of intra-abdominal hypertension in patients with severe acute pancreatitis with continuous hemofiltration using a polymethyl methacrylate membrane hemofilter. *Ther Apher Dial* 2005;9(4):355–61.
- [55] Oda S, Hirasawa H, Shiga H, et al. Management of intra-abdominal hypertension in patients with severe acute pancreatitis with continuous hemodiafiltration using a polymethyl methacrylate membrane hemofilter. *Ther Apher Dial* 2005;9(4):355–61.
- [56] Bloomfield G, Saggi B, Blocher C, et al. Physiologic effects of externally applied continuous negative abdominal pressure for intra-abdominal hypertension. *J Trauma* 1999;46(6): 1009–14.
- [57] Asbaugh DG, Bigelow DB, Petty TL, et al. Acute respiratory distress syndrome in adults. *Lancet* 1967;2:319–23.
- [58] Davey-Quinn A, Gedney JA, Whiteley SM, et al. Extravascular lung water and acute respiratory distress syndrome—oxygenation and outcome. *Anaesth Intensive Care* 1999;27(4): 357–62.
- [59] Rhee P, Koustova E, Alam HB. Searching for the optimal resuscitation method: recommendations for the initial fluid resuscitation of combat casualties. *J Trauma* 2003;54:52–62.
- [60] Pinsky MR. Targets for resuscitation from shock. *Minerva Anesthesiol* 2003;69(4):237–44.

- [61] Younes RN, Yin KC, Amino CJ, et al. Use of pentastarch in the treatment of patients with hemorrhagic hypovolemia: randomized phase II study in the emergency room. *World J Surg* 1998;22(1):2–5.
- [62] Kaplan LJ, Frangos S. Clinical review: acid-base abnormalities in the intensive care unit—part II. *Crit Care* 2005;9(2):198–203.
- [63] Toutouzas KG, Karaiskakis M, Kaminski A, et al. Nonoperative management of blunt renal trauma: a prospective study. *Am Surg* 2002;68:1097–103.

Laboratory Testing in the Intensive Care Unit

Michael E. Ezzie, MD, Scott K. Aberegg, MD, MPH,
James M. O'Brien, Jr, MD, MSc*

*Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, The Ohio State University
Medical Center, 201 Davis HLRI, 473 West 12th Avenue, Columbus, OH 43210, USA*

Scope and cost of laboratory testing

Laboratory testing is ubiquitous among hospitalized patients. Patients in intensive care units (ICUs) are subject to a higher number of blood draws, resulting in greater blood loss per day and greater phlebotomy during the entire hospitalization. Patients with arterial lines; those in teaching rather than nonteaching ICUs; and patients with higher severity of illness and specific diagnoses, such as sepsis, have more frequent laboratory testing and phlebotomy [1,2]. There is also considerable variation in practice between physicians [3] and institutions [2]. Laboratory testing is more common early after admission with more than one third of laboratory tests performed within 24 hours of ICU admission [2]. A relatively small number of tests comprise most testing performed. In one study, fewer than 25 tests and profiles accounted for 80% of the laboratory testing in each of three ICUs [4]. Depending on the ICU, between 104 and 202 tests accounted for 99% of the total laboratory testing performed. Table 1 shows the tests and profiles from the top 80% of tests that were common to the three studied ICUs. The Ohio State University Medical Center charges for each of these tests are also shown. The authors' experience is that many practitioners are unaware of the costs of individual laboratory tests. Although charges are overestimations of cost and reimbursement, these values also do not include the expense incurred through phlebotomy. Providing such cost data to clinicians reduces laboratory requests [5].

This article was supported by NIH/NHLBI grant K23 HL075076 (to J.M. O'Brien).

* Corresponding author.

E-mail address: james.obrien@osumc.edu (J.M. O'Brien).

Table 1
Common laboratory tests among patients in the ICU and their charges

Laboratory test	Charge
Alkaline phosphatase	\$32
Alanine aminotransferase	\$58
Arterial blood gas (pH, PCO ₂ , PO ₂ , HCO ₃ , O ₂ saturation, base excess)	\$224
Aspartate aminotransferase	\$41
Basic metabolic panel (sodium, potassium, chloride, carbon dioxide, anion gap, glucose, blood urea nitrogen, creatinine)	\$194
Sodium	\$28
Potassium	\$28
Chloride	\$28
CO ₂	\$32
Blood urea nitrogen	\$25
Creatinine	\$28
Glucose	\$25
Ionized calcium	\$132
Inorganic phosphorus	\$28
Magnesium	\$37
Bilirubin, total	\$28
Bilirubin, direct	\$32
Lactate dehydrogenase	\$39
Partial thromboplastin time	\$67
Prothrombin time/international normalized ratio	\$58
Complete blood cell count (white blood cell count, red blood cell count, hemoglobin concentration, hematocrit, mean corpuscular volume, mean cell hemoglobin, mean cell hemoglobin concentration, red blood cell distribution width, platelet count, mean platelet volume)	\$209
White blood cell count	\$47
Hemoglobin	\$40
Hematocrit	\$37
Platelet count	\$44
White blood cell differential	\$41

These are the top 80% of laboratory tests ordered from medical, surgical and pediatric ICUs in a single center. Charge data are available at: http://medicalcenter.osu.edu/patientcare/hospitalsandservices/billing/charges_and_fees/.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Adapted from Frassica JJ. Frequency of laboratory test use in the intensive care unit and its implications for large-scale data collection efforts. *J Am Med Inform Assoc* 2005;12:232.

It is estimated that 10% to 25% of ICU costs are attributable to laboratory testing [6,7]. In a multicenter study of hospitalized patients, many of the diagnosis-related groups (DRGs) with the highest per-patient laboratory costs likely included an ICU stay (Table 2) [8]. Of the 33 conditions with identifiable median ICU costs, 7 had laboratory costs that exceeded other costs of ICU care. Regarding national estimates of expenditures, one study

Table 2

DRGs with the highest per-patient laboratory costs for patients in the University HealthSystems Consortium database

DRG	Median costs, \$1995	Median percentage of total costs
Liver transplant	8329	10.7
Heart transplant	6859	8.0
Bone marrow transplant	5928	9.4
Lung transplant	5260	7.6
Extensive burns with operating room procedure	4294	5.7
Craniotomy for multiple significant trauma	3750	8.1
Acute leukemia without major operating room procedure, age > 17 years	3693	12.1
Malignant breast disorders with complications or comorbidities	2221	8.9
Kidney transplantation	2086	4.9
Acute leukemia without major operating room procedures, age 0–17 years	1822	18.3
HIV with extensive operating room procedures	1780	13.6
Extreme immaturity or respiratory distress, neonate	1749	5.1
Respiratory system diagnosis with ventilatory support	1705	9.7
Cardiac valve procedure with cardiac catheterization	1644	5.3
Pancreas, liver, and shunt procedures with complications or comorbidities	1620	9.8
Coronary bypass with cardiac catheterization	1563	6.8

Adapted from Young DS, Sachais BS, Jefferies LC. Laboratory costs in the context of disease. Clin Chem 2000;46:970; with permission.

suggested that \$172 million is spent annually on initial testing at level I trauma centers for major trauma victims [9]. Considering that more than \$55 billion is spent on critical care in the United States [10], annual expenditures for laboratory testing in ICUs are in the range of \$5 to \$14 billion.

Recent data demonstrate that patients cared for by physicians who spend more money on laboratory tests do not have better outcomes [3]. Among patients cared for by intensivists with the highest discretionary spending, laboratory costs were \$273 higher per ICU stay than among the lowest spenders. The highest spenders also spent more on other discretionary costs, which could be driven by increased laboratory use, including pharmacy costs (eg, potassium supplementation for potassium levels outside of the reference interval) and blood banking costs (eg, red blood cell transfusion in a patient with anemia attributable to laboratory testing). Patients cared for by physicians who spent more did not have significantly different ICU lengths of stay (adjusted $P = .32$) or hospital mortality (adjusted $P = .83$). As with physicians, institutions with more frequent blood testing practices do not have lower associated hospital mortality ($r = -0.003$, $P = .98$) [2].

Reference intervals and what is “normal”

In most instances, a reference interval is developed from a cohort of individuals without apparent disease. All members of the cohort undergo testing, and the central 95% of the results are determined. Therefore, by definition, 5% of a “normal” population has test results outside of the reference interval. There is an obvious limitation in equating values outside of this range to the presence of disease. In addition, considerations of inherent biologic variation, interindividual differences, and the validity of using reference intervals generated on a different population to patients undergoing clinical evaluations are often ignored. These may be of particular relevance when considering laboratory testing in ICU populations.

In some instances, clinical laboratories provide comparison values that have diagnostic, therapeutic, or prognostic implications instead of being derived from reference intervals. For example, 21% of adults have a blood cholesterol level of at least 240 mg/dL [11]. Such a level carries an increased risk of cardiovascular events, and reduction of cholesterol levels is associated with a reduced risk [12]. Instead of providing the central 95% of cholesterol values in the population, it is more instructive to provide values driven by evidence of higher risk. Clinicians are not interested if a patient’s cholesterol is abnormal relative to a “healthy” population but, instead, if that patient’s cholesterol is dangerous or if treating cholesterol might improve outcome.

Unfortunately, little is known of the values of laboratory tests associated with harm in critically ill patients. An initial approach is to examine the values of tests included in validated severity-of-illness systems [13]. For example, in the Acute Physiology and Chronic Health Evaluation (APACHE) II system, patients with a sodium level of 130 have the same risk of hospital mortality as patients with a sodium level of 140, assuming all else is similar.

This is despite the fact that the first group of patients would be considered abnormal because of being outside of the laboratory reference interval.

Although examining severity-of-illness systems provides some instruction as to laboratory values associated with poorer outcome, there are significant limitations that may preclude these levels for clinical decision making. The cut points in these systems are based on the most abnormal value observed during the first 24 hours after ICU admission. It is incorrect to assume that correcting these “dangerous” values to a value within the “safe” range reduces the predicted risk. Furthermore, these systems were not designed or validated to perform such a function, and when applied to individual patients, they can be misleading [14]. A final consideration is that even though laboratory values are independently associated with hospital mortality, the individual contribution of any one test is overshadowed by the influence of other factors, such as age, chronic health conditions, and vital sign abnormalities. For example, in the APACHE III scoring system, more than 50% of the possible points are available in seven measures of age, vital signs, and chronic health conditions [15]. Age, vital signs, and chronic health conditions are consistently associated with outcome across the severity of illness systems, whereas individual laboratory tests are variably included in each system.

Context of laboratory testing in the intensive care unit

The authors are unaware of an existing exploration of indications for laboratory testing in the ICU. They suggest the framework outlined in [Table 3](#). Indications for testing are classified, based on the pretest probabilities of true abnormalities requiring intervention (for ease of discussion, the authors refer to these abnormalities requiring intervention as “disease”). Screening tests are those performed because a condition occurs within a patient population without any suggestion that the condition is more likely to be found in a particular patient undergoing testing. Homeostatic laboratory tests are those performed on an ongoing basis in a patient for whom prior measurement of that test showed no abnormality and nothing has changed to suggest that it should now be outside of the reference interval. Case-finding occurs when a patient does not have signs or symptoms of a disease but has another condition that raises the probability of the asymptomatic disease. Finally, diagnostic and therapeutic testing occurs in the context of a patient with clinical signs of a disease or undergoing therapies that produce measurable responses, respectively.

Although there are few data about the relative indications for various laboratory investigations in the ICU, there is circumstantial evidence that an excess of testing is performed. This is suggested by findings of efforts to reduce laboratory testing, in which a decreased volume of testing does not appreciably affect outcome [16–20]. It is likely that the tests omitted are those for which subsequent action is least likely to have a benefit for the patient, such as those

Table 3
A framework of indications for laboratory testing

Indication for laboratory testing	Description	Example(s)
Screening	Testing to detect asymptomatic abnormalities	Hemoglobin concentration in patient with sepsis; liver function tests in patient with status asthmaticus
Homeostatic	Testing performed on recurring basis to ensure prior "normal" test results remain within reference interval	Daily hemoglobin concentration in patients who are not bleeding; daily coagulation panel in patient not receiving anticoagulants
Case-finding	Testing to detect abnormalities associated with a documented disease or syndrome	Creatinine in patient with septic shock; phosphate in a patient failing spontaneous breathing trials
Diagnostic	Testing to confirm or refute a suspected clinical syndrome or disease	Toxicology analyses in patient with suicidal overdose; sodium in patient with delirium
Therapeutic	Testing to determine response to specific therapy, including adverse events and monitoring of therapeutic drug levels	Platelet counts in patient being treated for heparin-induced thrombocytopenia; creatinine in patient receiving aminoglycosides, aPTT in patient on intravenous heparin

with normal or falsely abnormal results. Another alternative is that the results of these tests are not associated with outcome or are so infrequently abnormal as to be of little clinical consequence. These situations are most likely to be encountered when a disease under consideration is least likely to be present or, in other words, when the pretest probability of disease is lowest. This is the case with screening and homeostatic laboratory tests. The authors' experience agrees with the circumstantial evidence that most laboratory tests are performed to ensure that there are no asymptomatic abnormal laboratory results rather than to detect the cause of apparent clinical problems (Fig. 1).

Potential benefits of laboratory testing

Screening and homeostatic testing

On the basis of the authors' framework, screening and homeostatic laboratory tests are those performed when the pretest probability of disease for

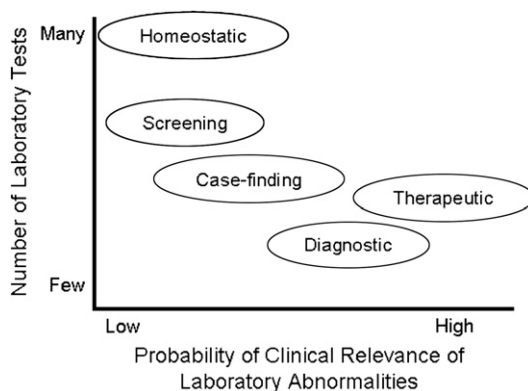


Fig. 1. Authors' perception of frequency of indications for laboratory testing in the medical ICU at Ohio State University Medical Center and relative probabilities of clinical relevance of any observed abnormalities.

an individual patient is not appreciably different than that for the general population. Because laboratory results in the critically ill are more likely to be outside of a reference interval [21], this raises the pretest probability of abnormal test results in patients in the ICU. Unlike ambulatory patients, many patients in the ICU cannot communicate signs and symptoms that would raise clinical suspicion and prompt further laboratory testing. Also, the physiology of the critically ill is probably more fragile and less able to tolerate severe derangements compared with other patients. Therefore, abnormal laboratory results might be of more clinical importance in critically ill patients, and frequent and comprehensive laboratory tests may provide early warning signs that might generate action to avert further deterioration.

Case-finding, diagnostic, and therapeutic testing

Case-finding testing, diagnostic testing, and therapeutic testing are situations in which a condition or disease is suspected or a test might affect the current therapeutic efforts. Among patients with specific suspected conditions or known prior abnormalities, confirming a diagnosis (or excluding one) allows for more focused therapies and clinical decision making. For example, using bronchoalveolar lavage for the diagnosis of acute eosinophilic pneumonia in a patient with acute respiratory failure confirms the diagnosis and informs specific therapy (eg, corticosteroids). It also excludes other diagnoses and avoids their associated therapies (eg, pneumonia and antibiotics). When patients are receiving a certain therapeutic regimen, laboratory results can also be used to guide drug dosing or to prompt investigation of therapeutic complications. Examples include assessment of drug levels and monitoring the platelet count of patients on heparin. Compared with screening and homeostatic testing, in case-finding, diagnostic, and

therapeutic testing, there is a higher likelihood of finding an abnormal value that truly requires attention (a true-positive result) rather than one that has no effect on the patient's course (a false-positive result).

The patient presenting with a severe infection allows for examples of case-finding, diagnostic, and therapeutic testing. Those with systemic signs of infection meet diagnostic criteria for sepsis and are at risk for organ dysfunction or severe sepsis [22]. Those developing severe sepsis are at higher risk of dying, and thus should have an evaluation for signs of organ dysfunction, including appropriate laboratory testing and cultures of sites of possible infection [23]. These are examples of case-finding and diagnostic testing, respectively. For the patient with severe sepsis, there is also evidence that early resuscitation (eg, first 6 hours after presentation) driven by a specific protocol improves outcome relative to usual care [24]. Candidates for this therapy are those with low blood pressure unresponsive to volume resuscitation or with an elevated lactate level (>4 mmol/L). Therefore, patients with sepsis should have early measurement of lactate to identify those for whom such therapy is appropriate. Resuscitation is then targeted to several end points, including continuous measurement of venous oxygen saturation. It has been suggested that when this catheter is not available, frequent monitoring of central venous blood gases may be a reasonable substitute [23]. Lactate and central venous oxygen saturation testing in the early resuscitation of patients with sepsis is thus considered therapeutic testing.

Drug monitoring is an additional form of therapeutic testing. Patients in the ICU commonly receive multiple drug therapies. Concurrent disease states or therapies may cause dose modification; thus, drug concentrations may be sampled for this information. For example, drugs excreted by the kidneys with a narrow therapeutic range are probably important to monitor because small changes in levels may alter treatment response. There are also situations when a practitioner needs to gauge the response to a drug therapy (eg, activated partial thromboplastin time [aPTT] testing during heparin therapy). Anticipatory monitoring for side effects and drug toxicity may prevent harm in critically ill patients treated by drugs with important side effects. In addition, drug monitoring may be necessary for select drugs to monitor therapeutic levels. The measurement of serum concentrations of drugs has limitations, including the effects of protein binding; the presence of interfering substances; assay limitations that may detect parent metabolites, precursors, and active metabolites; and pharmacokinetic variability [25]. Newer assays, such as those measuring the therapeutic free fraction of phenytoin, may overcome some of these limitations, but their effectiveness is largely unproven.

Risks of laboratory testing

Considering laboratory testing as part of therapy frames the decision to proceed with testing in the context of the balance between potential benefits

and risks. A useful laboratory test should have the potential to alter the management plan for a patient. If a laboratory test can only detect disease for which there are no therapeutic options, the test should not be performed. Therapeutic options need not be curative or disease directed. Confirmation of a fatal disease that may be appropriately treated with maintenance of comfort and referral to hospice care is a worthy goal of testing.

The probable benefits of testing are greatest when the pretest probability of a condition requiring action is highest and when the potential harms of testing are lowest. Therefore, an assessment of the risks of laboratory testing is necessary to determine the net benefit of testing. For such procedures as diagnostic cardiac catheterization, risks of the procedure, such as bleeding, dysrhythmias, myocardial infarction, and acute renal failure, are apparent. The risks of laboratory testing are more ambiguous. Because laboratory tests are so frequently performed, the cumulative effects of the small individual risks of laboratory testing cannot be ignored. Such risks include misguided therapy based on spurious results, misdiagnosis attributable to inadequate understanding of the limitations of test performance, risks of sample collection and repeated phlebotomy, and risks of misguided efforts in responding to laboratory “abnormalities” of uncertain significance.

False results and faulty decision making

A factor frequently neglected in clinical decision making is the accuracy of individual laboratory results. There are at least four potential sources of measurable error (or variance) in a laboratory measurement. First, factors associated with the acquisition and handling of specimens can alter results. Application of a tourniquet, length of time it was applied, temperature at which the specimen is collected and transported, anticoagulant used, time elapsed between collection and examination, appropriate labeling of the specimen, and time and speed of centrifugation are just a few of the factors that might affect measurement. This is particularly important if these factors are different than those observed when generating the reference interval. One study found that approximately 1 in 250 statim laboratory specimens from an ICU produced mistakes in the reported results [26]. Furthermore, surrogate measures are often used in laboratory testing because they are technically easier to perform than the true level of interest. For example, potassium is largely an intracellular ion, and blood levels can be affected by many stimuli that can produce shifts without changing whole-body levels. Other ions, such as magnesium and calcium, are highly protein bound, and total levels may provide an inaccurate measure of the biologically active fraction [27].

Other factors may affect the accuracy of laboratory results. There may be errors in laboratory testing because of problems with the equipment itself. This is the variance observed if a laboratory test is performed multiple times on the same sample under the same conditions. Considerable resources are

spent in reducing this error. There is also uncertainty attributable to intra-individual variability. This variability is rarely reported because it would require repeated testing of the same individual under the same conditions. This error is also attributed to the inability to measure all the biologic material of interest (eg, the sodium level in every milliliter of blood). Instead, the clinical laboratory reports an estimate of the true underlying value for sodium. This is akin to an average for a population derived from a sample of that population. Because we cannot measure all people, we use a sample to provide an estimate of the underlying true average. We also provide a measure of how confident we are of this estimate, which is the principle behind confidence intervals. In laboratory reporting, estimates of confidence in the reported value are rarely provided to the treating clinician. This may produce the belief that the reported value is the true value rather than an estimate. An additional source of error is found in the determination of reference intervals, as described previously.

For the clinician, laboratory tests are most useful when there is a level of a test result at which “disease” is discriminated from “health.” Unfortunately, for many tests used in patients in the ICU (eg, electrolytes), such thresholds for action are not established. This makes it difficult to interpret their value in the context of a therapeutic plan. In instances for which test results can be classified as normal and abnormal (or “negative” and “positive”), the performance of a test may best be expressed as a likelihood ratio (LR) [28]. This is the likelihood that a given test result would be expected in a patient with the target disorder compared with the likelihood that the same result would be expected in a patient without the disorder (in other words, $LR = \text{Sensitivity} / [1 - \text{Specificity}]$). The LR can then be used with the pretest probability of disease to determine the posterior probability of disease using a simple nomogram (Fig. 2). When the LR is 1, the test is not informative and does not alter the probability of disease. When disease is extremely likely or extremely unlikely, any single test is unlikely to alter the posttest probability to such a degree that the suspected diagnosis is reasonably excluded or confirmed. When the pretest probability of disease is equivocal (eg, 30%–70%), tests with an extremely high LR (eg, greater than 10) confirm disease and tests with an extremely low LR (eg, less than 0.1) reasonably exclude the diagnosis. Before ordering laboratory testing, a clinician should consider his or her pretest suspicion of disease and the LR of the test to determine the usefulness of the testing.

False test results are more common when the pretest probability of a condition is extremely low or high and the test result contradicts the pretest probability (eg, negative test result with a high pretest probability) or when the test has a LR close to 1. One can never truly know if the result obtained from testing is a true or false result, however. It is important to remember that we are always dealing with probabilities of disease rather than certainties. Assuming that a laboratory test never produces false results can lead to errors in clinical decision making. When a laboratory test produces

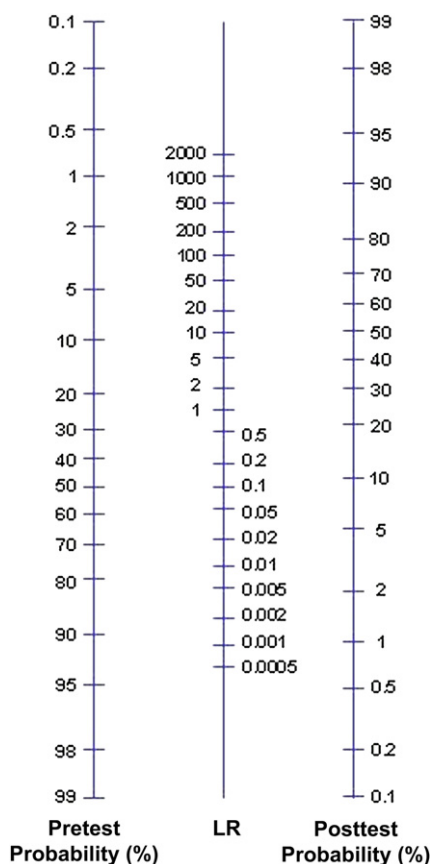


Fig. 2. Pretest probability, LR, and posttest probability of disease. Posttest probability can be determined by drawing a line from the pretest probability through the LR of the test. The end of the line is the posttest probability. The LR is calculated as the Sensitivity/(1 – Specificity).

a falsely abnormal result, clinicians may assume that the laboratory test result overrides any prior clinical suspicion and that the diagnosis is confirmed while overlooking the true culprit (eg, a high-probability ventilation-perfusion scan in a patient with low pretest clinical probability). This is more likely to occur when pretest probabilities are low (eg, screening or homeostatic laboratory testing) or the LR is believed to be much higher than it truly is. Alternatively, a falsely normal test result could reassure the clinician and cause him to exclude the condition under evaluation as a cause of the patient's problem (eg, normal cardiac stress test result in a patient at high risk of cardiovascular disease and classic angina). This may occur when pretest probabilities are high or the LR is believed to be lower than it truly is.

A further consideration in the interpretation of results from the clinical laboratory relates to multiple tests performed on a single sample [29]. Panels

of laboratory tests, such as basic metabolic panels, liver function panels, and complete blood cell counts (CBCs) with white blood cell differential counts, are common in clinical ICU practice. With increasing numbers of laboratory tests measured concurrently, the probability of at least one false-positive test result increases (Fig. 3) and the probability of true-negative results decreases (Fig. 4). So, with increasing numbers of laboratory tests performed, the probability of excluding abnormalities is reduced because of a decrease in the number of true-negative results. In addition, the probability of incorrectly concluding that there is an abnormality increases because of a rise in the number of false-positive results.

Risks of sample collection

Depending on the source of a specimen for laboratory study, there may be risks involved in collection. Such risks are more obvious with more invasive methods of obtaining the specimen, such as with biopsies, thoracentesis, paracentesis, and bronchoalveolar lavage. Phlebotomy carries minimal risk when performed in a sterile fashion but does involve minor discomfort. When using needles, there is also the risk of transmission of blood-borne infections (eg, hepatitis C virus, HIV) to health care workers. In the ICU, phlebotomy often occurs by accessing indwelling vascular devices, such as central venous and arterial catheters. If done with poor technique, this may increase the risk of catheter-related bloodstream infections.

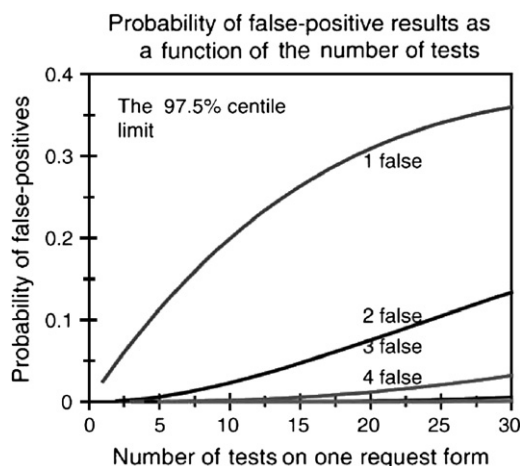


Fig. 3. Probability of false-positive results as a function of the number of tests performed concurrently with a standard reference interval. The 97.5% centile limit corresponds to the usual 95% reference interval. With 2 independent samples, there is a 4% probability of one false-positive result. With 10 samples, the probability is 20%, and with 39 samples, the probability is 37%. (From Jørgensen, et al. Should we maintain the 95 percent reference intervals in the era of wellness testing? A concept paper. Clin Chem Lab Med 2004;42(7):749; with permission.)

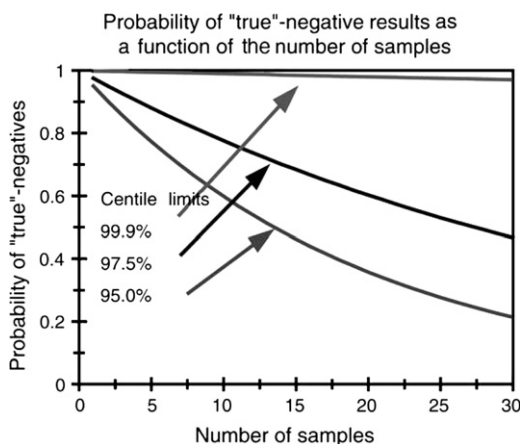


Fig. 4. Probability of true-negative test results as a function of the number of tests performed concurrently. Probabilities are provided for reference interval centile limits for 95%, 97.5% and 99.9%. These correspond to the traditional reference intervals of 90%, 95%, and 99.8%, respectively. (From Jørgensen, et al. Should we maintain the 95 percent reference intervals in the era of wellness testing? A concept paper. Clin Chem Lab Med 2004;42(7):748; with permission.)

Anecdotally, the authors have observed catheters kept in place to obtain daily laboratory tests in patients in whom it is difficult to obtain blood by other means.

Intensive care unit–acquired anemia and blood transfusion

In a multicenter study of almost 5000 patients in 284 ICUs in the United States, anemia was an almost universal finding [30]. Although the cause of anemia in the critically ill is multifactorial [31], true acquired iron deficiency is found in more than 50% of patients in the ICU within 2 weeks of admission [32]. Phlebotomy contributes considerably to iron deficiency [33] and accounts for greater blood loss than pathologic bleeding [32]. Patients in the ICU lose between 25 and 40 mL of blood daily through phlebotomy, which is more than three times the daily loss of patients on the ward [34]. Frequently, the blood collected for laboratory analysis exceeds the volume required, and a sizeable amount of blood is wasted [35]. The use of smaller collection tubes can reduce the volume of blood collected [36], but many automated laboratory instruments are not compatible with these tubes. Closed blood-conserving systems also reduce blood loss [37]; however, like small volume tubes, they are underused [38].

Observational studies suggest that anemia is associated with higher mortality in critically ill adults, particularly those with cardiovascular disease [39]. Because of concerns about decreased oxygen delivery in anemic patients [40], transfusion has become a common therapy. Eighty-five percent

of patients with an ICU stay longer than 1 week receive at least 1 U of blood, with an average of 9.5 U transfused [41]. There are risks associated with transfusion, however, including the transmission of infectious agents, an increased risk of nosocomial infections, transfusion-related acute lung injury, transfusion-associated circulatory overload, and transfusion-related graft-versus-host disease. Transfusions are also associated with greater organ dysfunction, length of stay, and mortality in patients in the ICU [42,43]. A multicenter randomized study of normovolemic, nonbleeding, anemic patients in the ICU found that a restrictive transfusion strategy (transfusion trigger of 7 g/dL to maintain levels from 7–9 g/dL) resulted in 3 U less of transfused blood than those randomized to the liberal transfusion strategy (transfusion trigger of 10 g/dL to maintain levels from 10–12 g/dL) [44]. Those in the restrictive arm showed a nonsignificant decrease in mortality and lower multiple organ dysfunction scores. These subjects also had fewer cardiac complications, including acute myocardial infarctions and pulmonary edema. Data are limited and conflicted regarding the value of transfusions in patients with coronary artery disease [45–47].

Therapeutic actions of uncertain benefit

In the authors' experience, ICU clinicians have an inclination toward "correcting" laboratory values, such as electrolytes, that fall outside of the reference interval. The authors are unable to find data supporting these routine efforts at "normalization" for unselected patients in the ICU. When attempts to mimic the normal physiologic state in ill patients have been subjected to clinical trials, the results have often been disappointing, including elimination of premature ventricular complexes in acute myocardial infarction [48] and normalization of acid-base and maximization of $\text{Pao}_2/\text{fraction of inspired oxygen (Fio}_2\text{)}$ ratios in patients with acute lung injury [49]. It is possible that the association between laboratory values outside of the reference interval and outcome in patients in the ICU is attributable to the response to the observed results (eg, "replacing" electrolytes) rather than to the deranged value itself. Further studies are necessary to determine if normalization of abnormal routine laboratory values in patients in the ICU confers net benefit.

In addition to correcting abnormal laboratory values, there is a tendency to recheck laboratory tests after the intervention. This may produce a clinician-perpetuating cycle of laboratory monitoring and intervention of no proven benefit. Meanwhile, the repeated testing increases the risk of ICU-acquired anemia. Time and attention of the nursing and medical staff are also required, which may distract them from providing other care. Finally, sampling rate can affect predicted probabilities of mortality produced by severity-of-illness measures [50]. These effects may be relevant as the comparison of risk-adjusted outcomes across providers and institutions gains momentum.

Recommendations for “routine” laboratory testing: screening and homeostatic laboratory tests

It has traditionally been assumed that because they have higher severity of illness, critically ill patients require more frequent determination of laboratory values [17]. Several observations suggest that the current intensity of laboratory testing is excessive, however. When “routine” laboratory tests are canceled by a protocol, clinicians rarely override the cancellation, and when unexpected abnormal values are encountered, they are often ignored [51,52]. Use of laboratory testing varies considerably among institutions [2] and providers within institutions [3] without differences in outcomes. Although there is a lack of evidence of benefit of the current practice of frequent laboratory testing in the ICU, this does not necessarily mean there is a true lack of benefit to such a strategy. Excessive costs, potential risks, and no proof of benefit do mandate a re-evaluation of the current approach to routine laboratory testing in the ICU, however.

Presumably, there is a threshold under which foregoing laboratory evaluation would worsen outcomes for patients in the ICU, but there are insufficient data to delineate this minimum volume of laboratory testing. Some have suggested that this discussion is difficult to frame, because there are not adequate definitions of “necessary” and “unnecessary” laboratory tests [53]. One study focused on redundant testing—tests that were high volume or high cost and for which an interval could be clearly defined in which a repeat test was likely to be uninformative and in which the preceding test result was within the reference interval [54]. Using charitable limits before defining a test as redundant (eg, routine urinalysis within 36 hours of a test result within the reference range), 28% of tests were performed earlier than the test-specific predefined interval. Excluding chest radiographs and manual white blood cell differentials, there was no clinical indication for early repeated tests in 92% of cases.

Although reduction of unnecessary and wasteful laboratory testing is a worthy goal, it is not clear which laboratory tests should be the first targets for elimination. The authors would not advocate admission laboratory testing as an initial target for reduction for several reasons. Admission laboratory tests are valuable to establish baseline values for comparison with later values. Moreover, before a diagnosis is established, casting a wide net with admission laboratory tests may facilitate recognition of rare diseases that might otherwise not be considered. It may also help to detect conditions contributing to the primary complaint (eg, myocardial infarction in a patient with diabetic ketoacidosis). The authors believe that such an approach encourages the clinician to maintain a broad differential and avoid premature closure of diagnostic and therapeutic possibilities. They would not advocate screening type testing as a matter of course for all patients (eg, thyroid-stimulating hormone [TSH] testing on all admissions), however, unless it has a direct impact on therapy (eg, pregnancy testing for women of child-bearing age).

Instead, admission testing should pursue diagnostic and therapeutic alternatives raised by the clinical presentation.

Routine, undirected, daily laboratory evaluation (eg, homeostatic laboratory testing) is a practice of questionable utility, and efforts to reduce it are warranted. For homeostatic testing to be justified, the value of the information obtained must exceed the risks. In the authors' opinion, this is seldom the case, and they have observed several instances in which laboratory tests are ordered as a matter of routine rather than necessity (Table 4). Substantial cost savings could be effected by simply increasing the intervals at which

Table 4
Situations in which repeated laboratory tests on a given day are not warranted

Clinical situation	Example(s)
Laboratory test repeated at too frequent intervals (before a meaningful change can reasonably be expected)	Daily albumin ordered to monitor nutritional status; every 4-hour hemoglobin ordered in a patient with gastrointestinal hemorrhage; free T ₄ ordered daily during treatment of hyperthyroidism
Redundant laboratory tests ordered concurrently	CK-MB and troponin ordered concurrently every 6 hours after myocardial infarction; creatinine and BUN ordered concurrently; AST and ALT ordered concurrently
Laboratory test ordered when clinical assessment is superior	Short-interval hematocrit testing in gastrointestinal hemorrhage; ABG to assess response to NIPPV; serial BNP measurement during treatment of CHF
Laboratory test ordered to confirm an expected response to a routine intervention	Repeat testing of electrolytes after replacement; repeat testing of hemoglobin after transfusion
Laboratory test ordered that does not affect management or prognostication	Frequent coagulation parameter testing in a patient with cirrhosis who is not bleeding

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CHF, congestive heart failure; CK, creatine kinase; NIPPV, non-invasive positive pressure ventilation; T₄, thyroxine.

homeostatic laboratory tests are obtained. If these laboratory tests were decreased in frequency from daily to every 3 days, a two-thirds reduction in associated direct costs could be expected. As a patient improves, the support for such routine testing becomes even less tenable.

Arterial blood gas (ABG) measurement merits specific discussion. Obtaining blood for ABG testing is invasive and painful in patients without intravascular catheters. Arterial lines confer risks of mechanical and infectious complications. To justify testing, the benefits of the information from an ABG measurement should exceed these risks and the information must not be otherwise available with lower risk and cost. ABG measurements provide data related to oxygenation, ventilation, and acid-base status. In most settings, oxygen saturation is a reliable surrogate for PaO_2 , and it parallels oxygen delivery along a wider range of values [55]. Pulse oximetry allows for continuous monitoring of oxygen saturation and is noninvasive, practically free of risk, and in routine use in most ICUs. Most situations resulting in spurious values of pulse oximetry result in falsely low values (eg, hypotension). These prompt further evaluation and are unlikely to cause harm. In a few situations, however, such as hypoxic patients with darkly pigmented skin [56], carbon monoxide poisoning [57], hypothermia [58], and rapid changes in arterial oxygen content [59], pulse oximetry can report higher values than obtained by direct measurement of an arterial sample. Excluding these situations, pulse oximetry should be used in lieu of ABG measurement for the routine assessment of oxygenation. Because most intubated patients homeostatically regulate ventilation to maintain pH in a safe physiologic range [60] and respiratory acidosis is generally benign [61], close monitoring of arterial pH and PaCO_2 is not necessary in most clinically stable mechanically ventilated patients. Therefore, ABG sampling can be avoided in most instances in which the measure of interest is continuing assessment of oxygenation, ventilation, and acid-base status. Nonintubated patients and those receiving noninvasive positive-pressure ventilation can usually be safely managed without routine blood gas monitoring. Clinical assessment, with careful attention to mental status, vital signs, and work of breathing, is superior to ABG analysis in these patients, because rising PCO_2 is a late finding in respiratory failure and a normal ABG result may provide false reassurance that a patient with impending respiratory embarrassment is stable [62]. In mechanically ventilated patients in whom pulse oximetry is potentially inaccurate (particularly falsely high), in those unable to regulate their ventilation, and in those with acute clinical deterioration, judicious monitoring with ABG measurements may be necessary.

Strategies to reduce unneeded laboratory tests

Multiple strategies have been used in an effort to reduce laboratory testing and to ensure that ordered tests are appropriate for the clinical syndrome under investigation. These have included suggestions by pharmacists

on rounds to reduce phlebotomy [63], a laboratory interpretation and consultative service [64], changes in processes of test ordering [17,19,65,66], the use of guidelines for laboratory testing [16–20,66], and providing physicians with prices of various laboratory tests [5]. Most published studies show some degree of reductions in laboratory testing, costs, and transfusions. Importantly, no significant adverse events attributable to decreased laboratory testing were reported.

Although many interventions reduced the volume of laboratory testing, this does not mean that all unnecessary testing was eliminated. For example, an intervention to reduce the number of ABG measurements in a surgical intensive care unit (SICU) resulted in an almost 50% reduction in the number of blood gas measurements performed [67]. There were still 4.8 ABG measurements performed per patient-day, however. Another study reduced laboratory testing with guideline-driven orders but continued to recommend measuring basic metabolic panels daily [68]. Such observations and the lack of poorer outcomes with fewer laboratory tests suggest that further reduction is possible.

Specific laboratory tests in the critically ill

Cardiac biomarkers in critical illness: troponin and natriuretic peptides

Assays for troponin isoforms and brain natriuretic peptide (BNP) and variants (eg, N-terminal [NT]-pro-BNP) have received attention as potentially useful diagnostic and prognostic tests in critically ill patients. The increasing popularity of these tests stems from the ease with which they can be obtained as well as their proven utility as diagnostic tests outside of the ICU. In patients presenting with symptoms of myocardial infarction, troponin assays are sensitive and highly specific tests for the diagnosis of acute coronary syndromes [69]. Likewise, in patients presenting to the emergency department with dyspnea, assays for BNP are useful aids in the differentiation of cardiac and noncardiac dyspnea [70]. Because critically ill patients were not among the populations in which these tests were originally validated, use of these assays in the ICU may be problematic. Many conditions common in critically ill patients (eg, sepsis, pulmonary embolism, shock, cor pulmonale) can cause elevations of these biomarkers, resulting in unacceptably high rates of false-positive test results [71,72].

The diagnosis of acute coronary syndromes and detection of impaired left ventricular (LV) function have been suggested as potential diagnostic uses of troponin in critically ill patients. In critically ill patients, the positive predictive value of an abnormal troponin assay is disappointingly low—only 28% to 55% of patients with a positive test result are confirmed to have an acute coronary syndrome [73–76]. The low positive predictive value of troponin in the critically ill results from the frequent occurrence of other diseases that can cause its elevation. As a result, an isolated troponin elevation in a critically

ill patient is not diagnostic of acute coronary syndrome, and additional testing is needed for confirmation. Therefore, the authors do not recommend its routine use in critical care settings, except in patients with electrocardiographic abnormalities or symptoms suggestive of myocardial infarction. Elevated troponin levels are associated with LV dysfunction in critical illness, but the documented correlations, although statistically significant, have generally been weak [73]. Therefore, in patients in whom LV dysfunction is suspected, an elevated troponin level does not preclude confirmatory testing that allows quantification of LV impairment. There are no data demonstrating that detection of subclinical LV impairment with determination of troponin levels leads to changes in therapy with beneficial impacts on clinically important outcomes. In addition, it is not clear if there is a level of troponin under which LV dysfunction is unlikely, obviating further testing.

BNP and variants (NT-pro-BNP) have been studied as biomarkers of LV dysfunction in critical illness [77]. Like troponin, elevated BNP levels are nonspecific findings and are observed in such conditions as pulmonary hypertension, pulmonary embolism, LV hypertrophy, renal failure, acute coronary syndromes, atrial fibrillation, lung cancer, and sepsis [78]. There are inconsistent reports of an association between BNP levels and cardiac filling pressures and patient volume status [79–82]. Most of these studies were exploratory and did not use a validation cohort to confirm reproducibility of results. Results of BNP testing rarely obviate further testing, and thus add little to the evaluation of volume status and LV dysfunction in most critically ill patients [83]. One possible exception is that low levels of BNP (<350) may be useful to rule out cardiogenic shock (95% negative predictive value) [84].

One promising recent study demonstrated the potential of NT-pro-BNP to facilitate the diagnosis of LV dysfunction in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD). A level of NT-pro-BNP less than 1000 had a negative predictive value of 94%, largely excluding LV dysfunction. The utility of a level greater than 2500 for confirming LV dysfunction was more modest, with an LR of 5.16 [85]. Another small study ($n = 19$) demonstrated the ability of NT-pro-BNP to detect cardiac dysfunction as a cause of weaning failure in patients with acute exacerbations of COPD [86]. If these results can be validated in a larger cohort of patients, NT-pro-BNP may find a use in differentiating cardiac from noncardiac causes of weaning failure.

In most studies, troponin and BNP correlate with prognosis. It has been suggested that prognostication may be a valid indication for measuring their levels [87,88]. It is not clear how information from these biomarkers can be used for the benefit of patients, however. Neither assay consistently provides prognostic information beyond that available by using traditional scoring systems, making their prognostic role of questionable clinical utility.

Although troponin and BNP have proven their utility in non-critical care settings, current use of these cardiac biomarkers in the ICU is largely of

research interest. It is most important for clinicians to remember that many disease processes can cause troponin and BNP to be nonspecifically elevated in the ICU. Future studies of the use of these markers to guide clinicians in the care of critically ill patients should carefully identify the study population, use a “gold standard” for the outcome of interest in all patients, validate any cutoff level prospectively, and ensure that the outcome of interest is clinically relevant.

D-dimer and thromboembolic disease

D-dimer is a protein produced when cross-linked fibrin is degraded by plasmin. When coagulation and fibrinolysis are coactivated, elevated levels of D-dimer are found. This occurs in clinical settings of venous thromboembolism (VTE), trauma, or recent surgery. D-dimer may also be detected in sepsis, malignancy, pregnancy, and myocardial infarction [89]. There are numerous available D-dimer assays, and the performance of one assay should not be generalized to all [90]. Outpatients with VTE tend to have elevated levels of D-dimer [91,92], and negative D-dimer assays have negative predictive values similar to Doppler ultrasound examination in select inpatients not in the ICU [93]. In critically ill patients, however, the diagnosis of VTE is extremely challenging and patients are at high risk for the disease. Among medical-surgical critically ill patients, only 3.6% to 15.9% have negative D-dimer test results, regardless of the presence or absence of thromboembolic disease [94]. The negative predictive value of testing in one study is 84.7% to 92.1% depending on the type of assay used [95]. Among critically ill patients with a low pretest probability of VTE, D-dimer may be useful if the result is negative. A positive result, however, does not confirm the presence of VTE.

D-dimer testing has been evaluated as a predictor of mortality in the ICU. Among 321 critically ill patients, D-dimer levels measured within 24 hours of admission were associated with mortality, sepsis, and multiorgan system failure [96]. D-dimer did not add prognostic information beyond that available by using traditional severity-of-illness scoring systems, however. Shorr and colleagues [97] showed that D-dimer levels correlated with activation of the proinflammatory cytokine pathway and identified patients at increased risk for multiorgan system failure and death. These results highlight the importance of the coagulation system in sepsis, but D-dimer testing alone should not be used to treat coagulation abnormalities in patients with critical illness.

Blood cultures

Bacteremia is found in up to 10% of patients in the ICU and is an important cause of morbidity and mortality [98]. In the evaluation of fevers, there are specific guidelines for blood cultures that include indications, number of

cultures, appropriate interval, and interpretation [99]. Use of this approach has been shown to optimize treatment and outcome [100]. Among patients already receiving antibiotics, blood cultures routinely ordered for fever are relatively insensitive [101,102]. In one study, repeat blood cultures identified a new pathogen in only 2.5% of cases, with no growth in 83.4%, the same pathogen in 9.1%, and contamination in 5.0% [103]. Despite this low sensitivity, repeat blood cultures accounted for one third of all such samples in this laboratory. False-positive results attributable to contamination are increased with each additional culture [104]. The suspected site of infection may also affect the yield of blood cultures. For example, there are fewer true-positive blood cultures in the setting of nosocomial urinary tract infections than in the setting of endocarditis or central venous catheter-associated infections.

An expert task force concluded that a new fever in a patient in the ICU should generate a careful clinical assessment rather than trigger an automatic battery of laboratory tests and cultures [105]. Clinicians should be sensitive to the cost and limited value of repeated cultures. Unfortunately, the ability to identify bacteremia based on clinical evaluation alone is limited [106]. Therefore, repeat blood cultures may be necessary in patients in whom clinical evaluation does not reveal an alternative source of fever. Surveillance blood cultures (eg, those performed without clinical suspicion of bacteremia) add little to the management of patients in the ICU, are expensive, and should be avoided [107].

Emerging trends in laboratory testing

Point-of-care testing

Caring for critically ill patients involves medical decision making that can be time-sensitive, and information crucial to these decisions may be needed within minutes. As patient acuity increases, the need for rapid collection, processing, and interpretation of laboratory tests becomes more urgent. For these reasons and others, point-of-care (POC) technologies have become a considered alternative for critical care medicine. POC refers to the performance of diagnostic tests at or near the patient. The excellent accuracy, validity, and reliability of POC testing results have been reviewed [108]. These tests can be performed at the bedside by portable instruments in minutes and can measure many blood analytes using small amounts of whole blood.

The scientific advances that make POC testing possible include whole-blood biosensors, ion-selective electrodes, substrate-specific electrodes, polarography, and potentiometry [109]. As a result, laboratory measurements can be made for pO_2 , pCO_2 , pH, sodium, potassium, chloride, magnesium, calcium, urea nitrogen, lactate, creatinine, glucose, hematocrit, cardiac enzymes, co-oximetry, and coagulation studies [110]. The primary advantage

of POC testing over traditional methods is decreased turnaround time and fewer steps [108]. POC testing can also decrease blood loss to laboratory testing. The main disadvantage of POC testing is the need for quality control outside of the central laboratory to ensure accurate and reliable measurements. Additional issues are cost, competency, and education. POC testing has become the standard of care in diabetes management, with patients instructed to respond to the result in a specific manner, but requires careful consideration among the critically ill. Compared with laboratory-based venous plasma measurements (eg, the gold standard), POC testing tends to report higher glucose levels when using arterial or capillary sources and in anemic, hypoxic, hypothermia, or hypotensive patients [111]. These conditions may result in a falsely reassuring low-normal glucose level when the patient is, in fact, hypoglycemic. Because symptoms of hypoglycemia are difficult to recognize in patients in the ICU, protocols endorsing “tight” control of glucose should be mindful of this confounder.

Noninvasive testing

Noninvasive testing by pulse oximetry offers a continuous determination of oxygen saturation and has become a standard in many ICUs. Several other noninvasive technologies are currently available. End-tidal CO_2 determination can confirm endotracheal tube placement after intubation and may also be beneficial in resuscitative efforts [112]. The GlucoWatch (<http://www.glucowatch.com/>) measures blood glucose levels through reverse iontophoresis and has been approved by the US Food and Drug Administration (FDA) [113]. The Bilichek by Spectrix (Murrysville, Pennsylvania) measures the concentration of bilirubin directly on the forehead of newborns by light reflectance and requires no reagents or calibration [114]. The Hemoscan CBC device is an optical device that focuses on the microvasculature of the eye to capture images of circulating blood cells, allowing computation of a CBC [115]. Further developments of accurate and reliable noninvasive testing would be beneficial by sparing the need for biologic sampling and reduction in risks of ICU-acquired anemia.

Continuous sampling

Continuous ABG monitoring has been performed on pediatric and adult patients [116,117]. Intra-arterial fiberoptic sensors can continuously measure PO_2 , PCO_2 , and pH [118]. Ex vivo techniques have been used in neonates with in-line analyzers that allow for return of the specimen to the patient and blood conservation [119]. Technologies for continuous monitoring of mixed venous oxygen samples with fiberoptic pulmonary catheters have been available since 1994 [120]. Because critically ill patients often have arterial or central venous lines, taking advantage of this access with continuous sampling techniques may be of benefit. The current intra-arterial technology has

a high cost, however, with catheters that are fragile and not reliable at measuring PaO_2 [121]. In the future, this technology may save on blood loss and give real-time results.

Suggestions for future research and current practice

As outlined throughout, there are few data to guide clinicians in regard to laboratory testing in critically ill patients. Patients in the ICU have significantly more testing performed than any other single group of patients. This testing is not without risk, ranging from ICU-acquired anemia to misguided decision making. Multiple studies found that the volume of testing can be dramatically reduced without appreciably affecting outcomes. This suggests that at least a portion of the current laboratory practice provides no marginal benefit for patients. The authors believe there is adequate evidence to suggest the following:

1. Each institution should examine its own practices in regard to laboratory testing and determine areas of excess or inappropriate testing that might be targets for action.
2. The practice of bundling multiple laboratory tests together (eg, the basic metabolic panel) for the convenience of the provider should be abandoned.
3. Routine testing of multiple laboratories on an ongoing basis (homeostatic laboratories) should be stopped.
4. Laboratory testing should be pursued as a part of a therapeutic response to a clinical problem rather than as a search for abnormal values to be corrected. Testing in the context of higher pretest probabilities of disease should be emphasized.
5. Efforts at blood conservation, such as the use of low-volume sample tubes and closed-line sampling devices and the removal of arterial and venous catheters, should be encouraged.
6. Attempts to change the practice of laboratory testing are more likely to be successful if pursued in an interdisciplinary fashion, addressing predisposing, enabling, and reinforcing factors.
7. Research is desperately needed to examine the role of the clinical laboratory in critical care. Such work should include efforts to define the levels of common laboratory test results that are associated with greater risk so as to determine if attempting to correct these abnormal test results is associated with improved (or worse) outcomes, to delineate the appropriate level of laboratory testing for various groups of critically ill patients, to validate selected diagnostic tests for ICU populations, and to develop alternative technologies to replace sampling of biologic materials.

For the clinician practicing with current data and technology, one is left without answers as to a rational approach to laboratory testing. The authors suggest revisiting the indication for laboratory testing for guidance. For the

undifferentiated patient in the ICU, the authors suggest there are few laboratory tests that should be routinely ordered for all (Table 5). Instead, they believe that testing should be guided by the clinical presentation and therapeutic efforts (Table 6). This is by no means a complete list, and each clinician should review the evidence to produce his or her own “batteries” of tests prompted by specific clinical scenarios. The authors also emphasize that these recommendations are not based on high-level evidence. The sense of a “need to know” is so ingrained in training that the authors found themselves hesitant to exclude testing, despite the limitations and dangers outlined previously. As more ICUs move to computerized order entry and electronic documentation, such technology can be leveraged to supply

Table 5
Suggestions for initial laboratory tests for patients in the ICU

Situation	Suggested laboratory tests
All patients in the ICU on admission	White blood cell count and differential Hemoglobin or hematocrit Platelets Sodium Chloride Potassium Bicarbonate Creatinine Glucose Inorganic phosphate Bilirubin ALT or AST PTT PT/INR Urine pregnancy test (women of child-bearing age only)
All ventilated patients after intubation	ABG (to show correlation with pulse oximetry and minute ventilation requirements)
All patients with sepsis on recognition of sepsis	Admission laboratory tests, plus Lactate ABG Blood cultures before antibiotics Urinalysis Urine culture, if pyuria on urinalysis Other appropriate cultures Central venous saturation (within 6 hours of presentation if hypotensive or elevated lactate)
Patients with shock on presentation	Admission laboratory tests, plus ABG BNP

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

Table 6

An incomplete list of laboratory tests indicated by clinical situations or therapeutic efforts

Clinical situation/therapeutic effort	Suggested laboratory tests	Suggested interval for testing
Pulse oximetry does not correlate reasonably (eg, within $\pm 4\%$) with measured PaO_2	ABG	Daily while on $> 50\% \text{ FiO}_2$
Patients with abnormal ventilatory control (eg, pharmacologic paralysis)	ABG or venous blood gas	Daily while on $> 50\% \text{ FiO}_2$
Acute drop in SpO_2 or change in respiratory rate	ABG	With event
Acute drop in blood pressure (eg, $> 20\%$) or rise in heart rate	ABG Hemoglobin or hematocrit	With event
Dysrhythmia	ABG or venous blood gas Potassium Magnesium	With event
New bleeding	Hemoglobin or hematocrit Platelet count PTT PT/INR Type and screen	With event
Patient receiving potentially nephrotoxic drugs	Creatinine	Daily
Patient receiving drugs with narrow therapeutic window or need for minimal blood level for effectiveness and measurable drug levels	Therapeutic drug levels	Consult with pharmacy to ensure appropriate timing
Delirium	Sodium Creatinine Ionized Calcium Glucose Bilirubin B_{12} level Thiamine level	With diagnosis of delirium
Failure of patient to perform well on spontaneous breathing trials	Delirium laboratory tests, if delirious Inorganic phosphate	With failure of spontaneous breathing trial
Patient receiving volume resuscitation	Sodium	Daily while receiving volume replacement
Patient with significant volume loss, therapeutic (eg, furosemide) or pathologic (eg, diarrhea)	Sodium Potassium Magnesium Ionized calcium Creatinine	Daily while volume loss ongoing

Abbreviations: PT, prothrombin time; PTT, partial thromboplastin time; SpO_2 , transcutaneous oxygen saturation.

laboratory testing as indicated by suspected diagnoses and ongoing and future therapies. This should also reduce the anxiety that some clinicians feel in letting go of the daily homeostatic laboratory tests. One can feel reassured that the correct test, as guided by evidence and collaboration with clinical laboratory experts, is going to be ordered at appropriate intervals to ensure maximum benefit for the patient.

Summary

Laboratory testing in critically ill patients represents a large proportion of the cost of caring for these patients. Much of this testing seems to be unsupported by evidence of efficacy and often does not lead to meaningful changes in therapy. The unnecessary risks and costs of excessive laboratory testing in the ICU could be minimized by a carefully developed framework of accepted or suggested laboratory tests for critically ill patients, supplemented by investigations to determine the “appropriate” intensity of testing. Until such evidence is available, the authors recommend a judicious approach to laboratory testing in the ICU, guided by pretest probabilities, test performance characteristics, and a priori determinations of how each test can meaningfully influence the care of the individual patient. This approach should be tempered by knowledge of the risks of testing, including blood loss, iatrogenic anemia, and misguided therapy.

References

- [1] Smoller BR, Kruskall MS. Phlebotomy for diagnostic laboratory tests in adults. Pattern of use and effect on transfusion requirements. *N Engl J Med* 1986;314(19):1233–5.
- [2] Zimmerman JE, Seneff MG, Sun X, et al. Evaluating laboratory usage in the intensive care unit: patient and institutional characteristics that influence frequency of blood sampling. *Crit Care Med* 1997;25(5):737–48.
- [3] Garland A, Shaman Z, Baron J, et al. Physician-attributable differences in intensive care unit costs: a single-center study. *Am J Respir Crit Care Med* 2006;174(11):1206–10.
- [4] Frassica JJ. Frequency of laboratory test utilization in the intensive care unit and its implications for large-scale data collection efforts. *J Am Med Inform Assoc* 2005;12(2):229–33.
- [5] Seguin P, Bleichner JP, Grolier J, et al. Effects of price information on test ordering in an intensive care unit. *Intensive Care Med* 2002;28(3):332–5.
- [6] Chalfin DB. Analysis of cost-effectiveness in intensive care: an overview of methods and review of applications to problems in critical care. *Curr Opin Anaesthesiol* 1996;9:129–33.
- [7] Klepzig H, Winten G, Thierolf C, et al. [Treatment costs in a medical intensive care unit: a comparison of 1992 and 1997]. *Dtsch Med Wochenschr* 1998;123(23):719–25.
- [8] Young DS, Sachais BS, Jefferies LC. Laboratory costs in the context of disease. *Clin Chem* 2000;46(7):967–75.
- [9] Asimos A. The trauma panel: laboratory test utilization in the initial evaluation of trauma patients. *Emerg Med Rep* 1997;18:22–31.
- [10] Halpern NA, Pastores SM, Greenstein RJ. Critical care medicine in the United States 1985–2000: an analysis of bed numbers, use, and costs. *Crit Care Med* 2004;32(6):1254–9.

- [11] National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES). Centers for Disease Control 2007 3-20-0007. Ref Type Electronic Citation.
- [12] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106(25):3143–421.
- [13] Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13(10):818–29.
- [14] Lemeshow S, Klar J, Teres D. Outcome prediction for individual intensive care patients: useful, misused, or abused? *Intensive Care Med* 1995;21(9):770–6.
- [15] Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991;100(6):1619–36.
- [16] Barie PS, Hydo LJ. Learning to not know: results of a program for ancillary cost reduction in surgical critical care. *J Trauma* 1996;41(4):714–20.
- [17] Wang TJ, Mort EA, Nordberg P, et al. A utilization management intervention to reduce unnecessary testing in the coronary care unit. *Arch Intern Med* 2002;162(16):1885–90.
- [18] Roberts DE, Bell DD, Ostryzniuk T, et al. Eliminating needless testing in intensive care—an information-based team management approach. *Crit Care Med* 1993;21(10):1452–8.
- [19] Neilson EG, Johnson KB, Rosenbloom ST, et al. The impact of peer management on test-ordering behavior. *Ann Intern Med* 2004;141(3):196–204.
- [20] Pilon CS, Leathley M, London R, et al. Practice guideline for arterial blood gas measurement in the intensive care unit decreases numbers and increases appropriateness of tests. *Crit Care Med* 1997;25(8):1308–13.
- [21] Dighe AS, Rao A, Coakley AB, et al. Analysis of laboratory critical value reporting at a large academic medical center. *Am J Clin Pathol* 2006;125(5):758–64.
- [22] American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20(6):864–74.
- [23] Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32(3):858–73.
- [24] Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345(19):1368–77.
- [25] Gross AS. Best practice in therapeutic drug monitoring. *Br J Clin Pharmacol* 1998;46(2):95–9.
- [26] Plebani M, Carraro P. Mistakes in a stat laboratory: types and frequency. *Clin Chem* 1997;43(8 Pt 1):1348–51.
- [27] Koch SM, Warters RD, Mehlhorn U. The simultaneous measurement of ionized and total calcium and ionized and total magnesium in intensive care unit patients. *J Crit Care* 2002;17(3):203–5.
- [28] Irwig L, Tosteson AN, Gatsonis C, et al. Guidelines for meta-analyses evaluating diagnostic tests. *Ann Intern Med* 1994;120(8):667–76.
- [29] Cebul RD, Beck JR. Biochemical profiles. Applications in ambulatory screening and pre-admission testing of adults. *Ann Intern Med* 1987;106(3):403–13.
- [30] Corwin HL, Gettinger A, Pearl RG, et al. The CRIT Study: anemia and blood transfusion in the critically ill—current clinical practice in the United States. *Crit Care Med* 2004;32(1):39–52.
- [31] Raghavan M, Marik PE. Anemia, allogenic blood transfusion, and immunomodulation in the critically ill. *Chest* 2005;127(1):295–307.
- [32] von Ahsen N, Muller C, Serke S, et al. Important role of nondiagnostic blood loss and blunted erythropoietic response in the anemia of medical intensive care patients. *Crit Care Med* 1999;27(12):2630–9.
- [33] Woodhouse S. Complications of critical care: lab testing and iatrogenic anemia. *MLO Med Lab Obs* 2001;33:28–31.

- [34] Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. *JAMA* 2002;288(12):1499–507.
- [35] Dale JC, Ruby SG. Specimen collection volumes for laboratory tests. *Arch Pathol Lab Med* 2003;127(2):162–8.
- [36] Smoller BR, Kruskall MS, Horowitz GL. Reducing adult phlebotomy blood loss with the use of pediatric-sized blood collection tubes. *Am J Clin Pathol* 1989;91(6):701–3.
- [37] Silver MJ, Li YH, Gragg LA, et al. Reduction of blood loss from diagnostic sampling in critically ill patients using a blood-conserving arterial line system. *Chest* 1993;104(6):1711–5.
- [38] O'Hare D, Chilvers RJ. Arterial blood sampling practices in intensive care units in England and Wales. *Anaesthesia* 2001;56(6):568–71.
- [39] Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996;348(9034):1055–60.
- [40] Russell JA, Phang PT. The oxygen delivery/consumption controversy. Approaches to management of the critically ill. *Am J Respir Crit Care Med* 1994;149(2 Pt 1):533–7.
- [41] Corwin HL. Blood transfusion in the critically ill patient. *Dis Mon* 1999;45(10):409–26.
- [42] Moore FA, Moore EE, Sauaia A. Blood transfusion. An independent risk factor for post-injury multiple organ failure. *Arch Surg* 1997;132(6):620–4.
- [43] Vamvakas EC, Carven JH. Allogeneic blood transfusion, hospital charges, and length of hospitalization: a study of 487 consecutive patients undergoing colorectal cancer resection. *Arch Pathol Lab Med* 1998;122(2):145–51.
- [44] Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;340(6):409–17.
- [45] Hebert PC, Yetisir E, Martin C, et al. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med* 2001;29(2):227–34.
- [46] Wu WC, Rathore SS, Wang Y, et al. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001;345(17):1230–6.
- [47] Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA* 2004;292(13):1555–62.
- [48] Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. *N Engl J Med* 1989;321(6):406–12.
- [49] Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342(18):1301–8.
- [50] Suistomaa M, Kari A, Ruokonen E, et al. Sampling rate causes bias in APACHE II and SAPS II scores. *Intensive Care Med* 2000;26(12):1773–8.
- [51] Hindmarsh JT, Lyon AW. Strategies to promote rational clinical chemistry test utilization. *Clin Biochem* 1996;29(4):291–9.
- [52] Williamson JW, Alexander M, Miller GE. Continuing education and patient care research. Physician response to screening test results. *JAMA* 1967;201(12):938–42.
- [53] van Walraven C, Naylor CD. Do we know what inappropriate laboratory utilization is? A systematic review of laboratory clinical audits. *JAMA* 1998;280(6):550–8.
- [54] Bates DW, Boyle DL, Rittenberg E, et al. What proportion of common diagnostic tests appear redundant? *Am J Med* 1998;104(4):361–8.
- [55] Hall JB, Schmidt GA, Wood LDH. Principles of critical care. New York: The McGraw-Hill Company, Inc.; 1998.
- [56] Bickler PE, Feiner JR, Severinghaus JW. Effects of skin pigmentation on pulse oximeter accuracy at low saturation. *Anesthesiology* 2005;102(4):715–9.
- [57] Hampson NB. Pulse oximetry in severe carbon monoxide poisoning. *Chest* 1998;114(4):1036–41.

- [58] MacLeod DB, Cortinez LI, Keifer JC, et al. The desaturation response time of finger pulse oximeters during mild hypothermia. *Anaesthesia* 2005;60(1):65–71.
- [59] Stoneham MD. Uses and limitations of pulse oximetry. *Br J Hosp Med* 1995;54(1):35–41.
- [60] Mason RJ, Broaddus VC, Murray JF, et al. *Murray and Nadel's textbook of respiratory medicine*. 4th edition. Philadelphia: WB Saunders; 2005.
- [61] Frumin MJ, Epstein RM, Cohen G. Apneic oxygenation in man. *Anesthesiology* 1959;20:789–98.
- [62] Tulaimat A, Mokhlesi B. Noninvasive ventilation for persistent weaning failure. *Am J Respir Crit Care Med* 2004;169(9):1073–4.
- [63] Pell LJ, Martin BS, Shirk MB. Epoetin alfa protocol and multidisciplinary blood-conservation program for critically ill patients. *Am J Health Syst Pharm* 2005;62(4):400–5.
- [64] Laposata ME, Laposata M, Van Cott EM, et al. Physician survey of a laboratory medicine interpretive service and evaluation of the influence of interpretations on laboratory test ordering. *Arch Pathol Lab Med* 2004;128(12):1424–7.
- [65] Clemmer TP, Spuhler VJ, Oniki TA, et al. Results of a collaborative quality improvement program on outcomes and costs in a tertiary critical care unit. *Crit Care Med* 1999;27(9):1768–74.
- [66] van Walraven C, Goel V, Chan B. Effect of population-based interventions on laboratory utilization: a time-series analysis. *JAMA* 1998;280(23):2028–33.
- [67] Merlani P, Garnerin P, Diby M, et al. Quality improvement report: linking guideline to regular feedback to increase appropriate requests for clinical tests: blood gas analysis in intensive care. *BMJ* 2001;323(7313):620–4.
- [68] Mehari SM, Havill JH, Montgomery C. A written guideline implementation can lead to reductions in laboratory testing in an intensive care unit. *Anaesth Intensive Care* 1997;25(1):33–7.
- [69] Zimmerman J, Fromm R, Meyer D, et al. Diagnostic marker cooperative study for the diagnosis of myocardial infarction. *Circulation* 1999;99(13):1671–7.
- [70] Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347(3):161–7.
- [71] Roongsritong C, Warraich I, Bradley C. Common causes of troponin elevations in the absence of acute myocardial infarction: incidence and clinical significance. *Chest* 2004;125(5):1877–84.
- [72] Phua J, Lim TK, Lee KH. B-type natriuretic peptide: issues for the intensivist and pulmonologist. *Crit Care Med* 2005;33(9):2094–103.
- [73] Ammann P, Maggiorini M, Bertel O, et al. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. *J Am Coll Cardiol* 2003;41(11):2004–9.
- [74] Lim W, Qushmaq I, Cook DJ, et al. Elevated troponin and myocardial infarction in the intensive care unit: a prospective study. *Crit Care* 2005;9(6):R636–44.
- [75] Lim W, Cook DJ, Griffith LE, et al. Elevated cardiac troponin levels in critically ill patients: prevalence, incidence, and outcomes. *Am J Crit Care* 2006;15(3):280–8.
- [76] Lim W, Qushmaq I, Devereaux PJ, et al. Elevated cardiac troponin measurements in critically ill patients. *Arch Intern Med* 2006;166(22):2446–54.
- [77] Charpentier J, Luyt CE, Fulla Y, et al. Brain natriuretic peptide: a marker of myocardial dysfunction and prognosis during severe sepsis. *Crit Care Med* 2004;32(3):660–5.
- [78] Schwam E. B-type natriuretic peptide for diagnosis of heart failure in emergency department patients: a critical appraisal. *Acad Emerg Med* 2004;11(6):686–91.
- [79] Forfia PR, Watkins SP, Rame JE, et al. Relationship between B-type natriuretic peptides and pulmonary capillary wedge pressure in the intensive care unit. *J Am Coll Cardiol* 2005;45(10):1667–71.
- [80] Jelic D, Lee JW, Jelic D, et al. Utility of B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide in evaluation of respiratory failure in critically ill patients. *Chest* 2005;128(1):288–95.

- [81] Dokainish H, Zoghbi WA, Lakkis NM, et al. Optimal noninvasive assessment of left ventricular filling pressures: a comparison of tissue Doppler echocardiography and B-type natriuretic peptide in patients with pulmonary artery catheters. *Circulation* 2004;109(20):2432–9.
- [82] Witthaut R, Busch C, Fraunberger P, et al. Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: impact of interleukin-6 and sepsis-associated left ventricular dysfunction. *Intensive Care Med* 2003;29(10):1696–702.
- [83] Dokainish H, Zoghbi WA, Lakkis NM, et al. Comparative accuracy of B-type natriuretic peptide and tissue Doppler echocardiography in the diagnosis of congestive heart failure. *Am J Cardiol* 2004;93(9):1130–5.
- [84] Tung RH, Garcia C, Morss AM, et al. Utility of B-type natriuretic peptide for the evaluation of intensive care unit shock. *Crit Care Med* 2004;32(8):1643–7.
- [85] Abroug F, Ouanes-Besbes L, Nciri N, et al. Association of left-heart dysfunction with severe exacerbation of chronic obstructive pulmonary disease: diagnostic performance of cardiac biomarkers. *Am J Respir Crit Care Med* 2006;174(9):990–6.
- [86] Grasso S, Leone A, De Michele M, et al. Use of N-terminal pro-brain natriuretic peptide to detect acute cardiac dysfunction during weaning failure in difficult-to-wean patients with chronic obstructive pulmonary disease. *Crit Care Med* 2007;35(1):96–105.
- [87] Brueckmann M, Huhle G, Lang S, et al. Prognostic value of plasma N-terminal pro-brain natriuretic peptide in patients with severe sepsis. *Circulation* 2005;112(4):527–34.
- [88] Landesberg G, Vesselov Y, Einav S, et al. Myocardial ischemia, cardiac troponin, and long-term survival of high-cardiac risk critically ill intensive care unit patients. *Crit Care Med* 2005;33(6):1281–7.
- [89] Raimondi P, Bongard O, de Moerloose P, et al. D-dimer plasma concentration in various clinical conditions: implication for the use of this test in the diagnostic approach of venous thromboembolism. *Thromb Res* 1993;69(1):125–30.
- [90] Dempfle CE, Zips S, Ergul H, et al. The Fibrin Assay Comparison Trial (FACT): evaluation of 23 quantitative D-dimer assays as basis for the development of D-dimer calibrators. FACT Study Group. *Thromb Haemost* 2001;85(4):671–8.
- [91] Ginsberg JS, Brill-Edwards PA, Demers C, et al. D-dimer in patients with clinically suspected pulmonary embolism. *Chest* 1993;104(6):1679–84.
- [92] Bounameaux H, Cirafici P, de Moerloose P, et al. Measurement of D-dimer in plasma as diagnostic aid in suspected pulmonary embolism. *Lancet* 1991;337(8735):196–200.
- [93] Wells PS, Anderson DR, Bormanis J, et al. Application of a diagnostic clinical model for the management of hospitalized patients with suspected deep-vein thrombosis. *Thromb Haemost* 1999;81(4):493–7.
- [94] Crowther MA, Cook DJ, Griffith LE, et al. Neither baseline tests of molecular hypercoagulability nor D-dimer levels predict deep venous thrombosis in critically ill medical-surgical patients. *Intensive Care Med* 2005;31(1):48–55.
- [95] Kollef MH, Zahid M, Eisenberg PR. Predictive value of a rapid semiquantitative D-dimer assay in critically ill patients with suspected venous thromboembolic disease. *Crit Care Med* 2000;28(2):414–20.
- [96] Kollef MH, Eisenberg PR, Shannon W. A rapid assay for the detection of circulating D-dimer is associated with clinical outcomes among critically ill patients. *Crit Care Med* 1998;26(6):1054–60.
- [97] Shorr AF, Thomas SJ, Alkins SA, et al. D-dimer correlates with proinflammatory cytokine levels and outcomes in critically ill patients. *Chest* 2002;121(4):1262–8.
- [98] Marik PE. Fever in the ICU. *Chest* 2000;117(3):855–69.
- [99] Aronson MD, Bor DH. Blood cultures. *Ann Intern Med* 1987;106(2):246–53.
- [100] Ibrahim EH, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000;118(1):146–55.

- [101] Grace CJ, Lieberman J, Pierce K, et al. Usefulness of blood culture for hospitalized patients who are receiving antibiotic therapy. *Clin Infect Dis* 2001;32(11):1651–5.
- [102] Pazin GJ, Saul S, Thompson ME. Blood culture positivity: suppression by outpatient antibiotic therapy in patients with bacterial endocarditis. *Arch Intern Med* 1982;142(2):263–8.
- [103] Tabriz MS, Riederer K, Baran J Jr, et al. Repeating blood cultures during hospital stay: practice pattern at a teaching hospital and a proposal for guidelines. *Clin Microbiol Infect* 2004;10(7):624–7.
- [104] Bates DW, Goldman L, Lee TH. Contaminant blood cultures and resource utilization. The true consequences of false-positive results. *JAMA* 1991;265(3):365–9.
- [105] O'Grady NP, Barie PS, Bartlett J, et al. Practice parameters for evaluating new fever in critically ill adult patients. Task Force of the American College of Critical Care Medicine of the Society of Critical Care Medicine in collaboration with the Infectious Disease Society of America. *Crit Care Med* 1998;26(2):392–408.
- [106] Smith-Elekes S, Weinstein MP. Blood cultures. *Infect Dis Clin North Am* 1993;7(2):221–34.
- [107] Levin PD, Hersch M, Rudensky B, et al. Routine surveillance blood cultures: their place in the management of critically ill patients. *J Infect* 1997;35(2):125–8.
- [108] Salem M, Chernow B, Burke R, et al. Bedside diagnostic blood testing. Its accuracy, rapidity, and utility in blood conservation. *JAMA* 1991;266(3):382–9.
- [109] Woo J, Henry JB. The advance of technology as a prelude to the laboratory of the twenty-first century. *Clin Lab Med* 1994;14(3):459–71.
- [110] Harvey MA. Point of care laboratory testing in critical care. *Am J Crit Care* 1999;8(2):72–83.
- [111] Dungan K, Chapman J, Braithwaite SS, et al. Glucose measurement: confounding issues in setting targets for inpatient management. *Diabetes Care* 2007;30(2):403–9.
- [112] Callaham M, Barton C. Prediction of outcome of cardiopulmonary resuscitation from end-tidal carbon dioxide concentration. *Crit Care Med* 1990;18(4):358–62.
- [113] Uehling M. Under the skin: sorting through the hype and hope for noninvasive POC devices. *CAP Today* 2000;14(7):52–68.
- [114] Rubaltelli FF, Gourley GR, Loskamp N, et al. Transcutaneous bilirubin measurement: a multicenter evaluation of a new device. *Pediatrics* 2001;107(6):1264–71.
- [115] Bissell M. Point of care testing at the millennium. *Crit Care Nurs Q* 2001;24(1):39–43.
- [116] Weiss IK, Fink S, Harrison R, et al. Clinical use of continuous arterial blood gas monitoring in the pediatric intensive care unit. *Pediatrics* 1999;103(2):440–5.
- [117] Zollinger A, Spahn DR, Singer T, et al. Accuracy and clinical performance of a continuous intra-arterial blood-gas monitoring system during thoracoscopic surgery. *Br J Anaesth* 1997;79(1):47–52.
- [118] Haller M, Kilger E, Briegel J, et al. Continuous intra-arterial blood gas and pH monitoring in critically ill patients with severe respiratory failure: a prospective, criterion standard study. *Crit Care Med* 1994;22(4):580–7.
- [119] Widness JA, Kulhavy JC, Johnson KJ, et al. Clinical performance of an in-line point-of-care monitor in neonates. *Pediatrics* 2000;106(3):497–504.
- [120] Inomata S, Nishikawa T, Taguchi M. Continuous monitoring of mixed venous oxygen saturation for detecting alterations in cardiac output after discontinuation of cardiopulmonary bypass. *Br J Anaesth* 1994;72(1):11–6.
- [121] Roupie EE. Continuous assessment of arterial blood gases. *Crit Care* 1997;1(1):11–4.

Endocrine Assessments During Critical Illness

Olga V. Sakharova, MD^{a,b}, Silvio E. Inzucchi, MD^{a,c,*}

^a*Yale University School of Medicine, Department of Internal Medicine,*

Section of Endocrinology, 333 Cedar Street, New Haven, CT 06520-8020, USA

^b*Hospital of Saint Raphael, 1450 Chapel Street, New Haven, CT 06511-4440, USA*

^c*Yale-New Haven Hospital, 20 York Street, New Haven, CT 06510-3202, USA*

Hormonal aberrations in the critically ill present unique challenges to the care of patients in the ICU. This article reviews proper assessment of the effects of severe illness on glucose homeostasis and adrenal and thyroid function.

Assessment of glycemic status

Stress-induced hyperglycemia, defined as a transient increase in blood glucose concentrations during acute physiological illness, is common among critical care patients, frequently even those without a prior history of diabetes [1]. Critical illness is associated with the number of alterations in carbohydrate metabolism, including: dramatic increases in glucose counter-regulatory hormones and various cytokines; an accelerated catabolic state (increased lipolysis, increased proteolysis, increased glycolysis); enhanced hepatic glucose production; and impaired insulin-mediated glucose uptake by skeletal muscles [2].

The ongoing increase in glucose production by the liver, together with decreased peripheral glucose use, is considered the major mechanism of stress hyperglycemia. Additional factors contributing to hyperglycemia in the ICU includes treatment with corticosteroids, vasopressors, provision of enteral or parenteral nutrition, or large amounts of dextrose-containing infusions, and bed rest itself [3]. As a result, critical illness significantly increases insulin requirements, leading to greater demands upon the pancreatic β cell. The glucose level is in some way the reflection of the battle

* Corresponding author. Yale University School of Medicine, Section of Endocrinology, 333 Cedar Street, New Haven, CT 06520-8020, USA.

E-mail address: silvio.inzucchi@yale.edu (S.E. Inzucchi).

between the counter-regulatory hormones and underlying β -cell reserve. Critical illness therefore can be considered a significant stress for the β cells, the function of which needs to be augmented substantially to maintain euglycemia. Although a correlation exists between the severity of critical illness and the levels of counter-regulatory hormones, not all patients in the ICU develop hyperglycemia [4–6]. Relative insulin deficiency is required for stress hyperglycemia to develop. Hypoinsulinemia might result from several independent mechanisms, such as the blunting of insulin secretion by means of glucose toxicity, various drugs, the unmasking of pre-existing pancreatic β -cell dysfunction during stress, or the direct effects of an inflammatory milieu on islet function [1,2].

For years, stress hyperglycemia was viewed as an adaptive response to ensure adequate fuel delivery to noninsulin-dependent tissues or was considered merely a marker of severity of the disease. As a result, until recently, glycemic control in hospitalized patients had not been a major therapeutic focus. A growing body of evidence, however, demonstrates that tight glycemic control actually may improve clinical outcomes among certain patient populations, with the strongest evidence for those in the ICU [7–12], particularly in those remaining in the surgical or medical ICU for at least 3 days [9,12]. Importantly, the benefits of aggressive glucose management in these studies were not confined to patients with diabetes. Aggressive control of blood glucose in the critical care setting has, as a result, become widely accepted and is now emerging as a standard used to measure the quality of ICU care. In 2004, the American College of Endocrinology recommended in its Position Statement on Inpatient Diabetic and Metabolic Control a target blood glucose of less than 110 mg/dL in the ICU [13]. Currently, the American Diabetes Association recommends a similar target, “as close to 110 mg/dL as possible,” and “generally less than 180 mg/dL” for critically ill patients [13]. This area is not without controversy, especially, regarding the specific threshold and which patient types benefit most [14].

The major concern in regard to aggressive glucose management in the ICU remains the risk of hypoglycemia. In the only randomized controlled trials of tight glycemic control in this setting, hypoglycemia, defined as a blood glucose less than 40 mg/dL, was substantially more common in the intensively treated group than in the group receiving conventional treatment. This was substantially more common in medical (18.7% versus 3.1%) than in surgical (5.2 % versus 0.7%) patients [9,12]. Obviously, if a higher threshold to define hypoglycemia was employed, its frequency would be significantly higher. Although in these studies, hypoglycemia was not associated with hemodynamic compromise or seizures, its consequences for neurocognitive functioning and clinical outcomes in critically ill patients remain unknown. Additionally, in the medical ICU trial, hypoglycemia was an independent predictor of the risk of death [12].

The diagnosis of hypoglycemia in the ICU setting is based necessarily on glucose measurements because of patients’ often altered mental status. In

the obtunded or sedated patient in the ICU, the usual adrenergic or neuroglycopenic symptoms of hypoglycemia may be missing. Safe implementation of aggressive glucose management depends on both the safety of the insulin infusion algorithm being employed and the frequency and accuracy of glucose monitoring.

Continuous intravenous infusion is the preferred way of administering insulin in the critical care setting. Because of its short-half life (several minutes) when administered intravenously, the insulin infusion rate can be adjusted frequently, usually hourly. This indeed is required given the fluctuating severity of illness, alterations in medications that affect glucose levels, changes in nutritional delivery, and the requirement for off-unit tests and procedures. Optimally, a nurse-driven standardized algorithm for insulin infusion should be implemented [15]. Various insulin infusion protocols have been suggested in the literature [16,17]. The most efficient protocols take into consideration not only the current blood glucose level, but also the insulin infusion rate and the velocity of the glycemic change [18]. Insulin infusion therapy necessitates frequent monitoring to achieve and maintain blood glucose within the target range and prevent hypoglycemia. Thus, together with implementation of continuous insulin infusion protocols, fastidious glucose monitoring is becoming a cornerstone of ICU management. Of note, exact thresholds for the initiation of insulin infusion and exact glycemic targets remain hotly debated [19].

Glycemic monitoring in hospitals generally involves point-of-care glucose testing of capillary blood glucose concentrations with portable meters [20–22]. With the widespread availability of these devices, routine laboratory glucose testing, which has its requisite delays, is not used for insulin infusion adjustments. The frequency of glucose measurement is dictated by the particular insulin infusion protocol used and the blood glucose level, and usually varies from every 1 hour to every 4 hours. Meters provide data quickly, often in less than 20 seconds. The result should be documented on the critical care flow sheet or within the electronic medical records, so that trends can be analyzed and acted upon. Many portable meters have download capabilities that facilitate the display of glucose values and trends, limit operator errors while transcribing the data, and minimize nursing workload. Creation of the interface between the particular portable glucose meter and a hospital's information system is extremely helpful. Ideally, wireless downloading of data should be the ultimate goal of glucose documentation in the hospital, especially the ICU.

Technical aspects

Point-of-care meter accuracy

Important technological advances have resulted in improved clinical accuracy and superior performance of the latest portable meters [22]. Recent studies report 91% to 100% accuracy of various point-of-care glucose

testing devices in hospitalized patients [23]. It is important to realize, however, that some error is allowed when accuracy of these devices is tested [20]. For example, the National Committee for Clinical Laboratory Standards recommends the difference between a glucose meter and a conventional laboratory not to exceed plus or minus 15% for glucose concentration less than 100 mg/dL and plus or minus 20% for glucose concentrations greater than 100 mg/dL [20]. Although not typically considered, such errors may be significant when trying to establish tight glycemic control in the ICU. Because of the limitation in accuracy of all current point-of-care glucose devices, it is imperative, that in any circumstance when there is a discrepancy between the measured glucose level and a patient's clinical condition, that the glucose concentration be confirmed by central laboratory measurement. Because of these inherent inaccuracies in currently employed glucose monitoring techniques, the authors feel that the lower target for blood glucose control should be 90 mg/dL or higher. In this case, even a 20% error will result in a glucose concentration that is maintained above 70 mg/dL, at which point the counter-regulatory adrenergic response begins.

Sample source and type

The actual concentration of glucose (amount of glucose per volume of specimen) differs significantly between plasma and whole blood, because glucose dissolves in the aqueous but not the solid components of the specimen [24]. When specimens of similar volumes are compared, the glucose concentration will be higher where the water concentration is higher. As plasma has higher water concentration than whole blood (which includes cellular elements), the actual concentration of glucose in plasma is significantly higher than for whole blood. Glucose also traverses the erythrocyte membrane; its dissolution in water is identical inside and outside the red cell. The amount of water within the red cell inversely depends on the protein concentration (mainly hemoglobin). Therefore, a higher hemoglobin concentration results in a lower red blood cell glucose concentration. As whole blood glucose is the sum of the plasma glucose concentration and the red blood cell concentration, the higher hemoglobin results in a lower blood glucose concentration. When using a bedside glucose meter, which measures whole blood (but reports a plasma value), the measured reading can be adjusted for the hematocrit with the formula, $\text{glucose} \times [1.0 - (0.0024 \times \% \text{ hematocrit})]$ [25]. This rarely is done in the busy ICU setting. Thus, the patient's hematocrit can influence the results of glucose measurement significantly when whole blood is used.

On the contrary, the measurement of glucose in plasma is independent of red cell mass and hematocrit values, thus rendering it the preferred blood fluid for this purpose. Measurement of glucose in serum is not recommended because its concentration decreases by approximately 0.6 mmol/L/h as a result of glycolysis during collection and processing [24]. Plasma glucose concentration is approximately 11% higher than that in whole blood. The

International Federation of Clinical Chemistry and Laboratory Medicine recommends using a constant factor of 1.11 to convert concentration in whole blood to the equivalent concentration in plasma [26]. Importantly, this conversion factor is most reliable with a hematocrit of 45%. Most bedside/home glucose meters actually convert their whole blood glucose results to the higher plasma equivalents, adjusting upwards by 10% to 15% depending on the meter. It is important that ICU providers know whether their hospital's device reports true whole blood glucose or converts it to plasma glucose. Also, individual institutions should specify blood glucose targets based on the local methodology of glucose testing.

The International Federation also recommends reporting glucose concentrations as the plasma equivalent, irrespective of sample type or measurement technique [26]. Such uniform conversion will provide harmonization of the results, facilitate the classification and care of patients, and lead to fewer therapeutic errors. Unfortunately, currently, plasma glucose and blood glucose are used interchangeably in the literature, contributing to significant risk of a misinterpretation. One example of such misinterpretation was revealed recently by Dunagn and colleagues [27]. In the Belgium studies mentioned previously, the researchers were using the HemoCue B glucose analyzer that measures and reports whole blood glucose. Their proposed glycemic target of 80 to 110 mg/dL refers to whole blood glucose [9,12]. Once converted to the plasma glucose testing (used by most glucose meters), the results are 90 to 120 mg/dL. Although the difference seems to be minimal, it might become more clinically significant in the near-hypoglycemic range.

In the ICU, arterial access is frequently available, and an arterial blood sample can be used for glucose measurement with point-of-care devices [28]. Although it is a reasonable alternative to capillary or venous blood testing in critically ill patients, it should be recognized that, because of glucose extraction by tissues, glucose measured from arterial blood is generally higher than from other sources. This is especially true in the postprandial state, which is usually not applicable to most critical care patients. Studies have demonstrated differences of up to 30 mg/dL, although usually the discrepancies are smaller [29–31]. Therefore, if arterial blood is used for glucose monitoring, the target should be kept at a higher range for safety purposes.

Patient and disease variables

Bedside glucometry is an accepted method for estimating blood glucose levels in the ambulatory and hospital ward settings. Among critically ill patients, however, such measurements have not been validated fully. The effects of various critical care variables on glucose meter performance have been reviewed recently (Fig. 1) [27]. These variations include hypotension, alterations in hematocrit, oxygenation or pH, and interference from various medications. In general, fingerstick glucose testing may not correlate accurately with venous plasma glucose in patients who have

Variable	Methodology affected*	
	GO	GD
Whole blood	↓	↓
Arterial		↑
Capillary	↑	↑
Postprandial state		↑
Hematocrit		
Anemia		↑
Polycythemia	↓	
Oxygen concentration		
Hypoxia	↑	—
Oxygen therapy	↓	—
pH	—	—
Low pH (<6.8)	—/	—
High pH (>7.55)	—/↑	—
Hypothermia		/
Hypotension		↓
Drugs		
Ascorbic acid	↓	↑/—
Acetaminophen		
Dopamine	—	↓
Icodextrin	—	
Mannitol		—

Fig. 1. Confounding variables of glucose measurements in critically ill patients. *Change relative to venous plasma measured at central laboratory. Abbreviations: GD, glucose-1-dehydrogenase method; GO, glucose oxidase method. (Data from Dungan K, Chapman J, Braithwaite SS, et al. Glucose measurement: confounding issues in setting targets for inpatient management. Diabetes Care 2007;30(2):403–9.)

hypoperfusion. As a result, clinical management errors can be made [30,32,33]. Studies that have compared the two modalities are inconsistent in their findings, with evidence for both lower and higher capillary readings in hypoperfused patients, as compared with measurement in venous

plasma. Using venous blood (from phlebotomy or indwelling central line) with the bedside meter, however, appears to minimize any differences and is the preferred method in hypotensive patients [32,33]. Both anemia and polycythemia may influence the results of glucose measurement on whole blood, with, as previously mentioned, increases in hematocrit decreasing glucose measurements and vice versa [23,34]. Thus, most point-of-care devices can overestimate glucose and miss hypoglycemia in patients who have anemia.

Oxygenation generally has a negligible effect on glucose values measured by bedside devices [32]. Very high oxygen tension (used for patients on oxygen therapy and/or patients undergoing cardiopulmonary bypass) can lower glucose readings falsely, but the elevation appears to be significant only when the PO_2 is greater than 100 mm Hg and when arterial blood is used [27]. Similarly, although marked fluctuations in pH (pH <6.95 and >7.85) can affect the performance of meters, this has not been shown to be a source of major error at the more common pH ranges [27].

Unfortunately, in the critical care setting, several variables can be present simultaneously, further contributing to erroneous glucose measures. Although on average, glucose testing by point-of-care devices provides reasonable estimates for plasma glucose, for an individual patient, occasional readings may be unreliable [23,35]. When there is any discrepancy between the clinical condition and results of glucose monitoring with point-of-care meters, the venous blood sample should be sent to the central laboratory for confirmation.

Operator error

Bedside glucose measurements usually are performed by the nurses or other trained personnel. The caregiver must locate a glucose meter, perform a fingerstick, document the results, and make the necessary insulin drip adjustments; the process can easily take up to 5 minutes per hour. Operator error resulting from improper application and timing has been minimized by advances in technology [20]. Proper use of point-of-care glucose testing, however, requires consistent training, well-defined policies and procedures and regularly scheduled equipment testing and maintenance.

Continuous interstitial glucose monitoring

Continuous glucose monitoring systems are approved for the outpatient setting in patients with diabetes. Such systems can be used for up to 72 hours. The sensor component consists of a flexible electrode residing inside a permeable membrane, and it is inserted into the subcutaneous tissues of the abdomen or limbs. Interstitial glucose is measured by the glucose-oxidase method, and every 10 seconds a glucose measurement is sent to a monitor that records and may display an average glucose value every 5 minutes. Periodic calibration is required. The data subsequently can

be downloaded using special software. Current literature on the use of continuous monitoring in the ICU setting is limited. One study examined the accuracy of the Continuous Glucose Monitoring System (CGMS; Medtronic, Minneapolis, Minnesota) among critical care patients admitted to a medical ICU [36]. Reasonable accuracy was demonstrated; Pearson correlation coefficient was 0.88 as compared with capillary blood glucose testing, with 98.7% of glucose matches being clinically acceptable according to Clarke Error Grid analysis). Only a few glucose readings in this study were in the hypoglycemic range, however. Similar promising results for CGMS were reported recently for 424 blood samples from 45 ICU patients (Pearson correlation coefficient, 0.89; 100% clinically acceptable by Clarke Error Grid analysis) [31]. Although good accuracy was demonstrated for the euglycemia range, with hypoglycemia, CGMS was less accurate (62.8% of matches being clinically acceptable) [37]. If validated in larger studies, these devices may play a role as real-time glucose sensors for managing patients in the ICU. Until then, at the very least, they are of significant interest for purposes of clinical investigation.

Summary

Aggressive glucose management strategies in the critical care setting require implementation of rapid, reliable, and accurate glucose monitoring. The currently available techniques, which mainly involve periodic assessment of capillary, venous, or arterial blood samples, are somewhat limited. An understanding of the variables that might affect glucose measurements in the ICU will facilitate safe and appropriate glycemic control in critically ill patients. In the future, noninvasive continuous glucose monitoring may play a larger role in care practices.

Assessment of adrenal status

Critical illness is associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis [38]. The stress stimulus leads the hypothalamus to release corticotropin-releasing hormone (CRH), which acts on the pituitary to increase adrenocorticotrophic hormone (ACTH) production, which, in turn, stimulates the adrenal cortex to dramatically increase secretion of glucocorticoids. In general, the degree of activation of the HPA axis is proportionate to the severity of illness. This rise in cortisol concentration results in multiple downstream effects, of which preserving vascular reactivity and modulation of the immune response are pivotal for maintaining homeostasis during acute illness. Many factors, however, can impair the integrity of the HPA axis and blunt normal corticosteroid response leading to either transient or, rarely, permanent adrenal insufficiency in critically ill patients [39].

Symptoms, physical signs, and laboratory findings suggesting corticosteroid insufficiency have been reviewed elsewhere [39–41]. Although certain clinical features are helpful in making the diagnosis of adrenal insufficiency, very often these are nonspecific and particularly difficult to identify in the ICU setting. Because this is a potentially lethal condition, the threshold for laboratory evaluation of adrenal insufficiency should be low in any critically ill patient. Adrenal insufficiency should be suspected in any critically ill patient who has persistent hypotension and hemodynamic instability that persists despite adequate fluid resuscitation, abdominal pain with no obvious source, multiple organ dysfunction, and otherwise unexplained hypoglycemia, hyponatremia, or hyperkalemia [39].

Recently, much attention had been focused on so-called relative or functional adrenal insufficiency of critical illness, a condition defined as subnormal adrenal corticosteroid production in the absence of any structural defects of the HPA axis [38,39,42,43]. The explanation for the development of this condition is hypothetical exhaustion of the secretory adrenocortical reserve as a result of ongoing near-maximal stimulation. Other contributing factors may include the suppression of cortisol and ACTH production by circulating cytokines and other inflammatory mediators, as well as the development of target tissue resistance to glucocorticoids and/or adrenal cortex resistance to ACTH action [39]. The biochemical definition and clinical significance of this condition are neither widely accepted nor well understood. Notably, the benefits of early identification of patients with relative adrenal insufficiency and use of corticosteroid replacement has been demonstrated only in patients who had severe septic shock [44,45]. Although physiologic corticosteroid replacement might be beneficial in patients who have other critical illnesses in which there is evidence of relative hypoadrenalism, no data from large randomized studies are available [46–48]. This article therefore discusses the diagnosis of relative adrenal insufficiency only in relation to patients who have sepsis.

Diagnosis of hypoadrenalism

Laboratory investigation of adrenal insufficiency in the critically ill patient is challenging and controversial. Theoretically, obtaining a single measurement of a random serum cortisol concentration in the ICU should suffice to assess adrenal function and at least rule out a diagnosis of adrenal insufficiency. Stress from critical illness typically maximizes endogenous steroid output and, in and of itself, should suffice as a dynamic test to assess the integrity of the entire HPA axis. Normal values for the cortisol response during acute illness, however, have not been formally defined. Instead, many thresholds below which adrenal insufficiency is likely to be present have been suggested, ranging widely from 10 to 34 $\mu\text{g/dL}$ [38,39]. Indeed, it probably varies to some degree according to the underlying disease and severity of the condition. Because of these inconsistencies in defining

cutpoints for adequate random cortisol levels, the high-dose (250 µg) cosyntropin stimulation test (CST) was recommended as the first-line test used to evaluate adrenal cortical reserve in the ICU. It should be noted that the CST only evaluates the ability of the adrenal cortex to respond to (synthetic) ACTH, but not the integrity of the entire HPA axis. As a result, it may not be able to diagnose secondary adrenal insufficiency properly, particularly when long-standing. Although no cutpoint value has been defined rigorously as an appropriate response, a total cortisol level at 30 minutes poststimulation in excess of 20–25 µg/dL was considered adequate by many authorities to rule out the diagnosis of adrenal insufficiency [38,39]. Recently, the use of the increment rise above baseline in serum total cortisol levels (eg, >9 µg/dL) had been used to define adrenal dysfunction in patients who had septic shock, and this will be addressed below [44,49]. It is not known whether this definition is true for other forms of critical illnesses.

The best test of the entire HPA axis remains the insulin tolerance test to induce hypoglycemia. This is impractical and dangerous in critically ill patients, however, and should not be performed. The metyrapone test is similarly inappropriate in this setting. The low-dose (1 µg) CST has been proposed as a more sensitive test to evaluate patients for secondary adrenal failure, but there is little experience with this in the ICU.

Recently, much attention had been focused on the limitations of using total cortisol (protein-bound plus free fractions) instead of free cortisol to assess adrenal function in patients who are critically ill [50–54]. It is known that correct interpretation of the absolute level of any hormone is difficult without knowing the concentration of binding proteins. Their increase or decrease significantly affects measurement of total without any alteration in free hormone concentrations. Approximately 10% of cortisol is present free in the plasma, unbound to proteins. Of the remainder, 20% is bound loosely to albumin, and 70% is tightly bound to cortisol-binding globulin (CBG). In most circumstances, as long as these ratios are not perturbed, use of total cortisol (which is easier to measure) is acceptable. Critical illness, however, is known to be associated with both hypoalbuminemia and significant decreases in CBG concentrations [55,56]. Recent studies conducted on critically ill patients demonstrated significant discrepancy between total and free cortisol concentrations [51,52]. In one investigation, critically ill patients with hypoalbuminemia (<2.5 g/dL) had a baseline total cortisol level significantly lower than those with near-normal albumin concentrations (15.8 ± 7.4 versus 22.6 ± 8.9 µg/dL) [51]. Similarly, ACTH-stimulated cortisol levels were lower in critically ill patients with hypoalbuminemia (23.4 ± 9.5 versus 34.4 ± 10.3 µg/dL). In fact, 40% of hypoproteinemic critically ill subjects had a stimulated total cortisol level of less than 18.5 µg/dL in this study [38]. In contrast, all critically ill patients with near-normal serum protein concentrations had a stimulated total cortisol level above 20 µg/dL. In spite of these apparent problems with the measurement of total cortisol, however, the baseline and stimulated free cortisol levels were elevated

significantly and indistinguishable between the two groups. The limitation of using the total serum cortisol measurements and the importance of knowing the serum albumin concentration when interpreting total cortisol levels also has been demonstrated by others [52,57]. Other investigators demonstrated that the use of the increment in cortisol during CST might be preferred to absolute total levels while assessing adrenal function in hypoproteinemic patients, as it was not affected substantially by serum albumin [57].

In one investigation, baseline free cortisol concentration among all critically ill patients exceeded ACTH-stimulated concentrations in normal, unstressed subjects ($> 1.8 \mu\text{g/dL}$) by a factor of seven- to tenfold, while total cortisol was increased by only a factor of two to three [51]. Therefore, the random free cortisol level of $1.8 \mu\text{g/dL}$ has been suggested as a threshold to identify patients at risk for adrenal insufficiency during critical illness [38,58]. Based on this same study, the threshold for free cortisol level during CST was suggested to be $3.1 \mu\text{g/dL}$. These cutpoints have not been validated by other groups [54].

The use of a calculated free cortisol or a free cortisol index defined as the ratio of serum total cortisol (nmol/L ; $1 \mu\text{g/dL} = 27.59 \text{ nmol/L}$) over the serum CBG concentration (mg/L) has been suggested as an alternative to measuring free cortisol, which is not widely available in most hospitals [50,56,59,60]. In the postoperative setting, 23% of patients have been found to have low total cortisol (in this study, defined as $< 25 \mu\text{g/dL}$), most of whom had low CBG concentrations [50]. When the free cortisol index was used, however, there were no difference between the groups. Similarly, another method of calculation of free cortisol index (Coolens' equation) demonstrated good correlation between the measured and calculated serum cortisol in patients who had septic shock [50]. These methods, however, require the measurement of CBG and do not take into consideration any effects of hypoalbuminemia. Additionally, the threshold values will require more extensive validation in various critical care settings before this calculated method can be used.

Other promising approaches to evaluating the HPA axis in the critically ill care setting include the measurement of salivary cortisol and other ACTH-dependent adrenal steroids such as DHEA and DHEAS [38]. These data are too preliminary to consider using these tests in the clinical setting.

Patients with septic shock

The evaluation of HPA axis and current recommendations for the use of steroids in patients who have sepsis deserves separate discussion. The initial interest in the use of glucocorticoids in this setting evolved from their potential beneficial anti-inflammatory action. The short-term use of glucocorticoids at supraphysiological doses, however, had no favorable effects on morbidity and mortality in unselected patients with sepsis [61]. More recently, the use of low-dose corticosteroids (terminology that is inaccurate,

as such doses conventionally are used in the treatment of acute adrenal crisis) in patients who have established septic shock in the ICU has been associated with substantial benefits [44]. The definition of relative or functional adrenal insufficiency in this population is based on the results of high-dose CST that takes into account not an absolute cortisol level but the incremental rise in cortisol in excess of 9 $\mu\text{g/dL}$. This definition was proposed by Annane and colleagues [49], who initially tested high dose CST as a prognostic factor in patients with septic shock. Those with a blunted cortisol response had a higher risk of death independent of their baseline cortisol level. The best clinical outcomes (28-day mortality rate 26%) were observed in patients who had baseline cortisol levels less than 34 $\mu\text{g/dL}$ and the cortisol response to high dose CST of greater than 9 $\mu\text{g/dL}$, suggesting adequate adrenal reserve and response to stress during critical illness. Importantly, patients with a high baseline cortisol ($> 34 \mu\text{g/dL}$) but with a blunted response to CST ($\leq 9 \mu\text{g/dL}$) had the worst prognosis (28-day mortality rate 82%) [49].

Subsequently, these collaborators demonstrated that the use of hydrocortisone (50 mg intravenously every 6 hours) and fludrocortisone (50 μg by mouth daily) for 7 days in 300 patients who had septic shock significantly reduced mortality and duration of vasopressor therapy [44]. Importantly, approximately two thirds of patients were found to have inadequate adrenal response, and the benefits of corticosteroid replacement were restricted primarily to these nonresponders. In this subgroup analysis, 28-day mortality was significantly less among those who received steroids (53%) compared with placebo (63%; $P = .02$). No such difference, however, was evident in patients who had adequate adrenal reserve. Moreover, there was a nonsignificant trend to higher mortality among responders who were treated with steroids (61%) compared with placebo (53%, $=.96$), suggesting that steroid therapy might be detrimental in patients with septic shock whose cosyntropin response appeared normal. Several additional studies have demonstrated beneficial clinical effects on shock reversal, suggesting that steroids restore hemodynamic responsiveness to adrenergic stimuli [62–64].

These results have been influential and have led to a change in clinical practice. Presently, the Surviving Sepsis guidelines endorse the use of corticosteroids (200 mg of hydrocortisone per day in divided doses) in patients who have refractory septic shock [65]. Although a reasonable recommendation, the authors would point out that this essentially is based on a single study from a single center that has not been confirmed adequately [45]. Until additional placebo-controlled studies confirm the benefits of steroids in patients who have sepsis in the absence of shock, the treatment should be limited only to patients who resemble those studied by Annane: nonresponders with severe septic shock on mechanical ventilation who have hypotension unresponsive to fluids and pressors and evidence of other organ dysfunctions (Box 1).

Box 1. Recommendations for the evaluation and management of adrenal insufficiency in patients with septic shock*Testing*

Perform a screening high-dose CST upon admission to ICU.

Obtain baseline serum cortisol level.

Intravenous bolus of 250 µg cosyntropin.

Repeat serum cortisol after 30 minutes.

Treatment

Immediately initiate corticosteroid replacement (hydrocortisone 100 mg intravenously every 6 hours) while waiting for the results of CST.

Discontinue treatment if maximum stimulated cortisol is greater than 20 µg/dL and the incremental cortisol response is greater than 9 µg/dL at 30 minutes^a.

Continue treatment if maximum cortisol is greater than 20 µg/dL or if the incremental cortisol response is less than 9 µg/dL^a.

Because hydrocortisone has intrinsic mineralocorticoid activity, and because patients who have septic shock often are treated aggressively with intravenous crystalloid solutions, it is not clear if fludrocortisone is necessary^b.

Further evaluation

In patients who have profoundly abnormal CST results, frank adrenal failure should be investigated further by measuring ACTH levels (cannot be done after cosyntropin injection), plasma renin activity, and consideration of adrenal and/or pituitary imaging, based on the clinical picture.

Duration

Treatment should be considered for 7 days. A fixed duration protocol has been used in some studies, while in others, therapy was tapered gradually after clinical improvement. The authors recommend tapering steroid doses after shock resolution by approximately 25% per day.

Follow-up

Despite the often transient nature of relative adrenal insufficiency in patients who have septic shock, the authors feel that all patients who have this diagnosis deserve retesting upon recovery to exclude permanent adrenal insufficiency.

^a Some authorities advised the discontinuation of therapy if stressed cortisol exceeds 34 µg/dL independent of incremental cortisol response.

^b The original Ananье et al study [44] used 50 µg/d.

Recommendations

It is the authors' belief that once fully standardized and widely used, the measurement of free cortisol will become the gold standard for evaluating of the HPA axis during critical illness. Free cortisol measurements will shed light on the exact adaptation mechanisms and most likely change the current understanding of HPA adaptation during severe stress. Until this occurs, the use of serum total cortisol is the only acceptable surrogate. When using the total cortisol level, however, one should take into account the prevailing albumin concentration [38,47]. Because of inconsistencies in random cortisol levels, the authors still recommend full-dose CST as a first-line evaluation, with interpretation of the absolute stimulated cortisol level. The use of the cortisol increment should be limited to assessing patients who have septic shock for reasons already discussed. Albumin concentrations of 2.5 mg/dL or less appear to influence measured total cortisol [51,57]. In critically ill patients who have an albumin level of more than 2.5 gm/dL, the stimulated total cortisol level above 20 µg/dL should rule out the diagnosis of adrenal insufficiency adequately (Table 1). In critically patients who have an albumin level less than 2.5 µg/dL, the suggested threshold for total cortisol in CST is 15 µg/dL [51,57]. These recommendations are likely to be refined in the future as more data emerge. It should be pointed out that alteration in the HPA axis during critical illness is a dynamic process, and the reassessment of adrenal status may need to be considered as the clinical scenario evolves.

Summary

Evaluating adrenal function in the critically ill can be very challenging, and there is little agreement at this time on the ideal test. Moreover, what signifies a normal from an abnormal adrenal response in this setting remains controversial. Practitioners therefore should incorporate the biochemical with the clinical assessment to optimize patient management.

Table 1
Diagnostic criteria for adrenal insufficiency in ICU

	Albumin >2.5 mg/dL	Albumin <2.5 g/dL
Total cortisol (µg/dL) ^a		
Baseline	<15	<10
Stimulated	<20	<15
Free cortisol (µg/dL)		
Baseline	<1.8	<1.8
Stimulated	<3.0	<3.0

^a 1 µg/dL of cortisol equals 27.59 nmol/L.
Adapted from Marik PE. The diagnosis of adrenal insufficiency in the critically ill patient: does it really matter? Crit Care 2006;10(6):176.

Assessment of thyroid function

Acute illness also often is associated with significant abnormalities in thyroid function tests (TFTs), often termed the euthyroid sick syndrome (ESS) or nonthyroidal illness (NTI) syndrome [66–68]. To correctly interpret TFT results in the patient in intensive care, the clinician should be familiar with the changes that occur in the regulation of the hypothalamic-pituitary-thyroid (HPT) axis and in thyroid hormone metabolism, and the effects of commonly used medications on thyroid physiology.

Measuring and assessing T4 and T3 levels

The initial and most common abnormality observed in any person who has significant acute illness is a fall in total T3 concentrations. Unlike T4, which is produced solely by the thyroid gland, most of the circulating pool of T3 is derived from peripheral conversion from T4, a reaction that is catalyzed by 5'-monodeiodinase (or type 1 deiodinase) located in the kidney, liver, and muscle. It is believed that this decline is caused by a block of extrathyroidal conversion caused by inhibition of this enzyme. High concentrations of glucocorticoids (from endogenous or exogenous sources) [69,70], free fatty acids [71], and medications, such as amiodarone [72], iodinated contrasts, and high-dose propranolol also have been shown to decrease type 1 deiodinase activity. Additionally, the block in T4 to T3 conversion occurs whenever caloric intake is reduced markedly, especially when manifested by carbohydrate restriction [73,74]. Notably, degradation of T4 still occurs through the conversion to reverse T3 (rT3), which has no known biological activity [75]. Degradation of rT3 also is reduced, resulting in significant accumulation of rT3 in patients who have nonthyroidal illnesses [76].

As the severity of illness progresses, a drop in total T4 concentrations also occurs, which, together with the change in T3, results in a low T3-T4 state. The initial decline is caused mainly by a reduction in the concentrations of serum thyroid hormone-binding proteins, among which thyroxine-binding globulin (TBG) predominates [77,78]. Total T4, however, is often low in critically ill patients, even when the TBG concentration is clearly normal [79]. Thus, other factors such as abnormal T4 binding caused by altered glycosylation of TBG and increased clearance of this protein may be contributing factors [80]. Additional influences may be the presence of circulating inhibitors of T4 binding. These include high concentrations of fatty acids often observed in the critically ill [81,82]. Many drugs (salicylates, phenytoin, carbamazepine, furosemide) may inhibit thyroid hormone binding to TBG competitively, resulting in an acute increase in free T4, with a subsequent physiological decrease in total T4 concentrations. Some drugs (including phenytoin, carbamazepine, rifampin, phenobarbital) also may contribute to low total T4 concentration by accelerating its clearance.

Importantly, despite the presence of low total T4 in these situations, serum concentrations of free T4, as measured by the gold standard equilibrium dialysis technique, typically remain in the normal range (or actually may be elevated) in most patients unless the illness is severe and protracted [83]. Unfortunately, however, all currently available free T4 assays lack accuracy when used in patients who have NTI [84]. The free hormone methods employed by most laboratories do not include physical separation of bound from free hormone. As a result, they do not measure free hormone concentrations directly, and they are thus prone to artifacts when used to assess patients with binding protein abnormalities [85]. In general, these assays overestimate free T4 levels at high protein concentrations and underestimate free T4 when protein concentrations are low. As a result, these analog methods widely used by many laboratories actually measure free T4 in the presence of binding proteins and frequently give falsely low results in the ICU patient [86].

The serum free T4 measurement by equilibrium dialysis is a more accurate approach but is technically demanding, time-consuming, and quite expensive. It actually uses a two-step approach to first physically separate free from protein-bound hormone through a dialysis membrane, and then measure the free concentration. Serum free T4 fraction measured by this method is usually normal or slightly high, but never low in patients who have nonthyroidal illness (unless there is verifiable, superimposed thyroid dysfunction) [67,87]. A high free T4 with this test is most likely caused by the factors that inhibit protein binding of T4 than to true hyperthyroidism. Another well-known in vitro artifact to falsely elevate free T4 results is the heparin effect [88]. Heparin induces lipase activity in the blood sample, resulting in nonesterified fatty acid generation from plasma triglycerides, which may displace T4 from binding sites on TBG. Computed estimates of free T4, such as the free T4 index (sometimes referred to as the calculated free T4 or the T7) generally perform well in the absence of significant alterations in binding proteins. At the very low range of TBG concentration, however, these methods fail to adequately correct for the binding protein deficiency and may give falsely low results [89]. Because of the wide range of assay artifacts concerning free T4 in the setting of acute illness, this test always must be analyzed in conjunction with measurement of thyroid stimulating hormone (TSH), which has its own caveats in the critically ill.

Measuring and assessing TSH levels

Another common alteration in thyroid metabolism is a decrease in the pituitary secretion of TSH that typically occurs in parallel with the decline in serum T4 concentrations [90]. The causes are multifactorial and attributed to effects of the illness per se, malnutrition, and the suppressive effects of cytokines [91] and medications such as corticosteroids [92] and dopamine [93]. Interestingly, decreased biological activity of TSH caused by

abnormalities in TSH glycosylation with subsequent diminished thyroidal response also has been described [94]. Of note, infusion of the hypothalamic peptide, thyrotropin-releasing hormone (TRH) is able to overcome this apparent block, resulting in an increase in serum TSH, T4, and T3 concentrations in the critically ill. This observation suggests a block at the level of the hypothalamus [95]. If the illness persists, reduced TSH secretion likely contributes to low total and eventually low free T4 concentrations. Clinically, low T3 and T4 levels, in association with normal, low-normal or decreased TSH suggest the development of a variant of central hypothyroidism [83]. Such changes may be a self-protective adaptation to illness, as the body attempts to conserve energy. This state is usually transient, resolving once the patient shows signs of improvement. The recovery of the thyroidal axis begins with a rise in serum TSH and is followed eventually by normalization in T4 concentrations [96]. Because of the difference in half-lives of T4 (days) and TSH (hours), the normalization of T4 lags behind the increase in TSH. As a result, the picture during the resolution of euthyroid sick syndrome may suggest primary hypothyroidism.

For the most accurate interpretation of TSH values among critically ill patients, a highly sensitive third-generation assay is required [97]. This method has a detection limit of 0.01 mU/L and is usually able to separate between the suppressed TSH values of hyperthyroidism from the low, but still detectable, values in NTI [98,99]. When hospitalized, nonhyperthyroid patients with TSH less than 0.1 mU/L on a second-generation assay were reassessed with the more sensitive TSH assay, 86% had low, but measurable TSH values [98]. In contrast, TSH was suppressed to less than 0.01 in 96% of hospitalized hyperthyroid patients. Thus, the use of a modern TSH assay among critically ill patients increases the number in whom overt hyperthyroidism can be excluded. Yet, any suppressed TSH results in an ICU patient are notable, and require careful clinical evaluation, including the interpretation of circulating thyroid hormone levels and knowledge of the recent medication history and current clinical status of the patient. Additionally, some hospitalized patients might have elevated TSH concentrations as observed during the recovery phase from nonthyroidal illness [96]. In most of these patients, TSH normalizes subsequently. Patients who have TSH concentrations greater than 20 mU/L usually have primary hypothyroidism. The timing and aggressiveness of thyroid hormone replacement therapy (ie, levothyroxine) should take into account the patient's underlying medical condition [100].

Recommendations

It remains controversial whether development of the aforementioned changes in thyroid metabolism reflect a protective mechanism or a maladaptive process during illness. Because the presence of euthyroid sick syndrome is associated with an increased mortality among critically ill patients [101,102], it could indicate an aberration that may delay recovery from

acute illness and therefore would require intervention [103,104]. To date, however, thyroid hormone therapy has not been demonstrated to improve clinical outcomes in critically ill patients. Therefore it is not recommended [105–108]. Indeed, generally speaking, TFTs should not be checked routinely in the intensive care setting unless there is a suspicion of thyroid dysfunction, based on past history or clinical evaluation. The goal of TFT measurement in the ICU mainly should be the identification of previously unrecognized thyroid dysfunction (hypothyroidism, hyperthyroidism) that would require therapeutic intervention. When such disease is suspected in critically ill patients, measurement of a complete thyroid panel (at a minimum to include free T4 and TSH) is required. Routine assessment of the more labile T3 is not advised.

If hypothyroidism is suspected clinically in an ICU patient (eg, hypothermia, bradycardia, respiratory acidosis, pleural effusions, failure to wean), a major dilemma arises when the evaluation suggests central hypothyroidism. It should be recalled, however, that such hormone levels are statistically much more likely to be indicative of euthyroid sick syndrome, whose prevalence is much higher than otherwise unrecognized pituitary or hypothalamic disease. This is particularly the case in the absence of any prior history of pituitary tumors or cranial irradiation. In difficult cases, assessment of other pituitary-related hormones (cortisol, prolactin) may elucidate the integrity of the hypothalamic-pituitary unit further. It should be noted, however, that the gonadal axis commonly also is suppressed during acute illness. As a result, assessment of the estradiol/testosterone levels and LH and FSH frequently will reveal a pattern that suggests central hypogonadism. Such testing is therefore rarely helpful. In certain circumstances, measuring free T4 by equilibrium dialysis is indicated to better elucidate actual thyroid function. Rarely, the measurement of serum concentrations of rT3 may assist in the diagnostic evaluation [109].

If hyperthyroidism is suspected (eg, tachyarrhythmias, widened pulse pressure, respiratory alkalosis, high-output heart failure), and a low TSH is measured, it remains unlikely that the patient has true hyperthyroidism, unless the TSH is suppressed fully on a third-generation assay, and the free T4 is elevated, or at least in the upper limits of the normal range. If the free T4 is low or low-normal, the patient is probably not hyperthyroid. Because of inaccuracy of all free T4 assays in this setting, however, repeating the free T4 by another method is advised before firmly establishing the diagnosis, especially if clinical suspicion persists.

Summary

The evaluation of thyroid function in critically ill patients is challenging and has many pitfalls. Normal reference ranges should be applied cautiously. Establishing thyroid dysfunction based on a single set of TFTs may be misleading. Careful clinical evaluation, knowledge of the hospital course,

and recent therapies are essential for the correct interpretation of such testing in this setting. Early pursuit of endocrine consultation may be helpful in difficult situations.

References

- [1] McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. *Crit Care Clin* 2001;17:107–24.
- [2] Mizock BA. Alterations in carbohydrate metabolism during stress: a review of the literature. *Am J Med* 1995;98:75–84.
- [3] Inzucchi SE GP, Dziura JD, Siegel M, et al. Risk factors for poor glycemic control in a medical intensive care unit [abstract]. *Diabetes Care* 2003;52:A96.
- [4] Lind L, Lithell H. Impaired glucose and lipid metabolism seen in intensive care patients is related to severity of illness and survival. *Clin Intensive Care* 1994;5:100–5.
- [5] Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc* 2003;78:1471–8.
- [6] Ligtenberg JJ, Meijering S, Stienstra Y, et al. Mean glucose level is not an independent risk factor for mortality in mixed ICU patients. *Intensive Care Med* 2006;32:435–8.
- [7] Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin–glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995;26:57–65.
- [8] Malmberg K. Prospective randomised study of intensive insulin treatment on long-term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) study group. *BMJ* 1997;314:1512–5.
- [9] van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001;345:1359–67.
- [10] Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 2004;79:992–1000.
- [11] Furnary AP, Wu Y. Clinical effects of hyperglycemia in the cardiac surgery population: the Portland Diabetic Project. *Endocr Pract* 2006;12(Suppl 3):22–6.
- [12] Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006;354:449–61.
- [13] Garber AJ, Moghissi ES, Bransome ED Jr, et al. American College of Endocrinology position statement on inpatient diabetes and metabolic control. *Endocr Pract* 2004;10:77–82.
- [14] American College of Endocrinology and American Diabetes Association consensus statement on inpatient diabetes and glycemic control. *Endocr Pract* 2006;12(Suppl 3):4–13.
- [15] Goldberg PA. Memoirs of a root canal salesman: the successful implementation of a hospital-wide intravenous insulin infusion protocol. *Endocr Pract* 2006;12(Suppl 3):79–85.
- [16] Meijering S, Corstjens AM, Tulleken JE, et al. Towards a feasible algorithm for tight glycaemic control in critically ill patients: a systematic review of the literature. *Crit Care* 2006;10:R19.
- [17] Wilson M, Weinreb J, Hoo GW. Intensive insulin therapy in critical care: a review of 12 protocols. *Diabetes Care* 2007;30:1005–11.
- [18] Goldberg PA, Siegel MD, Sherwin RS, et al. Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit. *Diabetes Care* 2004;27:461–7.
- [19] Malhotra A. Intensive insulin in intensive care. *N Engl J Med* 2006;354:516–8.
- [20] Sacks DB, Bruns DE, Goldstein DE, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem* 2002;48:436–72.

- [21] Association AD. Bedside blood glucose monitoring in hospitals. *Diabetes Care* 2004; 25(Suppl 1):S104.
- [22] Goldstein DE, Little RR, Lorenz RA, et al. Tests of glycemia in diabetes. *Diabetes Care* 2004;27:1761–73.
- [23] Louie RF, Tang Z, Sutton Dv, et al. Point-of-care glucose testing: effects of critical care variables, influence of reference instruments, and a modular glucose meter design. *Arch Pathol Lab Med* 2000;124:257–66.
- [24] Brunkhorst FM, Wahl HG. Blood glucose measurements in the critically ill: more than just a blood draw. *Crit Care* 2006;10:178.
- [25] Blake DR, Nathan DM. Point-of-care testing for diabetes. *Crit Care Nurs Q* 2004;27: 150–61.
- [26] D'Orazio P, Burnett RW, Fogh-Andersen N, et al. Approved IFCC recommendation on reporting results for blood glucose: International Federation of Clinical Chemistry and Laboratory Medicine Scientific Division, Working Group on Selective Electrodes and Point-of-Care Testing (IFCC-SD-WG-SEPOCT). *Clin Chem Lab Med* 2006;44: 1486–90.
- [27] Dungan K, Chapman J, Braithwaite SS, et al. Glucose measurement: confounding issues in setting targets for inpatient management. *Diabetes Care* 2007;30:403–9.
- [28] Ray JG, Hamielec C, Mastracci T. Pilot study of the accuracy of bedside glucometry in the intensive care unit. *Crit Care Med* 2001;29:2205–7.
- [29] Maser RE, Butler MA, DeCherney GS. Use of arterial blood with bedside glucose reflectance meters in an intensive care unit: are they accurate? *Crit Care Med* 1994;22: 595–9.
- [30] Kulkarni A, Saxena M, Price G, et al. Analysis of blood glucose measurements using capillary and arterial blood samples in intensive care patients. *Intensive Care Med* 2005; 31:142–5.
- [31] Corstjens AM, Ligtenberg JJ, van der Horst IC, et al. Accuracy and feasibility of point-of-care and continuous blood glucose analysis in critically ill ICU patients. *Crit Care* 2006;10:R135.
- [32] Atkin SH, Dasmahapatra A, Jaker MA, et al. Fingerstick glucose determination in shock. *Ann Intern Med* 1991;114:1020–4.
- [33] Sylvain HF, Pokorny ME, English SM, et al. Accuracy of fingerstick glucose values in shock patients. *Am J Crit Care* 1995;4:44–8.
- [34] Tang Z, Lee JH, Louie RF, et al. Effects of different hematocrit levels on glucose measurements with handheld meters for point-of-care testing. *Arch Pathol Lab Med* 2000;124: 1135–40.
- [35] Finkielman JD, Oyen LJ, Afessa B. Agreement between bedside blood and plasma glucose measurement in the ICU setting. *Chest* 2005;127:1749–51.
- [36] Goldberg PA, Siegel MD, Russell RR, et al. Experience with the continuous glucose monitoring system in a medical intensive care unit. *Diabetes Technol Ther* 2004;6: 339–47.
- [37] Clarke WL, Anderson S, Farhy L, et al. Evaluating the clinical accuracy of two continuous glucose sensors using continuous glucose error grid analysis. *Diabetes Care* 2005;28: 2412–7.
- [38] Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. *J Clin Endocrinol Metab* 2006;91:3725–45.
- [39] Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003;348:727–34.
- [40] Goldberg PA, Inzucchi SE. Critical issues in endocrinology. *Clin Chest Med* 2003;24: 583–606, vi.
- [41] Oelkers W. Adrenal insufficiency. *N Engl J Med* 1996;335:1206–12.
- [42] Burchard K. A review of the adrenal cortex and severe inflammation: quest of the eucorticoi-
d state. *J Trauma* 2001;51:800–14.

- [43] Rothwell PM, Udwadia ZF, Lawler PG. Cortisol response to corticotropin and survival in septic shock. *Lancet* 1991;337:582–3.
- [44] Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862–71.
- [45] Luce JM. Physicians should administer low-dose corticosteroids selectively to septic patients until an ongoing trial is completed. *Ann Intern Med* 2004;141:70–2.
- [46] Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med* 2005;171:242–8.
- [47] Marik PE, Gayowski T, Starzl TE. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. *Crit Care Med* 2005;33:1254–9.
- [48] Huang CJ, Lin HC. Association between adrenal insufficiency and ventilator weaning. *Am J Respir Crit Care Med* 2006;173:276–80.
- [49] Annane D, Sebille V, Troche G, et al. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA* 2000;283:1038–45.
- [50] le Roux CW, Chapman GA, Kong WM, et al. Free cortisol index is better than serum total cortisol in determining hypothalamic-pituitary-adrenal status in patients undergoing surgery. *J Clin Endocrinol Metab* 2003;88:2045–8.
- [51] Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum-free cortisol in critically ill patients. *N Engl J Med* 2004;350:1629–38.
- [52] Vogeser M, Groetzner J, Kupper C, et al. Free serum cortisol during the postoperative acute phase response determined by equilibrium dialysis liquid chromatography–tandem mass spectrometry. *Clin Chem Lab Med* 2003;41:146–51.
- [53] Ho JT, Al-Musalhi H, Chapman MJ, et al. Septic shock and sepsis: a comparison of total and free plasma cortisol levels. *J Clin Endocrinol Metab* 2006;91:105–14.
- [54] Annane D, Maxime V, Ibrahim F, et al. Diagnosis of adrenal insufficiency in severe sepsis and septic shock. *Am J Respir Crit Care Med* 2006;174:1319–26.
- [55] Pugeat M, Bonneton A, Perrot D, et al. Decreased immunoreactivity and binding activity of corticosteroid-binding globulin in serum in septic shock. *Clin Chem* 1989;35:1675–9.
- [56] Beishuizen A, Thijs LG, Vermes I. Patterns of corticosteroid-binding globulin and the free cortisol index during septic shock and multitrauma. *Intensive Care Med* 2001;27:1584–91.
- [57] Salgado DR, Verdeal JC, Rocco JR. Adrenal function testing in patients with septic shock. *Crit Care* 2006;10:R149.
- [58] Marik PE. The diagnosis of adrenal insufficiency in the critically ill patient: does it really matter? *Crit Care* 2006;10:176.
- [59] Bonte HA, van den Hoven RJ, van der Sluijs Veer G, et al. The use of free cortisol index for laboratory assessment of pituitary–adrenal function. *Clin Chem Lab Med* 1999;37:127–32.
- [60] le Roux CW, Sivakumaran S, Alaghband-Zadeh J, et al. Free cortisol index as a surrogate marker for serum-free cortisol. *Ann Clin Biochem* 2002;39:406–8.
- [61] Cronin L, Cook DJ, Carlet J, et al. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. *Crit Care Med* 1995;23:1430–9.
- [62] Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. *Crit Care Med* 1999;27:723–32.
- [63] Bollaert PE, Charpentier C, Levy B, et al. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med* 1998;26:645–50.
- [64] Oppert M, Schindler R, Husung C, et al. Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. *Crit Care Med* 2005;33:2457–64.
- [65] Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32:858–73.

- [66] Wartofsky L, Burman KD. Alterations in thyroid function in patients with systemic illness: the euthyroid sick syndrome. *Endocr Rev* 1982;3:164–217.
- [67] Docter R, Krenning EP, de Jong M, et al. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism. *Clin Endocrinol (Oxf)* 1993;39:499–518.
- [68] Chopra IJ. Nonthyroidal illness syndrome or euthyroid sick syndrome? *Endocr Pract* 1996;2:45–52.
- [69] Chopra IJ, Williams DE, Orgiazzi J, et al. Opposite effects of dexamethasone on serum concentrations of 3,3',5'-triiodothyronine (reverse T3) and 3,3',5-triiodothyronine (T3). *J Clin Endocrinol Metab* 1975;41:911–20.
- [70] Bianco AC, Nunes MT, Hell NS, et al. The role of glucocorticoids in the stress-induced reduction of extrathyroidal 3,5,3'-triiodothyronine generation in rats. *Endocrinology* 1987;120:1033–8.
- [71] Chopra IJ, Huang TS, Beredo A, et al. Evidence for an inhibitor of extrathyroidal conversion of thyroxine to 3,5,3'-triiodothyronine in sera of patients with nonthyroidal illnesses. *J Clin Endocrinol Metab* 1985;60:666–72.
- [72] Martino E, Bartalena L, Bogazzi F, et al. The effects of amiodarone on the thyroid. *Endocr Rev* 2001;22:240–54.
- [73] Harris AR, Fang SL, Vagenakis AG, et al. Effect of starvation, nutriment replacement, and hypothyroidism on in vitro hepatic T4 to T3 conversion in the rat. *Metabolism* 1978;27:1680–90.
- [74] Suda AK, Pittman CS, Shimizu T, et al. The production and metabolism of 3,5,3'-triiodothyronine and 3,3',5-triiodothyronine in normal and fasting subjects. *J Clin Endocrinol Metab* 1978;47:1311–9.
- [75] Chopra IJ, Chopra U, Smith SR, et al. Reciprocal changes in serum concentrations of 3,3',5-triiodothyronine (T3) in systemic illnesses. *J Clin Endocrinol Metab* 1975;41:1043–9.
- [76] Chopra IJ. An assessment of daily production and significance of thyroidal secretion of 3, 3', 5'-triiodothyronine (reverse T3) in man. *J Clin Invest* 1976;58:32–40.
- [77] Afandi B, Schussler GC, Arafeh AH, et al. Selective consumption of thyroxine-binding globulin during cardiac bypass surgery. *Metabolism* 2000;49:270–4.
- [78] Afandi B, Vera R, Schussler GC, et al. Concordant decreases of thyroxine and thyroxine-binding protein concentrations during sepsis. *Metabolism* 2000;49:753–4.
- [79] Chopra IJ, Solomon DH, Hepner GW, et al. Misleadingly low free thyroxine index and usefulness of reverse triiodothyronine measurement in nonthyroidal illnesses. *Ann Intern Med* 1979;90:905–12.
- [80] Jirasakuldech B, Schussler GC, Yap MG, et al. A characteristic serpin cleavage product of thyroxine-binding globulin appears in sepsis sera. *J Clin Endocrinol Metab* 2000;85:3996–9.
- [81] Chopra IJ, Teco GN, Mead JF, et al. Relationship between serum-free fatty acids and thyroid hormone-binding inhibitor in nonthyroid illnesses. *J Clin Endocrinol Metab* 1985;60:980–4.
- [82] Jaume JC, Mendel CM, Frost PH, et al. Extremely low doses of heparin release lipase activity into the plasma and can thereby cause artifactual elevations in the serum-free thyroxine concentration as measured by equilibrium dialysis. *Thyroid* 1996;6:79–83.
- [83] Chopra IJ. Clinical review 86: euthyroid sick syndrome: is it a misnomer? *J Clin Endocrinol Metab* 1997;82:329–34.
- [84] Baloch Z, Carayon P, Conte-Devolx B, et al. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid* 2003;13:3–126.
- [85] Ekins R. Analytic measurements of free thyroxine. *Clin Lab Med* 1993;13:599–630.
- [86] Wong TK PA, Hoo GS, Bradley ME, et al. Comparison of methods measuring free thyroxine in nonthyroidal illness. *Clin Chem* 1992;38:720–4.

- [87] Chopra IJ. Simultaneous measurement of free thyroxine and free 3,5,3'-triiodothyronine in undiluted serum by direct equilibrium dialysis/radioimmunoassay: evidence that free triiodothyronine and free thyroxine are normal in many patients with the low triiodothyronine syndrome. *Thyroid* 1998;8:249–57.
- [88] Mendel CM FP, Kunitake ST, Cavalieri RR. Mechanism of the heparin-induced increase in the concentration of free thyroxine in plasma. *J Clin Endocrinol Metab* 1987;65:1259–64.
- [89] Wang R NJ, Weiss RM, Wilcox RB. Accuracy of free thyroxine measurements across natural ranges of thyroxine binding to serum proteins. *Thyroid* 2000;10:31–9.
- [90] Wehmann RE, Gregerman RI, Burns WH, et al. Suppression of thyrotropin in the low-thyroxine state of severe nonthyroidal illness. *N Engl J Med* 1985;312:546–52.
- [91] Papanicolaou DA. Euthyroid sick syndrome and the role of cytokines. *Rev Endocr Metab Disord* 2000;1:43–8.
- [92] Faglia G, Ferrari C, Beck-Peccoz P, et al. Reduced plasma thyrotropin response to thyrotropin-releasing hormone after dexamethasone administration in normal subjects. *Horm Metab Res* 1973;5:289–92.
- [93] Van den Berghe G, de Zegher F, Lauwers P. Dopamine and the sick euthyroid syndrome in critical illness. *Clin Endocrinol (Oxf)* 1994;41:731–7.
- [94] Lee HY, Suhl J, Pekary AE, et al. Secretion of thyrotropin with reduced concanavalin A-binding activity in patients with severe nonthyroid illness. *J Clin Endocrinol Metab* 1987;65:942–5.
- [95] Van den Berghe G, Wouters P, Weekers F, et al. Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone-releasing peptide and thyrotropin-releasing hormone in patients with protracted critical illness. *J Clin Endocrinol Metab* 1999;84:1311–23.
- [96] Hamblin PS, Dyer SA, Mohr VS, et al. Relationship between thyrotropin and thyroxine changes during recovery from severe hypothyroxinemia of critical illness. *J Clin Endocrinol Metab* 1986;62:717–22.
- [97] Stockigt JR. Guidelines for diagnosis and monitoring of thyroid disease: nonthyroidal illness. *Clin Chem* 1996;42:188–92.
- [98] Spencer CA, LoPresti JS, Patel A, et al. Applications of a new chemiluminometric thyrotropin assay to subnormal measurement. *J Clin Endocrinol Metab* 1990;70:453–60.
- [99] Franklyn JA, Black EG, Betteridge J, et al. Comparison of second- and third-generation methods for measurement of serum thyrotropin in patients with overt hyperthyroidism, patients receiving thyroxine therapy, and those with nonthyroidal illness. *J Clin Endocrinol Metab* 1994;78:1368–71.
- [100] Attia J, Margetts P, Guyatt G. Diagnosis of thyroid disease in hospitalized patients: a systematic review. *Arch Intern Med* 1999;159:658–65.
- [101] Slag MF, Morley JE, Elson MK, et al. Hypothyroxinemia in critically ill patients as a predictor of high mortality. *Jama* 1981;245:43–5.
- [102] Maldonado LS, Murata GH, Hershman JM, et al. Do thyroid function tests independently predict survival in the critically ill? *Thyroid* 1992;2:119–23.
- [103] Van den Berghe GH. Acute and prolonged critical illness are two distinct neuroendocrine paradigms. *Verh K Acad Geneesk Belg* 1998;60:487–518 [discussion: 518–20].
- [104] DeGroot LJ. Non-thyroidal illness syndrome is functional central hypothyroidism, and if severe, hormone replacement is appropriate in light of present knowledge. *J Endocrinol Invest* 2003;26:1163–70.
- [105] Gardner DF, Kaplan MM, Stanley CA, et al. Effect of tri-iodothyronine replacement on the metabolic and pituitary responses to starvation. *N Engl J Med* 1979;300:579–84.
- [106] Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. *J Clin Endocrinol Metab* 1986;63:1–8.
- [107] Klemperer JD, Klein I, Gomez M, et al. Thyroid hormone treatment after coronary artery bypass surgery. *N Engl J Med* 1995;333:1522–7.

- [108] Bennett-Guerrero E, Jimenez JL, White WD, et al. Cardiovascular effects of intravenous triiodothyronine in patients undergoing coronary artery bypass graft surgery. A randomized, double-blind, placebo-controlled trial. Duke T3 study group. *Jama* 1996;275:687–92.
- [109] Burmeister LA. Reverse T3 does not reliably differentiate hypothyroid sick syndrome from euthyroid sick syndrome. *Thyroid* 1995;5:435–41.

The Cognitive Consequences of Critical Illness: Practical Recommendations for Screening and Assessment

Max L. Gunther, MS^{a,b}, James C. Jackson, PsyD^{a,c},
E. Wesley Ely, MD, MPH^{a,c,d,*}

^a*VA Tennessee Valley Geriatric Research, Education and Clinical Center (GRECC)
1310 24th Ave. S, Nashville, TN 37212-2637, USA*

^b*Department of Psychology - Clinical, University of Georgia,
Psychology Building Athens, GA 30602-3013, USA*

^c*Center for Health Services Research, 6100 Medical Center East,
Nashville, TN 37232-8300, USA*

^d*Division of Allergy/Pulmonary/Critical Care Medicine,
D-3100 MCN, Vanderbilt University School of Medicine,
Nashville, TN 37232-2358, USA*

In older individuals, the quality of life has increasingly become the currency of trade compared with survival alone [1]. Recent evidence suggests that critical illness may pose substantial risks for long-term cognitive impairment (LTCI) and has the potential to severely impact the quality and independence of one's life. Of the 55,000 intensive care unit (ICU) patients who are treated daily in the United States [2], approximately 40% require mechanical ventilation [3]. Patients who are ventilated for three or more days represent only 4% to 10% of hospital admissions yet seem to account for the use of 30% to 50% of an ICU's resources [4]. Demographic data suggest that approximately 60% of all days spent in the ICU are patients who are 65 years of age or older [5]. Although the total number of hospital beds has been reduced in the United States over the last 15 years, the number of critical care beds has increased by 26% [2]. With the burgeoning number of elderly individuals in the current population, these statistics take on vital importance when considering the accumulating data which links critical illness to LTCI. Unfortunately, it is only in the last decade that researchers and

* Corresponding author. Center for Health Services Research, 6100 Medical Center East, Nashville, TN 37232-8300.

E-mail address: wes.ely@vanderbilt.edu (E.W. Ely).

clinicians have begun to document the cognitive declines associated with this vulnerable population, despite that neurologic organ dysfunction has been studied extensively in other populations [6]. Additionally, other lines of investigation suggest that CNS degradation is not only linked to declines in quality of life but also an independent predictor of mortality [7].

The prevalence of ICU-related cognitive impairments

Critical illness frequently results in *de novo* cognitive impairments. Estimates suggest that 25% to 78% of patients suffer clinically significant declines in cognitive functioning following stays in the ICU and that in many cases this decline may be permanent [8].

Although the specific mechanism or mechanisms by which the neurologic degradation occurs remain under investigation, it is clear that the development of delirium (ie, an acute cerebral dysfunction) is a major precursor to post-ICU cognitive decline. In reviewing the studies that have examined this phenomenon, it is a challenge to draw conclusions because most reports to date vary widely in their population of interest, prospective or retrospective reports, and their operational definition and quantification of LTCI. Nonetheless, the authors believe that this remains a useful exercise. This article reviews 10 studies of primary relevance and interest that have examined patients' cognitive impairments following ICU treatment [9–19] (note: an exhaustive treatment of these and similar studies is beyond the scope of this article). These investigations include 2 studies in general ICU patients, 5 studies in acute respiratory distress syndrome (ARDS) patients, and 1 study each in respiratory and acute lung injury (ALI) patients. Most of these reports assessed participants within the first year of hospital discharge; however, three investigations have assessed patients within a longer time frame. Two studies examined participants approximately 2 years following discharge, and 1 study tested individuals at 1 and 2 years post ICU, respectively.

The studies listed highlight the long-term cognitive consequences of critical illness and strongly suggest that the neurologic degradation may indeed be persistent and in some cases permanent, particularly in geriatric populations, especially in those suffering from pre-existing conditions, such as mild cognitive impairment (MCI), traumatic brain injury (TBI), or dementia. Whatever the specific mechanism of the ICU-related cognitive decline, these pre-existing risk factors seem to compound patients' cognitive losses, hastening the pace of dementia.

Premorbid risk factors

It is clear that ICU delirium is related to emerging cognitive impairment; however, many questions remain regarding the specific mechanism by which

ICU delirium may lead to cognitive decline. Although delirium indicates emerging cognitive impairment, it is not the case that all patients who experience delirium have pre-existing cognitive conditions. Jackson and colleagues demonstrated this in a study [20] that excluded patients who suffered from suspected dementia before their admittance to the ICU. Of the remaining sample, nearly one third of individuals in the ICU who were suffering from delirium had cognitive impairments 6 months later. It thus seems that even in cognitively intact individuals, the development of delirium in the context of critical illness is associated with adverse neuropsychologic outcomes.

Although delirium is often discussed as a unitary construct, in fact there exists a great deal of heterogeneity regarding the presentation and course of the condition. In reality, delirium is a dynamic state characterized by both hypo- and hyperactive behaviors. Moreover, it is common in ICU populations for patients to oscillate frequently between these states, painting a complex clinical picture [21]. Between these two extremes, the level of delirium can fluctuate widely also. Given the heterogeneity of this construct, it is not surprising that debate continues to exist regarding the conceptualization and measurement of delirium's duration and severity [22–24]. It is clear, however, and generally agreed on, that a spectrum of severity exists and that variables, such as duration, cause, delirium subtype, and the level of severity, likely prove to be important factors for predicting long-term neuropsychologic outcomes. To date, only one study has examined this relationship explicitly. To summarize, although the quantification of delirium duration is straightforward, several challenges remain regarding the measurement of delirium and its severity.

Although pre-existing risk factors, such as TBI or MCI, have been found to interact with ICU-related cognitive decline, several potentially deleterious variables have consistently yielded no associated risk. Specifically, data suggest that there is no link between LTCI and illness severity (APACHE-II) [25], length of time in the ICU, time on mechanical ventilation, total days under sedation, narcotic and paralytic medication, or tidal volume [16,17,19,26,27]. Although a need for much additional research remains, determining that these potentially confounding variables do not seem to play a primary causal role in the development of LTCI has been an important step in furthering our understanding of ICU delirium and neurologic degeneration. In doing so it allows investigators and clinicians alike to focus their attention on uncovering potential causal variables to reduce the likelihood and prevalence of LTCI in the critically ill.

How does patient age relate to critical illness and cognitive decline? Of the studies mentioned [9–19], most have examined adult patients who were either young or middle-aged (mean age = 54; SD = 11). In these studies, age of participant is not significantly related to level of cognitive impairment ($r = 0.262$; not significant) [17]. In a multivariate analysis, Jackson and colleagues [16] examined the individual contribution of age in predicting the

overall outcomes of a patient's cognitive measure and found that age was not a significant risk factor. At time of discharge, there is a moderate relationship between decline in executive abilities and age, although this relationship loses significance at 2-month follow up [10]. Other evidence does suggest, however, that a patient's global mental status, visuospatial/constructional ability, and visual memory may decline more rapidly for patients older than 60 years following ICU treatment [16]. Although all of the studies mentioned enrolled elderly patients (defined as older than 65 years), only one study contained participants with a mean age greater than 65 [14]. This finding is unfortunate given that the elderly account for nearly half of all critical care admissions and more than half of all days spent by patients in the ICU [5]. Most studies that have examined cognitive outcomes excluded patients who had known pre-existing or comorbid cognitive impairments. It would be helpful for future research to include patients who have premorbid impairments to help paint a more accurate picture of ICU delirium and LTCI.

Several recent studies of non-ICU cohorts have identified a long list of potential environmental risk factors for the development of delirium and LTCI [28–31] with certain variables emerging as potential high-risk conditions. In particular, patients who possess three or more individual risk factors seem to be at elevated risk compared with controls [28–31]. Although several demographic variables cannot be modified (eg, age, socioeconomic status, and so forth), others have potential to serve as useful points of intervention. For example, specific types of sedatives and analgesic medications [30–37] seem to be good candidates. In line with this reasoning, benzodiazepines and meperidine have been shown to be related to the development of delirium in ICU patients [31,32]. Additionally, benzodiazepines, narcotics, and other psychoactive agents have been reported to correspond with 3- to 11-fold increases in the prevalence of delirium. Recent survey data indicate that lorazepam is frequently administered in the ICU for the treatment of delirium and may be prescribed at more than 50 mg/d. Finally, other reports suggest that fluid and electrolyte disturbance, gastrointestinal bleeding [38], and alcohol abuse [28] may also represent important clinically modifiable conditions related to the development of ICU delirium. Given that delirium seems to be a major causal variable related to the development of cognitive impairment, the identification and modification of these risk factors is paramount to the prevention and treatment of adverse cognitive outcomes.

Long-term cognitive impairment following delirium

Mounting evidence suggests that delirium may be the causal link between critical illness and LTCI. Although most studies examining this relationship have been conducted in non-ICU populations, the authors believe that these data are still relevant. To date, nine studies have assessed the association between delirium and cognitive impairment in non-ICU patients. From

these studies, when compared with controls, patients diagnosed with delirium were much more likely to experience a significant decline in cognitive functioning at follow-up. It is important to highlight an essential distinction between dementia and delirium. Although dementia and LTCI tend to be relatively stable conditions, delirium is characterized by rapidly fluctuating changes in consciousness [39].

A study of patients who had hip fracture excluding individuals who had dementia found that participants who had delirium were nearly two times as likely to suffer from cognitive impairments at 2-year follow-up compared with controls who did not have delirium [40]. Another investigation, which examined hospitalized geriatric patients in community housing, observed that individuals who experienced delirium had poorer Mini Mental Status Examination (MMSE) scores at 6 months and suffered from greater cognitive declines during the 18 months following hospitalization when compared with controls who did not have delirium [41]. Furthermore, patients in this study were matched case-wise by highest hospital MMSE score, suggesting that the observed cognitive decline in patients who have delirium cannot be accounted for by premorbid cognitive impairment. McCusker and colleagues [42] reported that on discharge, hospitalized elderly who were admitted to emergency services had MMSE scores that were on average five points below (ie, worse than) patients free from delirium. To account for potential alternative explanations, the authors of this study controlled for premorbid dementia, overall functioning, comorbid disease, and illness severity, suggesting once again that delirium may be the critical factor impacting patients' cognitive outcomes. In a separate study examining individuals in geriatric nursing homes [43], while also accounting for premorbid cognitive impairments, investigators reported that patients who developed delirium while hospitalized demonstrated significant cognitive declines when compared with controls.

Four additional studies report greater occurrence of dementia in elderly patients following delirious episodes while hospitalized. Specifically, when investigating a sample of geriatric patients hospitalized for acute delirium, 14 individuals immediately following remission of their delirium and an additional 14 patients were diagnosed as demented at 2-year follow-up [44]. This proportion of patients suffering from dementia was significantly higher than that in a typical geriatric population with no demented episodes. A separate sample of patients 85 years or older who were not demented who suffered an episode of delirium were significantly more likely to be diagnosed with dementia at 3-year follow-up than were individuals who did not have delirium. Specifically, rates of dementia climbed from 5.6% with no delirium to 18.1% per year with delirium [45]. Finally, Koponen and colleagues [46] observed that one third of psychiatric patients hospitalized for delirium had evidence of cognitive decline.

To date, one study has assessed the relationship between delirium and LTCI in the critically ill [20]. In this investigation, a trend between delirium

and LTCI was observed. This study differed from previous reports in that the population was significantly younger (mean age = 53.2).

Delirium as a causal mechanism for long-term cognitive impairment

Certain lines of inquiry have speculated that delirium indicates a more subtle dementia that may not become apparent to either patients or clinicians for several years. In particular, for frail populations [47] minor incidents may result in major impacts that could lead to LTCI and functional disabilities [48]. ICU-induced delirium may in fact qualify as just such an incident. In this regard, delirium could represent the precipitating factor that causes patients to cross a critical threshold eventually resulting in LTCI. Consistent with this prediction, several studies suggest that like other diseases of the central nervous system (CNS) [49], the neurodegeneration linked to Alzheimer disease may be present, possibly even for decades, prior to the manifestation of observable functional impairment. In this view, cognitive functioning may teeter on a neurodegenerative cliff until a precipitating event, in this case a stay in the ICU, pushes the patient over a vital threshold, resulting in LTCI.

Other studies have suggested that a common pathogenic mechanism may underlie Alzheimer disease and delirium [50]. Of particular interest are the inflammatory processes, such as elevated levels of cytokines (IL-1) that may contribute to delirium and Alzheimer disease [51,52]. Change in an individual's potential for neuroplasticity may also serve as a mediator for neurologic atrophy and cognitive declines [53,54]. Not surprisingly, reduction in neuronal tissue is closely linked to dementia and cognitive impairments [54–57]. An alternative line of reasoning suggests that delirium is related to the degradation of vital subcortical structures, such as the brainstem and thalamus [38], along with mnemonic (ie, hippocampus) and executive structures, such as the prefrontal and parietal cortices (Fig. 1). This reasoning makes intuitive sense when considering that critical illness survivors often suffer from losses in attention and memory also [20,25].

Neuroimaging

Research has only recently begun to use neuroimaging techniques to answer important questions regarding the nature of ICU delirium and LTCI. Neuroimaging has the potential to be a powerful tool that could allow investigators to answer a wide range of questions related to post-ICU cognitive decline. Traditional structural imaging techniques, such as CT and MRI, have already shed light onto the nature of the white and gray matter degradation that seems to be occurring in certain ICU patients [46,58–60]. Newer methods of neuroimaging are allowing researchers to shed light on not only anatomic changes in the brain but also functional and molecular signatures. An early CT study reported atrophy surrounding the cerebral ventricles in elderly psychiatric patients experiencing delirium compared with matched

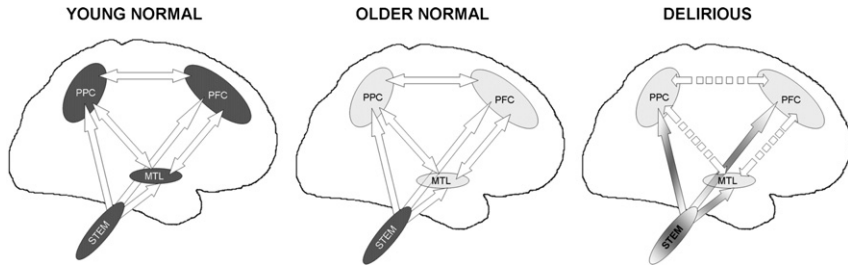


Fig. 1. Delirium in critical illness is related to grey and white matter degradation in the CNS. Disruption of this critical circuit in the key brain regions for cognition depicted below may result in the decoupling of functional connectivity leading to long-term cognitive impairment. (1) Young normal: In healthy individuals there is normal and consistent connectivity between the PPC, MTL, and PFC. This circuit is innervated, activated, and maintained by the ARAS arising from the brainstem by way of the thalamus. (2) Older normal: Elderly individuals begin to show signs of grey matter atrophy in the PPC, MTL, and PFC. Although functional connectivity between these regions remains intact, the strength of the connections is no longer as robust as it once was in the healthy CNS. This circuit continues to be activated and maintained by the ARAS directly and by way of the thalamus. (3) Delirious: Individuals treated in the ICU are subject to several medical and pharmacologic challenges that may disrupt normal CNS connectivity. Serious illnesses, such as sepsis, ARDS, and ALI, as well as sedative and analgesic medications commonly prescribed in the ICU, have the potential to weaken functional links between the cortical regions depicted above. This situation is particularly likely for processes impacting the ARAS. Fluctuations in activation arising from the brainstem may be sufficient in elderly individuals to cause a disruption that may surpass a critical threshold of functional connectivity necessary to maintain normal consciousness. In combination with exposure to other ICU-related threats to cognitive function, prolonged decoupling of this circuit may lead to deleterious neurodegenerative consequences, such as excitotoxicity. Over time this has the potential to result in apoptosis and long-term cognitive impairment. PPC, posterior parietal cortex; PFC, prefrontal cortex; MTL, medial temporal lobe; ARAS, ascending reticular activating system. (From Gunther ML, Jackson JC, Ely EW. Loss of IQ in the ICU: Brain injury without the insult. *Med Hypotheses* 2007; in press. doi:10.1016/j.mehy.2007.03.039; with permission.)

controls [57]. Furthermore, the degree of atrophy was related to patients' MMSE scores. Patients in these studies also displayed cerebral infarctions and hemorrhages in frontal and parietal regions [49]. Another study that examined the effects of electroconvulsive shock therapy in patients who had delirium found white matter abnormalities and lesions in the basal ganglia [61].

Further evidence suggests that there are major neuroanatomic changes that occur in patients experiencing prolonged delirium, diminished level of consciousness, alerted state of mental status, or confusion [59]. In one study, CT scanning revealed that 61% of critically ill patients who suffered from these conditions were found to have either gross white and gray matter atrophy, white matter lesions/hyperintensities, cortical and subcortical lesions, or ventricular enlargement [59]. Additionally, Hopkins and colleagues [55] observed similar findings when using CT to examine anatomic changes associated with poor cognitive outcomes in patients who have ARDS. In this study, structural lesions were found in the brainstem (pons) and

posterior parietal cortex (PPC), along with atrophy in the medial temporal lobe (MTL; eg, hippocampus). Significant white matter intensity changes were identified in cortical and subcortical white matter tracts [55].

Buckner and colleagues [62] examined potential mechanisms underlying neurophysiologic changes associated with Alzheimer disease by using multimodal imaging. Gray matter degradation in the PPC, MTL, and prefrontal cortex (PFC) was observed to correlate with functional (blood oxygen level-dependent) declines in activation for these known mnemonic regions while engaged in memory tasks.

Additionally, the brain's primary arousal mechanism, the ascending reticular activating system (ARAS) may also play an important role in the modulation of delirium [63]. Excitatory projections originating in the myelencephalon innervate the midbrain and cortex directly and are hypothesized to be critically involved in general attention [63,64]. Because many anesthetic agents are believed to act in the brainstem region, it is possible that perturbation of the ARAS circuit may lead to fluctuations in arousal, perception, attention, and executive function. Excitatory pontine afferents may therefore be involved in maintaining an equilibrium between top-down regulation by way of cortical structures and bottom-up arousal levels originating in the brainstem (see Fig. 1). For individuals who have pre-existing neuronal degradation, transient interference in either or both areas could have the potential for major cognitive disruption. Gross longitudinal changes in brain physiology are known to impact metabolic cellular mechanisms [62,65,66]. If such changes persist for a sufficient length of time, either hyper- or hypometabolic modifications can lead to apoptosis, gray matter atrophy, and axonal degradation. Once again, patients who have prior CNS deterioration or insults may be particularly at risk for this hypothesized deleterious mechanism depicted in Fig. 1. Although this model of ICU-linked cognitive impairment remains highly speculative, our hope is that it may generate novel hypotheses for the investigation of potential explanations for ICU delirium and LTCI.

Clinical awareness of cognitive impairment

Recent reports suggest that individuals recovering from critical illness rarely have the opportunity for cognitive rehabilitation. Hopkins and colleagues [25] found that although 42% of ARDS survivors enrolled in general rehabilitation therapy, only 12% participated in cognitive rehabilitation. Cognitive decline seems to be grossly under-recognized by intensive care and rehabilitation professionals. Unfortunately, this oversight is not restricted to critically ill patients. One study suggested that most physicians fail to recognize or accurately assess potential cognitive impairment in non-ICU settings [67]. Furthermore, cognitive dysfunction is rarely evaluated in the critically ill [20] and is likely to go unnoticed in approximately half of all cases [68]. These unsettling statistics are at least in part likely to be because

of the subtlety by which cognitive impairment may manifest itself, especially if patients are alert, oriented, and seem to be mentally intact overall. The authors believe that the education of medical care providers regarding neuropsychologic decline is imperative. Raising the awareness of physicians and nurses alike to this issue is of vital importance. Accordingly, a major aim of this article is to raise awareness within the ICU community and to increase referrals for rehabilitation and neuropsychologic testing and to speech and language therapists who could potentially provide interventions and services to aide patients' cognitive remediation. Furthermore, in light of the paucity of relevant data regarding cognitive rehabilitation, the authors also hope to stimulate future research on the topic with the goal that such interventions for the critically ill can eventually be realized.

Dementia screening guidelines developed by the United States Preventative Services Task Force recommend that clinicians assess cognitive function whenever cognitive impairment or deterioration is suspected [69]. Although rates of cognitive impairment at ICU discharge are high, screening all ICU survivors at discharge is clinically unwieldy and impractical. Alternatively, screening individuals who have an increased likelihood of developing cognitive impairment may prove to be more useful. Although a protocol or clinical decision tree to inform the process of cognitive screening of ICU survivors has yet to be developed, it may be that patients who have certain risk factors (eg, ARDS, advanced age, sepsis, bacterial meningitis, hypoxemia) should be screened [11,70–77]. Possible red flags suggesting a need for screening (which could be done using brief cognitive questionnaires such as MMSE or Mini-cog) could be problems such as obvious memory difficulties or other marked symptoms of cognitive impairment and disorientation, particularly in the absence of delirium (eg, confusion; repeating the same question; difficulty with instrumental activities of daily living; social problems; neglect of appearance, nutrition, or hygiene; loss of interest in hobbies; social withdrawal; or behavioral problems, such as irritability, wandering, agitation, or apathy).

In addition to being impractical, another potential problem with routinely screening all patients at hospital discharge is that it has the potential to result in a high false-positive rate because of the transient effects of medication and acute illness. In cases in which significant questions regarding a patient's cognitive functioning exist or in those instances in which screening indicates the presence of possible problems, patients should be referred to a clinical neuropsychologist for consultation and further evaluation. Few neuropsychologists are actively involved in the assessment and management of survivors of critical illness at the present time; however, they are the appropriate professionals to assess cognitive function in these individuals. Unfortunately, neuropsychologists may not be available in many small hospitals or rural areas but are frequently used in neurology, rehabilitation medicine, or psychiatry departments in most moderately sized or large medical centers. If a neuropsychologist is unavailable, it is appropriate to refer

patients to a clinical psychologist who is trained in performing basic cognitive evaluations.

ICU diagnosis and monitoring of sedation and delirium

Delirium is a dynamic state characterized by change in mental status. Specifically, it is associated with inattention and an altered level of consciousness [39]. The Society of Critical Care Medicine (SCCM) suggested in its 2002 guidelines for sedation and analgesia that all critically ill patients should be monitored for level of sedation and delirium concurrently [78]. Unfortunately, evidence has repeatedly shown that neither nurses nor physicians are able to consistently diagnose delirium using clinical judgment alone. For this reason, it is necessary to use well-validated and reliable yet brief assessment tools to monitor a patient's level of consciousness. The authors recommend a streamlined two-step process designed to track sedation and delirium.

First, the ICU professional should assess an individual's level of consciousness using an objective and reliable assessment instrument. This assessment is recommended to avoid over-sedation and to provide a common language by which a treatment team can communicate when discussing the treatment of patients in the ICU. Fortunately, there are various instruments that can be used to assess level of consciousness.

The Ramsay Sedation Scale was the first instrument used to reliably quantify the behavioral characteristics of sedation [79]. It was not until several decades later that other scales, such as the Calmness Scale, the Sedation Agitation Scale [80,81], the Motor Activity Assessment Scale [82], and the Vancouver Interactive [83], were added. More recently, the Richmond Agitation Sedation Scale [84] (RASS; Fig. 2) was developed and has helped validate the construct of sedation by adding ability to follow direct verbal instructions to the list of observable patient behaviors. Along with the Ramsay, the RASS is widely used because it is a reliable and valid measurement of critically ill patients' verbal reports and their reactions to physical stimuli [80,84,85]. The RASS (along with other validated sedation scales) serves as a neurologic assessment instrument, irrespective of whether the patient is sedated. Such validated measures improve the accuracy of assessment by standardizing and operationalizing level of arousal. The authors believe that this need not be restricted to situations of iatrogenic modification of consciousness; rather, applications often can, and indeed should, be much broader than this. Other ICU assessment tools of note include the Intensive Care Delirium Screening Checklist developed by Skrobik and colleagues that is frequently used in clinical and research settings. This instrument also has robust statistical properties, including a high sensitivity (99%) and moderate specificity (64%).

A patient's depth of sedation should be tailored to his or her idiographic needs. To accomplish this, treatment teams should uniformly and regularly assess patients using a validated sedation instrument. This assessment

Richmond Agitation Sedation Scale (RASS)

+4	Combative	Combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements are not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening & contact > 10 sec)
-2	Light sedation	Briefly awakens to voice (eye opening & contact < 10 sec)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Sessler, et al., *AJRCM* 2000; 161:A506
Ely, et al., *JAMA* 2003; 286, 2983-2991

Feature I: Acute Onset or Fluctuating Course

- A. Is there evidence of an acute change in mental status from the baseline? or
- B. Did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go, or increase and decrease in severity as evidenced by fluctuation on a sedation scale (e.g. RASS), GCS, or previous delirium assessment?

Feature II: Inattention

Did the patient have difficulty focusing attention as evidenced by a score of *less than 8* on either the visual or auditory component of the Attention Screening Examination (ASE)?

ASE – Visual and Auditory:

1. Visual: Picture Recognition (Refer to picture packet)
2. Auditory: Vigilance “A” Random Letter Test
Directions: Say to the patient, “I am going to read you a series of 10 letters. Whenever you hear the letter ‘A,’ indicate by squeezing my hand.” Read letters from the following letter list in a normal tone.

S A H E V A R A T

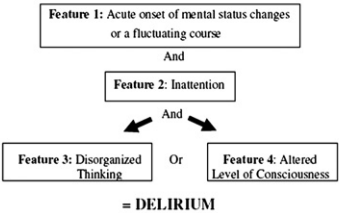
Scoring: Errors are counted when patient fails to squeeze on the letter “A” and when the patient squeezes on any letter other than “A.”

Linking Sedation and Delirium Monitoring:
A Two Step Approach to Assess Consciousness

Step One: Sedation Assessment (RASS)

If RASS is -4 or -5, then Stop and Reassess patient at later time
If RASS is above -4 (-3 through +4) then Proceed to Step 2

Step Two: Delirium Assessment (CAM-ICU)



Ely, *JAMA* 2001; 286, 2703-2710. Ely, *Crit Car Med* 2001; 29, 1370-1379.
Copyright © 2002, E. Wesley Ely, MD, MPH and Vanderbilt University, all rights reserved

Feature III: Disorganized Thinking

Is there evidence of disorganized or incoherent thinking as evidenced by *incorrect answers to 2 or more of the 4 questions* and/or inability to follow the commands?

- Questions: Set A
1. Will a stone float on water?
 2. Are there fish in the sea?
 3. Does one pound weigh more than two pounds?
 4. Can you use a hammer to pound a nail?
- Set B
1. Will a leaf float on water?
 2. Are there elephants in the sea?
 3. Do two pounds weigh more than one pound?
 4. Can you use a hammer to cut wood?

Other:

1. Are you having any unclear thinking?
2. Hold up this many fingers. (Examiner holds two fingers in front of patient).
3. Now do the same thing with the other hand (not repeating the # of fingers).

Feature IV: Altered Level of Consciousness

Is the patient's LOC anything *other than alert*? (e.g., RASS other than “0” at time of assessment):

- Alert** spontaneously fully aware of environment and interacts appropriately
Vigilant hyperalert
Lethargic drowsy but easily aroused, unaware of some elements in the environment, or not spontaneously interacting appropriately with the interviewer; becomes fully aware and appropriately interactive when prodded minimally
Stupor becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli, and as soon as the stimulus ceases, stuporous subject lapse back into the unresponsive state

Fig. 2. Definition of delirium according to the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), using criteria of the Diagnostic and Statistical Manual IV (SM-IV) of the American Psychiatric Association.

facilitates communication across an entire treatment team by using a common metric and allows nurses, physicians, and pharmacists to coordinate and empirically guide the course of sedation over time.

Following a broad assessment of the patient’s arousal, the second step in monitoring individuals in the ICU is to assess patients who respond to verbal stimuli for delirium. In 2001, Ely and colleagues [86–88] published the first nonverbal instruments designed to specifically assess delirium for intubated patients. The Confusion Assessment Method for the ICU (CAM-ICU) has a sensitivity and specificity of approximately 95% with an inter-rater reliability (Kappa) of 0.96 [86,87]. The CAM-ICU was specifically designed for bedside use by nurses or physicians, is easy to use, requires minimal training, and on average only takes 1 minute to administer. Furthermore, it incorporates four key features derived from the Diagnostic

and Statistical Manual–IV (DSM-IV) definition of delirium [39]. These features are: (1) change in mental status from baseline or fluctuating course of mental status, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. According to the DSM-IV and the CAM-ICU definitions, a patient is considered delirious when both conditions 1 and 2 are present along with either condition 3 or 4. The CAM-ICU has now been translated into 13 languages and has become part of a mainstream component of clinical monitoring of the CNS in ICU patients in dozens of countries. Management issues of ICU patients often must be informed by the knowledge of whether or not the patient is experiencing delirium. More specifically, we recommend that patients be monitored multiple times daily by bedside nurses so that data can be recorded and presented to the full medical team. The most current and detailed information is available at www.icudelirium.org with updated protocols, manuals and training material.

Summary

A growing body of literature is helping to increase awareness in clinicians and researchers alike regarding the importance of delirium and LTCI in the critically ill. Although the relationship between delirium and cognitive decline is well documented in non-ICU populations [57], it is becoming evident that a homologous relationship seems to exist for the critically ill. Several causal models have been proposed to elucidate potential mechanisms for this phenomenon; unfortunately, none have emerged as clear winners. One finding that has come to light, however, is that delirium in the ICU can no longer be thought of as harmless. Rather, it seems to pose serious risks for a patient's long-term and immediate health. Until more detailed data are available to explain the pathway by which ICU delirium leads to LTCI, it will likely be necessary to appeal to neuroscience and gerontology to provide further clues for how to overcome this widespread and devastating public health issue. Although the causes of LTCI after critical illness remain to be fully determined, it is clear that screening for cognitive impairment and delirium in ICU patients is a priority that should be reflected in clinical and research contexts. Although methods of screening patients for delirium have progressed substantially, less is known about how to best assess cognitive impairment in the ICU. Through the development of more sophisticated screening procedures, it is hoped that patients who have early manifestations of LTCI will one day receive targeted care, which in turn will lead to better clinical outcomes.

References

- [1] Van Dijk D, Keizer AM, Diephuis JC, et al. Neurocognitive dysfunction after coronary artery bypass surgery: a systematic review. *The Journal Of Thoracic And Cardiovascular Surgery* 2000;120(4):632–9.

- [2] Halpern NA, Pastores SM, Greenstein RJ. Critical care medicine in the United States 1985–2000: an analysis of bed numbers, use, and costs. *Crit Care Med* 2004;32:1254–9.
- [3] Esteban A, Anzueto A, Alia I, et al. How is mechanical ventilation employed in the intensive care unit? An international utilization review. *Am J Respir Crit Care Med* 2000;161(5):1450–8.
- [4] Cohen IL, Booth FV. Cost containment and mechanical ventilation in the United States. *New Horizons* 1994;2:283–90.
- [5] Angus DC, Kelley MA, Schmitz RJ, et al. Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? *JAMA* 2000;284(21):2762–70.
- [6] Raja PV, Blumenthal JA, Doraiswamy PM. Cognitive deficits following coronary artery bypass grafting: prevalence, prognosis, and therapeutic strategies. *CNS Spectrums* 2004;9(10):763–72.
- [7] Russell JA, Singer J, Bernard G, et al. Changing pattern of organ dysfunction in early human sepsis is related to mortality. *Crit Care Med* 2000;28:3405–11.
- [8] Hopkins RO, Jackson JC. Long-term neurocognitive function after critical illness. *Chest* 2006;130(3):869–78.
- [9] Marquis KA, Curtis JR, Caldwell ES, et al. Neuropsychological sequelae in survivors of ARDS compared with critically ill control patients. *Am J Respir Crit Care Med* 2000;161:A383.
- [10] Jones C, Griffiths RD, Slater T, et al. Significant cognitive dysfunction in non-delirious patients identified during and persisting following critical illness. *Intensive Care Med* 2006.
- [11] Hopkins RO, Weaver LK, Pope D, et al. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;160(1):50–6.
- [12] Hopkins RO, Jackson JC, Wallace CJ. Neurocognitive impairments in ICU patients with prolonged mechanical ventilation. *International Neuropsychological Society 33rd Annual Meeting Program and Abstracts* 2005;61.
- [13] Hopkins RO, Weaver LK, Chan KJ, et al. Quality of life, emotional, and cognitive function following Acute Respiratory Distress Syndrome. *Journal of the International Neuropsychological Society* 2004;10:1005–17.
- [14] Sukantarat KT, Burgess PW, Williamson RCN, et al. Prolonged cognitive dysfunction in survivors of critical illness. *Anaesthesia* 2005;60:847–53.
- [15] Al-Saidi F, McAndrews MP, Cheung AM, et al. Neuropsychological sequelae in ARDS survivors. *Am J Respir Crit Care Med* 2003;167:A737.
- [16] Jackson JC, Gordon SM, Burger D, et al. Acute respiratory distress syndrome and long term cognitive impairment: A case study. *Archives of Clinical Neuropsychology* 2003;18:688.
- [17] Rothenhausler HB, Ehrentraut S, Stoll C, et al. The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. *Gen Hosp Psychiatry* 2001;23(2):90–6.
- [18] Suchyta MR, Hopkins RO, White J. The incidence of cognitive dysfunction after ARDS. *American Journal of Respiratory Crit Care Med* 2004;169:A18.
- [19] Christie JD, DeMissie E, Gaughan C. Validity of a brief telephone-administered battery to assess cognitive function in survivors of the Adult Respiratory Distress Syndrome (ARDS). *American Journal of Respiratory Critical Care Medicine* 2004;169:A781.
- [20] Jackson JC, Hart RP, Gordon SM, et al. Six-month neuropsychological outcome of medical intensive care unit patients. *Crit Care Med* 2003;31(4):1226–34.
- [21] Peterson JF, Pun BT, Dittus RS, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc* 2006;54(3):479–84.
- [22] Otter H, Martin J, Bäsell K, et al. Validity and reliability of the DDS for severity of delirium in the ICU. *Neurocrit Care* 2005;2(2):150–8.
- [23] McCusker J, Cole MG, Dendukuri N, et al. The delirium index, a measure of the severity of delirium: new findings on reliability, validity, and responsiveness. *J Am Geriatr Soc* 2004;52:1744–9.

- [24] de Jonghe JF, Kalisvaart KJ, Timmers JF, et al. Delirium-O-Meter: a nurses' rating scale for monitoring delirium severity in geriatric patients. *International Journal Of Geriatric Psychiatry* 2005;20(12):1158–66.
- [25] Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13(10):818–29.
- [26] Hopkins RO, Weaver LK, Collingridge D, et al. Two-Year Cognitive, Emotional, and Quality-of-Life Outcomes in Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2005;171(4):340–7.
- [27] Christie JD, Biester RCP, Taichman DB, et al. Formation and validation of a telephone battery to assess cognitive function in acute respiratory distress syndrome survivors. *Journal Of Critical Care* 2006;21(2):125–32.
- [28] Elie M, Cole MG, Primeau FJ, et al. Delirium risk factors in elderly hospitalized patients. *J Gen Intern Med* 1998;13(3):204–12.
- [29] Marcantonio ER, Goldman L, Mangione CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA* 1994;271(2):134–9.
- [30] Inouye SK, Schlesinger MJ, Lydon TJ. Delirium: a symptom of how hospital care is failing older persons and a window to improve quality of hospital care. *Am J Med* 1999;106(5):565–73.
- [31] Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA* 1994;272(19):1518–22.
- [32] Dubois MJ, Bergeron N, Dumont M, et al. Delirium in an intensive care unit: a study of risk factors. *Intensive Care Med* 2001;27(8):1297–304.
- [33] Wrigge H, Zinserling J, Stuber F, et al. Effects of mechanical ventilation on release of cytokines into systemic circulation in patients with normal pulmonary function. *Anesthesiology* 2000;93:1413–7.
- [34] Fish DN. Treatment of delirium in the critically ill patient. *Clin Pharm* 1991;10:456–66.
- [35] Francis J. Drug-induced delirium: diagnosis and treatment. *CNS Drugs* 1996;5:103–14.
- [36] Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA* 1996; 275(11):852–7.
- [37] Jones RN, Kiely DK, Bergman M, et al. Delirium persistence: relationship to opioid analgesic use among patients in post-acute care. *AGS* 2004;S57–8.
- [38] Korevaar JC, van Munster BC, de Rooij SE. Risk factors for delirium in acutely admitted elderly patients: a prospective cohort study. *BMC Geriatr* 2005;5:6.
- [39] APA. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association; 1994.
- [40] Dolan MM, Hawkes WG, Zimmerman SI, et al. Delirium on hospital admission in aged hip fracture patients: prediction of mortality and 2-year functional outcomes. *J Gerontol. A Biol Sci Med Sci* 2000;55:M527–34.
- [41] Francis J, Kapoor WN. Prognosis after hospital discharge of older medical patients with delirium. *J Am Geriatr Soc* 1992;40(6):601–6.
- [42] McCusker J, Cole M, Dendukuri N, et al. Delirium in older medical inpatients and subsequent cognitive and functional status: a prospective study. *CMAJ* 2001;165(5):575–83.
- [43] Katz IR, Curyto KJ, TenHave T, et al. Validating the diagnosis of delirium and evaluating its association with deterioration over a one-year period. *Am J Geriatr Psychiatry* 2001;9(2): 148–59.
- [44] Rahkonen T, Luukkainen-Markkula R, Paanilla S, et al. Delirium episode as a sign of undetected dementia among community dwelling subjects: a 2 year follow up study. *Journal of Neurology, Neurosurgery, Psychiatry* 2000;69:519–21.
- [45] Rockwood K, Cosway S, Carver D, et al. The risk of dementia and death after delirium. *Age Ageing* 1999;28(6):551–6.
- [46] Koponen H, Steinbeck U, Mattila E. Delirium among elderly persons admitted to a psychiatric hospital: clinical course during the acute stage and one year follow up. *Acta Psychiatry Scandinavia* 1989;79:579–85.

- [47] Hammerman D. Toward an understanding of frailty. *Ann Intern Med* 1999;130:945–50.
- [48] Nourhashemi F, Andrieu S, Gillett-Guyonet S, et al. Instrumental activities of daily living as a potential marker of frailty: a study of 7364 community dwelling elderly women (the EPIDOS Study). *Journal of Gerontology: Medical Sciences* 2001;56A:M448–53.
- [49] Carlson NR. *Physiology of Behavior*. 9th ed. Boston: MA Allyn & Bacon; 2006.
- [50] Eikelenboom P, Hoogendijk WJG. Do delirium and Alzheimer's dementia share specific pathogenetic mechanisms? *Dementia Geriatr Cogn Disord* 1999;10:319–24.
- [51] Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition—the case for a head-to-toe inflammatory paradigm. *Journal Of The American Geriatrics Society* 2002;50(12):2041–56.
- [52] Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. *Cancer* 2005;104(4):788–93.
- [53] Blennow K, Gottfries CG, Nelson JG. Neurochemistry of aging, in *Geriatric Psychopharmacology*. New York: Marcel Dekker; 1998.
- [54] Watt DF. Review of the syndromes of delirium and confusional states. *Journal of Neurosciences*, 2005. In Press.
- [55] Hopkins RO, Gale SD, Weaver LK. Brain atrophy and cognitive impairment in survivors of acute respiratory distress syndrome. *Brain Inj* 2006;20(3):263–71.
- [56] Hopkins RO, Tate DF, Bigler ED. Anoxia versus traumatic brain injury: amount of tissue loss not etiology, alters cognitive and emotional function. *Neuropsychology* 2005;19:233–42.
- [57] Jackson JC, Gordon SM, Hart RP, et al. The association between delirium and cognitive decline: a review of the empirical literature. *Neuropsychol Rev* 2004;14(2):87–98.
- [58] Koponen H, Hurri L, Stenbäck U, et al. Computed tomography findings in delirium. *The Journal Of Nervous And Mental Disease* 1989;177(4):226–31.
- [59] Suchyta, M.R., A. Jephson, and R.O. Hopkins. Brain MR and CT findings associated with critical illness. *Proceedings of the American Thoracic Society* 2005;4:A426.
- [60] Lerner DM, Rosenstein DL. Neuroimaging in delirium and related conditions. *Seminars in Clinical Neuropsychiatry* 2000;5:98–112.
- [61] Figiel GS, Coffey CE, Djang WT, et al. Brain magnetic resonance imaging findings in ECT-induced delirium. *The Journal Of Neuropsychiatry And Clinical Neurosciences* 1990;2(1):53–8.
- [62] Buckner RL, Snyder AZ, Shannon BJ, et al. Molecular, Structural, and Functional Characterization of Alzheimer's Disease: Evidence for a Relationship between Default Activity, Amyloid, and Memory. *J. Neurosci* 2005;25(34):7709–17.
- [63] Mesulam MM. *Principles of behavioral and cognitive neurology* (2nd ed). Oxford University Press; 2000.
- [64] Joseph JT, Cardoso DL eds. *Functional neuroanatomy: An interactive text and manual*. 2nd ed. Surgical Neurology. Wiley-Liss: Hoboken, NJ; 2004.
- [65] Liu RSN, Lemieux L, Bell GS, et al. A longitudinal study of brain morphometrics using quantitative magnetic resonance imaging and difference image analysis. *NeuroImage* 2003;20(1):22.
- [66] Akiyama H, Meyer JS, Mortel KF, et al. Normal human aging: factors contributing to cerebral atrophy. *Journal of the Neurological Sciences* 1997;152(1):39–49.
- [67] Callahan CM, Hendrie HC, Tierney WM. Documentation and evaluation of cognitive impairment in elderly primary care patients. *Ann Intern Med* 1995;15:422–9.
- [68] Wilkes MM, Navickis RJ. Patient survival after human albumin administration. *Annals of Internal Medicine* 2001;135:149–64.
- [69] Boustani M, Peterson B, Hanson L, et al. Screening for dementia in primary care: a summary of the evidence for the U.S. Preventive services task force. *Ann of Intern Med* 2003;138:927–36.
- [70] Johnson SC, O'Meara ES, Manolio TA, et al. Cognitive impairment and decline are associated with carotid artery disease in patients without clinically evident cerebrovascular disease. *Ann Intern Med* 2004;140:237–47.

- [71] van de Beek D, Schmand B, De Gans J, et al. Cognitive impairment in adults with good recovery after bacterial meningitis. *The Journal of Infectious Diseases* 2002;186:1047–52.
- [72] Wu JH, Haan MN, Liang J, et al. Impact of diabetes on cognitive function among older Latins: a population based cohort study. *J Clin Epidemiol* 2003;56:686–93.
- [73] Rozzini R, Sabe T, Trabucchi M. Cognitive impairment and mortality in elderly patients with heart failure. *Am J Med* 2004;116:137–8.
- [74] Kozora E, Filley CM, Julian LJ, et al. Cognitive functioning in patients with chronic obstructive pulmonary disease and mild hypoxemia compared with patients with mild Alzheimer disease and normal controls. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology* 1999;12:178–83.
- [75] Grant I, Prigatano GP, Heaton RK, et al. Progressive neuropsychologic impairments and hypoxemia: relationship in chronic obstructive pulmonary disease. *Archives of General Psychiatry* 1987;44:999–1006.
- [76] Browne SM, Halligan PW, Wade DT, et al. Postoperative hypoxia is a contributory factor to cognitive impairment after cardiac surgery. *J Thorac Cardiovasc Surg* 2003;126:1061–4.
- [77] van der Post J, Noordzij LA, de Kam ML, et al. Evaluation of tests of central nervous system performance after hypoxemia for a model of cognitive impairment. *J Psychopharmacol* 2002;16:337–43.
- [78] Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Critical Care Medicine* 2002;30(1):119–41.
- [79] Ramsay MA, Savege TM, Simpson BR, et al. Controlled sedation with alphaxalone-alpha-dolone. *British Medical Journal* 1974;2(5920):656–9.
- [80] Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. *Critical Care Medicine* 1999;27(7):1325–9.
- [81] Riker R, Fraser G, Cox P. Continuous infusion of haloperidol controls agitation in critically ill patients. *Crit.Care.Med* 1994;22:433–40.
- [82] Devlin JW, Boleski G, Mlynarek M, et al. Motor activity assessment scale: a valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit. *Crit. Care Med* 1999;27:1271–5.
- [83] De Lemos J, Tweeddale M, Chittock DR. Measuring quality of sedation in adult mechanically ventilated critically ill patients: The Vancouver interaction and calmness scale. *J Clin Epidemiol* 2000;53:908–19.
- [84] Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *American Journal Of Respiratory And Critical Care Medicine* 2002;166(10):1338–44.
- [85] Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA: The Journal Of The American Medical Association* 2003;289(22):2983–91.
- [86] Bergeron N, Dubois MJ, Dumont M, et al. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Medicine* 2001;27(5):859–64.
- [87] Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA: The Journal Of The American Medical Association*; 2001.
- [88] Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Critical Care Medicine* 2001;29(7):1370–9.

Multimodality Monitoring in Neurocritical Care

Katja Elfriede Wartenberg, MD^{a,d},
J. Michael Schmidt, PhD^{a,b},
Stephan A. Mayer, MD, FCCM^{a,b,c,*}

^aNeurological Intensive Care Unit, New York Presbyterian Hospital, Columbia University Medical Center, 710 W. 168th Street, New York, NY 10032, USA

^bDepartment of Neurology, College of Physicians and Surgeons of Columbia University, 710 W. 168th Street, New York, NY 10032, USA

^cDepartment of Neurological Surgery, College of Physicians and Surgeons of Columbia University, 710 W. 168th Street, New York, NY 10032, USA

^dSection of Stroke and Neurological Intensive Care, Department of Neurology, Carl Gustav Carus University Hospital Dresden, Fetscherstrasse 74, 01307 Dresden, Germany

A brief history of monitoring in neurocritical care

Monitoring in most ICUs between 1960 and 1980 was restricted to clinical examination, heart and respiratory rate, blood pressure, oxygen saturation, body temperature, and central venous pressure. With the advent of the pulmonary artery catheter, monitoring of cardiac output and right-sided cardiac filling pressures became possible, providing new understanding and acting as a guide to therapy for the resuscitation of cardiogenic and septic shock.

Neurologic ICUs (NICUs) at that time focused almost exclusively on the care of postoperative neurosurgical patients, and neuromonitoring was restricted primarily to serial neurologic examination and, in some units, intracranial pressure (ICP) monitoring. These “neuro checks” often did not reveal changes in cerebral function until they were irreversible. The idea was to detect clinical deterioration as soon as possible, enabling prompt efforts to reverse or correct any injurious process. This era can be thought of as the age of *clinical neuromonitoring*.

* Corresponding author. Neurological Institute, Columbia University, 710 W. 168th Street, New York, NY 10032, USA.

E-mail address: sam14@columbia.edu (S.A. Mayer).

Between 1980 and 2000, use of ICP monitoring became more widespread, although even today its use is far from routine, particularly when critically injured patients are admitted to nonspecialty NICUs. The accepted paradigm at this time, which can be thought of as the age of *physiologic neuro-monitoring*, was to detect and treat increases in ICP *before* they led to obvious and often irreversible clinical deterioration. Neurocritical care demanded a quick and accurate diagnosis, with monitoring and management based on brain-derived physiologic information to detect secondary injury in its earliest phase. However, at that time, ICP monitoring was the only widely used technique, with jugular venous oxygen saturation monitoring used at only a small number of centers focusing on neurotrauma.

In our view, the future of neurocritical care will bring us into the age of multimodality monitoring and *neurophysiologic decision support*. Advanced monitoring techniques that can provide real-time information regarding the relative health or distress of the brain, such as brain tissue oxygen tension, signal-processed continuous electroencephalography, and neurochemical analysis using microdialysis will be used to create and maintain an optimal physiologic environment for the comatose injured brain. Rather than using neuromonitoring to alarm the clinician when critical deviations occur, real-time physiologic end points will be used to guide goal-directed therapy, in the same way that targeted therapy to avoid a low venous oxygen saturation in the acute phase of septic shock has been shown to improve survival. Conceptually, rather than reacting to harmful physiologic intracranial events, the idea will be to prevent them altogether with a proactive strategy (Fig. 1).

In the twenty-first century, advanced neuromonitoring techniques and improvements in the surgical, endovascular, and medical management of intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), acute ischemic stroke, and severe traumatic brain injury (TBI) will contribute to improved outcomes from these devastating diseases. Preliminary experiences with real-time monitoring of brain oxygen tension, metabolism, and continuous electroencephalography in patients with severe brain injury already allow prediction of long term-outcome [1–6]. These associations with patient-centered outcomes provide a rationale for using these monitoring techniques as end points for therapy during the acute phase of injury. Future clinical trials will then be needed to demonstrate that goal-directed ICU therapy produces better outcomes. This review provides an overview of the current state of multimodality monitoring in neurocritical care.

Cerebral perfusion and intracranial pressure

Cerebral perfusion and intracranial pressure (CPP) is the driving force of cerebral blood flow (CBF) and is the principal determinant of the autoregulatory response of the cerebral vasculature. Under normal physiologic conditions, a mean arterial pressure (MAP) of 80 to 100 mm Hg and an ICP of

Logic Model of the Paradigm Shift to a New Proactive Treatment Model

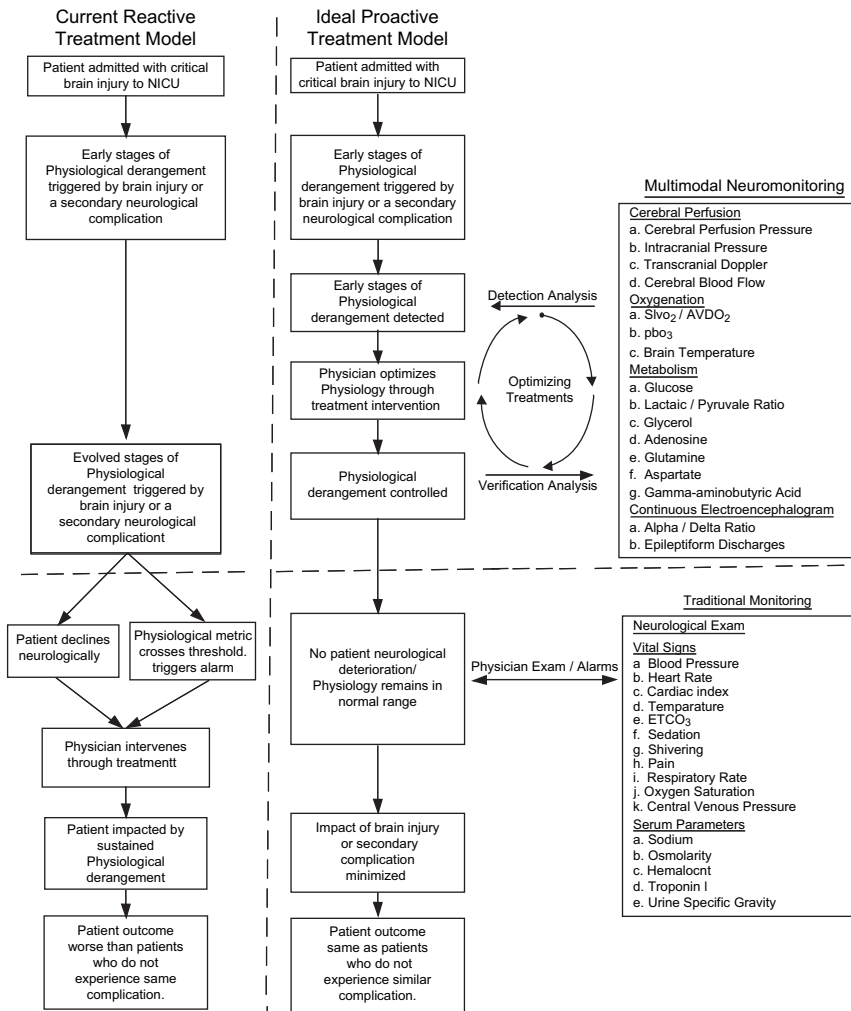


Fig. 1. Simultaneous monitoring of brain oxygen tension (PBO_2), brain temperature, ICP, CPP, CBF, and cerebral metabolism in addition to TCD ultrasonography, cEEG, and cardiovascular parameters offers the potential to impact neurologic outcome by enabling detection of early changes in brain physiology and is shifting the treatment from a reactive model to a proactive one. (From Wartenberg KE, Schmidt JM, Krieger DW. The future of the brain support: multimodality monitoring. *Future Neurology* 2006;1:480; with permission.)

5 to 10 mm Hg generate a CPP of 70 to 85 mm Hg [7]. However, true CPP may vary ± 27 mm Hg from measurements with MAP [8]. Accurate MAP measurements require the placement of an arterial pressure catheter. The transducer of the arterial pressure catheter should be positioned at the level

of the foramen of Monroe to accurately measure CPP. Transcranial Doppler (TCD) ultrasonography has been proposed as a noninvasive method to assess the adequacy of CPP [8], but it requires constant adjustment of probe placement by experienced staff.

ICP values can be obtained by inserting ventricular, subdural, epidural, or intraparenchymal microtransducers. The microtransducers have the advantage of low infection and hemorrhage rates, but can have a considerable zero-drift over monitoring periods of a few days and cannot be re-zeroed after insertion. Intraventricular drains connected to external pressure transducers are still the gold standard for ICP monitoring. They provide the most accurate measurements, allow for ICP control by drainage of cerebrospinal fluid (CSF), and can be re-zeroed externally. However, the risk of infection is approximately 10% and increases with longer duration of the monitoring period. Antibiotic coating of intraventricular drains may prevent or delay the onset of infectious ventriculitis [9–12]. Most ICP monitors are MRI-compatible.

ICP waveforms contain additional valuable information regarding compliance of the cerebrospinal system, CBF autoregulation, and CSF absorption capacity (Fig. 2) [9]. Continuous assessment of brain compliance with the Spiegelberg Brain Compliance Monitor and ICP pulse waveform analysis at the bedside may be helpful to predict impending neurologic decompensation and herniation [9].

An interesting approach to noninvasive ICP monitoring is tissue resonance analysis [13]. Unilateral mass effect can be discovered by way of TCD ultrasonography demonstrating depressed ipsilateral mean flow velocities, increased ipsilateral pulsatility index, and reduced ipsilateral-to-

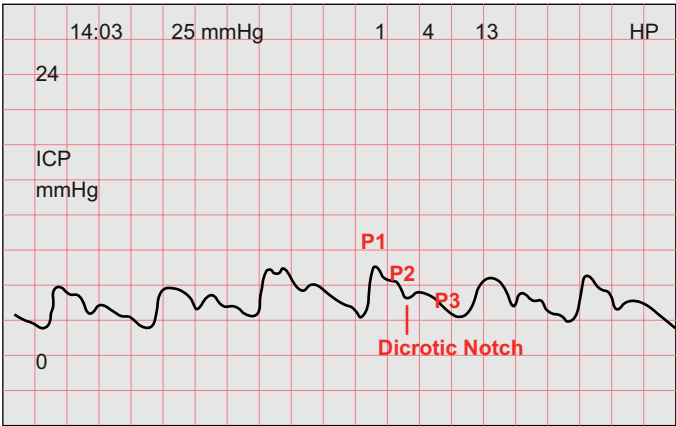


Fig. 2. Example of intracranial pressure waveforms. P1, percussion wave with a sharp and constant amplitude; P2, tidal wave (ends at the dicrotic notch); P3, dicrotic wave. These waveforms are influenced by arterial and venous pressure, blood volume, CSF volume, and mass lesions.

contralateral pulsatility index ratio in ICH with a volume greater than 25 mL [14]. Further studies are needed to evaluate whether ultrasound monitoring of hemispheric mass lesions can complement ICP monitoring by providing information regarding compartmentalized mass effect.

Invasive ICP and CPP monitoring is a standard of care in most neurocritical care units, but the management protocols and therapeutic targets that are used differ considerably. Most brain injuries result in disturbed autoregulation, meaning that CPP and ICP monitoring is necessary to ensure normal cerebral perfusion. Moreover, in patients with depressed mental status (Glasgow Coma Scale score ≤ 8), ICP monitoring is considered a standard of care given the insensitivity of the clinical examination for detecting clinical deterioration. For example, ICP elevations after SAH may result from CSF outflow obstruction and cerebral edema and cause secondary neurologic injury [15]. ICP control is essential before treatment of the aneurysm and is associated with more favorable outcome by protection against cortical injury and facilitation of surgical exposure of the aneurysm [16].

With autoregulatory failure, sufficient brain perfusion is even more dependent on CPP (Fig. 3). A minimum CPP threshold of 60 mm Hg is generally accepted, but the question remains which CPP is optimal for each

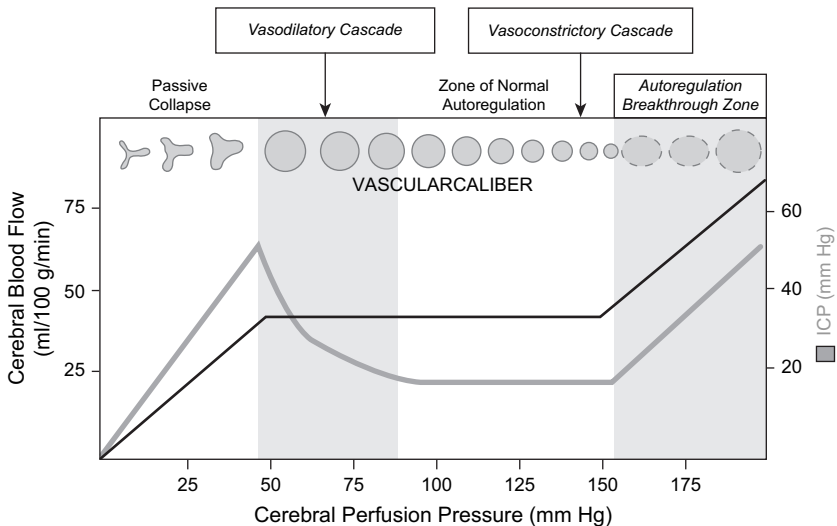


Fig. 3. Relationship between extremes of cerebral perfusion pressure (CPP) and intracranial pressure (ICP) in states of normal (black line) and reduced intracranial compliance (gray line). In the vasodilatory cascade zone, CPP insufficiency and intact pressure autoregulation lead to reflex cerebral vasodilation and increased ICP; the treatment is to raise CPP. In the autoregulation breakthrough zone, pressure and volume overload, which overwhelms the brain's capacity to autoregulate, leads to increased cerebral blood volume and ICP; the treatment is to lower CPP. (Reproduced from Rose JA, Mayer SA. Optimizing blood pressure in neurological emergencies. *Neurocrit Care* 2004;1:289; with kind permission of Springer Science and Business Media.)

individual patient at different times [9,17]. Hypoxic and ischemic events have been observed despite maintaining a CPP of > 70 mm Hg in patients with TBI [18]. On the other hand, once the CPP reaches the lower threshold of the autoregulatory breakthrough zone, hyperemia and secondary increase in ICP may result [7]. Current management of patients with severe brain injury resulting in intracranial hypertension should be directed at ICP and CPP management. To balance the issue of hypo- and hyperperfusion, additional guidance can be provided by monitoring of jugular venous oxygen saturation, microdialysis (eg, lactate/pyruvate ratio), global or regional CBF, and brain tissue oxygen pressure [7,18–20].

Cerebral blood flow

Cerebral blood flow can normally be maintained over a certain range of CPP. This relationship is nonlinear in injured brain as a consequence of disturbed autoregulation [21]. Therefore, direct monitoring of CBF would be helpful for managing patients with severe brain injury. The Kety-Schmidt Technique, the gold standard of CBF measurement, involves direct measurement of arterial and jugular venous concentrations of an inert, freely diffusible indicator such as nitrous oxide and calculation of global CBF from the uptake rate of the indicator into cerebral tissue [22,23]. CBF can be estimated with use of radioisotopes such as krypton-85 or xenon-133 combined with compact scintillation detectors and microprocessors [24,25], the still-developing indocyanine green dye dilution technique using noninvasive near-infrared spectroscopy [26], and the thermodilution method. Thermodilution CBF measurements are based on bedside recording of a temperature difference between the site of constant injection of a blood compatible fluid with a lower temperature into the jugular bulb and 25 mm downstream from the injection site [27]. Other techniques that assess CBF include xenon-enhanced CT scanning [28], single photon emission CT (SPECT), oxygen-15-positron emission tomography (PET), perfusion CT, or perfusion-weighted magnetic resonance (MR) imaging [29].

Alternatively, CBF can be estimated continuously and invasively by way of laser Doppler flowmetry and thermal diffusion limited to a specific region of interest (Bowman Perfusion Monitor). Laser Doppler flowmetry assesses the volume or concentration and the velocity of red blood cells in a small sample volume (1 mm^3), which generates a flow signal; this yields a qualitative estimate of local CBF [30]. Some laser Doppler flowmetry probes are compatible with MRI. Most of the probes are susceptible to artifacts. The thermal diffusion method provides a quantitative estimate of regional CBF in milliliters per 100 g per minute by using thermal diffusion based on the tissue's ability for dissipation of heat [31]. The MRI compatibility of the Bowman Perfusion Monitor is uncertain.

In comparison with xenon-enhanced CT, a cutoff for CBF of 15 mL/100 g/min was identified as a threshold for diagnosis of symptomatic vasospasm

in SAH for the thermal diffusion method (Table 1) [32]. In small prospective series, both ischemia rebound hyperemia related to temporary arterial clip placement during aneurysm surgery could be identified with a thermal diffusion probe [33]. A study of SAH and TBI patients found a correlation between CBF obtained by the thermal diffusion method and PBO_2 , indicating that tissue oxygen levels were determined by regional CBF [34]. This kind of real-time continuous perfusion assessment provides exciting new perspectives into regional cerebral autoregulation, especially if directly time-correlated with ICP and CPP.

Transcranial Doppler evaluation of cerebral autoregulation

The autoregulatory reserve of the cerebral vasculature can be assessed with TCD ultrasonography using several methods [35]:

- observation of alterations of flow velocity (FV) in the middle cerebral artery (MCA) during titration of MAP with vasopressors and calculation of the rise of autoregulation as percentage increase in vascular resistance (CPP/FV) divided by the percentage rise in CPP [36];
- cerebrovascular reactivity to carbon dioxide assessed by way of TCD ultrasonography provides information about the functional status of cerebral vasoreactivity and has been found to correlate with outcome after head trauma [37], but may increase ICP when the cerebral autoregulatory reserve has been exhausted [38];
- a stepwise decrease in arterial blood pressure by deflation of compressed leg cuffs during continuous TCD MCA FV recording can reveal the absence of normal pressure autoregulation [36];
- in the transient hyperemic response test, short-term compression of the common carotid artery normally results in a decrease in ipsilateral MCA FV, followed by transient hyperemia as a result of distal vasodilatation. The presence of the hyperemic response correlates with better outcome after head injury [39];
- with observation of the phase shift between continuously monitored MCA FV and superimposed respiratory and arterial blood pressure waves, a phase shift of zero suggests absent autoregulation, whereas a phase shift of 90° indicates intact autoregulation [40];
- the moving correlation coefficient between mean CPP and mean FV is positive when autoregulation is disturbed and zero or negative when autoregulation is intact (positive coefficients were linked to worse outcome in head trauma patients) [41]; or
- simultaneous recording of flow velocities in both MCAs combined with noninvasive beat to beat finger blood pressure measurements can allow for assessment of diurnal variations of FV, regional autoregulation, and the dependency of FV on cardiac output and stroke volume [42].

Table 1

Multimodal monitoring reference values for cerebral health and pathologic conditions

Multimodal monitoring device	Physiologic parameter	Normal range	Pathologic condition
Continuous EEG	Brain activity	Alpha/delta ratio <50%	Alpha/delta ratio > 50%
	Epileptiform discharges	No epileptiform discharges	Epileptiform discharges
		Reactivity to stimuli	No reactivity
Transcranial Doppler ultrasound	Mean blood flow velocity	FVm MCA: 30–75 cm/s	MCA FVm 140–200 cm/s; intermediate probability of vasospasm after SAH
	Pulsatility index	FVm ACA: 20–75 cm/s	MCA FVm > 200 cm/s; high probability of vasospasm after SAH
	CO ₂ reactivity	FVm PCA: 15–55 cm/s	CO ₂ R; <2% increase
	Lindgaard index	FVm/VA: 13–66 cm/s	Ipsilateral-to-contralateral Pi ratio > 1.25; suspicious for compartmentalized ICP and mass effect
		Pi: 0.9–1.2	LgI > 3:1; mild vasospasm
		CO ₂ R: ≥2% increase	LgI > 6:1; severe vasospasm
		LgI <3:1	
ICP monitor	ICP	<20 mm Hg	≥20 mm Hg
ICP monitor and arterial blood pressure catheter	CPP	≥60 mm Hg	≤60 mm Hg
NeuroSensor cerebral blood flow and intracranial pressure system (Bowman perfusion monitor)	CBF ^a	50 mL/100 g/min	≤20 mL/100 g/min; loss of neuronal function and threshold for ischemia
Jugular venous oximetry	SjO ₂	50%–75%	<50%; increased OEF, indicative ischemia
			>75%; reduced OEF, indicative of hyperemia
Brain tissue oxygen monitor (Licox, Neurotrend)	PBO ₂ ^a	20 mm Hg in white matter	<20 mm Hg indicative of cerebral hypoxia
		35–40 mm Hg in gray matter	<8 mm Hg definite hypoxia/ischemia
	Brain tissue carbon dioxide ^a	43–50 mm Hg	>60 mm Hg in brain tissue hypercarbia
	Brain tissue pH ^a	7.2	<7.15 indicative of tissue acidosis
	Brain temperature ^a	Correlates with core body temperature (normal 37°C)	<36.8°C or >37.2°C

Cerebral Microdialysis

Glucose ^a	1170 ± 900 (1000–4000)	100 ± 200 µmol/L
Lactate ^a	µmol/L (1500–2000 µmol/L)	8900 ± 6500 µmol/L
Pyruvate ^a	2900 ± 900 (1000–3000)	31 ± 47 µmol/L
Lactate/pyruvate ratio ^a	µmol/L (2000 µmol/L)	>40 indicative of ischemia and anaerobic metabolism
Glutamate ^a	166 ± 47 µmol/L (120 µmol/L)	381 ± 236 µmol/L
Glycerol ^a	10–40 (15–20)	573 ± 427 µmol/L
	16 ± 16 (2–10) µmol/L	Increased glutamate and lactate: earliest markers of impending ischemia, followed by increased actate/pyruvate ratio, decreased glucose and increased glycerol
	82 ± 44 (10–50) µmol/L	

^a Suggested thresholds are drawn from a summary of experimental data cited in the text.

Cutoff values for VFm and PI represent the standard values of our Doppler ultrasound laboratory.

Abbreviations: CO₂R, CO₂ reactivity; FVm, mean blood flow velocity; MCA, middle cerebral artery; OEF, oxygen extraction fraction; Pi, pulsatility index; LgI, Lindegaard index; SAH, subarachnoid hemorrhage.

Modified from Wartenberg KE, Mayer SA. multimodal brain monitoring in the neurological intensive care unit: where does continuous EEG fit in? J Clin Neurophysiol 2005;22:124–7; with permission.

All of these methodologies are capable of qualitative assessment of cerebral autoregulation, but most are not available continuously. None of these methods has an established role in routine clinical practice, which may be due in large part to operator expertise and time required to perform these studies.

Further applications of transcranial Doppler ultrasonography

TCD ultrasonography has long been used to support the diagnosis of arterial vasospasm after SAH and to identify patients at risk for development of delayed ischemia. Correlation of increased mean FV in proximal intracranial vasculature with the diagnosis of vasospasm by cerebral angiography has been established [43,44]. Vasospasm is defined by an increase of mean FV above 200 cm/s by TCD ultrasonography and suspected if mean FV ranges from 140 to 200 cm/s. Comparing the highest FV in the MCA with the highest FV in the extracranial internal carotid artery (Lindegaard Index) eliminates the influence of systemically increased blood flow causing hyperemia (see Table 1) [45]. Vasospasm is considered to be present if the Lindegaard index is greater than 3:1 [45]. Detection of high-intensity transient signals, which are thought to reflect microemboli in stroke patients with cardiac valvular disease, patent foramen ovale, and carotid disease, is another application of TCD ultrasonography [46]. TCD studies have shown high specificity for the confirmation of intracranial circulatory arrest in brain death. Brief systolic forward flow spikes with reversed or absent diastolic flow found bilaterally or in three different arteries are accepted TCD criteria for supporting the diagnosis of brain death [47,48].

Application of TCD ultrasonography for diagnostic monitoring requires experienced and skilled operators. Examination of 200 patients is required to be considered adept at the technique [49]. Other limitations of TCD ultrasonography include inadequacy of the acoustic windows (5%–20%), dependency of the accuracy of the flow velocities on the angle of insonation, and anatomic variants [50].

New developments include continuous TCD monitoring, which requires constant readjustment of the probes, and color-coded transcranial Doppler (TCCD). TCCD can visualize the entire circle of Willis, turbulences within the blood vessels, direction of flow, and increased flow velocities. Direct sampling of defined volumes within blood vessels and obtaining angle-corrected flow velocities provide improved accuracy of measurement [49].

Cerebral oxygenation monitoring

Monitoring of cerebral oxygenation after brain injury may lead to the detection or prevention of secondary episodes of ischemia. There are four methods of measuring brain oxygenation: jugular venous bulb oximetry,

direct brain tissue oxygen tension measurement, near infrared spectroscopy, and oxygen-15 PET [29].

Jugular venous oxygen saturation

Retrograde placement of a jugular venous catheter equipped with an oximeter can provide continuous measurements of jugular venous oxygen saturation (S_{jvO_2}). It is advisable to cannulate the dominant internal jugular vein to correctly assess global cerebral oxygenation. The dominant internal jugular vein can be determined by compression of each internal jugular vein, observing the greater ICP rise if an ICP monitor is present. The catheter tip should be positioned in the jugular bulb and the position confirmed by lateral skull radiograph. After the insertion and every 8 to 12 hours the catheter requires calibration [51,52]. Jugular bulb catheters are compatible with MRI.

S_{jvO_2} is the result of the difference between cerebral oxygen delivery (supply) and the cerebral metabolic rate of oxygen (demand), given that arterial oxyhemoglobin saturation, hemoglobin concentration, and the hemoglobin dissociation curve remain stable. It provides an indirect measurement of CBF. If S_{jvO_2} is low ($<50\%$ for >10 minutes in duration) it indicates hypoperfusion (decreased supply) or an increase in cerebral metabolism (increased demand) (see Table 1). The arteriovenous difference in oxygen supply ($AVDO_2 = CMRO_2/CBF$, $CMRO_2$ = cerebral metabolic rate of oxygen consumption) is a better estimate of the balance between cerebral metabolism and blood flow [21]. Changes in S_{jvO_2} should be confirmed by measuring the oxygen saturation in a blood sample withdrawn from the jugular venous catheter, and the catheter should be recalibrated if the difference is $>4\%$ [51]. Jugular venous oximetry is mainly applied in comatose patients ($GCS \leq 8$) with head trauma, where frequent episodes of cerebral venous oxygen desaturation secondary to hypocapnia, hypoperfusion, and increased ICP are found within the first 48 hours [53]. Monitoring of S_{jvO_2} can also be used in the treatment of SAH [54] and during neurosurgical procedures [55].

Reliability of jugular venous oximetry is limited by changes in arterial oxygen content, hemodilution, prone position of the jugular bulb catheter, necessity for frequent calibrations, and infrequent complications related to catheter insertion such as infection, increase in ICP, thrombosis, arterial puncture, and pneumothorax [52]. Jugular venous oximetry reflects global cerebral oxygenation and does not detect regional ischemia in smaller regions of the brain ipsilateral to the catheter or in the contralateral hemisphere [56].

Brain tissue oxygen pressure

Brain tissue oxygen tension of a region of interest can be measured continuously with a small flexible microcatheter inserted into brain parenchyma.

The brain tissue oxygen pressure (PBO_2) value is a marker of the balance between regional oxygen supply and use. Depending on the device, either ICP and brain temperature (Licox, Integra Neurosciences) or the tissue partial pressure of carbon dioxide ($PBCO_2$) and pH (Neurotrend, Johnson & Johnson) can be monitored in addition to PBO_2 . The Licox device measures tissue oxygenation through a polarographic technique by means of a Clark electrode, whereas the Neurotrend uses “optimal luminescence” to measure pH, $PBCO_2$, and PBO_2 [57,58]. The catheter can be inserted directly into a given region of interest, eg, any hypoperfused area as determined by CT or MRI perfusion studies, and preferably should pass through gray matter into white matter for optimal value referencing and data comparison. The catheter may either be tunneled after craniotomy or placed through a double or triple lumen bolt (Fig. 4). The measured tissue volume is approximately 17 mm^3 . Normal PBO_2 varies depending on the region being measured; levels are highest in regions with a dense population of neurons such as cortex and hippocampus and lower in white matter [59]. Measured PBO_2 and amplitude of changes are generally lower with Neurotrend compared with Licox device [60]. Licox and Neurotrend probes are generally compatible with MRI, but may cause artifact in the region of interest.

Monitoring of PBO_2 using Licox probes has been validated in comparison with fiberoptic jugular oxygen saturation monitoring, xenon-enhanced CT scanning, and SPECT to determine an ischemic threshold. In a study, CBF levels of $18\text{ mL}/100\text{ g}/\text{min}$ by xenon-enhanced CT corresponded to a PBO_2 of 22 mm Hg [61]. During episodes of ischemia as determined by SPECT PBO_2 averaged to $10 \pm 5\text{ mm Hg}$ compared with $37 \pm 12\text{ mm Hg}$ in normal brain [62]. The likelihood of mortality after severe TBI is increased with prolonged periods with PBO_2 reduction $<15\text{ mm Hg}$, or with any value $<8\text{ mm Hg}$ [63,64]. In TBI patients, jugular venous oxygen desaturations below 50%, which indicate a marked global reduction in oxygen delivery, were shown to correlate with critically reduced mean PBO_2 level of 8.5 mm Hg [65]. In a study of 24 patients with TBI, PBO_2 was identified

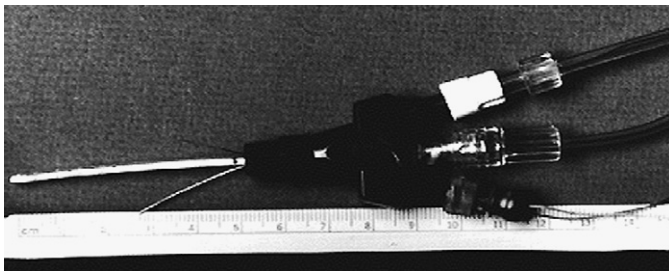


Fig. 4. Photograph of a triple-lumen transcranial bolt for fixation of the microdialysis probe (top), along with an oxygen sensor (lower). (From Wartenberg KE, Mayer SA. Multimodal brain monitoring in the neurological intensive care unit: where does continuous EEG fit in? *J Clin Neurophysiol* 2005;22:124–7; with permission.)

as the most powerful predictor of outcome in a multivariate model; levels consistently exceeding 35 mm Hg correlated with good recovery, 26 to 35 mm Hg corresponded with moderate to severe disability, and levels below 25 mm Hg correlated with poor outcome [2]. In regions of focal pathology after TBI, SjvO₂ monitoring was found to be insensitive to critical PBO₂ reductions detected with a Licox probe [66]. In a larger study comparing PBO₂ and SjvO₂ monitoring, the sensitivity to detect global cerebral ischemia was 64% for PBO₂ catheters and 70% for SjvO₂ catheters; in 90% of the ischemic episodes, PBO₂ and SjvO₂ decreased together. The sensitivity for identification of ischemia due to intracranial hypertension or systemic hypotension by the two methods was not different, but SjvO₂ was significantly more sensitive during ischemic episodes caused by hypocapnia [51].

Based on these studies, the cutoff point for cerebral ischemia with PBO₂ monitoring seems to be in the range of 8 to 25 mm Hg (see Table 1). A small preliminary nonrandomized study comparing ICP/CPP directed management (ICP <20 mm Hg, CPP >60 mm Hg) with PBO₂-targeted therapy (PBO₂ >25 mm Hg) in 53 patients with severe TBI was the first to demonstrate a trend toward decreased mortality with PBO₂-targeted management strategy [67]. In another study, 52 patients with severe TBI were treated with normobaric hyperoxia for 24 hours within 6 hours after admission. Compared with historical controls, hyperoxia treatment resulted in increased PBO₂ levels, reduced levels of glutamate and lactate in cerebral microdialysate that extended beyond the 24-hour treatment window, slightly decreased ICP, and a trend toward higher Glasgow Outcome Scale scores 6 months after injury [68].

Brain oxygen tension measurements have mainly been studied in patients with severe TBI, SAH, and large hemispheric infarctions and in patients undergoing neurosurgical procedures. PBO₂ monitoring can provide real-time information regarding autoregulation (Figs. 5 and 6) and has been shown to have a clear impact on the management of patients with TBI and large hemispheric infarction [18,67,69]. Multimodality monitoring, which integrates data from multiple physiologic monitors, is capable of showing strong intercorrelations between PBO₂ and various drivers of brain perfusion, including MAP, CPP, and end tidal carbon dioxide (CO₂) (see Fig. 6) [2,20,51,59,68,70–80]. Novel methods for correlational data analysis and display may enhance the ability of clinicians to understand complex physiologic relationships and identify optimal physiologic targets (see Figs. 1 and 6). PBO₂ monitoring allows for the determination of critical perfusion thresholds [18,20], identification of impaired autoregulation in large hemispheric infarction by means of a pressure oxygen reactivity index (see Fig. 6) [6], and monitoring for ischemia during hyperventilation [81,82], vasospasm [83,84], and hypothermia for severe TBI [85]. It also contributes to better understanding of the pathophysiology of the brain. Appropriate probe placement into the region of interest and probe depth are key for successful monitoring, optimization of cerebral oxygenation and CBF, and prediction of prognosis. PBO₂

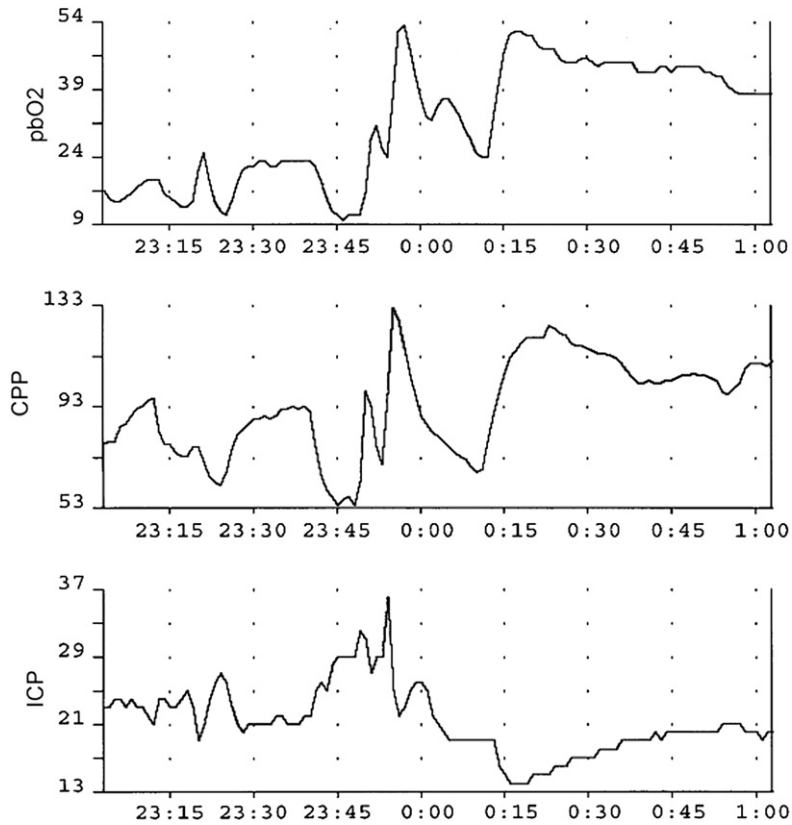


Fig. 5. Real-time relationship of the physiological parameters brain oxygen tension (PBO₂), cerebral perfusion pressure (CPP), and intracranial pressure (ICP) over 2 hours in a patients with intracerebral hemorrhage complicated by intracranial hypertension. Note the striking parallel relationship between PBO₂ and CPP, indicative of autoregulatory failure. (From Wartenberg KE, Schmidt JM, Krieger DW. The future of the brain support: Multimodality monitoring. *Future Neurology* 2006;1(4):473; with permission.)

monitoring may be most useful in brain injury with suspected regional ischemia such as traumatic brain injury, SAH, and ischemic stroke.

Near infrared spectroscopy

Near infrared spectroscopy (rSO₂) is a noninvasive technique to measure regional cerebral oxygen saturation by analyzing the difference of absorption spectra of oxygenated and deoxygenated hemoglobin and cytochrome aa₃. Simultaneous monitoring of transmittance across the brain at two or more wavelengths enables alterations of optical attenuation of the spectra to be converted into changes of cerebral oxygenation [86,87]. Current

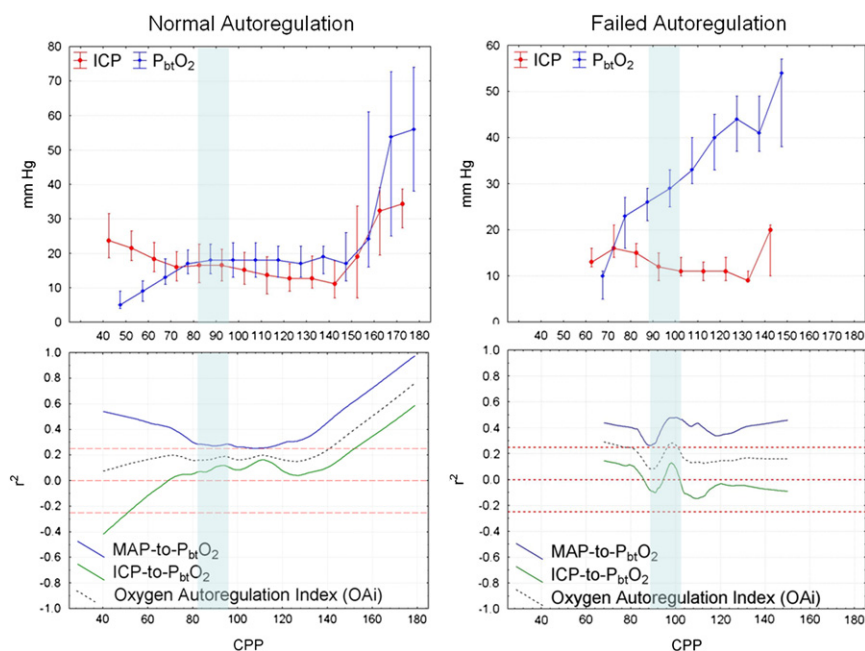


Fig. 6. Use of PBO₂ monitoring for the evaluation of cerebral autoregulation. Top panels show plots of PBO₂ and ICP as a function of CPP. Bottom panels show the correlation coefficients between PBO₂-MAP and PBO₂-ICP.

methods include time-resolved, spatially resolved, and phase-resolved spectroscopy [88]. The change in total hemoglobin is directly related to the change in blood volume [89]. The INVOS system provides a numerical value for oxygen saturation using rSO₂; 60% to 80% has been reported as the normal range [90]. NIRO oximeters continuously present values for oxygenated and total hemoglobin concentration, cytochrome aa₃, and a tissue oxygen index [91].

Applications of continuous cerebral oxygen saturation measurements with good sensitivity and specificity in adults include detection of changes during carotid cross-clamping during carotid endarterectomy [88,92] and during cardiac surgery [93]. The combination of indocyanine green dye dilution and near infrared spectroscopy might assist in the detection and treatment of cerebral vasospasm causing delayed cerebral ischemic deficit after SAH [94] and in the assessment of perfusion reductions in acute ischemic stroke [95]. The changes of hemodynamics and cerebral oxygenation acquired by rSO₂ in ventilated newborns with hypoxic-ischemic encephalopathy were reconstructed to a three-dimensional image using optical tomography to map brain structure and physiology [89].

Infrared spectroscopy is attractive because it is noninvasive and applied simply by attaching pads to the forehead or other regions of interest.

However, concerns have been raised about the limited and variable penetration of infrared light through the skull (2–3 mm, limited to gray matter), contamination by extra- and intracranial sources (mixture of capillary, venous, and arterial blood), and uniform distribution of infrared light in the CSF layer. The degree of scatter of infrared light in adults is unpredictable, especially in the presence of scalp swelling and hematomas [88,96,97]. In a small series comparing rSO₂ of dead and healthy subjects using the INVOS device, 6 out of 18 dead showed rSO₂ values above the lowest obtained values for healthy subjects, raising further doubts about the validity of these measurements [98]. These disadvantages and inconsistent impact of monitoring of decreased oxygenation on neurologic outcome [99–101] have restricted the use of near infrared spectroscopy for adults in the NICU.

Cerebral metabolism

Brain metabolism can be assessed by PET and magnetic resonance spectroscopy, jugular venous oxygen saturation, CBF monitoring, and microdialysis. PET scanning gives a topographic overview of glucose metabolism, and magnetic resonance spectroscopy demonstrates lactate content of a particular cerebral structure qualitatively. The cerebral metabolic rate of oxygen (CMRO₂) represents the product of CBF and AVDO₂ and can be obtained by simultaneous recording of hemispheric CBF (calculated as the average of 16 hemispheric brain regions using the intracarotid ¹³³xenon washout method) and AVDO₂ (obtained by jugular venous oxygen saturation monitoring) [102]. The relationship between CMRO₂ and CBF allows for an estimate of the balance between cerebral metabolism and blood flow, but does not offer the opportunity for simple continuous real-time assessment of cerebral metabolism [56].

With the introduction of cerebral microdialysis, it became possible to monitor neurotransmitters (glutamate), substrates (glucose), metabolites (lactate, pyruvate), and other extracellular neurochemicals (glycerol, acetylcholine, choline) in the extracellular space of specific brain regions in hourly intervals at the bedside (Fig. 7). With microdialysis, a 0.62-mm-wide catheter lined with a polyamide dialysis membrane at the tip is placed into the brain and perfused with Ringer solution or normal saline at ultra-low flow rates (0.1–2.0 µL/min) with a precision pump. Molecules below the cut-off size of the semipermeable membrane (usually 10,000–20,000 daltons) diffuse from the extracellular space into the perfusion fluid, which is collected into vials [103–105]. The diffusion of glucose, lactate, pyruvate, glutamate, acetylcholine, choline, and glycerol from the surrounding brain tissue into the perfusion fluid is approximately 70% at a flow rate of 0.3 µL/min [106]. The vials are changed every 10 to 60 minutes and analyzed by enzyme spectrophotometry or high-performance liquid chromatography at the bedside [103–105]. Recovery of cerebral metabolites into dialysate is maximized

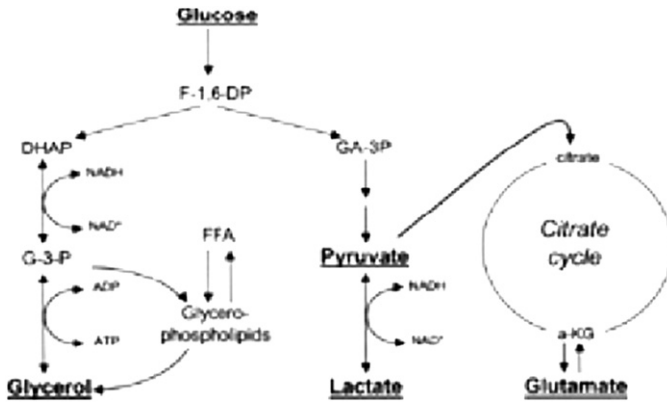


Fig. 7. Simplified diagram of intermediary metabolism of the glycolytic chain and its relation to the formation of glycerol and glycerophospholipids and to the citric acid cycle. Abbreviations: a-KG, a-ketoglutarate; DHAP, dihydroxyacetone-phosphate; F-1,6-DP, fructose-1,6-diphosphate; FFA, free fatty acids; G-3-P, glycerol-3-phosphate; GA-3P, glyceraldehydes-3-phosphate. Underlining indicates metabolites that are measured by microdialysis. (Adapted from Wartenberg KE, Schmidt JM, Krieger DW. The future of the brain support: Multimodality monitoring. *Future Neurology* 2006;1(4):475; with permission.)

by increasing the length of the membrane, decreasing the flow rate, and increasing the size of the membrane pores. Semipermeable membranes with a higher limit in size (100,000–300,000 daltons) also allow for the passage of polypeptides and proteins from the extracellular space, such as cytokines, antibiotics, and free phenytoin. Recovery rates for smaller relevant biochemical markers through a membrane with a larger cutoff may be similar to those obtained with the standard microdialysis catheter (cutoff 20,000 daltons) [106–109]. However, microdialysis of larger proteins require slower buffer flow rates, large pore probes, and attention to water loss from the probe [110]. The microdialysis catheter can be placed into the cerebral parenchyma tunneled underneath the scalp through a craniotomy site, through a burrhole, or directly through a bolt fixed to the cranium [103–105]. They are MRI-compatible.

All substances pass the interstitial space between cells and blood capillaries. Monitoring the interstitial fluids provides important information about the biochemistry of neurons and glia potentially subjected to ischemia, hyperemia, trauma, vasospasm, seizures, hemorrhage, and neurosurgical and medical interventions [104,105]. The catheter should be inserted into areas at risk of ischemia such as the vascular territory most likely affected by vasospasm or brain regions surrounding a mass lesion, or in a standardized location such as the right frontal lobe in diffuse brain injury [105]. A decrease in glucose is thought to signify reduced capillary perfusion, decreased systemic supply, or increased cellular uptake of glucose. In the context of multimodality monitoring, simultaneous measurements of cerebral oxygen tension and cerebral blood flow is thought to clarify whether a decrease in

glucose is due to ischemia (eg, when accompanied by a reduction in CBF and PBO₂), or caused by hypermetabolism (normal or increased CBF and PBO₂) [2]. Alternatively, an increase in dialysate glucose may be due to hyperemia (increased supply), increased systemic glucose levels, or decreased cellular metabolism. Under aerobic conditions, glucose gets metabolized to pyruvate-producing adenosine triphosphate (see Fig. 7).

During hypoxia and ischemia, the end product of pyruvate is lactate and results in an increase of the lactate/pyruvate ratio [111,112]. The diagnosis of an ongoing ischemic event may be further supported by a simultaneous decrease in CBF and PBO₂. Ischemia also results in a release of glutamate. Glycerol is an end product of lipolysis during destruction of cell membranes caused by energy failure. Choline is also released from damaged cell membranes. These changes in the penumbral extracellular milieu often precede the manifestation of definite neurologic deficits. Other substances that can be measured include adenosine, urea, amino acids, nitrate, and nitrite concentrations [59].

Microdialysis monitoring has been shown to be useful in patients with severe TBI with regional or global ischemia [2,105,111–117], SAH and acute or delayed ischemia [71,105,118–120], large hemispheric ischemic stroke [6,121–123], ICH [124], and intraoperatively when episodes of regional ischemia may occur [125–128]. In patients with SAH, metabolic derangements seen by microdialysis are a better predictor of symptomatic vasospasm than TCD ultrasonography and cerebral angiography [118]. Increased lactate/glucose ratios [111,112] as well as reduced glucose along with elevated lactate and hypoxia [2] were found to be predictive of poor outcome after TBI. After ICH, glutamate levels are elevated in the perihematomal zone and decrease with stereotactic aspiration and thrombolysis [124]. Measuring the concentration of antibiotics, anticonvulsants, and other therapeutic agents is another growing field of application for microdialysis [109,129–131].

Microdialysis offers monitoring of brain cell metabolism and is helpful in detecting secondary insults and predicting outcome in patients with severe TBI. Currently, the use of microdialysis is limited more to the observation of trends than the targeting of threshold values for metabolites and neurotransmitters within a small region of interest. However, several catheters can be placed in different locations and monitor cerebral metabolism simultaneously. The microdialysis catheter can be inserted together with the brain oxygen probe, an ICP monitor, or a CBF monitor within a three-lumen cranial bolt (see Fig. 4). If used in combination with PBO₂ monitoring, “stunned” brain tissue can be distinguished from brain regions undergoing active ischemic injury.

Neuroimaging

Modern imaging techniques provide the opportunity of high-quality diagnosis of disease states and insight into pathophysiology and

hemodynamics of vascular disease. CT and MRI are used frequently for diagnosis of disease states in NICU patients.

[^{18}F]2-deoxy-D-glucose and oxygen-15 PET is used to obtain a quantitative assessment of brain metabolism and CBF [29,132], but it is not widely available. CBF can be evaluated qualitatively by way of SPECT as well and is more readily available [29].

Xenon-enhanced CT scanning [28], perfusion CT, and perfusion-weighted imaging (PWI) [29] add diagnostic capability to a qualitative image of the cerebral perfusion status which can be assessed by comparison of mean transit time (MTT), CBF, and cerebral blood volume (CBV) between different brain regions. PWI allows for calculation of perfusion maps and the delay of MTT comparing selected locations. Furthermore, MRI detects ischemia early by an increase in signal on diffusion-weighted imaging (DWI) and reduction of the apparent diffusion coefficient within 30 minutes of onset of symptoms. Simultaneous PWI and DWI enable identification of viable areas that lack adequate perfusion and are at risk for infarction. The PWI/DWI mismatch concept has been used in patients with acute stroke symptoms to determine risk and benefit of thrombolysis; however, absolute CBF and CBV values may be more accurate for evaluation of the true perfusion deficit [133].

PET, SPECT, perfusion CT, and MRI are noninvasive methods that assess the cerebral perfusion status and metabolism globally. Most of the time, the imaging facilities are located outside the NICU; consequently, skilled personnel are required to minimize the risk involved with transporting critically ill patient and ventilated patients on continuous drips. Imaging gives a comprehensive evaluation of cerebral perfusion at only one point in time, whereas cerebral autoregulation is a dynamic process. Therefore, supplementation of global one-time assessment of CBF with regional continuous CBF, pO_2 , and microdialysis monitoring at the bedside may be helpful.

Continuous EEG

Digital video continuous electroencephalographic monitoring (cEEG) provides prolonged monitoring of brain activity in critically ill patients with altered mental status and at risk for secondary ischemia after acute brain injury. Indications for cEEG include:

- (1) detection of nonconvulsive seizures or status epilepticus in patients with unexplained fluctuating mental status and after convulsive status epilepticus;
- (2) characterization of spells such as sudden posturing, rigidity, tremors, chewing, twitching, nystagmus, eye deviation, and agitation, and unexplained changes in heart rate and blood pressure;

- (3) assessment of level of consciousness during sedation and paralysis including identification of clinically silent events, management of burst-suppression in anesthetic coma;
- (4) detection of ischemia after SAH, during neurosurgical and neuroendovascular procedures, in patients with hemodynamic lesions or at risk for acute ischemia; and
- (5) prognostication [134,135].

In a study of 570 hospitalized patients who underwent cEEG monitoring, seizures were seen in 19%, 95% of which were nonconvulsive [136]. Up to 34% of patients in a smaller NICU patient population experienced nonconvulsive seizures, and 76% of these were in nonconvulsive status epilepticus [137]. Nonconvulsive seizures or status epilepticus are associated with increased morbidity and mortality regardless of etiology [138,139], especially after SAH [140–142]. Seizure duration and time to diagnosis are predictors of outcome in patients with nonconvulsive status. Mortality is 36% after 30 minutes in nonconvulsive status, and 75% after more than 24 hours [143]. Seizures occurring after cerebral hemorrhage or brain injury may increase brain edema, midline shift, and intracranial hypertension [144].

Continuous EEG was first applied to monitor for reversible ischemia intraoperatively, during carotid endarterectomy [145,146]. Because certain cEEG patterns such as broad, repetitive slow waves (“axial bursts”) are highly correlated with the clinical and angiographic occurrence of vasospasm [147], quantitative analysis was developed to detect delayed cerebral ischemia in SAH by cEEG in awake and comatose SAH patients [148–150] and to predict outcome after traumatic brain injury [151]. Quantitative cEEG allows for evaluation of a large amount of data over long periods of time (raw EEG waveforms) in the form of a summary as compressed spectral array, density spectral array, compressed EEG pattern analysis, bandwidth power trends with ratios of power, geographic power/bandwidth display, burst suppression monitor, and level of sedation monitor in real time. Spectra or power ratios that are easily interpretable with scoring systems or alarms make quantitative cEEG a very useful monitoring tool in the neurologic intensive care unit [134,135,152,153]. Trend analysis of total power (1–30 Hz) [149], variability of relative alpha (6–14 Hz/1–20 Hz) even up to 2 days before clinical changes [150,151], and poststimulation alpha/delta ratio (8–13 Hz/1–4 Hz) [148] were found to correlate with clinical cerebral ischemia or angiographically confirmed vasospasm after SAH and with poor prognosis after SAH and TBI.

Another future application of cEEG may include electrocorticography with observation and measurement of cortical spreading depression, seen in about 50% of patients following an acute brain injury. Transient or prolonged repeated depolarizations of brain tissue surrounding a cortical lesion and slow potential changes (0.005–0.05 Hz) may contribute to expansion of the initial focal injury [154].

Technical requirements such as digital analysis and data reduction; constant fixation of electrodes for agitated, physically moved, and transported NICU patients; altered cranial anatomy (catheters, monitoring devices, skull defects, scalp edema); electrical artifacts due to a noisy NICU environment; availability of 24-hour coverage of experienced electroencephalographers; availability of networking with real-time and event respond access; automated alerting systems; and accessibility of remote online analysis resources currently limit the use of continuous EEG for immediate clinical decision-making and therapy [135,136,148]. Furthermore, EEG electrodes interfere with the quality of imaging studies, which are frequently obtained in NICU patients, and with procedures such as insertion of extraventricular drains and ICP monitors. Most of the EEG electrodes are not compatible with MRI.

Power spectrographic displays that compress several hours of recordings into a single image that reveals certain patterns such as recurrent seizures or changes of ratios, quantitative analysis, analysis programs at the bedside, and networking with Web-based links can facilitate the review of large quantities of EEG data by the electroencephalographer and enable a closer-to-real-time assessment of brain dysfunction [155,156]. Video-assisted EEG could also allow expert review of documentation of a neurologic assessment.

Somatosensory-evoked potentials (SSEPs), brain stem auditory-evoked response, and long latency cortical auditory-evoked responses are valuable tools for prognostication in comatose NICU patients. The bilateral absence of the N20 cortical component of SSEPs obtained in patients with hypoxic-ischemic encephalopathy after cardiopulmonary resuscitation is associated with poor neurologic recovery [157]. Normal SSEP conduction times for the components N13 and N20 bilaterally obtained within 48 hours of admission to the hospital signify a good neurologic outcome after severe brain trauma at 12 months in 60% of patients. If any cortical potential is delayed, the chances for a satisfactory recovery of neurologic function are less than 30%. With absent SSEPs, the most likely outcome is death or disability [158]. Combined continuous EEG and SSEP monitoring has recently become available [159]. Long latency cortical auditory-evoked responses are more sensitive for detection of severity and extent of cerebral dysfunction in traumatic brain injury compared with brain stem auditory-evoked responses [160].

Multimodality monitoring

The true richness of multimodal neuromonitoring lies not in the addition of new metrics but in the analysis of relationships among these metrics. During rounds in the NICU with multimodality monitoring, a physician may be confronted with more than 200 variables [161]. Unassisted human beings, however, are not able to judge the degree of relatedness between more than two variables [162]. Computer-assisted graphical analysis can play

a role in the intensive care unit to reap the benefits of intensive neuromonitoring [163–170]. Understanding these relationships may allow earlier identification and treatment of critical patient conditions, ideally before permanent secondary injury can occur.

Several groups have examined the relationships among physiologic metrics to monitor dynamic cerebral autoregulation and pinpoint patient-specific physiologic targets using varying statistical techniques [163–167,171,172]. This research is grounded by the fact that cerebrovascular pressure reactivity can be determined by observing the response of ICP to changes in MAP [168]. With intact pressure reactivity, spontaneous increases in MAP lead to vasoconstriction and a reduction in cerebral blood volume within 5 to 15 seconds, subsequently decreasing ICP. However, if pressure reactivity is disturbed, the absence of vasoconstriction in response to elevations in MAP results in passive increases in cerebral blood volume and ICP. If MAP decreases, the opposite occurs (see Fig. 3) [169]. Additionally, intracranial pressure, cerebral perfusion pressure, and regional cerebral blood flow have been found to be dynamically correlated to decreased brain tissue oxygen [18–20].

Dynamic analysis of these metrics may yield new tools to maintain adequate cerebral oxygenation. Steiner and colleagues [168] analyzed the relation of MAP and ICP to identify a CPP target and demonstrated that patients with a mean CPP closer to their “optimum” CPP target had a better outcome. However, this method failed to identify a target CPP for 40% of patients. An assumption of autoregulatory failure is that the cerebral vasculature is unresponsive to changes in blood pressure, effectively eliminating the negative correlation normally observed between MAP and ICP that is used to indicate a CPP target. This likely accounts for why a target could not be identified in most cases. Soehle and colleagues [165] evaluated the relationship between CPP and PBO_2 to quantify autoregulation dysfunction. An increased correlation among the two parameters is related to worsening autoregulation dysfunction. Furthermore, SAH patients with elevated CPP and PBO_2 correlations were at significantly greater risk for infarction from vasospasm than those with intact autoregulation [170]. We reported preliminary results on the feasibility to generate a CPP target by monitoring the correlation of MAP to PBO_2 simultaneously with the correlation of ICP to PBO_2 and identifying the observed CPP when these relationships change (see Fig. 6) [173]. Though in need of further study, the primary advantage of using brain oxygenation data to identify a patient-specific CPP target is that such a target should be identifiable regardless of autoregulation status.

Complex multidimensional data analysis has been studied to identify complication specific data patterns to good effect. Gather and colleagues [174] applied graphical modeling techniques to physiologic data collected in an ICU revealing distinct partial correlation patterns among physiologic parameters such as heart rate, arterial pressure, SpO_2 , and central venous pressure for distinct clinical states, including congestive heart failure,

pulmonary hypertension, and use of vasopressors. In the future, multidimensional data analysis might also be used to generate compound patient-specific physiologic targets—for example, generating targets MAP and end tidal CO₂ that will produce the lowest ICP without adversely impacting PBO₂. Dynamic analysis of neuromonitoring data has a bright future and will continue to have an increasing role in physician decision support at the bedside.

Summary

Traditional monitoring in the NICU relegates physicians and nurses to treating patients reactively, only after the patients have declined neurologically and a physiologic process has become abnormal. Real-time monitoring of brain oxygen tension, brain temperature, ICP, CPP, CBF, and cerebral metabolism—in addition to TCD ultrasonography, cEEG, and cardiovascular parameters—gives the neurointensivist immediate insight in the physiologic and metabolic state of brain regions at risk for ischemia and injury and enhances the potential of early effective interventions to reverse pathologic states on an individual basis. Specifically, the combination of ICP/ CPP monitoring, complemented by brain oxygen tension and lactate/pyruvate ratio monitoring, may distinguish areas of the brain at risk that might respond to manipulations of MAP or CPP.

Initial research using this information at the bedside has enabled proactive treatment of patients in the form of patient-specific physiologic targets. Ideally, multimodal analysis of physiologic data will enable neurointensivists to optimize a patient's physiology, minimizing the impact of neurologic derangement, and ultimately transforming the NICU treatment model. To get there, more research and actual application of these techniques is needed to confirm reference values for brain health and to standardize clinical management (see [Table 1](#)). Optimization of CPP and ICP, hyperventilation, hyperosmolar therapy, hypothermia, weaning from liberation from ventilation, diagnosis and treatment of vasospasm, and temporary occlusion of arteries during radiologic or surgical interventions can be guided by these novel technologies. Clinical informatics tools and decision support research will be needed to reduce the quantity and increase the quality of information neurointensivists must sift through when managing their patients. Multimodal monitoring should become the standard of every NICU and offers tremendous potential.

References

- [1] Charbel FT, Hoffman WE, Misra M, et al. Cerebral interstitial tissue oxygen tension, pH, HCO₃, CO₂. *Surg Neurol* 1997;48(4):414–7.
- [2] Zauner A, Doppenberg EM, Woodward JJ, et al. Continuous monitoring of cerebral substrate delivery and clearance: initial experience in 24 patients with severe acute brain injuries. *Neurosurgery* 1997;41(5):1082–91.

- [3] van Santbrink H, vd Brink WA, Steyerberg EW, et al. Brain tissue oxygen response in severe traumatic brain injury. *Acta Neurochir (Wien)* 2003;145(6):429–38 [discussion: 438].
- [4] Sarrafzadeh A, Haux D, Kuchler I, et al. Poor-grade aneurysmal subarachnoid hemorrhage: relationship of cerebral metabolism to outcome. *J Neurosurg* 2004;100(3):400–6.
- [5] Vespa PM, Nenov V, Nuwer MR. Continuous EEG monitoring in the intensive care unit: early findings and clinical efficacy. *J Clin Neurophysiol* 1999;16(1):1–13.
- [6] Dohmen C, Bosche B, Graf R, et al. Identification and clinical impact of impaired cerebrovascular autoregulation in patients with malignant middle cerebral artery infarction. *Stroke* 2007;38(1):56–61.
- [7] Vespa P. What is the optimal threshold for cerebral perfusion pressure following traumatic brain injury? *Neurosurg Focus* 2003;15(6):E4.
- [8] Czosnyka M, Matta BF, Smielewski P, et al. Cerebral perfusion pressure in head-injured patients: a noninvasive assessment using transcranial Doppler ultrasonography. *J Neurosurg* 1998;88(5):802–8.
- [9] Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. *J Neurol Neurosurg Psychiatry* 2004;75(6):813–21.
- [10] Hamilton AJ, Orozco J, Narotam P, et al. Efficacy of vancomycin/tri-iododecylmethyl ammonium chloride-coated ventriculostomy catheters in reducing infection. *Neurosurgery* 1997;40(5):1043–9.
- [11] Schmidt B, Czosnyka M, Raabe A, et al. Adaptive noninvasive assessment of intracranial pressure and cerebral autoregulation. *Stroke* 2003;34(1):84–9.
- [12] Mourad P. Noninvasive ICP monitoring. New York: Grand Rounds; 2005.
- [13] Michaeli D, Rappaport ZH. Tissue resonance analysis; a novel method for noninvasive monitoring of intracranial pressure. Technical note. *J Neurosurg* 2002;96(6):1132–7.
- [14] Mayer SA, Thomas CE, Diamond BE. Asymmetry of intracranial hemodynamics as an indicator of mass effect in acute intracerebral hemorrhage. A transcranial Doppler study. *Stroke* 1996;27(10):1788–92.
- [15] Johnson WD, Bolognese P, Miller JI, et al. Continuous postoperative ICBF monitoring in aneurysmal SAH patients using a combined ICP-laser Doppler fiberoptic probe. *J Neurosurg Anesthesiol* 1996;8(3):199–207.
- [16] Rordorf G, Ogilvy CS, Gress DR, et al. Patients in poor neurological condition after subarachnoid hemorrhage: early management and long-term outcome. *Acta Neurochir (Wien)* 1997;139(12):1143–51.
- [17] Robertson CS. Management of cerebral perfusion pressure after traumatic brain injury. *Anesthesiology* 2001;95(6):1513–7.
- [18] Meixensberger J, Jaeger M, Vath A, et al. Brain tissue oxygen guided treatment supplementing ICP/CPP therapy after traumatic brain injury. *J Neurol Neurosurg Psychiatry* 2003;74(6):760–4.
- [19] Nordstrom CH. Assessment of critical thresholds for cerebral perfusion pressure by performing bedside monitoring of cerebral energy metabolism. *Neurosurg Focus* 2003;15(6):E5.
- [20] al-Rawi PG, Hutchinson PJ, Gupta AK, et al. Multiparameter brain tissue monitoring—correlation between parameters and identification of CPP thresholds. *Zentralbl Neurochir* 2000;61(2):74–9.
- [21] Robertson CS, Contant CF, Gokaslan ZL, et al. Cerebral blood flow, arteriovenous oxygen difference, and outcome in head injured patients. *J Neurol Neurosurg Psychiatry* 1992;55(7):594–603.
- [22] Kety SS, Schmidt CF. The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. *Am J Physiol* 1945;143:53–66.
- [23] Cook DJ, Anderson RE, Michenfelder JD, et al. Cerebral blood flow during cardiac operations: comparison of Kety-Schmidt and xenon-133 clearance methods. *Ann Thorac Surg* 1995;59(3):614–20.

- [24] Obrist WD, Thompson HK Jr, Wang HS, et al. Regional cerebral blood flow estimated by 133-xenon inhalation. *Stroke* 1975;6(3):245–56.
- [25] Cohan SL, Mun SK, Petite J, et al. Cerebral blood flow in humans following resuscitation from cardiac arrest. *Stroke* 1989;20(6):761–5.
- [26] Keller E, Nadler A, Alkadhi H, et al. Noninvasive measurement of regional cerebral blood flow and regional cerebral blood volume by near-infrared spectroscopy and indocyanine green dye dilution. *Neuroimage* 2003;20(2):828–39.
- [27] Melot C, Berre J, Moraine JJ, et al. Estimation of cerebral blood flow at bedside by continuous jugular thermodilution. *J Cereb Blood Flow Metab* 1996;16(6):1263–70.
- [28] Yonas H, Jungreis C. Xenon CT cerebral blood flow: past, present, and future. *AJNR Am J Neuroradiol* 1995;16(1):219–20.
- [29] Latchaw RE. Cerebral perfusion imaging in acute stroke. *J Vasc Interv Radiol* 2004;15(1 Pt 2):S29–46.
- [30] Bolognese P, Miller JJ, Heger IM, et al. Laser-Doppler flowmetry in neurosurgery. *J Neurosurg Anesthesiol* 1993;5(3):151–8.
- [31] Carter LP, Weinand ME, Oommen KJ. Cerebral blood flow (CBF) monitoring in intensive care by thermal diffusion. *Acta Neurochir Suppl (Wien)* 1993;59:43–6.
- [32] Vajkoczy P, Horn P, Thome C, et al. Regional cerebral blood flow monitoring in the diagnosis of delayed ischemia following aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2003;98(6):1227–34.
- [33] Thome C, Vajkoczy P, Horn P, et al. Continuous monitoring of regional cerebral blood flow during temporary arterial occlusion in aneurysm surgery. *J Neurosurg* 2001;95(3):402–11.
- [34] Jaeger M, Soehle M, Schuhmann MU, et al. Correlation of continuously monitored regional cerebral blood flow and brain tissue oxygen. *Acta Neurochir (Wien)* 2005;147(1):51–6.
- [35] Aaslid R, Lindegaard KF, Sorteberg W, et al. Cerebral autoregulation dynamics in humans. *Stroke* 1989;20(1):45–52.
- [36] Tiecks FP, Lam AM, Aaslid R, et al. Comparison of static and dynamic cerebral autoregulation measurements. *Stroke* 1995;26(6):1014–9.
- [37] Steiger HJ, Aaslid R, Stooss R, et al. Transcranial Doppler monitoring in head injury: relations between type of injury, flow velocities, vasoreactivity, and outcome. *Neurosurgery* 1994;34(1):79–85.
- [38] Yoshihara M, Bando K, Marmarou A. Cerebrovascular carbon dioxide reactivity assessed by intracranial pressure dynamics in severely head injured patients. *J Neurosurg* 1995;82(3):386–93.
- [39] Smielewski P, Czosnyka M, Kirkpatrick P, et al. Evaluation of the transient hyperemic response test in head-injured patients. *J Neurosurg* 1997;86(5):773–8.
- [40] Diehl RR, Linden D, Lucke D, et al. Phase relationship between cerebral blood flow velocity and blood pressure. A clinical test of autoregulation. *Stroke* 1995;26(10):1801–4.
- [41] Czosnyka M, Kirkpatrick PJ, Pickard JD. Multimodal monitoring and assessment of cerebral haemodynamic reserve after severe head injury. *Cerebrovasc Brain Metab Rev* 1996;8(4):273–95.
- [42] Diamant M, Harms MP, Immink RV, et al. Twenty-four-hour non-invasive monitoring of systemic haemodynamics and cerebral blood flow velocity in healthy humans. *Acta Physiol Scand* 2002;175(1):1–9.
- [43] Wardlaw JM, Offin R, Teasdale GM, et al. Is routine transcranial Doppler ultrasound monitoring useful in the management of subarachnoid hemorrhage? *J Neurosurg* 1998;88(2):272–6.
- [44] Jarus-Dziedzic K, Juniewicz H, Wronski J, et al. The relation between cerebral blood flow velocities as measured by TCD and the incidence of delayed ischemic deficits. A prospective study after subarachnoid hemorrhage. *Neurol Res* 2002;24(6):582–92.

- [45] Lindegaard KF, Nornes H, Bakke SJ, et al. Cerebral vasospasm after subarachnoid haemorrhage investigated by means of transcranial Doppler ultrasound. *Acta Neurochir Suppl (Wien)* 1988;42:81–4.
- [46] Darbellay GA, Duff R, Vesin JM, et al. Solid or gaseous circulating brain emboli: are they separable by transcranial ultrasound? *J Cereb Blood Flow Metab* 2004;24(8):860–8.
- [47] Dosemeci L, Dora B, Yilmaz M, et al. Utility of transcranial doppler ultrasonography for confirmatory diagnosis of brain death: two sides of the coin. *Transplantation* 2004;77(1):71–5.
- [48] Ducrocq X, Braun M, Debouverie M, et al. Brain death and transcranial Doppler: experience in 130 cases of brain dead patients. *J Neurol Sci* 1998;160(1):41–6.
- [49] Gahn G, von Kummer R. Ultrasound in acute stroke: a review. *Neuroradiology* 2001;43(9):702–11.
- [50] Rajamani K, Gorman M. Transcranial Doppler in stroke. *Biomed Pharmacother* 2001;55(5):247–57.
- [51] Gopinath SP, Valadka AB, Uzura M, et al. Comparison of jugular venous oxygen saturation and brain tissue PO₂ as monitors of cerebral ischemia after head injury. *Crit Care Med* 1999;27(11):2337–45.
- [52] Goetting MG, Preston G. Jugular bulb catheterization: experience with 123 patients. *Crit Care Med* 1990;18(11):1220–3.
- [53] Lewis SB, Myburgh JA, Reilly PL. Detection of cerebral venous desaturation by continuous jugular bulb oximetry following acute neurotrauma. *Anaesth Intensive Care* 1995;23(3):307–14.
- [54] Chieragato A, Targa L, Zatelli R. Limitations of jugular bulb oxyhemoglobin saturation without intracranial pressure monitoring in subarachnoid hemorrhage. *J Neurosurg Anesthesiol* 1996;8(1):21–5.
- [55] Gunn HC, Matta BF, Lam AM, et al. Accuracy of continuous jugular bulb venous oximetry during intracranial surgery. *J Neurosurg Anesthesiol* 1995;7(3):174–7.
- [56] Feldman Z, Robertson CS. Monitoring of cerebral hemodynamics with jugular bulb catheters. *Crit Care Clin* 1997;13(1):51–77.
- [57] De Georgia MA, Deogaonkar A. Multimodal monitoring in the neurological intensive care unit. *Neurologist* 2005;11(1):45–54.
- [58] Wartenberg KE, Mayer SA. Multimodal brain monitoring in the neurological intensive care unit: where does continuous EEG fit in? *J Clin Neurophysiol* 2005;22(2):124–7.
- [59] Sarrafzadeh AS, Kiening KL, Unterberg AW. Neuromonitoring: brain oxygenation and microdialysis. *Curr Neurol Neurosci Rep* 2003;3(6):517–23.
- [60] Hoelper BM, Alessandri B, Heimann A, et al. Brain oxygen monitoring: in-vitro accuracy, long-term drift and response-time of Licox- and Neurotrend sensors. *Acta Neurochir (Wien)* 2005;147(7):767–74.
- [61] Doppenberg EM, Zauner A, Watson JC, et al. Determination of the ischemic threshold for brain oxygen tension. *Acta Neurochir Suppl* 1998;71:166–9.
- [62] Hoffman WE, Charbel FT, Edelman G. Brain tissue oxygen, carbon dioxide, and pH in neurosurgical patients at risk for ischemia. *Anesth Analg* 1996;82(3):582–6.
- [63] Valadka AB, Gopinath SP, Contant CF, et al. Relationship of brain tissue PO₂ to outcome after severe head injury. *Crit Care Med* 1998;26(9):1576–81.
- [64] Bardt TF, Unterberg AW, Hartl R, et al. Monitoring of brain tissue PO₂ in traumatic brain injury: effect of cerebral hypoxia on outcome. *Acta Neurochir Suppl* 1998;71:153–6.
- [65] Kiening KL, Unterberg AW, Bardt TF, et al. Monitoring of cerebral oxygenation in patients with severe head injuries: brain tissue PO₂ versus jugular vein oxygen saturation. *J Neurosurg* 1996;85(5):751–7.
- [66] Gupta AK, Hutchinson PJ, Al-Rawi P, et al. Measuring brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. *Anesth Analg* 1999;88(3):549–53.

- [67] Stiefel MF, Spiotta A, Gracias VH, et al. Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. *J Neurosurg* 2005; 103(5):805–11.
- [68] Tolias CM, Reinert M, Seiler R, et al. Normobaric hyperoxia-induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: a prospective historical cohort-matched study. *J Neurosurg* 2004;101(3): 435–44.
- [69] Reithmeier T, Lohr M, Pakos P, et al. Relevance of ICP and ptiO₂ for indication and timing of decompressive craniectomy in patients with malignant brain edema. *Acta Neurochir (Wien)* 2005;147:947–52.
- [70] Kett-White R, Hutchinson PJ, Al-Rawi PG, et al. Cerebral oxygen and microdialysis monitoring during aneurysm surgery: effects of blood pressure, cerebrospinal fluid drainage, and temporary clipping on infarction. *J Neurosurg* 2002;96(6):1013–9.
- [71] Kett-White R, Hutchinson PJ, Al-Rawi PG, et al. Adverse cerebral events detected after subarachnoid hemorrhage using brain oxygen and microdialysis probes. *Neurosurgery* 2002;50(6):1213–21.
- [72] Kett-White R, Hutchinson PJ, Czosnyka M, et al. Effects of variation in cerebral haemodynamics during aneurysm surgery on brain tissue oxygen and metabolism. *Acta Neurochir Suppl* 2002;81:327–9.
- [73] Kett-White R, Hutchinson PJ, Czosnyka M, et al. Multi-modal monitoring of acute brain injury. *Adv Tech Stand Neurosurg* 2002;27:87–134.
- [74] Gupta AK, Hutchinson PJ, Fryer T, et al. Measurement of brain tissue oxygenation performed using positron emission tomography scanning to validate a novel monitoring method. *J Neurosurg* 2002;96(2):263–8.
- [75] Menzel M, Doppenberg EM, Zauner A, et al. Cerebral oxygenation in patients after severe head injury: monitoring and effects of arterial hyperoxia on cerebral blood flow, metabolism and intracranial pressure. *J Neurosurg Anesthesiol* 1999;11(4):240–51.
- [76] van Santbrink H, Maas AI, Avezaat CJ. Continuous monitoring of partial pressure of brain tissue oxygen in patients with severe head injury. *Neurosurgery* 1996;38(1):21–31.
- [77] Niklas A, Brock D, Schober R, et al. Continuous measurements of cerebral tissue oxygen pressure during hyperbaric oxygenation—HBO effects on brain edema and necrosis after severe brain trauma in rabbits. *J Neurol Sci* 2004;219(1–2):77–82.
- [78] Longhi L, Valeriani V, Rossi S, et al. Effects of hyperoxia on brain tissue oxygen tension in cerebral focal lesions. *Acta Neurochir Suppl* 2002;81:315–7.
- [79] Menon DK, Coles JP, Gupta AK, et al. Diffusion limited oxygen delivery following head injury. *Crit Care Med* 2004;32(6):1384–90.
- [80] Meixensberger J, Vath A, Jaeger M, et al. Monitoring of brain tissue oxygenation following severe subarachnoid hemorrhage. *Neurol Res* 2003;25(5):445–50.
- [81] Dings J, Meixensberger J, Roosen K. Brain tissue pO₂-monitoring: catheterstability and complications. *Neurol Res* 1997;19(3):241–5.
- [82] Kiening KL, Hartl R, Unterberg AW, et al. Brain tissue PO₂-monitoring in comatose patients: implications for therapy. *Neurol Res* 1997;19(3):233–40.
- [83] Vath A, Kunze E, Roosen K, et al. Therapeutic aspects of brain tissue pO₂ monitoring after subarachnoid hemorrhage. *Acta Neurochir Suppl* 2002;81:307–9.
- [84] Charbel FT, Du X, Hoffman WE, et al. Brain tissue PO₂(2), PCO₂(2), and pH during cerebral vasospasm. *Surg Neurol* 2000;54(6):432–7 [discussion: 438].
- [85] Gupta AK, Al-Rawi PG, Hutchinson PJ, et al. Effect of hypothermia on brain tissue oxygenation in patients with severe head injury. *Br J Anaesth* 2002;88(2):188–92.
- [86] Jobsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 1977;198(4323):1264–7.
- [87] Wray S, Cope M, Delpy DT, et al. Characterization of the near infrared absorption spectra of cytochrome aa₃ and haemoglobin for the non-invasive monitoring of cerebral oxygenation. *Biochim Biophys Acta* 1988;933(1):184–92.

- [88] Al-Rawi PG, Smielewski P, Kirkpatrick PJ. Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head. *Stroke* 2001;32(11):2492–500.
- [89] Hebden JC, Gibson A, Austin T, et al. Imaging changes in blood volume and oxygenation in the newborn infant brain using three-dimensional optical tomography. *Phys Med Biol* 2004;49(7):1117–30.
- [90] Misra M, Stark J, Dujovny M, et al. Transcranial cerebral oximetry in random normal subjects. *Neurol Res* 1998;20(2):137–41.
- [91] Gupta AK. Monitoring the injured brain in the intensive care unit. *J Postgrad Med* 2002; 48(3):218–25.
- [92] Kirkpatrick PJ, Smielewski P, Whitfield PC, et al. An observational study of near-infrared spectroscopy during carotid endarterectomy. *J Neurosurg* 1995;82(5):756–63.
- [93] Daubeney PE, Smith DC, Pilkington SN, et al. Cerebral oxygenation during paediatric cardiac surgery: identification of vulnerable periods using near infrared spectroscopy. *Eur J Cardiothorac Surg* 1998;13(4):370–7.
- [94] Keller E, Wolf M, Martin M, et al. Estimation of cerebral oxygenation and hemodynamics in cerebral vasospasm using indocyanine green dye dilution and near infrared spectroscopy: a case report. *J Neurosurg Anesthesiol* 2001;13(1):43–8.
- [95] Terborg C, Bramer S, Harscher S, et al. Bedside assessment of cerebral perfusion reductions in patients with acute ischaemic stroke by near-infrared spectroscopy and indocyanine green. *J Neurol Neurosurg Psychiatry* 2004;75(1):38–42.
- [96] Germon TJ, Kane NM, Manara AR, et al. Near-infrared spectroscopy in adults: effects of extracranial ischaemia and intracranial hypoxia on estimation of cerebral oxygenation. *Br J Anaesth* 1994;73(4):503–6.
- [97] Germon TJ, Young AE, Manara AR, et al. Extracerebral absorption of near infrared light influences the detection of increased cerebral oxygenation monitored by near infrared spectroscopy. *J Neurol Neurosurg Psychiatry* 1995;58(4):477–9.
- [98] Schwarz G, Litscher G, Kleinert R, et al. Cerebral oximetry in dead subjects. *J Neurosurg Anesthesiol* 1996;8(3):189–93.
- [99] Ausman JI, McCormick PW, Stewart M, et al. Cerebral oxygen metabolism during hypothermic circulatory arrest in humans. *J Neurosurg* 1993;79(6):810–5.
- [100] Brown R, Wright G, Royston D. A comparison of two systems for assessing cerebral venous oxyhaemoglobin saturation during cardiopulmonary bypass in humans. *Anaesthesia* 1993;48(8):697–700.
- [101] Harris DN, Bailey SM. Near infrared spectroscopy in adults. Does the Invos 3100 really measure intracerebral oxygenation? *Anaesthesia* 1993;48(8):694–6.
- [102] Cold GE. The relationship between cerebral metabolic rate of oxygen and cerebral blood flow in the acute phase of head injury. *Acta Anaesthesiol Scand* 1986;30(6):453–7.
- [103] Johnston AJ, Gupta AK. Advanced monitoring in the neurology intensive care unit: microdialysis. *Curr Opin Crit Care* 2002;8(2):121–7.
- [104] Ungerstedt U, Rostami E. Microdialysis in neurointensive care. *Curr Pharm Des* 2004; 10(18):2145–52.
- [105] Bellander BM, Cantais E, Enblad P, et al. Consensus meeting on microdialysis in neurointensive care. *Intensive Care Med* 2004;30(12):2166–9.
- [106] Hillman J, Milos P, Yu ZQ, et al. Intracerebral microdialysis in neurosurgical intensive care patients utilising catheters with different molecular cut-off (20 and 100 kD). *Acta Neurochir (Wien)* 2006;148:319–24.
- [107] Schwalbe O, Buerger C, Plock N, et al. Urea as an endogenous surrogate in human microdialysis to determine relative recovery of drugs: analytics and applications. *J Pharm Biomed Anal* 2005;41:233–9.
- [108] Clough GF. Microdialysis of large molecules. *AAPS J* 2005;7(3):E686–92.
- [109] Tisdall M, Russo S, Sen J, et al. Free phenytoin concentration measurement in brain extracellular fluid: a pilot study. *Br J Neurosurg* 2006;20(5):285–9.

- [110] Rosenbloom AJ, Sipe DM, Weedn VW. Microdialysis of proteins: performance of the CMA/20 probe. *J Neurosci Methods* 2005;148(2):147–53.
- [111] Goodman JC, Valadka AB, Gopinath SP, et al. Extracellular lactate and glucose alterations in the brain after head injury measured by microdialysis. *Crit Care Med* 1999; 27(9):1965–73.
- [112] Valadka AB, Goodman JC, Gopinath SP, et al. Comparison of brain tissue oxygen tension to microdialysis-based measures of cerebral ischemia in fatally head-injured humans. *J Neurotrauma* 1998;15(7):509–19.
- [113] Vespa PM, O'Phelan K, McArthur D, et al. Pericontusional brain tissue exhibits persistent elevation of lactate/pyruvate ratio independent of cerebral perfusion pressure. *Crit Care Med* 2007;35(4):1153–60.
- [114] Sakowitz OW, Stover JF, Sarrafzadeh AS, et al. Effects of mannitol bolus administration on intracranial pressure, cerebral extracellular metabolites, and tissue oxygenation in severely head-injured patients. *J Trauma* 2007;62(2):292–8.
- [115] Stahl N, Møllergaard P, Hallström A, et al. Intracerebral microdialysis and bedside biochemical analysis in patients with fatal traumatic brain lesions. *Acta Anaesthesiol Scand* 2001; 45(8):977–85.
- [116] Zauner A, Doppenberg E, Woodward JJ, et al. Multiparametric continuous monitoring of brain metabolism and substrate delivery in neurosurgical patients. *Neurol Res* 1997;19(3): 265–73.
- [117] Nordström CH, Reinstrup P, Xu W, et al. Assessment of the lower limit for cerebral perfusion pressure in severe head injuries by bedside monitoring of regional energy metabolism. *Anesthesiology* 2003;98(4):809–14.
- [118] Sarrafzadeh AS, Sakowitz OW, Kiening KL, et al. Bedside microdialysis: a tool to monitor cerebral metabolism in subarachnoid hemorrhage patients? *Crit Care Med* 2002;30(5): 1062–70.
- [119] Nilsson OG, Brandt L, Ungerstedt U, et al. Bedside detection of brain ischemia using intracerebral microdialysis: subarachnoid hemorrhage and delayed ischemic deterioration. *Neurosurgery* 1999;45(5):1176–84.
- [120] Samuelsson C, Hillered L, Zetterling M, et al. Cerebral glutamine and glutamate levels in relation to compromised energy metabolism: a microdialysis study in subarachnoid hemorrhage patients. *J Cereb Blood Flow Metab* 2007;27:1309–17.
- [121] Schneweis S, Grond M, Staub F, et al. Predictive value of neurochemical monitoring in large middle cerebral artery infarction. *Stroke* 2001;32(8):1863–7.
- [122] Berger C, Sakowitz OW, Kiening KL, et al. Neurochemical monitoring of glycerol therapy in patients with ischemic brain edema. *Stroke* 2005;36(2):e4–6.
- [123] Berger C, Schabitz WR, Georgiadis D, et al. Effects of hypothermia on excitatory amino acids and metabolism in stroke patients: a microdialysis study. *Stroke* 2002;33(2):519–24.
- [124] Miller CM, Vespa PM, McArthur DL, et al. Frameless stereotactic aspiration and thrombolysis of deep intracerebral hemorrhage is associated with reduced levels of extracellular cerebral glutamate and unchanged lactate pyruvate ratios. *Neurocrit Care* 2007;6(1):22–9.
- [125] Mendelowitsch A, Sekhar LN, Wright DC, et al. An increase in extracellular glutamate is a sensitive method of detecting ischaemic neuronal damage during cranial base and cerebrovascular surgery. An in vivo microdialysis study. *Acta Neurochir (Wien)* 1998;140(4): 349–55 [discussion: 356].
- [126] Bachli H, Langemann H, Mendelowitsch A, et al. Microdialytic monitoring during cerebrovascular surgery. *Neurol Res* 1996;18(4):370–6.
- [127] Xu W, Møllergaard P, Ungerstedt U, et al. Local changes in cerebral energy metabolism due to brain retraction during routine neurosurgical procedures. *Acta Neurochir (Wien)* 2002; 144(7):679–83.
- [128] Hutchinson PJ, Al-Rawi PG, O'Connell MT, et al. Biochemical changes related to hypoxia during cerebral aneurysm surgery: combined microdialysis and tissue oxygen monitoring: case report. *Neurosurgery* 2000;46(1):201–5 [discussion: 205–6].

- [129] Mindermann T, Zimmerli W, Gratzl O. Rifampin concentrations in various compartments of the human brain: a novel method for determining drug levels in the cerebral extracellular space. *Antimicrob Agents Chemother* 1998;42(10):2626–9.
- [130] Bouw R, Ederoth P, Lundberg J, et al. Increased blood-brain barrier permeability of morphine in a patient with severe brain lesions as determined by microdialysis. *Acta Anaesthesiol Scand* 2001;45(3):390–2.
- [131] Joukhadar C, Derendorf H, Muller M. Microdialysis. A novel tool for clinical studies of anti-infective agents. *Eur J Clin Pharmacol* 2001;57(3):211–9.
- [132] Noske DP, Peerdeman SM, Comans EF, et al. Cerebral microdialysis and positron emission tomography after surgery for aneurysmal subarachnoid hemorrhage in grade I patients. *Surg Neurol* 2005;64(2):109–15 [discussion: 115].
- [133] Grandin CB. Assessment of brain perfusion with MRI: methodology and application to acute stroke. *Neuroradiology* 2003;45(11):755–66.
- [134] Hirsch LJ. Continuous EEG monitoring in the intensive care unit: an overview. *J Clin Neurophysiol* 2004;21(5):332–40.
- [135] Wittman JJ Jr, Hirsch LJ. Continuous electroencephalogram monitoring in the critically ill. *Neurocrit Care* 2005;2(3):330–41.
- [136] Claassen J, Mayer SA, Kowalski RG, et al. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology* 2004;62(10):1743–8.
- [137] Jordan KG. Neurophysiologic monitoring in the neuroscience intensive care unit. *Neurol Clin* 1995;13(3):579–626.
- [138] Jaitly R, Sgro JA, Towne AR, et al. Prognostic value of EEG monitoring after status epilepticus: a prospective adult study. *J Clin Neurophysiol* 1997;14(4):326–34.
- [139] DeLorenzo RJ, Waterhouse EJ, Towne AR, et al. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. *Epilepsia* 1998;39(8):833–40.
- [140] Claassen J, Peery S, Kreiter KT, et al. Predictors and clinical impact of epilepsy after subarachnoid hemorrhage. *Neurology* 2003;60(2):208–14.
- [141] Dennis LJ, Claassen J, Hirsch LJ, et al. Nonconvulsive status epilepticus after subarachnoid hemorrhage. *Neurosurgery* 2002;51(5):1136–43 [discussion: 1144].
- [142] Butzkueven H, Evans AH, Pitman A, et al. Onset seizures independently predict poor outcome after subarachnoid hemorrhage. *Neurology* 2000;55(9):1315–20.
- [143] Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. *Neurology* 1996;47(1):83–9.
- [144] Vespa PM, O'Phelan K, Shah M, et al. Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. *Neurology* 2003;60(9):1441–6.
- [145] Sharbrough FW, Messick JM Jr, Sundt TM Jr. Correlation of continuous electroencephalograms with cerebral blood flow measurements during carotid endarterectomy. *Stroke* 1973;4(4):674–83.
- [146] Zampella E, Morawetz RB, McDowell HA, et al. The importance of cerebral ischemia during carotid endarterectomy. *Neurosurgery* 1991;29(5):727–30.
- [147] Rivierez M, Landau-Ferey J, Grob R, et al. Value of electroencephalogram in prediction and diagnosis of vasospasm after intracranial aneurysm rupture. *Acta Neurochir (Wien)* 1991;110(1–2):17–23.
- [148] Claassen J, Hirsch LJ, Kreiter KT, et al. Quantitative continuous EEG for detecting delayed cerebral ischemia in patients with poor-grade subarachnoid hemorrhage. *Clin Neurophysiol* 2004;115(12):2699–710.
- [149] Labar DR, Fisch BJ, Pedley TA, et al. Quantitative EEG monitoring for patients with subarachnoid hemorrhage. *Electroencephalogr Clin Neurophysiol* 1991;78(5):325–32.
- [150] Vespa PM, Nuwer MR, Juhasz C, et al. Early detection of vasospasm after acute subarachnoid hemorrhage using continuous EEG ICU monitoring. *Electroencephalogr Clin Neurophysiol* 1997;103(6):607–15.

- [151] Hebb MO, McArthur DL, Alger J, et al. Impaired percent alpha variability on continuous electroencephalography is associated with thalamic injury and predicts poor long-term outcome after human traumatic brain injury. *J Neurotrauma* 2007;24(4):579–90.
- [152] Claassen J, Mayer SA, Hirsch LJ. Continuous EEG monitoring in patients with subarachnoid hemorrhage. *J Clin Neurophysiol* 2005;22(2):92–8.
- [153] Shah AK, Agarwal R, Carhuapoma JR, et al. Compressed EEG pattern analysis for critically ill neurological-neurosurgical patients. *Neurocrit Care* 2006;5(2):124–33.
- [154] Fabricius M, Fuhr S, Bhatia R, et al. Cortical spreading depression and peri-infarct depolarization in acutely injured human cerebral cortex. *Brain* 2005;129:778–90.
- [155] Scheuer ML. Continuous EEG monitoring in the intensive care unit. *Epilepsia* 2002; 43(Suppl 3):114–27.
- [156] Kull LL, Emerson RG. Continuous EEG monitoring in the intensive care unit: technical and staffing considerations. *J Clin Neurophysiol* 2005;22(2):107–18.
- [157] Nakabayashi M, Kurokawa A, Yamamoto Y. Immediate prediction of recovery of consciousness after cardiac arrest. *Intensive Care Med* 2001;27(7):1210–4.
- [158] Sleigh JW, Havill JH, Frith R, et al. Somatosensory evoked potentials in severe traumatic brain injury: a blinded study. *J Neurosurg* 1999;91(4):577–80.
- [159] Fossi S, Amantini A, Grippo A, et al. Continuous EEG-SEP monitoring of severely brain injured patients in NICU: methods and feasibility. *Neurophysiol Clin* 2006;36(4): 195–205.
- [160] Rappaport M, Hemmerle AV, Rappaport ML. Short and long latency auditory evoked potentials in traumatic brain injury patients. *Clin Electroencephalogr* 1991;22(4):199–202.
- [161] Morris G, Gardner R. Computer applications. In: Hall J, Schmidt G, Wood L, editors. *Principles of critical care*. New York: McGraw-Hill; 1992. p. 500–14.
- [162] Jennings D, Amabile T, Ross L. Informal assessments: data-based versus theory-based judgments. In: Kahnemann D, Slovic P, Tversky A, editors. *Judgments under uncertainty: heuristics and biases*. Cambridge (UK): Cambridge University Press; 1982. p. 211–30.
- [163] Menzel M, Soukup J, Henze D, et al. Brain tissue oxygen monitoring for assessment of autoregulation: preliminary results suggest a new hypothesis. *J Neurosurg Anesthesiol* 2003; 15(1):33–41.
- [164] Czosnyka M, Smielewski P, Piechnik S, et al. Cerebral autoregulation following head injury. *J Neurosurg* 2001;95(5):756–63.
- [165] Soehle M, Jaeger M, Meixensberger J. Online assessment of brain tissue oxygen autoregulation in traumatic brain injury and subarachnoid hemorrhage. *Neurol Res* 2003;25(4): 411–7.
- [166] Steiner LA, Coles JP, Johnston AJ, et al. Assessment of cerebrovascular autoregulation in head-injured patients: a validation study. *Stroke* 2003;34(10):2404–9.
- [167] Lang EW, Czosnyka M, Mehdorn HM. Tissue oxygen reactivity and cerebral autoregulation after severe traumatic brain injury. *Crit Care Med* 2003;31(1):267–71.
- [168] Steiner LA, Czosnyka M, Piechnik SK, et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit Care Med* 2002;30(4):733–8.
- [169] Rosner MJ, Becker DP. Origin and evolution of plateau waves. Experimental observations and a theoretical model. *J Neurosurg* 1984;60(2):312–24.
- [170] Jaeger M, Schuhmann MU, Soehle M, et al. Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. *Stroke* 2007;38(3):981–6.
- [171] Panerai RB, Eames PJ, Potter JF. Variability of time-domain indices of dynamic cerebral autoregulation. *Physiol Meas* 2003;24(2):367–81.
- [172] Panerai RB, Chacon M, Pereira R, et al. Neural network modelling of dynamic cerebral autoregulation: assessment and comparison with established methods. *Med Eng Phys* 2004;26(1):43–52.

- [173] Schmidt J, Wartenberg KE, Wong A, et al. Graphical correlation analysis of brain tissue oxygen and intracranial pressure data for cerebral perfusion pressure optimization: a pilot study. 3rd Neurocritical Care Society Meeting 2006. Baltimore, MD, 2006 [poster presentation].
- [174] Gather U, Imhoff M, Fried R. Graphical models for multivariate time series from intensive care monitoring. *Stat Med* 2002;21(18):2685–701.

Thoracic Imaging in the ICU

Ami N. Rubinowitz, MD^{a,*}, Mark D. Siegel, MD^{b,c},
Irena Tocino, MD^a

^a*Department of Diagnostic Radiology, Thoracic Imaging Section, Yale University School of Medicine, 333 Cedar Street, Post Office Box 208042, New Haven, CT 06520, USA*

^b*Medical Intensive Care Unit, Yale-New Haven Hospital,
20 York Street, New Haven, CT 06510, USA*

^c*Department of Pulmonary & Critical Care Medicine, Yale University School of Medicine,
333 Cedar Street, Post Office Box 208057, New Haven, CT 06520, USA*

Imaging in the ICU plays a crucial role in patient care. The portable chest radiograph (CXR) is the most commonly requested radiographic examination, and, despite its limitations, it often reveals abnormalities that may not be detected clinically. Interactions between radiology and the bedside ICU clinical team have been transformed by the introduction and now widespread use of computer radiology (CR) and picture archiving and communication systems (PACS). Recent advances in CT technology have made it possible to obtain diagnostic-quality images even in the most dyspneic patient. This article reviews the significant contribution thoracic imaging makes in the diagnosis and management of critically ill patients.

Portable chest radiograph

The CXR is one of the most commonly requested radiographic examinations and is an integral supplement to the physical examination in the critically ill patient. At their institution, the authors perform, on average, 250 portable CXRs per day, half of which are on adult patients in the ICU. They are readily available, easy and quick to perform at the patient's bedside, and much less expensive than any other imaging modality. The CXR plays a key role in aiding diagnosis and management and monitoring response to therapy. Often, the physical examination is limited or difficult to perform in patients who are intubated, uncooperative, or unresponsive. Important problems may be clinically silent or difficult to detect in the

* Corresponding author.

E-mail address: ami.rubinowitz@yale.edu (A.N. Rubinowitz).

ICU, or the physical examination may be unreliable. Examples of disorders and problems for which the CXR is indispensable include malposition of invasive devices (particularly endotracheal tubes), identification of emergencies (pneumothorax), early detection of new problems (ventilator associated pneumonia or atelectasis), and assessment of volume status. The CXR is vital, often providing bedside clinicians with information they otherwise would not have.

Picture archiving and communication systems

Before the introduction of CR and PACS, radiology departments struggled to offer prompt, reliable access to ICU CXRs; a certain number of films would be lost either temporarily or permanently when frustrated clinicians would remove them from the radiology department for rounds and patient management. This occasionally would result in overlooking subtle but important findings and delay the radiologist's interpretation, potentially resulting in a negative impact on patient care.

The introduction and now widespread use of CR and PACS in most large medical centers has transformed interactions between radiology and the ICU. PACS are composed of image acquisition devices, network display devices, image servers or image archivers, and storage devices [1]. Images used for formal interpretation by the radiologist are viewed on high-resolution monitors. These are typically two or more $2k \times 2k$ grayscale monitors positioned side by side in a reading room with good control of background lighting. Sometimes high-quality, high-resolution monitors are placed in other hospital locations outside of the radiology department, providing sufficient resolution for clinical viewing purposes at substantial cost savings. Some institutions committed to the implementation of electronic medical records have opted for installation of flat panel monitors at the bedside for convenient access to images and reports, expediting patient evaluation and offering guidance when tubes, lines, and other devices need manipulation. When patients are not doing well, when problems become complex, or when abnormalities are suspected on the CXR, studies should be reviewed on high-resolution monitors, because important findings (such as a pneumothorax or malpositioned support device) may be missed on lower quality monitors or in suboptimal viewing environments.

There are many advantages to the combination of CR with PACS and few disadvantages. Some of these advantages include:

- More consistent acquisition of diagnostic-quality radiographs

- The ability to manipulate images by adjusting window levels and settings after the image has been obtained to overcome exposure problems

- The ability to rapidly transmit images over computer networks so they may be viewed simultaneously by the radiologist and the consulting physicians (eg, images may be reviewed from remote sites such as

home to allow the team on call to consult with the attending physician on specific circumstances)

Improved efficiency of the radiologist

Increased diagnostic accuracy and confidence of the radiologist with the help of the many tools available on the workstation such as scrolling, image navigation, image layout, window/level measurements, pan, zoom, magnification, annotation of images, including arrows calling attention to the location of tubes and catheters, and measurements for adjusting devices to ideal position (Fig. 1)

In the case of CT images, PACS offer the ability to perform instant multi-planar reconstructions, a helpful feature in evaluation of CT pulmonary angiography [1]. The integration of hospital information systems with PACS and digital voice recognition reporting systems has streamlined the flow of information between ICU physicians and radiologists further and improved the quality and content of such information. Computerized physician order entry offers an opportunity to capture essential clinical information to guide selection of appropriate studies and provides the radiologist with instant clinical content to aide in protocolling studies and in their interpretation. This computer-driven paperless environment, coupled with the ability to create reports with voice recognition, allows almost simultaneous access to images and interpretation from multiple sites, including at the bedside as in many institutions, or from home for after-hours consultation.

Ready access to the information is no substitute for direct daily communication between radiologist and clinical team. The implementation of

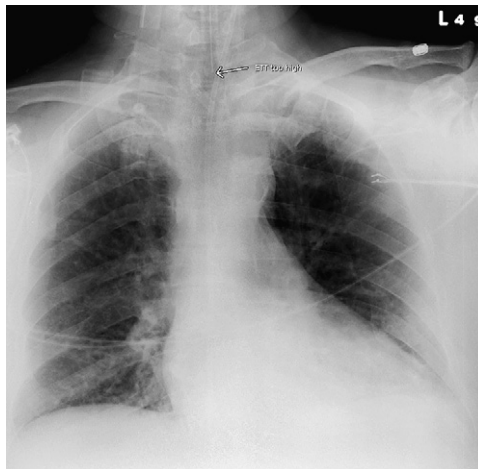


Fig. 1. AP chest radiograph in a 62-year-old man obtained after intubation. The endotracheal tube tip is too high, located above the thoracic inlet (at T1 level). This has been annotated on the picture archiving and communication systems workstation by the radiologist for the clinicians to view. A feeding tube is also present, adequately positioned.

PACS often results in a significant increase in the number of clinicians viewing their patients' images from off-site monitors and a decrease in the direct communication between the radiologist and the clinician. A study by Kundel and colleagues [2] demonstrated not only a dramatic decrease in the number of radiology consultations but also a significant increase in clinical action without first consulting the radiologist (from 6% to 40%). It is natural for the clinicians to want to review the films themselves. But interpretations leading to action should be done with caution, as subtle but important findings can be missed or overlooked easily on the lower-resolution monitors and suboptimal viewing conditions commonly encountered in the ICU. The final radiology report always should be read and taken into consideration. Clinicians sometimes use PACS as a substitute for conferences or rounds with the radiologist, especially as they have the images and radiologic report at their fingertips. This decline in communication between the clinician and radiologist may have a negative impact on patient care. Routine conferences or clinical rounds with the radiologist can facilitate communication and explanation of major or important findings on the images. They also can improve the radiologists' reports, because clinicians can provide valuable clinical or laboratory data that may narrow a differential diagnosis or lead to the appropriate diagnosis. Thus the valuable exchange of information between the radiologist and the clinician is of the utmost importance to ensure high-quality patient care. Despite the implementation of PACS, the authors actively promote and execute daily radiology rounds with several different clinical teams, 7 days a week. Conferences based around the high-resolution PACS monitors in the radiology department are more efficient with the ability to review multimodality studies and previous studies, spending more time per case and less overall time for each conference when compared with viewing hard-copy films [3]. In addition to daily rounds, the radiologist is responsible for communicating urgent and unexpected findings verbally to the ICU team in a timely manner, and documentation of such communication should be included in the radiology report. The explicit list of what constitutes an urgent finding and the appropriate recipient should be agreed upon by radiology and ICU and serve as an internal guideline [4].

Chest radiographs: technical issues

The quality of the portable CXR can be highly variable, ranging from good to uninterpretable. Obtaining diagnostic quality studies on unstable, uncooperative patients, or patients who have numerous support devices poses unique challenges to the technologist and is not always possible. There are limitations to obtaining quality portable CXRs, including the inability of critically ill patients to cooperate, the nature of the ICU environment with critically ill patients (some on life-support machines in tight quarters), difficulty in controlling scattered radiation in obese patients, and wide

differences in film exposure [5]. An uncooperative patient may move while the radiograph is being taken, or an exposure may be too long in large patients, or motion artifact may result when using grids to control scattered radiation. Patients who have many support lines and tubes may be difficult to move and position adequately for the film. This can result in parts of the chest being imaged incompletely and in rotation artifact.

To avoid these pitfalls and to standardize technique, at their institution, the authors obtain the portable CXR with the patient supine and with the cassette in vertical dimension so that the upper airway and upper abdomen are included, allowing evaluation of endotracheal tubes, feeding tubes, subpulmonic pneumothorax, and pneumoperitoneum, among other important findings. A focus to patient distance of 50 inches should be kept to avoid magnification and facilitate comparison of anatomic structures such as the width of the vascular pedicle, heart, and pulmonary vessels. The radiograph should be obtained at peak inspiration using 80 to 100 Kvp and short exposure times to minimize respiratory artifact. Clips, telemetry wires, and other external objects should be removed from the field as much as possible to better identify the position of lines, tubes, and the subtle findings of pneumothorax and early consolidation.

Recommendations for routine studies

Daily chest films often are ordered routinely in the ICU. The rationale for this practice, given unanswered questions about accuracy, efficacy, and cost-effectiveness, is debatable [6]. A recent survey among 65 ICU facilities shows a lack of consensus on the utility of the CXR, with only 63% of ICUs ordering routine daily CXRs [7]. Even those adhering to a daily request found the CXR helpful in no more than 30% of daily routine CXRs. The CXR was considered most helpful for the assessment of devices in 87% of daily CXRs, pneumothorax, 82% of daily CXRs, pneumonia, 74% of daily CXRs, and acute respiratory distress syndrome (ARDS) in 69% of daily CXRs. In the most recent efficacy study, new or important findings were present in 5.8% of routine CXRs, but the new findings influenced management in only 2.2% of the daily routine CXRs [8]. The results of this prospective study led the authors to the conclusion that daily routine CXRs are not necessary in the ICU. Other authors have shown that changing from routine to an on-demand strategy could result in a reduction of 36% of CXRs at considerable savings [9].

According to the American College of Radiology's "Appropriateness of Services Criteria," daily routine radiographs are indicated in patients who have acute cardiopulmonary disorders and those receiving mechanical ventilation [10]. This recommendation is based on previous literature of the 1980s and early 1990s showing a wide variety of results, with new radiographic findings reported anywhere from 6% to 91% of ICU chest radiographs. In two reports, 34.5% and 65% of studies showed abnormalities

or important changes, including malpositioned monitoring devices or altered cardiopulmonary status [11,12]. The yield was higher in radiographs performed for clinical problems than for those done routinely. In another study, consecutive routine chest films were evaluated in 94 medical ICU (MICU) patients [13]. Fifteen percent had an unsuspected abnormality, of which 93% precipitated a management change. The yield was higher in patients who had pulmonary and unstable cardiac disease, regardless of whether they were mechanically ventilated. Seventeen percent of these patients had unexpected findings, compared with 3% with other diseases. Films performed when two or more tubes or catheters were in place had a 16% chance of showing unsuspected findings, usually not involving device malposition, compared with 6% in those with none. The lack of standardization of methodology in these earlier studies precludes a formal meta-analysis, but a detailed review by Graat and colleagues [14] suggests that most of the findings identified on the routine daily CXR were either not new, or did not alter management. Routine studies may not be necessary in patients admitted to surgical ICUs [15,16]. For example, in one report, 164 routine radiographs were evaluated in 34 relatively young mechanically ventilated patients, most of whom were admitted for trauma [17]. Only 1% of radiographs had findings that could not be predicted clinically and affected management. Similarly, the yield of routine studies in postcardiothoracic surgery patients is also low [18,19], and a more selective use of films in these settings could save resources [15]. At present, it is prudent to recommend obtaining ICU chest radiographs on demand for the monitoring of devices and for deterioration of clinical condition.

Approach to interpreting the portable chest radiograph

A systematic approach is essential for interpreting the portable CXR. The steps are as follows:

- Assess the technical quality of the study.
- Evaluate the location of all catheters, tubes, and support devices.
- Assess the cardiovascular status of the patient.
- Check for abnormal parenchymal opacities.
- Search for evidence of barotrauma.
- Look for pleural effusions.
- Compare with the prior studies; does the patient look the same, better, or worse?

Attention should be directed to disorders common in the critically ill. Comparison always should be made with prior films, if available. The quality of the chest radiograph should be taken into account when reviewing the film. All support devices (tubes and catheters) should be evaluated for appropriate positioning and for possible complications of placement (ie, pneumothorax or mediastinal hematoma). The mediastinal width and contour

then should be assessed in addition to the cardiovascular status of the patient, with attention to the vascular pedicle width and heart size. Next, the lungs should be inspected for abnormal airspace opacities. Finally, the presence of abnormal air collections (such as pneumothorax, pneumomediastinum, pneumopericardium, or free air beneath the diaphragm) and pleural fluid collections should be sought [20]. It is important to remember that the appearance of the chest differs in the supine versus upright position. The anterior-posterior (AP) supine position magnifies the cardiac silhouette and will result in apparent vascular redistribution. This, in combination with low lung volumes (<eight posterior ribs visible on inspiration), can accentuate the cardiac silhouette and pulmonary vasculature even further, and artificially cause widening of the superior mediastinum with a widened vascular pedicle, mimicking congestive heart failure (CHF) when the patient is normal (Fig. 2). Although more difficult to detect on supine films, the appearances of pneumothoraces and pleural effusions have been described and are discussed in detail.

Invasive devices

The CXR readily identifies the position of invasive devices placed for monitoring or therapy, such as pulmonary artery catheters, central venous lines, temporary pacemakers, chest tubes, endotracheal tubes (ETTs), and nasogastric tubes (NGTs) [6,21]. Most invasive devices require radiographic

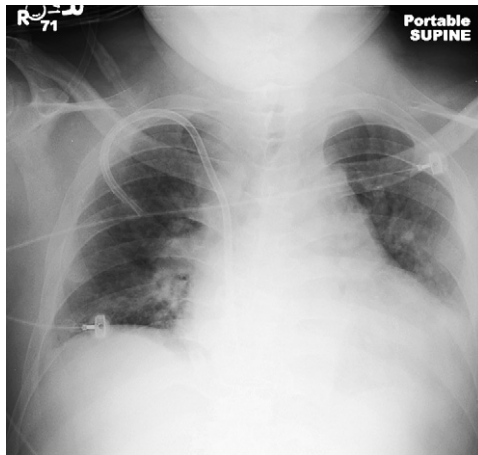


Fig. 2. Normal supine AP chest radiograph obtained with a poor inspiratory effort in a 44-year-old man. The AP and supine positioning of the patient accentuate the heart size and cause vascular redistribution, respectively. Combined with the poor inspiratory effort, the findings of apparent cardiomegaly, widened vascular pedicle, and redistributed blood flow in the upper lobe pulmonary veins give the appearance of congestive heart failure.

confirmation of position after placement, because improper positioning may not be clinically apparent. Studies also are needed to rule out procedure-related complications. Malposition caused by improper placement or migration is frequent and may cause complications. In one study, 14% of radiographs taken on admission to the ICU showed incorrectly positioned tubes or catheters [11].

Endotracheal tubes

After intubation, it is critical to ensure that the ETT is positioned appropriately within the airway. The tube should be approximately 5 cm above the carina or at the level of the aortic knob when the patient's head is in the neutral position. Flexion or extension of the head can move the ETT 2 to 4 cm in either direction [22]. Placement too high can cause inadvertent extubation or misplacement of the occluding cuff. Placement too close to the carina may lead to selective intubation of a main bronchus or irritation of the carina. Intubation too high or too low within the trachea is difficult to detect clinically, because breath sounds are generally normal. Right mainstem intubation may cause unequal breath sounds and high peak airway pressures and, in severe cases, may cause hypoxemia and hemodynamic compromise. Mainstem intubation can be clinically occult, however, and only revealed on the CXR. In one study, 60% of patients who had mainstem intubation had symmetric breath sounds [23]. In addition to inappropriate positioning, radiographic signs of right mainstem intubation include hyperinflation of the right lung and atelectasis of the right upper lobe, which may occur if the ETT reaches the bronchus intermedius. Selective intubation also may result in iatrogenic pneumothorax.

Malpositioning is common and may be missed clinically, justifying the requirement for CXRs immediately after intubation. In one study of 219 critically ill patients evaluated after ETT placement, 5% had mainstem intubation, and 14% needed repositioning [24]. In another study, 15.5% of ETTs were placed inappropriately by radiographic criteria, despite previous clinical evaluation [23]; 61.9% of these cases occurred in women, and the most common problem was placement too close to the carina [25].

Tracheal rupture is a rare but devastating complication of intubation, occurring most commonly in the peri-intubation period [26]. Rupture usually occurs through the membranous trachea within 7 cm of the carina. Risk factors include use of a stylet, an inexperienced operator, and emergency intubation. The most dramatic cases present as bilateral pneumothorax and massive subcutaneous emphysema, but clinical signs may be delayed as long as 24 hours in up to 70% of cases. In such cases, tracheal rupture is suggested radiographically by an oblique orientation of the ETT to the right and inflation of the cuff beyond the normal tracheal boundaries. Other radiographic signs include migration of the balloon cuff toward the tip of the ETT and pneumomediastinum or subcutaneous emphysema [26]. Rupture can be confirmed by CT if necessary [27].

Another complication of endotracheal intubation is damage to the tracheal mucosa caused by cuff overinflation and consequent ischemia. This usually is prevented by limiting inflation pressures and by the daily radiographic evaluation of the cuff and noting that it does not exceed the diameter of the trachea [5]. A rare but devastating complication is intubation of the esophagus. This should be demonstrated clinically by severe hypoxemia and detection of CO₂ in exhaled gas, but could be missed in the setting of severe cardiopulmonary disarray. Radiographic signs include inflation of the ETT beyond the diameter of the normal trachea, distention of the stomach, or an air column lateral to the tracheal air column.

Central venous catheters

Central venous, generally multilumen, catheters are placed commonly for hemodynamic monitoring and delivery of fluid and medication. The internal jugular and subclavian approaches are the most commonly used routes. A portable CXR should be done after line placement to confirm position and rule out procedure-related complications, especially pneumothorax [28]. Up to one third of catheters are malpositioned when initially placed [5]. To accurately measure central venous pressure, the catheter tip must be intrathoracic and beyond all the venous valves, the last of which are located distal to the anterior first rib on the CXR. For fluid and medication delivery, all line ports must be within the vessel. The ideal position for the line tip is in the superior vena cava (SVC) slightly above the right atrium. If placed higher, the proximal port, located 5 cm from the catheter tip, may be outside the vessel or above the valves. More distal placement may put the catheter tip within the heart, risking possible arrhythmias, myocardial rupture, and pericardial tamponade, although the actual risk of rupture if the catheter is in the right atrium is probably quite low [29]. In addition, when the central line tip is in the right atrium, venous blood sampled from the distal port will include blood from the lower half of the body, which is important to consider when venous saturation is being used to evaluate oxygen delivery [30]. Pneumothorax follows line placement in up to 6% of procedures and is probably more common with the subclavian than the internal jugular approach [24]. Because a pneumothorax can be devastating, a CXR should be done after each attempt at line placement, even if unsuccessful. An immediate CXR generally is not needed when a line is changed over a wire [31].

Delayed complications of central venous line placement include catheter embolization, venous obstruction leading to SVC syndrome, and vessel perforation [27]. Perforation of the SVC may result in infusion of fluid into the mediastinum or pericardium, and this may be manifested radiographically by mediastinal widening, enlargement of the cardiac silhouette, or a new pleural effusion. Radiographic signs that suggest impending perforation include curving of the catheter tip or direct placement of the catheter tip against the wall of the SVC [32].

Chest CT

Chest CT plays a crucial role in the care of the critically ill patient. A study performed by Miller and colleagues [33] concluded that the most common indications for requesting a CT scan were sepsis of unknown origin, evaluation of pleural effusion, evaluation of patient with malignancy, and assessment of complications of thoracic surgery. At the authors' institution, approximately 25 chest CTs are performed on ICU patients per month. It is not uncommon for the clinicians to request a CT in the patient who is acutely decompensating to try to elucidate possible causes, such as pulmonary embolism, source of bleeding in a postoperative patient, empyema, aortic dissection, or aortic intramural hematoma, especially as the portable CXR may be limited, nonspecific, or noncontributory. Pleural effusions can be difficult to detect on a portable CXR, and their appearance also can mimic airspace consolidation. Thus, chest CT in many instances may be the only way to accurately assess for both the presence and size of a pleural effusion. Although pleural fluid can be detected readily at CT, CT is of limited value in differentiating transudates from exudates. CT, however, does have the advantage over ultrasound when it comes to diagnosing empyema (and differentiating it from lung abscess) and in the characterization of malignant effusions [34]. Features on CT that favor empyema over lung abscess include: presence of sharp margin, thin wall, lenticular shape, the split-pleura sign (which will be discussed later in the article), and lung parenchyma displaced by the pleural fluid collection. In contrast, a lung abscess typically has an irregular margin and a thick wall. Additionally, it is round; the pleural surface is not seen, and lung tissue maintains normal position [35]. CT is also extremely useful and commonly requested to guide procedures such as drainage of pleural effusions or to assess the position of drainage catheters.

There are few drawbacks and many more advantages to performing CT in ICU patients (Box 1). The major disadvantage is the need to transport patients out of the closely monitored ICU environment. Many patients have relative contraindications to the use of intravenous (IV) contrast (particularly an increased risk of contrast-induced nephropathy). Fortunately, IV contrast seldom is needed except to evaluate the aorta or look for pulmonary emboli. CT exposes the patient to substantially more radiation compared with the CXR. Finally, the CT may not always provide additional information to the nonspecific CXR, especially when the patient has diffuse airspace disease, which often yields the same differential diagnosis raised on the portable study.

On the other hand, CT is more sensitive than CXR and can provide valuable information that may change patient management [36–38]. Not uncommonly, clinically occult or unsuspected abnormalities (such as a small pneumothorax or incidental pulmonary emboli) can be detected readily by CT. CT also may reveal a source of sepsis that CXR may not demonstrate (such as an empyema or lung abscess) (Fig. 3). Evaluation of chest tube

Box 1. Advantages and disadvantages of chest CT compared with portable chest radiograph**Advantages**

Much more sensitive

Evaluates

Lungs

Heart

Mediastinum

Pleura

Chest wall

Upper abdomen

Localizes disease

Guidance of interventional procedures

Can detect occult pneumothorax or effusions

Evaluates chest tube placement

Can contribute new information

May detect unsuspected abnormalities

Disadvantages

Risk of transporting patient out of the ICU environment

Significant increased radiation

Risks of intravenous contrast (if given)

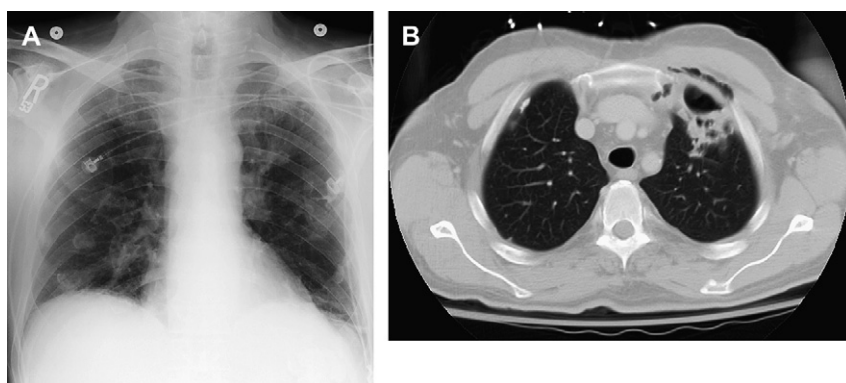


Fig. 3. 64-year-old immunocompromised man with a staphylococcal lung abscess that is difficult to identify on AP chest radiograph, but is visible at CT. (A) AP CXR shows bilateral amorphous densities consistent with pleural plaques in the middle to lower lungs. An abscess is not appreciated. (B) Axial CT image obtained the same day as the chest radiograph in A demonstrates a left upper lobe complex cavitary lesion consistent with a lung abscess. Gas is in the chest wall beneath the left pectoralis minor muscle secondary to adjacent extension of the abscess through the chest wall.

placement, which can be limited on a portable CXR and inadequate positioning, is performed more easily and confidently with the use of CT. Chest CT also can reveal significant or unsuspected findings in the upper abdomen (which routinely is included as part of the chest CT scan), such as free intraperitoneal air secondary to perforation of a viscus, colitis, hemoperitoneum, or retroperitoneal hematoma (Fig. 4).

As many ICU patients are at increased risk for thromboembolic disease, chest CT is not only useful in the diagnosis of pulmonary embolism, but it also provides additional information as it evaluates the lung parenchyma, heart and mediastinum, pleura and chest wall. As many as two thirds of patients will have an alternative diagnosis established by CT [36,37]. Because most of these patients have abnormalities present on their CXR, ventilation perfusion (V/Q) scan is rarely diagnostically useful in this patient population, because, if the lungs are not clear, it will usually be rendered indeterminate [39].

Specific disease states

Pulmonary edema

Pulmonary edema can be divided into two categories depending on its etiology: cardiogenic or noncardiogenic (Fig. 5). In the ICU setting, the most common causes of pulmonary edema are CHF, fluid overload, and damage to the pulmonary microvasculature resulting in capillary leak edema [5]. There are many causes of noncardiogenic edema, some of which include uremia, sepsis, neurogenic, trauma, drug overdose, toxic fume inhalation, and near-drowning.

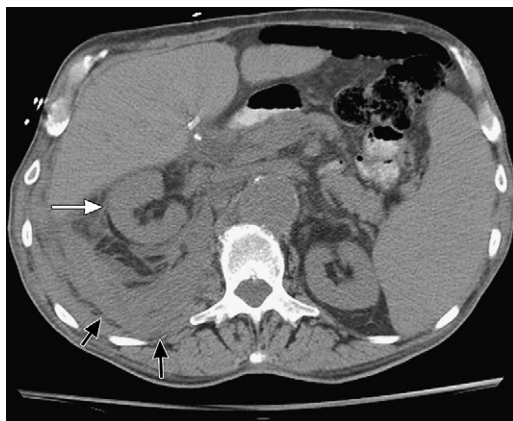


Fig. 4. 77-year-old man with sudden onset of tachycardia and dyspnea. Axial CT image of the upper abdomen, which was included as the last image of a chest CT, demonstrates a moderate-sized right retroperitoneal hematoma (black arrows) displacing the right kidney (white arrow) anteriorly. The remainder of the chest CT was normal. The patient was on Coumadin and had an elevated international normalized ratio.

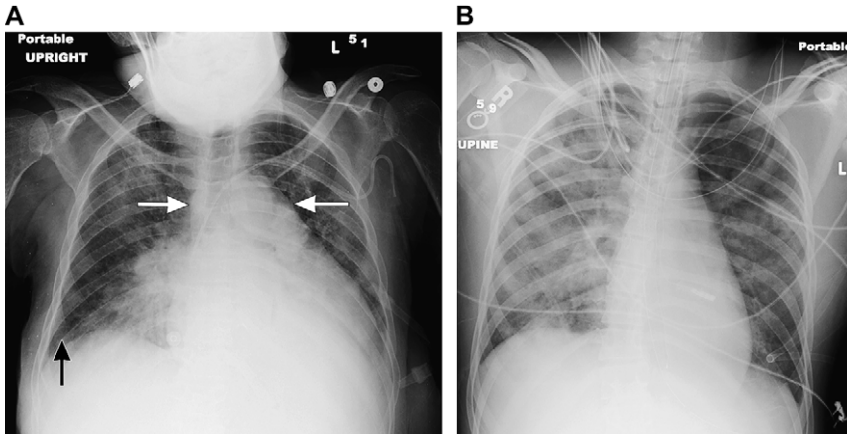


Fig. 5. AP chest radiographs (CXR) illustrating the differences in appearance of cardiogenic (A) versus noncardiogenic (B) edema. (A) 61-year-old woman with a left ventricular ejection fraction of 30% and cardiogenic edema demonstrates cardiomegaly, widened vascular pedicle (white arrows), engorged vessels, central ground glass opacities, Kerley B lines (black arrow), and haziness at the lung bases because of small pleural effusions. (B) CXR in a 39-year-old man with shortness of breath and acute respiratory distress syndrome following cocaine overdose. There are bilateral ground glass opacities with normal-sized heart, normal vascular pedicle width, without pulmonary venous congestion and lack of pleural effusions, which favor noncardiogenic cause of the edema.

Cardiogenic edema can be graded as mild, moderate, or severe. The upright CXR is more accurate than the supine portable CXR in depicting the findings of pulmonary edema. The earliest sign of pulmonary edema on CXR (mild edema) is vascular redistribution or cephalization of vessels, also known as pulmonary venous hypertension. With moderate (or interstitial) pulmonary edema corresponding signs on CXR include perihilar or vascular haziness, Kerley lines, and/or peri-bronchial cuffing, with or without pleural effusions. As intravascular hydrostatic pressures continue to rise, fluid begins to fill the airspaces, resulting in alveolar edema. Alveolar edema tends to produce airspace opacities in the middle to upper lung zones, but it can be present dependently in the lower lung fields, especially in patients who have diseases affecting the upper lobes, most commonly centrilobular emphysema. Thus alveolar edema in a patient who has chronic obstructive pulmonary disease (COPD) can mimic pneumonia radiographically. An important fact to remember that can help differentiate these two entities, is that interstitial or airspace opacities from edema can both appear and clear rapidly in contrast to airspace disease from pneumonia, which usually does not resolve completely within 24 hours (especially in a patient who has COPD).

Intravascular volume status can be estimated on the portable CXR by noting the vascular pedicle width [40,41]. The anatomic landmarks used for determining vascular pedicle width include the SVC and azygous vein complex on the right side of the mediastinum, and the proximal descending

thoracic aorta on the left (Fig. 6). A vascular pedicle width of greater than 7 cm is considered widened and can be used as an indirect sign of increased volume status [1]. Typically, the vascular pedicle width is widened in cardiogenic edema and edema secondary to fluid overload. On the other hand, the vascular pedicle width is normal or decreased in patients who have capillary leak edema not complicated by fluid overload or left ventricular dysfunction [5]. It is important to consider factors that can alter the vascular pedicle width artificially, however, such as patient rotation, supine positioning, a shallow inspiration, ventilator settings, and patients' body weight. It is important to take these factors into account and follow this landmark over serial portable CXRs performed with similar technique.

Although the portable CXR is relatively useful in detecting pulmonary edema, it is not always possible radiographically to distinguish between cardiogenic and noncardiogenic causes. In general, signs that favor CHF as the cause of edema include cardiomegaly, widened vascular pedicle, septal thickening, and pleural effusions. Airspace opacities with CHF tend to be central and uniformly distributed but can appear in different locations depending on patient positioning and presence of background emphysema. CT is much more sensitive for demonstrating these findings than portable CXR (Fig. 7). It also is important, however, to be aware of the fact that airspace edema, especially if resolving, may have different appearances on CT, and that the CT findings may not always be straightforward. The CT scan should not be reviewed in isolation. In these cases, it is usually helpful to also review recent serial CXRs, which may demonstrate rapidly changing airspace densities, thus favoring edema.

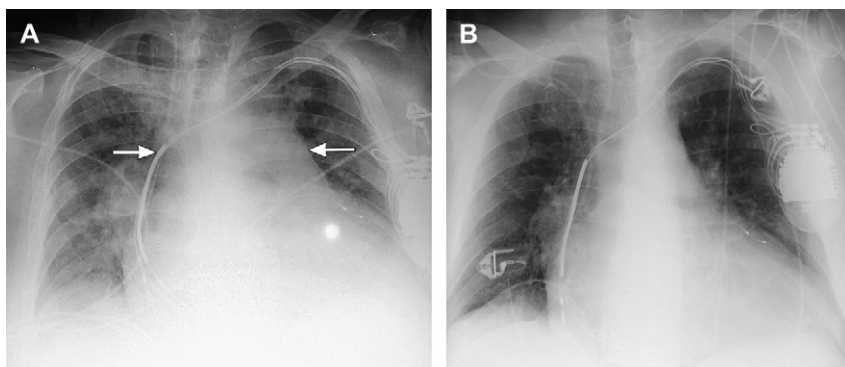


Fig. 6. Two chest radiographs (CXRs) of a 60-year-old man demonstrating a change in vascular pedicle width secondary to a change in volume status. (A) AP CXR demonstrates a widened vascular pedicle (arrows), cardiomegaly, pulmonary venous congestion, and bilateral pleural effusions consistent with congestive heart failure. (B) AP CXR after diuresis shows decrease in the vascular pedicle width, resolution of vascular congestion, and pleural effusions but persistent cardiomegaly. A pacemaker/defibrillator is also present and adequately positioned.

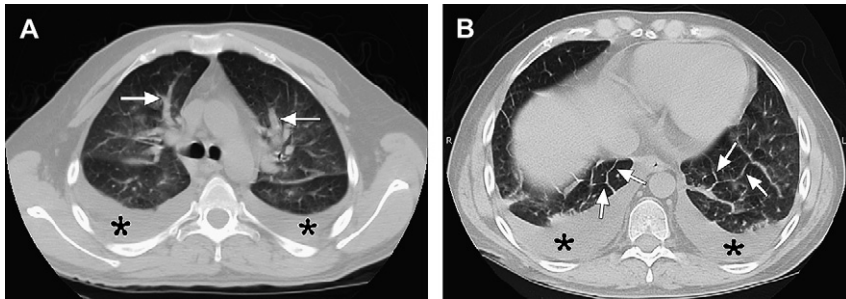


Fig. 7. 45-year-old man with shortness of breath secondary to acute myocardial infarction and congestive heart failure. Axial CT images obtained through the upper lungs (A) and lower lungs (B) demonstrate central ground glass opacities with an upper lobe predominance, engorged nondependent pulmonary veins (white arrows in A), and thickened interlobular septa (white arrows in B), which would produce Kerley lines on chest radiograph, and bilateral pleural effusions (asterisks).

Airspace opacities with capillary leak edema were found to be patchy and peripheral in 58% of patients compared with 13% in hydrostatic edema [42]. Imaging findings commonly associated with hydrostatic edema can be seen in patients who have capillary leak edema as well [42]. In addition, interstitial pneumonia, an acute noninfectious pneumonitis, or pulmonary hemorrhage can produce radiographic findings indistinguishable from pulmonary edema. Therefore, the imaging findings can only supplement the important information obtained from the physical examination and clinical history, which are crucial to making a correct diagnosis.

Acute respiratory distress syndrome

The radiographic manifestations of ARDS vary with the stages of the disease, the severity of the lung injury, and the associated complications such as barotrauma and pneumonia. The radiographic findings usually appear during the first 24 to 72 hours following the inciting clinical event (eg, shock, aspiration, sepsis) and most commonly present as bilateral patchy air space consolidation. This corresponds to the exudative phase of ARDS, when a large amount of protein-rich pulmonary edema leaks into the alveoli. The second phase is characterized by proliferation of type II pneumocytes and hyaline membrane formation. During the second phase, the initial patchy opacities progress to consolidation with a lower lobe predominance; these findings can remain stable for days, even weeks, offering a monotonous picture on the daily radiograph, in contrast with cardiogenic edema or pneumonia, where changes occur more rapidly. Few patients who have ARDS have a pure clinical or radiographic picture of capillary leak edema; the CXR can indicate superimposed fluid overload, with widening of the vascular pedicle, increasing pleural effusions, and soft tissue edema [40]. Pneumonia may be suspected in the presence of focal consolidation or worsening of

opacities after a relatively stable phase. In some cases, CT may be necessary to evaluate a persistent source of sepsis, the presence of nodules, or cavitation as a sign of fungal infection or septic emboli.

Evaluation of ARDS with CT has brought further understanding of the radiographic findings and corresponding pathophysiologic correlation [43,44]. On CT, the diffuse patchy consolidation on the portable CXR appears to be quite extensive involving the entire lung, but with more severe consolidation in the dependent zones explaining the severe ventilation–perfusion mismatch and shunting typical of ARDS (Fig. 8). According to Gattinoni and colleagues' [45] observations, a density and pressure gradient can be inferred from the CT images and corresponding Hounsfield numbers. The pressure and lung weight increase along the vertical axis, resulting in progressive alveolar collapse in the most dependent regions of the lungs. Gattinoni's model implies that some these alveoli can be recruited by increasing the levels of positive end-expiratory pressure (PEEP), whereas others are at risk of overdistention. Dependent consolidation and atelectasis provide a rationale for placing patients in the prone position. Although improvements in survival have not been shown, in many patients, prone positioning is associated with recruitment of dorsal lung zones and improved gas exchange [44]. When patients are managed in the prone position, the CXR may show a vanishing of the cardiac silhouette because of the contact of diaphragm and pleural effusions with the heart borders.

Barotrauma

Despite growing acceptance of ventilator strategies that emphasize lower tidal volumes and plateau pressures compared with approaches used in the past, barotrauma, particularly pneumothorax, but also pneumomediastinum, pneumopericardium, pneumoperitoneum, subcutaneous emphysema, and interstitial emphysema remain common ICU complications [46].

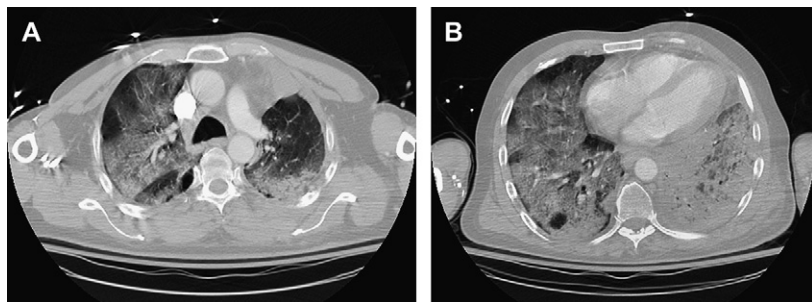


Fig. 8. Noncardiogenic edema (acute respiratory distress syndrome) secondary to fluid overload in a 59-year-old postoperative man with shortness of breath. Axial CT images through the upper (A) and lower (B) lungs demonstrate diffuse ground glass opacity and consolidation, which is most pronounced in the dependent lower lungs. The heart size is normal without pulmonary venous distension, and there are no pleural effusions.

Patients at high risk include those who have severe airway obstruction, especially status asthmaticus, and those who have ARDS [47]. Pneumothoraces quickly can become life threatening, especially in mechanically ventilated patients.

Pneumothoraces are missed frequently when interpreting the portable CXR. In one study, 32.1% of pneumothoraces were associated with delayed diagnosis [48]. Risk factors included an atypical location, mechanical ventilation, altered mental status, and development of pneumothorax during low physician staffing hours. The quality of the CXR and of the monitors available in the ICUs is also essential for diagnosing subtle pneumothoraces. Background light needs to be kept to a minimum, and ideally the reader should be able to manipulate the image to enhance the findings. Pneumothorax is especially difficult to diagnose in supine compared with upright patients, because the characteristic feature, a space between the parietal pleura and the chest wall at the apex, may not be present [49].

The characteristic appearance of pneumothoraces in supine patients has been described [49]. In the supine position, air tends to collect anteriorly and medially in the pleural space. This leads to increased radiolucency at the bases and sharp elongated (deep) cardiophrenic and costophrenic sulci (Fig. 9) [50]. Subpulmonic pneumothoraces may go undetected if the CXR is not

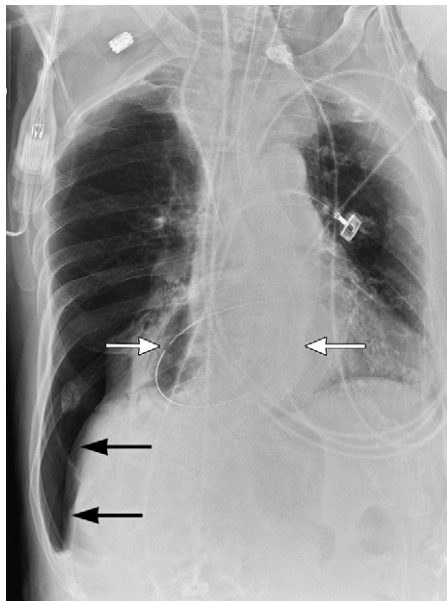


Fig. 9. Supine AP chest radiograph in a 93-year-old woman with shortness of breath and a right-sided pneumothorax. Lucency with absent lung markings at the right costophrenic angle is the deep sulcus sign (*black arrows*), indicative of a pneumothorax in the supine position. Other support devices including endotracheal tube and right internal jugular line are present, as well as an NG tube, which is coiled above the diaphragm in a hiatal hernia (*white arrow*).

done with the cassette in vertical orientation. Some pneumothoraces are occult on CXRs and are discovered only when the patient undergoes CT of the chest or abdomen [51]. CT also may be helpful for evaluating loculated air collections and the proper location of chest tubes when pneumothorax persists.

Signs of tension physiology may be difficult to detect in patients who have stiff lungs. There may be no mediastinal shift, and collapse may be minimal, so that the diagnosis may need to be made on clinical grounds alone [52]. Signs suggesting tension include depression of a hemidiaphragm and flattening of the heart border and vascular structures such as the superior vena cava and the inferior vena cava. If there is a delay in obtaining the portable CXR and the patient is clinically deteriorating, empiric treatment may be required.

Airspace disease

Patients in the ICU are at risk for many disorders initially that may be difficult to distinguish by CXR alone. Airspace disease is one of the most common abnormalities found on the CXR of an ICU patient. An alveolar filling process usually results in airspace disease and generally speaking can be secondary to pus, fluid, blood, or cells. Airspace opacification that rapidly appears and disappears can be secondary to cardiogenic edema (Fig. 10), noncardiogenic edema, hemorrhage, atelectasis, and aspiration pneumonitis [53]. Pneumonias not caused by aspiration usually do not completely clear rapidly (ie, within hours or a few days).

Pneumonia

In the critically ill patient, correctly establishing the diagnosis of pneumonia can be challenging. Airspace consolidation on CXR in this patient

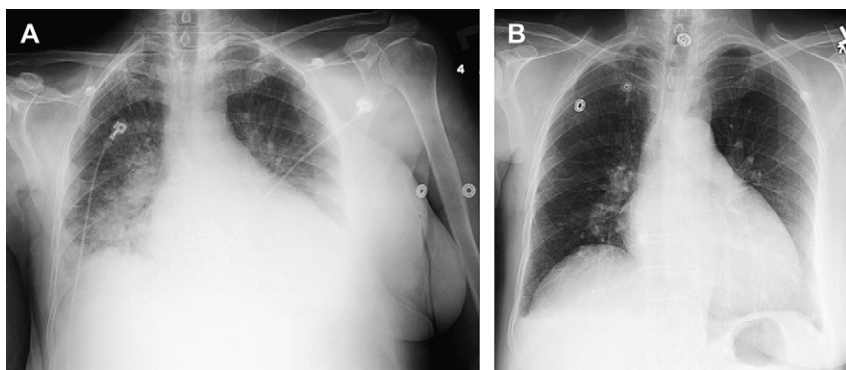


Fig. 10. Two chest radiographs (CXR) of a 77-year-old woman demonstrating rapid clearance of congestive heart failure (CHF). The initial CXR (A), obtained when patient was short of breath, demonstrates cardiomegaly, perihilar ground glass densities, vascular indistinctness, Kerley B lines, and bilateral pleural effusions consistent with CHF. One day later and after diuresis, the CXR (B) shows clear lungs without pleural effusions but a persistently enlarged heart.

population is not always caused by pneumonia and can be seen with other entities such as atelectasis, aspiration, pulmonary hemorrhage, noninfectious lung inflammation (such as because of a drug reaction), pulmonary edema, or ARDS. There are a few radiographic features that favor pneumonia over other disease processes (Table 1).

It is not uncommon for the portable CXR to demonstrate a nonspecific area of consolidation. CT often can help distinguish pneumonia from atelectasis (Fig. 11). Both pneumonia and atelectasis will appear as an area of consolidation, but CT can reveal signs of volume loss not apparent on the portable CXR, thus favoring the diagnosis of atelectasis over pneumonia. Findings favoring atelectasis include displacement of a fissure and crowding together of the segmental bronchi and vessels. Pneumonia on CT more typically will be space-occupying, involving a lobe or part of a lobe. None of these factors are entirely specific, however, and they must be considered in conjunction with the clinical parameters. The presence of air bronchograms is the result of an airspace (or alveolar) filling process surrounding bronchi that are not obstructed [54]. Air bronchograms more typically occur with, but are not specific for, pneumonia, and they also can be seen in other entities including atelectasis (if the airways are not obstructed), noninfectious lung inflammation, and in neoplastic etiologies including bronchioloalveolar carcinoma and pulmonary lymphoma. Pneumonia also can be present without air bronchograms (ie, if the airways are filled with mucus).

In patients who have nonspecific airspace disease on CXR, the CT scan can provide valuable clues to the diagnosis or sometimes even suggest an organism. Although there is a great deal of overlap, certain infections also can have a characteristic appearance. CT can demonstrate evidence of prior granulomatous exposure (such as calcified lymph nodes or calcified granulomas in the lung, liver, or spleen). Therefore, in a patient not responding to routine antibiotics, the presence of cavities, upper lobe (or superior segment lower lobe) airspace disease, or small airway disease, in conjunction with findings of prior granulomatous disease, suggests the possibility of reactivation tuberculosis (TB) (or an atypical mycobacterial infection). In a patient who has multiple peripheral lung nodules, some solid and some cavitary, the diagnosis of septic emboli should be considered, especially if the patient has an indwelling catheter, endocarditis, or history of IV drug abuse (Fig. 12). It

Table 1
Differentiating airspace opacities on portable chest radiograph

Pneumonia	Atelectasis	Pleural effusion
Nondependent	Volume loss	Homogeneous gradient of increased density
Slowly resolves	Appears or resolves rapidly	Change with position (if not loculated)
Lack of volume loss	Linear or band-like (if not lobar)	Blunted costophrenic angle
Sublobar, bilateral	Lobar–triangular or wedge-shaped	Apical cap

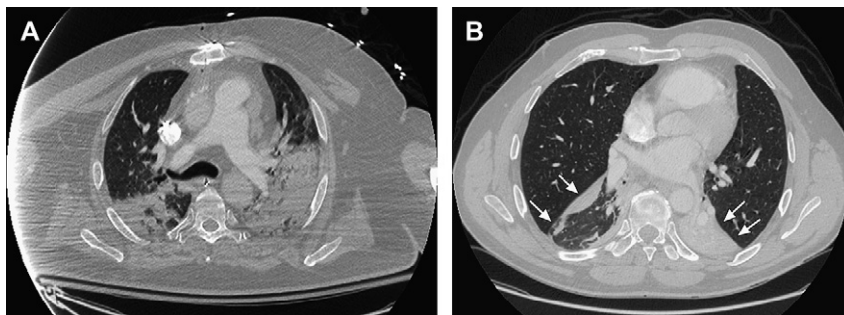


Fig. 11. Pneumonia versus atelectasis on CT. (A) Axial CT images through the middle chest in a 60-year-old man with pneumococcal pneumonia demonstrate bilateral airspace consolidation with air bronchograms and no volume loss. (B) 44-year-old man who is postoperative day 1 following spine surgery and with bilateral lower lobe atelectasis, left greater than right. Axial CT images through the chest at the level of the heart demonstrate complete collapse of the left lower lobe and partial collapse of the right lower lobe. Note the triangular shape of the collapsed left lower lobe with vessels crowded together, and posterior displacement of both major fissures (arrows) secondary to volume loss. The left lower lobe airways are not seen, as they are filled with mucus.

is important to remember, however, that no imaging appearance is entirely specific, and in reality, any infection can look just like any of the others.

Pneumonia in the immunocompromised patient

Cancer patients account for a large proportion of the critically ill. Chemotherapeutic agents can cause them to become immunocompromised, leaving them vulnerable to opportunistic or fungal infections. Other populations at risk for these life-threatening infections include patients who have AIDS, patients with organ transplants, and patients who have autoimmune or collagen vascular disease treated with immunosuppressive agents. In any immunocompromised patient, the presence of new ill-defined lung nodules, peribronchovascular consolidation, or pleural-based wedge-shaped

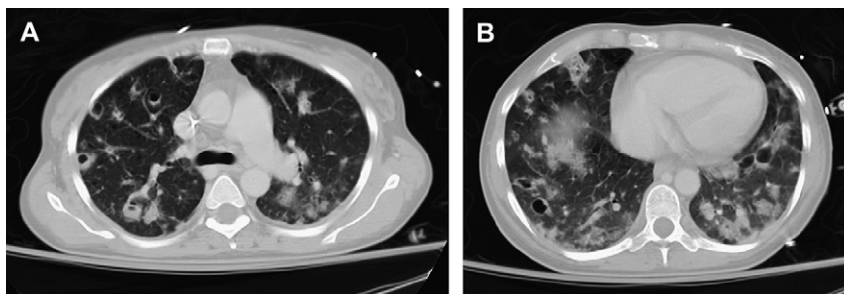


Fig. 12. 36-year-old woman IV drug abuser with recurrent endocarditis and septic emboli. Axial CT images obtained at levels of the upper (A) and lower (B) thorax demonstrate multiple peripheral solid and cavitary nodules consistent with septic emboli.

areas of consolidation should raise concern for fungal infection, in particular, invasive aspergillosis. The CT halo sign [55], which is a nodule or mass-like area of dense consolidation with surrounding ground glass opacity, is highly sensitive, but not specific, for invasive aspergillosis. The surrounding ground glass opacity is felt to reflect hemorrhage, as this organism is angioinvasive. If this sign is seen in an immunocompromised patient who has severe neutropenia, aggressive therapy aimed at this fungal organism should be instituted rapidly. This sign, however, is not unique to invasive aspergillosis, and it also can be seen with other infections, vasculitides, and neoplastic disease with surrounding hemorrhage (in particular Kaposi's sarcoma and metastatic angiosarcoma).

Aspiration

ICU patients are at risk for aspiration for several reasons. Predisposing factors include debilitation, general anesthesia, altered mental status, neuromuscular disorders, and abnormalities affecting the pharynx and esophagus. An endotracheal or tracheostomy tube is not entirely protective, because patients can aspirate around the cuff. The severity of clinical symptoms and extent of pulmonary complications depends on the type and amount of material aspirated into the tracheobronchial tree, and this can range anywhere from an asymptomatic focal inflammatory reaction with minimal or no radiographic findings to severe life-threatening disease [56]. The different clinical syndromes caused by aspiration include chemical pneumonitis, pneumonia, and airway obstruction. Aspiration of gastric acid with a pH of less than 2.5 can be fatal if massive, resulting in a severe chemical pneumonitis within minutes. The radiograph typically demonstrates focal consolidation that appears rapidly (within hours after the event), followed by the development of diffuse, bilateral airspace opacities characteristic of acute pulmonary edema. The opacities generally can clear as rapidly as they develop. Aspiration occurs most commonly on the right, caused by the steeper orientation of the right mainstem bronchus. When the patient is supine, the most frequently involved sites are the posterior segments of the upper lobes and superior segment of the lower lobes (Fig. 13).

In cases with aspiration of mixed bacterial flora from the oropharynx, a necrotizing pneumonia can ensue. In particular, patients who have advanced periodontal disease are at increased risk for developing pneumonia following aspiration. The anaerobic organisms present in the aspirate tend to produce airspace consolidation with necrosis and cavitation. Lung abscess formation, empyema, or bronchopleural fistula are the main complications of aspiration pneumonia.

Aspiration of solid material or of a foreign body can result in airway obstruction. It is not uncommon for a patient who is acutely decompensating to require emergent intubation. During this rapid and tense time period, a patient's tooth or piece of dental hardware could become dislodged into the airway. It is important to remain alert to this possibility when

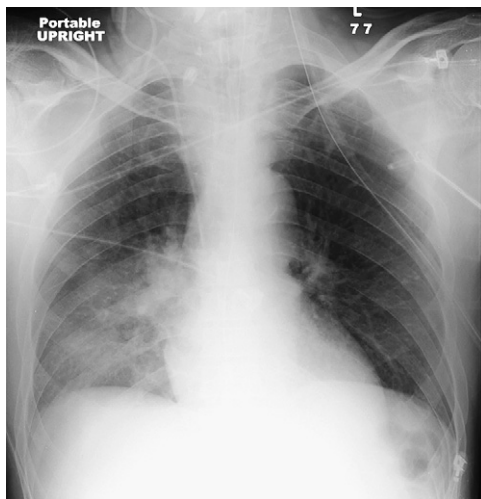


Fig. 13. 53-year-old alcoholic man with aspiration pneumonia following a drinking binge. AP chest radiograph with airspace opacity in the right lower lobe representing aspiration pneumonia. Support devices are positioned appropriately.

a radiopaque foreign body suddenly appears on the patient's CXR. It is easy to overlook this finding, especially in cases where there are numerous other abnormalities present. If a foreign body aspiration is suspected, this could be confirmed with CT if necessary.

It is important to note that the CXR is not always clear-cut, as aspiration can produce findings identical to other conditions such as pulmonary edema, nosocomial pneumonia, TB, or atelectasis. In the critical care setting, however, because many of these patients are increased risk for aspiration, this diagnosis should remain in the forefront, especially when rapidly appearing dependent airspace opacities are present radiographically.

Pleural effusions

Pleural effusions can be divided into two groups based on fluid analysis: transudates and exudates. In the ICU setting, pleural effusions are most commonly transudates that are small and uncomplicated. Pleural effusions are commonly present in patients following cardiothoracic or abdominal surgery, and in patients who have pulmonary edema. They can also be seen commonly secondary to atelectasis [57].

Small pleural effusions can be overlooked easily or difficult to accurately identify on a supine portable CXR, as the fluid level or meniscus sign typically present on upright CXR is not seen. Posterior-anterior (PA) and lateral CXR and/or decubitus views significantly increase detection rate and confidence in diagnosing small pleural effusions. If an effusion is uncomplicated and free-flowing, its appearance will differ with a change in patient positioning (Fig. 14). On a supine CXR, a pleural effusion usually results in

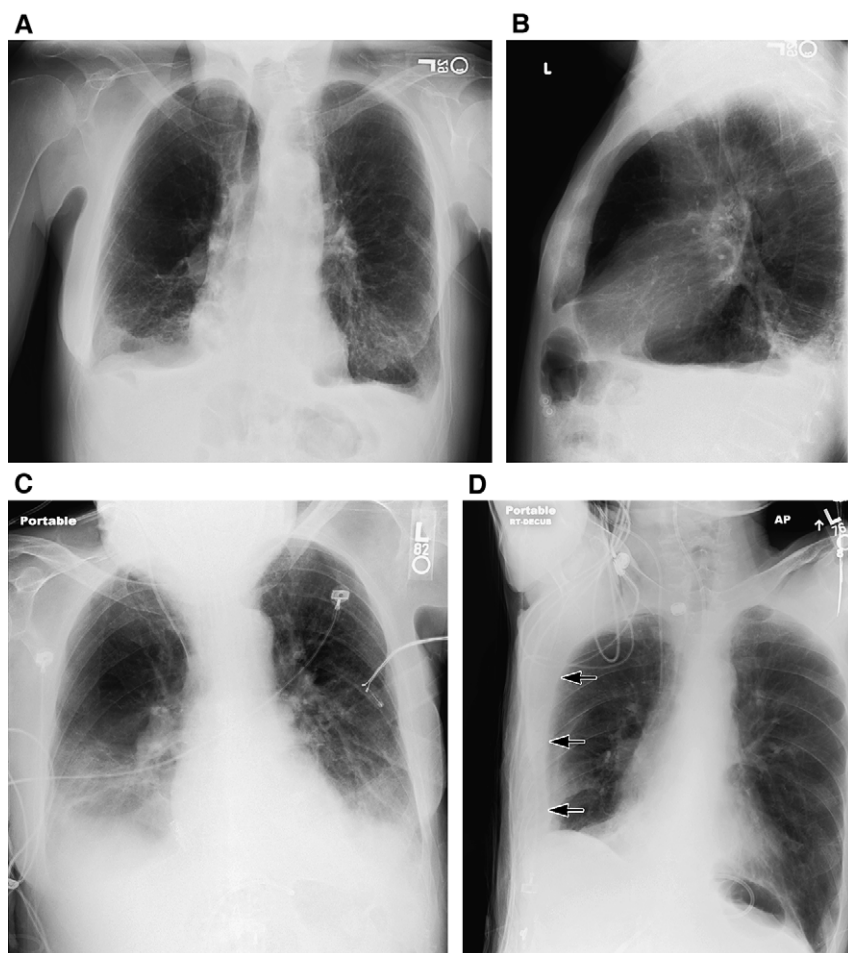


Fig. 14. 80-year-old man with small bilateral pleural effusions. (A, B) Posterior-anterior (PA) and lateral chest radiograph (CXR), respectively, show bilateral blunting of the costophrenic angles on both views and a meniscus caused by the effusions on the PA view. (C) Supine AP CXR demonstrates hazy increased density in the lower lungs. (D) Right decubitus CXR demonstrates the effusion layering along the right lateral hemithorax (arrows).

a gradient of homogeneous increased density over the lower lung fields without obscuration of vessels. Other entities such as atelectasis or an airspace opacity can produce a similar appearance.

In the ICU setting, if an effusion is suspected, then lateral decubitus views should be obtained if movement of the patient allows, as decubitus studies are more sensitive for detecting small effusions than a supine CXR [58]. A free-flowing effusion will layer on the decubitus view, and if it is at least 10 mm in width, it should be accessible by thoracentesis [59]. In contrast, if an effusion is loculated, it will not layer on the decubitus view.

CT is the most accurate examination for detecting and characterizing pleural effusions, and it has made a major impact on the diagnosis and management of pleural effusions. CT has the advantage over ultrasound in that it can evaluate the pleural surface better, and it is ideal to evaluate the lung parenchyma and tracheobronchial tree. For the most accurate assessment of the pleural surface, chest CT should be performed with IV contrast (providing there are no contraindications to the use of IV contrast). The evaluation of pleural enhancement, detection of pleural thickening, and the presence of pleural nodules are appreciated best on an IV contrast-enhanced CT examination. Although thoracentesis and analysis of the pleural fluid are the mainstay in identifying the etiology of pleural fluid, CT often can suggest the diagnosis. For example, in a patient who has a unilateral moderate-to-large pleural effusion without recent surgery, an exudative effusion should be suspected. Empyemas typically have a characteristic appearance on CT. When IV contrast is used, an empyema typically will show enhancement of both the parietal and visceral pleural surfaces, known as the split pleura sign (Fig. 15) [60]. In general, there should only be fat in the extrapleural space, whereas empyemas will have accompanying fluid/edema in the extrapleural space. Simple, free-flowing effusions should layer dependently and posteriorly in the pleural space when the patient is supine, whereas complicated effusions frequently are partially loculated within the chest [34].

In patients who are recently postoperative from cardiothoracic surgery, the presence of a rapidly enlarging pleural effusion should suggest the diagnosis of hemothorax. The density of pleural effusions can be measured easily on the PACS workstation. On chest CT, simple fluid has density



Fig. 15. 67-year-old man with lung cancer and tuberculosis empyema. Contrast-enhanced axial CT image at the level of the middle thorax demonstrates a large right pleural effusion with thickening and enhancement of both the parietal (*thin black arrows*) and visceral pleural surfaces (*white arrows*), known as the split pleura sign. Also note the fluid in the extrapleural space (*thick black arrow*). These findings are compatible with an empyema. The small bubbles of gas in the pleural space are caused by recent chest tube removal. Asterisk denotes the collapsed right lung secondary to central tumor (not shown).

measurements of no more than 20 Hounsfield units. Acute blood (ie, from hemothorax) has higher density measurements, typically in the range of 40 to 60 Hounsfield units. The radiologist should be aware of this and immediately alert the critical care team to this finding, as the patient may need to go back to the operating room for exploration and repair of a bleeding site.

In general, thoracentesis in critically ill patients should be performed with the help of CT or ultrasound guidance to decrease risk of complications, as positioning is difficult, and this procedure is more hazardous than in other settings. Ultrasound has advantages over CT for guiding thoracentesis, as it can be performed at the bedside and with the patient in any position. The risk of pneumothorax with ultrasound guidance is dramatically reduced, 3% as opposed to 18%, compared with clinical guidance alone [61,62]. Ideally, the effusion should be tapped at the time of the ultrasound so the patient's position is maintained. In the authors' experience, ultrasound may overlook small or even moderate-sized effusions, especially if the effusions are loculated or there is associated atelectatic lung compressed by the effusion.

CT has major advantages over ultrasound in the area of image-guided thoracentesis. CT provides a much more accurate evaluation of the size and location of the effusion, and a detailed evaluation of the pleural surface itself. CT also can assess the tracheobronchial tree and any associated intrathoracic complications such as necrotizing pneumonia, lung abscess, bronchopleural fistula, or empyema necessitans. CT is also useful in identifying location of drainage catheters, and it is extremely helpful in the guidance of catheters into loculated fluid collections.

Small pleural effusions that are too small to tap usually do not require drainage and typically will resolve with conservative management. In critically ill patients with acute respiratory failure, however, catheter drainage of even a small pleural effusion can improve oxygenation significantly [36,63]. Hemothoraces, moderate-to-large parapneumonic effusions, or empyemas should be treated with percutaneous catheter drainage. CT-guided catheter placement can be particularly useful when an effusion is suspected to be loculated to help ensure the catheter is positioned appropriately.

Pulmonary emboli

Patients in the ICU are at increased risk for thromboembolic disease, particularly because of factors such as immobility or hypercoagulable states. In any patient who has unexplained acute decompensation, particularly the development of shock or worsening oxygenation that cannot be explained otherwise, the diagnosis of pulmonary embolism should be considered. Most pulmonary emboli originate as thrombi in the deep veins of the lower extremity. If a deep vein thrombosis is suspected, lower extremity ultrasound can be useful in diagnosis. This examination is insensitive in

evaluating the calf veins and is limited (even for proximal clot) in obese patients, however. Ultrasound also does not pick up clot in the inferior vena cava (IVC) or iliac veins. CT venography combined with CT angiography can diagnose both DVTs and pulmonary emboli in a single imaging session with a single injection of IV contrast material. CT venography is reported to be just as sensitive and specific as ultrasound for detecting venous thrombosis [64].

The CXR is neither sensitive nor specific for diagnosing pulmonary embolism. In patients who have known pulmonary emboli, the most common radiographic finding is a normal CXR, followed by an area of subsegmental atelectasis or small pleural effusion [65,66]. Well-described CXR signs, which actually are seen rarely in practice but are much more suggestive of pulmonary embolism include:

- Westermarck sign (an area of relative oligemia distal to a large central clot)

- Hampton's hump, (a peripheral, wedge-shaped density representing pulmonary infarction)

- Fleischner sign, enlargement of central pulmonary artery by an acute clot [67]

Pulmonary infarcts are not common in patients who have documented pulmonary emboli (reportedly occur in less than 10% of cases) because of the dual blood supply to the lungs. V/Q scintigraphy is another noninvasive method for diagnosing pulmonary emboli. This test is highly sensitive but has a very poor specificity, and it commonly is rendered indeterminate in critically ill patients because of coexistent thoracic disease.

CT angiography

Within the last few years, the advent of faster and more technologically advanced CT scanners has helped to revolutionize the diagnosis of pulmonary embolism by noninvasive means. The older generation of CT scanners were very sensitive (85% to 90%) and specific (>90%) in diagnosing central and subsegmental emboli [68–70] but were less accurate in the detection of more peripheral clot. With an optimal examination performed on the newer multidetector CT scanners, however, small emboli out to the subsegmental level now can be diagnosed confidently. Three dimensional reformatted images clearly depict the pulmonary arterial tree in sagittal, coronal, and oblique orientations, which also can help to raise the level of confidence in diagnosing pulmonary embolism (Fig. 16). A meta-analysis evaluating CT pulmonary angiography has reported sensitivities ranging from 53% to 100% and specificities of 83% to 100% [71], with the numbers closer to 100% when performing the examination on the newer generation of CT scanners. CT angiography has become the mainstay for diagnosing pulmonary emboli and almost has replaced conventional pulmonary angiography (which has always been the gold standard of reference).

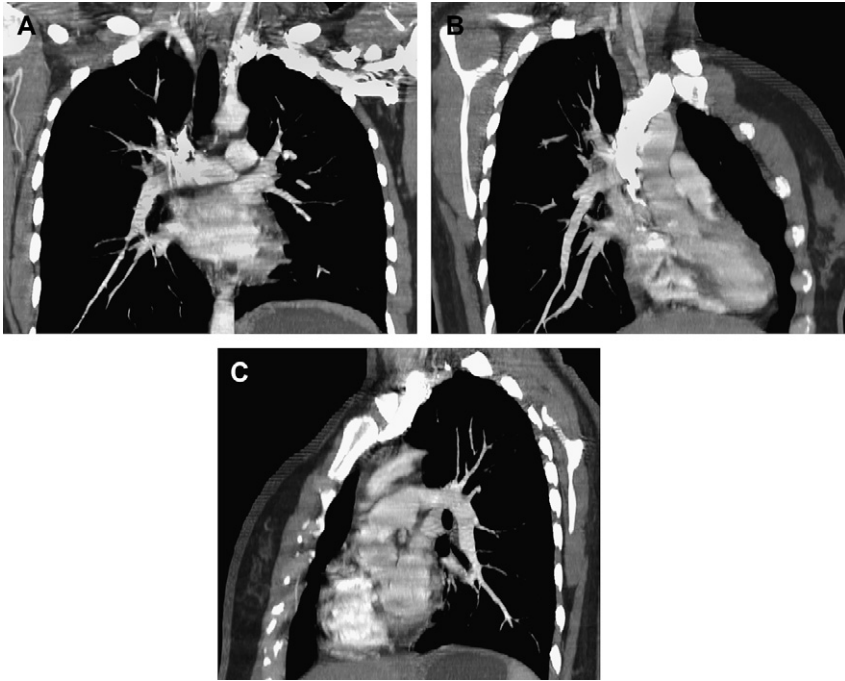


Fig. 16. Multiplanar reformatted images from a contrast-enhanced CT angiogram performed to evaluate for pulmonary embolism. In addition to obtaining thin section axial images (not shown), coronal (*A*), right oblique (*B*), and sagittal (*C*) reformatted images also are obtained routinely to evaluate for pulmonary emboli. This was a normal examination without evidence of pulmonary embolism.

A major advantage of CT compared with other diagnostic tests for pulmonary embolism is its ability to diagnose other potential causes of the patient's symptoms. In the occasional situation in which pulmonary embolism (PE) remains a concern despite the failure to find clot on the CT angiogram, a V/Q scan still might be employed, recognizing that these studies are frequently nondiagnostic in this population. If the CT is nondiagnostic for technical reasons (such as a poor IV contrast bolus or severe patient motion, among others), and a high clinical suspicion persists, then conventional pulmonary angiography should be considered. The main pitfalls of conventional angiography include: risk of major complications to this invasive test in approximately 1% of patients [72] and the fact that it is not any more accurate than CT in diagnosing small, subsegmental emboli [73].

With the advent of the newer-generation of CT scanners, a well-done CT pulmonary angiogram should allow the clinician to exclude pulmonary embolism if no clot is seen. The newer generation of CT scanners can pick up small emboli out to the subsegmental level confidently. A study by Tillie-LeBlond and colleagues [74] looking at the risk of pulmonary embolism after a negative CT pulmonary angiogram in patients with and without

pulmonary disease demonstrated a negative predictive value ranging from 98% (in patients with pulmonary disease) to 100% (in patients without pulmonary disease).

CT pulmonary angiograms are performed with IV contrast administered at least through a 22 gauge peripheral IV line (preferably 20 gauge or larger). If the patient has a contraindication to IV contrast material (such as severe contrast allergy or impaired renal function), then V/Q scan provides an important alternative. A V/Q, however, will not be technically possible if the patient is intubated.

When interpreting a CT pulmonary angiogram, several factors need to be evaluated, and a systematic approach by the radiologist is crucial. The first question that should be asked is: is this a diagnostic study? Reasons for non-diagnostic studies include poor contrast opacification of the pulmonary arterial tree, motion artifact, and artifact from other sources (such as presence of spinal hardware). Optimal contrast opacification is necessary when evaluating for the presence or absence of pulmonary emboli. Causes of suboptimal contrast opacification include: inaccurate timing of the contrast bolus by the CT technician, the presence of a congenital or acquired vascular shunt, severe obesity, and pregnancy (it is thought that the increased circulating blood volume dilutes out the contrast material). Occasionally, no apparent cause can be identified for the poor contrast bolus. In these cases, if the patient has normal renal function, it is not unreasonable to repeat the study the same day with the intent of achieving a diagnostic examination.

The next question that should be answered is: are there pulmonary emboli present, and what order vessels do they involve? Diagnostic criteria for acute pulmonary emboli on CT pulmonary angiogram include:

- An intravascular filling defect completely or partially surrounded by a rim of IV contrast (Fig. 17)
- An enlarged, occluded artery, which fails to enhance with contrast compared with adjacent patent vessels
- A peripheral filling defect that forms acute angles with the arterial wall [75].

If pulmonary emboli involve the large, central vessels, it is also important to note if a saddle embolus (clot crossing the bifurcation of the main pulmonary artery and involving the right and left main pulmonary arteries) is present. The presence of a saddle embolus in an acutely decompensating patient may lead to a more invasive intervention (such as thrombolysis or surgery for embolectomy).

After it is determined that pulmonary emboli are present, then the study should be evaluated for presence of right heart strain, which is associated with higher risk of complications and a potentially worse clinical outcome. Several small prospective studies have shown that right-sided heart strain as demonstrated on echocardiography is a predictor of early (within 30 days) death caused by acute pulmonary emboli [76–78]. CT findings also may

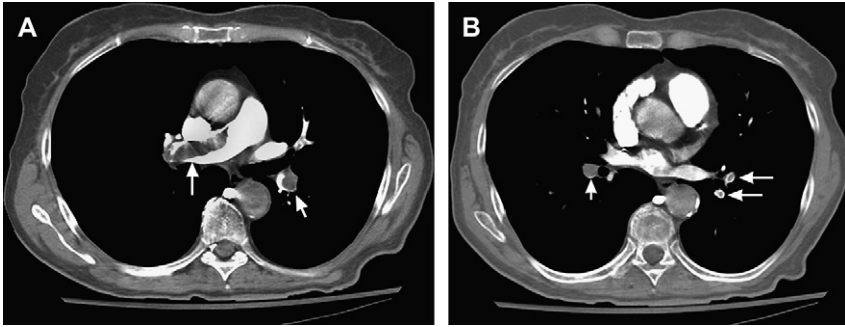


Fig. 17. CT of acute pulmonary emboli in an 80-year-old woman with tachycardia, shortness of breath, and an A-a gradient. (A) Contrast-enhanced CT image obtained at the midthorax level demonstrates low-density filling defects surrounded by a rim of contrast material in the right main pulmonary artery (PA) (*long arrow*) and the left interlobar PA (*short arrow*), consistent with pulmonary emboli. (B) Contrast-enhanced CT image obtained at the level of the heart shows low-density embolus expanding and filling almost the entire right interlobar PA with a minimal rim of surrounding contrast (*short arrow*). In addition, smaller emboli surrounded by contrast are within the segmental PAs to the left lower lobe (*long arrows*).

indicate right heart strain. Such findings include (Fig. 18) enlarged right heart chambers (short axis of right ventricle greater than short axis of left ventricle), leftward bowing of the interventricular septum, and reflux of contrast into the IVC and hepatic veins, which may or may not be enlarged [79]. The literature is mixed as to whether right ventricular (RV) enlargement on chest CT predicts early death in patients with acute pulmonary emboli. A retrospective study by Schoepf and colleagues [77] concluded that RV enlargement on initial chest CT in patients with acute pulmonary emboli helps to predict death within 30 days. However, a recently published retrospective study by Araoz and colleagues [76], failed to demonstrate a correlation between early death from acute pulmonary embolism in patients with RV enlargement or with high embolic burden.

There are several well-described pitfalls that potentially could lead to misdiagnosis of pulmonary embolism when evaluating a CT pulmonary angiogram. It is important that the radiologist interpreting these studies be familiar with these factors, which may be patient-related, technical, anatomic, or pathologic [75]. Examples include flow-related artifact secondary to suboptimal contrast bolus, partial volume averaging of adjacent lymph nodes, small vessel bifurcation, mucus plugs within adjacent bronchi, and pulmonary artery sarcoma—to name a few.

Atelectasis

Atelectasis is seen commonly in ICU patients, regardless of whether they are intubated or breathing spontaneously. The portable CXR is relatively nonspecific at revealing this diagnosis, and the appearance can be identical

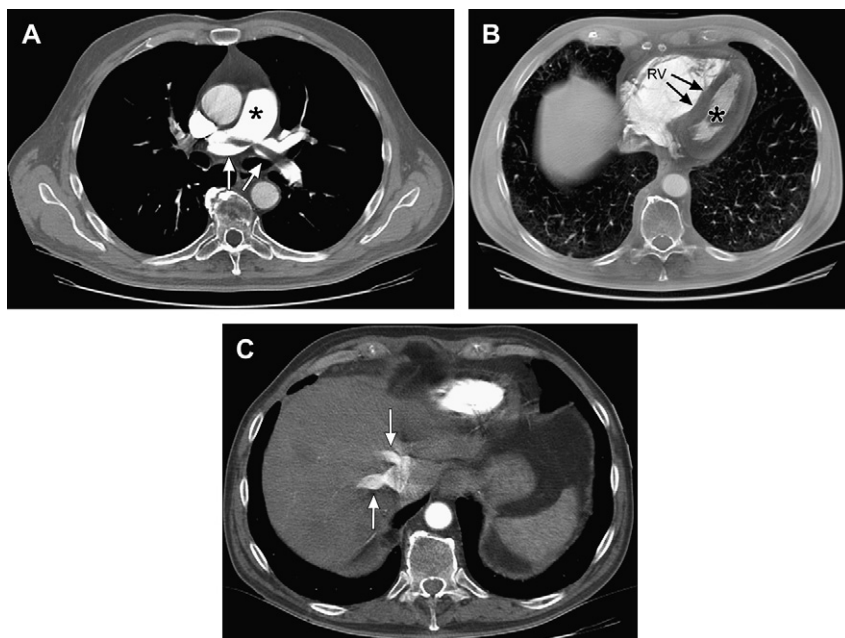


Fig. 18. 76-year-old man with a saddle embolus and signs of right heart strain. (A) Axial contrast-enhanced CT image obtained at the level of the main pulmonary artery (PA) (*asterisk*) shows low-density embolus (*arrows*) in the left and right main PA, crossing the bifurcation of the main PA. (B) Axial contrast-enhanced CT image obtained at the level of the heart shows leftward bowing of the interventricular septum (*arrows*), and the width of the right ventricle is larger than the left ventricle (*asterisk*), indicative of right heart strain. (C) Axial contrast-enhanced CT image shows reflux of intravenous contrast into prominent inferior vena cava and hepatic veins (*arrows*), which also suggests right heart strain.

to that produced by pneumonia or pleural effusion. The findings of atelectasis depend on the extent and location of collapsed lung. Subsegmental atelectasis usually manifests as linear or plate-like densities, and it tends to have a basilar distribution, whereas collapse of a bronchopulmonary segment may appear as a triangular, patchy, or wedge-shaped opacity. On a portable CXR, it may be difficult or impossible to differentiate lobar atelectasis from pneumonia, especially if signs of volume loss are not apparent. Both can appear as an area of consolidation with air bronchograms (that is, if the airways are not obstructed with mucus). Clinical signs often are relied upon to distinguish between the two, recognizing that atelectasis can become infected, resulting in fever and elevated white blood cell count, mimicking pneumonia both clinically and radiographically. An area of consolidation that clears quickly (within hours) or fluctuates, however, is more typically secondary to atelectasis [20,65]. CT also can help differentiate atelectasis from pneumonia, as the findings of volume loss with atelectasis usually are delineated much more clearly, and the segmental/subsegmental

bronchi tend to be crowded together in atelectasis when there is no associated endobronchial obstruction. Consolidation produced by pneumonia usually occupies space and maintains (or can even expand) the volume of the affected lobe. CT is also advantageous as it can identify tumor or a foreign body as the cause of the endobronchial obstruction.

The left lower lobe is by far the most common site affected, seen in 66% of ICU patients who have atelectasis, followed by the right lower lobe (22% of patients), and right upper lobe (11% of ICU patients) [80]. Several factors are thought to contribute to the increased susceptibility of critically ill patients to develop atelectasis. These include intubation, relative immobility with the patient maintained in the supine position, respiratory muscle weakness, impaired cough reflex, decreased ability to clear secretions, sedation, loss of surfactant, mucus plugging, foreign body aspiration, and neoplasms [5,20]. Mucus plugging can result from various causes; therefore it is the most common culprit producing atelectasis. This can be decreased significantly or improved with the use of aggressive chest physical therapy or routine suctioning. Because of the orientation of the left mainstem bronchus, however, blind suctioning is often unhelpful in relieving the airway obstruction, and in these cases, bronchoscopic suctioning should be considered [64,79].

Summary

ICU radiology plays an integral role in the care of the most critically ill patients in the hospital. Although there are limitations to the portable CXR, on a routine basis, it serves as an indispensable tool in evaluating these patients, especially when the physical examination is difficult to perform or noncontributory. A systematic approach should be applied when interpreting these films, and knowledge of the radiographic features of the disease states common to this group of patients is of the utmost importance.

Advances in technology have led to an improvement in patient care. The advent of PACS and digital radiography has transformed interactions between radiology and the ICU team. There are many advantages to the use of PACS, including the ability to view patient images simultaneously with the radiology report. It is important not to let it replace the valuable exchange that occurs between the clinicians and the radiologist during daily radiology rounds, however. CT imaging frequently detects pathology not visible on the portable CXR and often provides important information that may not be suspected clinically. It is useful in identifying effusions and is helpful in guiding treatment. CT pulmonary angiography can be performed rapidly and has become the imaging method of choice for evaluating pulmonary embolism. CT is also beneficial as it provides a detailed evaluation of the lungs, mediastinum, and chest wall and may reveal other unsuspected diagnoses in an acutely decompensating patient.

References

- [1] Trotman-Dickenson B. Radiology in the intensive care unit (Part I). *J Intensive Care Med* 2003;18:198–210.
- [2] Kundel HL, Seshadri SB, Langlotz CP, et al. Prospective study of a PACS: information flow and clinical action in a medical intensive care unit. *Radiology* 1996;199:143–9.
- [3] Kangarloo H. PACS—clinical experience at UCLA. *Comput Med Imaging Graph* 1991;15:201–3.
- [4] Kushner DC, Lucey LL. Diagnostic radiology reporting and communication: The ACR guideline. *Journal of the American College of Radiology* 2005;2(1):15–21.
- [5] Tocino I. Chest imaging in the intensive care unit. *Eur J Radiol* 1996;23:46–57.
- [6] Henschke CI, Yankelevitz DF, Wand A, et al. Chest radiography in the ICU. *Clin Imaging* 1997;21:90–103.
- [7] Graat ME, Hendrikse KA, Spronk PE, et al. Chest radiography practice in critical ill patients: a postal survey in the Netherlands. *BMC Med Imaging* 2006;6:8–13.
- [8] Graat ME, Choi G, Wolthuis EK, et al. The clinical value of daily routine chest radiographs in a mixed medical–surgical intensive care unit is low. *Crit Care* 2006;10(1):R11.
- [9] Hendrikse K, Gratama JW, Hove WT, et al. Low efficacy of daily routine chest radiographs in the ICU [abstract # SST03–08]. Presented at the Radiologic Society of North America 2006 meeting. Chicago, IL; November, 2006.
- [10] ACR appropriateness criteria—routine chest radiograph. American College of Radiology. 2006.
- [11] Henschke CI, Paternack GS, Schroeder S, et al. Bedside chest radiography: diagnostic efficacy. *Radiology* 1983;149:23–6.
- [12] Bekemeyer WB, Crapo RO, Calhoun S, et al. Efficacy of chest radiography in a respiratory intensive care unit. A prospective study. *Chest* 1985;88:691–6.
- [13] Strain DS, Kinasewitz GT, Vereen LE, et al. Value of routine daily chest x-rays in the medical intensive care unit. *Crit Care Med* 1985;13:534–6.
- [14] Graat ME, Stoker J, Vroom MB, et al. Can we abandon daily routine chest radiography in intensive care patients? *J Intensive Care Med* 2005;20:238–46.
- [15] Fong Y, Whalen GF, Hariri Rj, et al. Utility of routine chest radiographs in the surgical intensive care unit. A prospective study. *Arch Surg* 1995;130:764–8.
- [16] Silverstein DS, Livingston DH, Elcavage J, et al. The utility of routine daily chest radiography in the surgical intensive care unit. *J Trauma* 1993;35:643–6.
- [17] Bhagwanjee S, Muckart DJJ. Routine daily chest radiography is not indicated for ventilated patients in a surgical ICU. *Intensive Care Med* 1996;22:1335–8.
- [18] Hornick PI, Harris P, Cousins C, et al. Assessment of the value of the immediate postoperative chest radiograph after cardiac operation. *Ann Thorac Surg* 1995;59:1150–4.
- [19] Graham RJ, Mezziane MA, Rice TW, et al. Postoperative portable chest radiographs: optimal use in thoracic surgery. *J Thorac Cardiovasc Surg* 1998;115:45–50.
- [20] Siegel MD, Tocino I. Chest radiology in the intensive care unit, Part I. *Clinical Pulmonary Medicine* 1999;6(6):347–55.
- [21] Ravin CE, Putman CE, McCloud TC. Hazards of the intensive care unit. *AJR Am J Roentgenol* 1976;126:423–31.
- [22] Goodman LR, Conrardy PA, Laing F, et al. Radiographic evaluation of endotracheal tube position. *AJR Am J Roentgenol* 1976;127:433–4.
- [23] Brunel W, Coleman DL, Schwartz DE, et al. Assessment of routine chest roentgenograms and the physical examination to confirm endotracheal tube position after emergent intubation [see comments]. *Chest* 1989;96:1043–5.
- [24] Gray P, Sullivan G, Ostzyzniuk P, et al. Value of postprocedural chest radiographs in the adult intensive care unit. *Crit Care Med* 1992;20:1513–8.

- [25] Schwartz DE, Lieberman JA, Cohen NH. Women are at greater risk than men for malpositioning of the endotracheal tube after emergent intubation. *Crit Care Med* 1994;22:1127–31.
- [26] Rollins RJ, Tocino I. Early radiographic signs of tracheal rupture. *AJR Am J Roentgenol* 1987;148:695–8.
- [27] Tocino I. Chest imaging in the intensive care unit. In: Freundlich IM, Bragg DG, editors. *A radiologic approach to diseases of the chest*. Baltimore (MD): Williams & Wilkins; 1997. p. 321–42.
- [28] Yilmazlar A, Bilgin H, Korfali G, et al. Complications of 1303 central venous cannulations. *J R Soc med* 1997;90:319–21.
- [29] Frassinelli P, Pasquale MD, Cipolle MD, et al. Utility of chest radiographs after guidewire exchanges of central venous catheters. *Crit Care Med* 1998;26:611–5.
- [30] Turnaoglu S, Tugrul M, Camci E, et al. Clinical applicability of the substitution of mixed venous oxygen saturation with central venous oxygen saturation. *J Cardiothorac Vasc Anesth* 2001;15:574–9.
- [31] Amshel CE, Palesty JA, Dudrick SJ. Are chest x-rays mandatory following central venous recatheterization over a wire? *Am Surg* 1998;64:499–502.
- [32] Tocino IM, Watanabe A. Impending catheter perforation of superior vena cava: radiographic recognition. *AJR Am J Roentgenol* 1986;146:487–90.
- [33] Miller WR, Tino G, Friedburg JS. Thoracic CT in the intensive care unit: assessment of clinical usefulness. *Radiology* 1998;209:491–8.
- [34] Muller NL. Imaging of the pleura. *Radiology* 1993;186:297–306.
- [35] Naidich DP, Webb WR, Muller NL, et al. *Computed tomography and magnetic resonance of the thorax*. Philadelphia: Lippincott-Raven; 2007.
- [36] Trotman-Dickenson B. Radiology in the intensive care unit (part II). *J Intensive Care Med* 2003;18:239–52.
- [37] Hull R, Raskob GE, Ginsberg JS. A noninvasive strategy for the treatment of patients with suspected pulmonary embolism. *Arch Intern Med* 1994;154:289–97.
- [38] Mirvis SE, Tobin KD, Kostrubiak I, et al. Thoracic CT in detecting occult disease in critically ill patients. *AJR Am J Roentgenol* 1987;148:685–9.
- [39] The PIOPED investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). *JAMA* 1990;263:2753–9.
- [40] Milne EN, Pistolesi M, Miniati M, et al. The vascular pedicle of the heart and the vena azygous. Part I: the normal subject. *Radiology* 1984;152:1–8.
- [41] Pistolesi M, Milne EN, Miniati M, et al. The vascular pedicle of the heart and the vena azygous. Part II. Acquired heart disease. *Radiology* 1984;152:9–17.
- [42] Aberle DR, Wiener-Kronish JP, Webb WR, et al. Hydrostatic versus increased permeability pulmonary edema: diagnosis based on radiographic criteria in critically ill patients. *Radiology* 1988;168:73–9.
- [43] Owens CM, Evans TW, Keogh BF, et al. Computed tomography in established adult respiratory distress syndrome. *Chest* 1994;106:1815–21.
- [44] Gattinoni L, Caironi P, Pelosi P, et al. What has CT taught us about the acute respiratory distress syndrome? *Am J Respir Crit Care Med* 2001;164:1701–11.
- [45] Gattinoni LA, Pesenti A, Avalli L, et al. Pressure–volume curve of total respiratory system in acute respiratory failure: computed tomographic scan study. *Am Rev Respir Dis* 1985;132:800–4.
- [46] Tocino I, Westcott JL. Barotrauma. *Radiol Clin North Am* 1996;34:59–81.
- [47] Gammon RB, Shin MS, Groves RH Jr, et al. Clinical risk factors for pulmonary barotrauma: a multivariate analysis. *Am J Respir Crit Care Med* 1995;152:1235–40.
- [48] Kollef MH. Risk factors for the misdiagnosis of pneumothorax in the supine and semirecumbent critically ill adult. *Crit Care Med* 1991;19:906–10.
- [49] Tocino IM, Miller MH, Fairfax WR. Distribution of pneumothorax in the supine and semirecumbent critically ill adult. *AJR Am J Roentgenol* 1985;144:901–5.
- [50] Gordon R. The deep sulcus sign. *Radiology* 1980;136:25–7.

- [51] Tocino IM, Miller MH, Frederick PR, et al. CT detection of occult pneumothorax in head trauma. *AJR Am J Roentgenol* 1984;143:987–90.
- [52] Tocino I. Pneumothorax in the supine patient. *Radiographic anatomy. Radiographics* 1985; 5:557–86.
- [53] Webb RW, Higgins CB. *Thoracic imaging: pulmonary and cardiovascular radiology*. Philadelphia: Lippincott Williams & Wilkins; 2005.
- [54] Goodman LR, Felson B. *Felson's principles of chest roentgenology: a programmed text*. New York: W.B. Saunders; 1999.
- [55] Kuhlman JE, Fishman EK, Siegelman SS. Invasive pulmonary aspergillosis in acute leukemia: characteristic findings on CT, the CT halo sign, and the role of CT in early diagnosis. *Radiology* 1985;157:611–4.
- [56] Marom EM, McAdams HP, Erasmus JJ, et al. The many faces of pulmonary aspiration. *AJR Am J Roentgenol* 1999;172:121–8.
- [57] Mattison LE, Coppage L, Alderman DF, et al. Pleural effusions in the MICU: prevalence, causes, and clinical implications. *Chest* 1997;111:1018–23.
- [58] Woodring JH. Recognition of pleural effusions on supine radiographs: how much fluid is required? *AJR. Am J Roentgenol* 1984;142:59–64.
- [59] Light RW. Clinical practice. Pleural effusion. *N Engl J Med* 2002;346:1971–7.
- [60] Stark DD, Federle MP, Goodman PC, et al. Differentiating lung abscess and empyema: radiography and computed tomography. *AJR Am J Roentgenol* 1983;141:163–7.
- [61] Ratopoulos V, Davis LM, Lee G, et al. Factors affecting the development of pneumothorax associated with thoracentesis. *AJR Am J Roentgenol* 1991;156:917–20.
- [62] Grogan DR, Irwin RS, Channick R, et al. Complications associated with thoracentesis: a prospective randomized study comparing three different methods. *Arch Intern Med* 1990;150:873–7.
- [63] Talmor M, Hydo L, Gershenwald JG, et al. Beneficial effects of chest tube drainage of pleural effusion in acute respiratory failure refractory to positive end-expiratory pressure ventilation. *Surgery* 1998;123(2):137–43.
- [64] Loud PA, Katz DS, Klippenstein DL, et al. Combined CT venography and pulmonary angiography in suspected thromboembolic disease: diagnostic accuracy for deep venous evaluation. *AJR Am J Roentgenol* 2000;174:61–5.
- [65] Swensen SJ, Peters SG, LeRoy AJ, et al. Radiology in the intensive care unit [review]. *Mayo Clin Proc* 1991;66:396–410.
- [66] Henschke CI, Yankelevitz DF, Wand A, et al. Accuracy and efficacy of chest radiography in the intensive care unit. *Radiol Clin North Am* 1996;34:21–31.
- [67] Worsley DF, Alavi A, Aronchick JM, et al. Chest radiographic findings in patients with acute pulmonary embolism: observations from the PIOPED Study. *Radiology* 1993;189: 133–6.
- [68] Remy-Jardin M, Remy J, Wattinne I, et al. Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single breath-hold technique—comparison with pulmonary angiography. *Radiology* 1992;185:381–7.
- [69] van Rossum AB, Treurniet FE, Kieft GJ, et al. Role of spiral volumetric computed tomographic scanning in the assessment of patients with clinical suspicion of pulmonary embolism and abnormal ventilation/perfusion lung scan. *Thorax* 1996;51:23–8.
- [70] Mayo JR, Remy-Jardin M, Muller NL, et al. Pulmonary embolism: prospective comparison of spiral helical CT with ventilation–perfusion scintigraphy. *Radiology* 1997;205: 447–52.
- [71] Rathbun SW, Raskob GE, Whitsett TL. Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: a systematic review. *Ann Intern Med* 2000;132:227–32.
- [72] Zuckerman DA, Sterling KM, Oser RE. Safety of pulmonary angiography in the 1990s. *J Vasc Interv Radiol* 1996;7:199–205.

- [73] Stein PD, Henry JW, Gottschalk A. Reassessment of pulmonary angiography for the diagnosis of pulmonary embolism: relation of interpreter agreement to the order of the involved pulmonary arterial branch. *Radiology* 1999;210:689–91.
- [74] Tillie-LeBlond I, Mastora I, Radenne F, et al. Risk of pulmonary embolism after a negative spiral CT angiogram in patients with pulmonary disease: 1-year clinical follow-up study. *Radiology* 2002;223:461–7.
- [75] Wittram C, Maher MM, Yoo AJ, et al. CT angiography of pulmonary embolism: diagnostic criteria and causes of misdiagnosis. *Radiographics* 2004;24:1219–38.
- [76] Araoz PA, Gotway MB, Harrington JR, et al. Pulmonary embolism: prognostic CT findings. *Radiology* 2007;242:889–97.
- [77] Schoepf UJ, Kucher N, Kipfmüller F, et al. Right ventricular enlargement on chest computed tomography: a predictor of early death in acute pulmonary embolism. *Circulation* 2004;110:3276–80.
- [78] ten Wolde M, Sohne M, Quak E, et al. Prognostic value of echocardiographically assessed right ventricular dysfunction in patients with pulmonary embolism. *Arch Intern Med* 2004;164:1685–9.
- [79] Contractor S, Maldjian PD, Sharma VK, et al. Role of helical CT in detecting right ventricular dysfunction secondary to acute pulmonary embolism. *J Comput Assist Tomogr* 2002;26:587–91.
- [80] Shevland JE, Hirleman MT, Hoang KA, et al. Lobar collapse in the surgical intensive care unit. *Br J Radiol* 1983;56:531–4.

Monitoring the Mechanically Ventilated Patient

Vasileios Bekos, MD^a, John J. Marini, MD^{b,*}

^a*Department of Intensive Care, Naval Hospital of Athens, 229 Messogion Avenue,
15561 Cholargos, Athens, Greece*

^b*Department of Pulmonary and Critical Care Medicine, University of Minnesota,
Regions Hospital, MS11203B, 640 Jackson Street, St. Paul, MN 55101, USA*

The general purpose of monitoring is simple and clear—to follow in real time specific physiological values that can change rapidly and alter the patient's clinical status. Especially in the intensive care setting, in which the vast majority of patients are admitted because of a primary respiratory problem or of respiratory complications during their illness, monitoring of the cardiorespiratory system alerts the clinician to sudden untoward events, aids in diagnosis, helps manage diagnosis, facilitates prognosis, and enables assessment of therapeutic response. Monitoring techniques can be classified into those pertaining to the output of the ventilatory process and those that characterize the load and capacity of the respiratory system [1,2].

Monitoring gas exchange

Arterial blood gas analysis

Analysis of the arterial blood gases provides data that are fundamental to the diagnosis of respiratory and metabolic disturbances and to assessing the effect of therapeutic interventions.

Arterial O₂ tension and saturation

The physiologic significance of hypoxemia depends on chronicity, compensatory mechanisms, hypoxic ventilatory response, and the tolerance of the vital organs most at risk, such as the heart and the brain. So, while some patients must be kept as fully saturated as feasible, maintaining less than full saturation may be appropriate for patients who are exposed chronically to moderate hypoxemia or in whom full O₂ saturation can be achieved

* Corresponding author.

E-mail address: john.j.marini@healthpartners.com (J.J. Marini).

only at the expense of high airway pressures or elevated fractions of inspired oxygen. In the absence of carbon monoxide, methemoglobin, or abnormal hemoglobin, arterial O_2 saturation can be estimated with acceptable accuracy from the PaO_2 and pH alone. If the arterial O_2 content is required, or if carboxyhemoglobin or methemoglobin concentrations are high, direct analysis by co-oxymetry must be requested. When obtaining blood samples for arterial blood oxygen tension (PaO_2), 15 minutes should elapse to allow equilibration after an increment in inspired oxygen fraction content. In contrast, because of the body's acid-base buffering systems, arterial CO_2 concentrations respond exponentially after step changes in ventilation, with a half-time of more than 3 minutes during hyperventilation and a slower 16-minute half-time during CO_2 accumulation.

Acid-base status, pH, and $PaCO_2$

Normally, acids are generated by the hydration of CO_2 (respiratory acid) and by other processes of metabolism (metabolic acids). In disease states, hydrogen ion concentration can rise secondary to the production of excess lactate, generation of ketoacids, ingestion of certain types of alcohol or drugs, or failure of the body to excrete or metabolize the generated load of hydrogen ion. The body defends against radical changes in pH primarily by regulating its two pathways for eliminating acid: respiratory and renal. The Henderson-Hasselbach equation for the bicarbonate buffer system relates pH to the concentrations of bicarbonate and $PaCO_2$:

$$pH = 6.1 + \log \{HCO_3 / (0.03 PaCO_2)\}$$

In this expression, knowledge of $PaCO_2$ (lung excreted) and pH (measured) enables the calculation of the HCO_3^- (kidney excreted). Hydrogen ions are neutralized partially by combining with bicarbonate ion (producing CO_2) and by reversible oxidation of protein. The bicarbonate buffer system:



generates CO_2 when H^+ is added to the extra cellular fluid. Rising CO_2 and H^+ concentrations stimulate the respiratory center, effectively eliminating H^+ by driving the preceding equation leftward as CO_2 is eliminated. Several days later, the healthy kidney will adapt to hypercapnia or hypocapnia by adjusting the bicarbonate level to help restore the normal ratio between bicarbonate concentration and $PaCO_2$. Respiratory compensation for metabolic disturbances is generally incomplete and occurs more reliably and vigorously in response to metabolic acidosis than alkalosis. The bicarbonate buffer system is not the only one available, as skeletal calcium and certain proteins, chiefly hemoglobin, play a significant role.

The normal ranges are, for arterial pH: 7.38 to 7.44 and for arterial $PaCO_2$: 35 to 45 mm Hg. Acidosis and alkalosis may be pathogenic or

compensatory. A pH less than 7.35 indicates acidemia, caused by metabolic or renal depletion of bicarbonate, hypoventilation relative to metabolic need, or both. Mixed venous gases, representing an admixture from tissues throughout the body, generally have a PaCO_2 that is 4 to 8 mm Hg higher and a pH that is 0.05 to 0.10 units lower than the arterial value.

The information available from ABG analysis allows the clinicians to determine pH and the relative contributions of respiratory and metabolic mechanisms. Because compensation is virtually never complete, the dominant underlying mechanism—acidosis or alkalosis—is suggested by the pH. Intensive care unit (ICU) clinicians must be alert for “triple” acid-base disorders in which two metabolic derangements with opposing influences on pH are in play. The anion gap calculation usually aids in the appropriate interpretation.

The anion gap, the difference between the serum sodium concentration and the sum of chloride and the bicarbonate ions, is normally is 13 mEq or less. Because the serum proteins are anions, the calculated gap should be increased by approximately 2.0 to 2.5 mEq/L for each g/dL of hypoalbuminemia. Another useful bedside computation is the “ Δ/Δ ,” the ratio of the anion gap to bicarbonate gap. As lactic acidosis develops, the anion gap increases relatively more than the HCO_3^- falls because the HCO_3^- has a wider volume of distribution. The ratio varies, but averages approximately 1.5 in moderate lactic acidosis—less if the acuity is extreme and more as the severity worsens.

Monitoring oxygenation

The human eye is not very good at detecting or quantifying arterial hypoxemia. Perhaps the most popular recent innovation in gas exchange monitoring has been the application of oximetry to the online assessment of arterial (SaO_2) and mixed venous O_2 saturations (SvO_2). PaO_2 reflects the maximal tension driving O_2 to the tissues, whereas saturation reflects O_2 content per gram of hemoglobin. Reflectance oximetry is used when a fiber-optic catheter continuously samples oxygen saturation in the pulmonary or systemic arterial bloodstream.

Arterial pulse oximetry

For patients supported by mechanical ventilation, transcutaneous pulse oximetry continuously measures SaO_2 , enabling rapid adjustment of FiO_2 , mean airway pressure and positive end-expiratory pressure (PEEP) and warning of arterial desaturation during weaning, sleeping, or changes of body position. Trends in oximetry values hold greater significance than the absolute value of O_2 saturation.

Pulse oximetry probes consist of a photo detector and two light-emitting diodes [3–5]. Probes are most frequently placed on fingers, ear lobes, nasal bridge, or forehead. The relative absorption of these spectrophotometric beams as they pass through the tissue (which differs for O_2 saturated and

desaturated blood) is converted into the appropriate saturation value by computer-stored algorithms. Phasic variations in tissue volume separate the incoming arterial component from venous and background absorption. Most units display pulse rate, and many display a simulated arterial waveform or other visual indicator of pulse intensity. A tracing with a waveform that varies dramatically with ventilation strongly suggests variation of stroke output synchronous with respiratory cycle—a condition typical for gas trapping and auto-PEEP. The pulse rate should be correlated to the ECG measured rate to assess signal quality. With a good pulse signal, pulse oximeters are quite accurate in their upper range (saturation $>80\%$) but become less reliable as the patient desaturates or perfusion deteriorates [6,7]. Chaotic pulse rhythms (eg, atrial fibrillation) have unpredictable effects on the display values [8,9]. A direct determination of arterial blood saturation (preferably by co-oximetry) is the most definitive check of accuracy. Interpretation of pulse oximetry readings must account for a variety of factors that may artifactually influence the results. Common sources of artifact include inappropriate probe placement, motion artifact, ambient light, and electromagnetic radiation. Even if the device is functioning properly and is free from external interference, the results should be interpreted with particular caution in the presence of abnormal hemoglobin, nail polish, deeply pigmented skin, hypo perfusion, anemia, venous congestion, or tricuspid regurgitation or when certain vital dyes are used. It is important to fully understand the oxyhemoglobin dissociation relationship curve that is highly nonlinear (Fig. 1). A drop of a few percentage points in SaO_2 over the 95% to 100% interval reflects a much larger change in PaO_2 than does a similar decrement over the 80% to 85% interval. Other gas-measuring techniques (transcutaneous and transconjunctival measurements of O_2 and CO_2) have been used in recent years, but require frequent calibration, excellent skin and electrode preparation to ensure gas transfer to the skin surface, and regular site changes [10,11]. The validity of tissue oxygen saturation monitoring has yet to be verified in critically ill patients.

O₂ consumption

Oxygen consumption may be helpful when determining nutritional requirements as well as the severity of shock. Assuming a stable tissue need for oxygen, measurements of VO_2 may help to gauge the hemodynamic response to therapeutic measurements. The total body oxygen consumption (VO_2) is often difficult to measure accurately at the bedside. Two primary methods are in general use: direct analysis of inspired and expired gases and the Fick method (computation of VO_2 from the product of cardiac output $[\text{CO}]$ and the difference in O_2 content between samples of arterial and mixed venous blood). Neither method reflects average oxygen consumption when the patient's metabolic rate fluctuates during data collection. Unfortunately, VO_2 measurements are not highly reproducible, so their differences are unreliable in assessing breathing effort associated with an imposed or

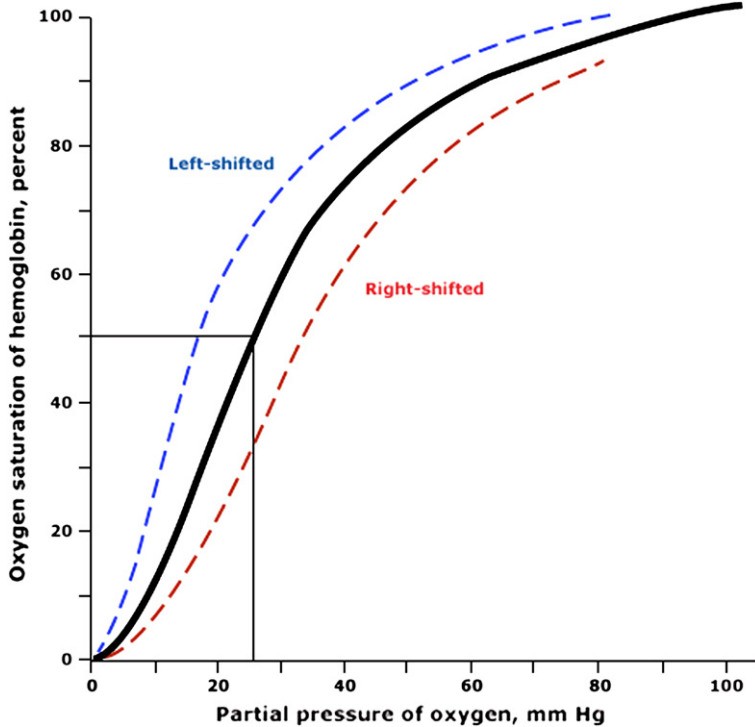


Fig. 1. Relationship of blood oxygen saturation (SaO_2) to blood oxygen tension (PaO_2) with the normal curve having a sigmoidal shape. The upper plateau of the relationship (90% saturation) reached at a PaO_2 of approximately 55 to 60 mm Hg.

relieved ventilatory stress, particularly when the patient inspired a high fraction of oxygen.

Efficiency of oxygen exchange

The ideal $\text{P}_{\text{A}}\text{O}_2$ is obtained from the modified alveolar gas equation:

$$\text{P}_{\text{A}}\text{O}_2 = \text{P}_{\text{I}}\text{O}_2 - (\text{P}_{\text{A}}\text{CO}_2/\text{R}) + [(\text{P}_{\text{A}}\text{CO}_2 \times \text{FiO}_2 \times (1 - \text{R}))/\text{R}]$$

Here R is the respiratory exchange ratio (which normally varies from about 0.7 to 1.0) and the $\text{P}_{\text{I}}\text{O}_2$ is the inspired oxygen tension.

At sea level with a normally ventilated patient breathing room air, the alveolar gas equation can be simplified to:

$$\text{P}_{\text{A}}\text{O}_2 = 0.21 \times (760 - 47) - 1.25 \times (\text{P}_{\text{A}}\text{CO}_2) \sim 100 \text{ mm Hg}$$

The difference between alveolar and arterial oxygen tensions, $\text{P}(\text{A}-\text{a})\text{O}_2$, takes account of alveolar CO_2 tension and therefore eliminates hypercapnia

from consideration as the sole cause of hypoxemia. The $P(A-a)O_2$ ranges from ~ 10 mm Hg (on room air) to ~ 100 mm Hg (on FiO_2 of 1.0), and changes nonlinearly with respect to FiO_2 as the extent of V/Q mismatch increases. Finally, the $P(A-a)O_2$ may be influenced by fluctuations in venous oxygen content. The O_2 content of mixed venous blood (SvO_2) exerts an increasingly important effect on SaO_2 , as ventilation/perfusion inequality or shunting develop [12–14]. Online measurements of SvO_2 with a fiber-optic Swan-Ganz catheter enable venous admixture (Qs/Qt) to be computed with relative ease. In the steady state:

$$Qs/Qt = (C_AO_2 - CaO_2)/(C_AO_2 - CvO_2)$$

where the oxygen content of alveolar capillary blood (C_AO_2), arterial blood (CaO_2), or mixed venous blood (CvO_2), are expressed in mL of O_2 per 100 mL of blood. Like $P(A-a)O_2$, the Qs/Qt is also influenced by variations in V/Q mismatching and by fluctuations in SvO_2 and FiO_2 . If Qs/Qt is abnormally high but all alveoli are patent, calculated admixture will diminish toward the normal physiologic value ($\sim 5\%$) as FiO_2 increases. Conversely, if the Qs/Qt abnormality results from blood bypassing patent alveoli through intrapulmonary communications or through an intracardiac defect, there will be no change in Qs/Qt , as FiO_2 increases (true shunt).

Several pragmatic approaches have been taken to simplify bedside assessment of O_2 exchange efficiency. The first is to quantify $P(A-a)O_2$ during the administration of pure O_2 . So, after a suitable wash-in time (5 to 10 minutes), pure shunt accounts for the entire $P(A-a)O_2$. Furthermore, if the hemoglobin is fully saturated with O_2 , dividing the $P(A-a)O_2$ by 20 approximates shunt percentage (at $FiO_2 = 1.0$). The PaO_2/FiO_2 ratio is a convenient and widely used bedside index of oxygen exchange that attempts to adjust for fluctuating FiO_2 . However, this simple ratio is affected by changes in SvO_2 and does not remain equally sensitive across the entire range of FiO_2 , especially when shunt is the cause of admixture. The PaO_2/P_AO_2 ratio is another easily calculated index, which does not require blood sampling from the central circulation, but in the same way loses reliability in proportion to the degree of shunting. All of these indices fail to account for changes in the functional status of the lung that result from alterations in PEEP, auto-PEEP, or changes in patient's position and ventilator settings. When measured under conditions of controlled ventilation, the oxygenation index:

$$PaO_2/(FiO_2 \times \text{mean } P_{aw})$$

reflects the influence of average lung volume as well as oxygen supplementation and has gained widespread popularity in neonatal and pediatric practice. Despite this rationale, this indicator is not (as yet) widely used in adult critical care.

Monitoring ventilation and carbon dioxide

Carbon dioxide production and exchange

Carbon dioxide stores (~ 120 L of CO_2) are held in several forms (dissolved, bound to protein, fixed as bicarbonate) and distributed in compartments that differ in their volumetric capacity and ability to exchange CO_2 rapidly with the blood. Well-perfused organs constitute a small reservoir for CO_2 that is capable of quick turnover. The existence of large CO_2 reservoirs with different capacities and time constants of filling and emptying means that equilibration to a new steady-state PaCO_2 after a step-change in ventilation takes longer than generally appreciated—especially for step reductions in alveolar ventilation. With such a large capacity and only a modest rate of metabolic CO_2 production, the CO_2 reservoir fills rather slowly, so that PaCO_2 raises only 6 to 9 mm Hg during the first minute of apnea and 3 to 6 mm Hg each minute thereafter [15,16]. Measurements of CO_2 excretion are valuable for metabolic assessment, computations of dead-space ventilation, and evaluation of hyperpnea. The rate of CO_2 elimination is a product of minute ventilation (VE) and the expired fraction of CO_2 in the expelled gas. This value represents metabolic CO_2 production only if the patient remains metabolically stable during the period of gas collection. The quantity of CO_2 generated per minute depends on acid-base fluctuations, perfusion adequacy, and ventilation status with respect to metabolic needs. The rate of CO_2 production falls to negligible values during circulatory arrest. Based on the linkage between lung perfusion and CO_2 discharge, partial rebreathing techniques have been developed to monitor cardiac output noninvasively.

The volume of CO_2 produced by the body tissues varies with metabolic rate (fever, pain, agitation, sepsis, and so forth). The PaCO_2 must be interpreted in conjunction with the VE, especially in mechanically ventilated patients. Many vagaries of CO_2 flux can be eliminated by controlling ventilation and muscular activity.

Deadspace and deadspace fraction

The physiologic deadspace (V_D) refers to the “wasted” portion of the tidal breath that fails to participate in CO_2 exchange. A breath can fail to accomplish CO_2 elimination either because fresh (CO_2 -free) gas is not brought to the alveoli or because fresh gas fails to contact systemic venous blood. A portion of tidal ventilation is wasted when CO_2 -laden gas is recycled to the alveoli with the next tidal breath, as when tidal breaths are very small. Deadspace also rises when fresh gas distributes to inadequately perfused alveoli, so that CO_2 -poor gas is exhausted during exhalation. Wasted ventilation is characterized as the sum of the “anatomic” deadspace and the “alveolar” deadspace. Because the airways fill with CO_2 -containing alveolar gas at the end of the tidal breath, the physical volume of the airways corresponds rather closely to their contribution to wasted ventilation. When

the parenchyma is well aerated and well perfused, the anatomic deadspace of a breath of normal size is relatively fixed at approximately 1 mL per pound of body weight and predominates over the alveolar component. Quite the opposite happens in patients with most lung diseases, in whom alveolar deadspace predominates. Here, the lung is composed of well and poorly perfused units, so that the mixed alveolar gas within the airways at end exhalation has a CO_2 concentration lower than that of pulmonary arterial blood. Deadspace increases with advancing age and body size and is reduced modestly by recumbency, extended breath holding, and decelerating inspiratory flow patterns. Supine position reduces deadspace by decreasing the average size of the lungs, thereby increasing the number of well-perfused lung units. An external apparatus attached to the airway may add to the series deadspace, whereas tracheostomy reduces it. Diseases that increase V_D include low output circulatory failure, pulmonary embolism, pulmonary vasoconstriction, vascular compression, mechanical ventilation with high tidal volume or PEEP, and diseases that destroy either the number or function of alveoli.

Except at very small tidal volumes, the fraction of wasted ventilation (V_D/V_T) tends to remain relatively constant as the depth of the breath varies [17,18]. The deadspace fraction can be estimated from analyzed specimens of arterial blood and mixed expired (P_{ECO_2}) gas:

$$(V_D/V_T) = (\text{PaCO}_2 - P_{\text{ECO}_2})/\text{PaCO}_2$$

where P_{ECO_2} is the CO_2 concentration in mixed expired gas, which can be determined on a breath-by-breath basis if exhaled volume is measured simultaneously. In healthy persons, the normal V_D/V_T during spontaneous breathing varies from ~ 0.35 to 0.15 depending on factors noted earlier (position, exercise, age, and so forth) [19,20]. In the settings of critical illness, it is not uncommon for V_D/V_T to rise to values that exceed 0.7 [21,22]. Dead-space accounts for most of the increase in the VE requirement and CO_2 retention that occur in the terminal phase of acute hypoxemic respiratory failure. In addition, changes in V_D/V_T occur during periods of hypovolemia or overdistention by high airway pressures, especially when progressive levels of PEEP are applied to support oxygenation [23–25]. Examination of the airway pressure tracing under conditions of controlled, constant inspiratory flow ventilation may demonstrate concavity or a clear point of upward inflection, indicating overdistention, accelerated deadspace formation, and escalating risk of barotrauma. Small reductions in PEEP or tidal volume may then dramatically reduce peak cycling pressure and V_D/V_T .

Monitoring of exhaled gas

Capnography analyzes the CO_2 concentration of the expiratory air stream, plotting CO_2 concentration against time or against exhaled volume, a display that provides more clinical information. After anatomic deadspace

has been cleared, the CO_2 rises progressively to its maximal value at end-exhalation, a number that reflects the CO_2 tension of mixed alveolar gas. When ventilation and perfusion are evenly distributed, as they are in healthy subjects, end-tidal PCO_2 (P_{ETCO_2}) closely approximates PaCO_2 . Normally P_{ETCO_2} underestimates PaCO_2 by 1 to 3 mm Hg, a gap that widens when ventilation and perfusion are matched suboptimally, as when alveolar dead-space admixes with CO_2 -rich gas from well-perfused alveoli. Plotting CO_2 concentration against exhaled volume can yield estimates for the anatomic deadspace, as well as for the end tidal and mixed expired CO_2 concentrations (Fig. 2). The latter can be used to determine CO_2 production when mixed expired PCO_2 , expressed as a percentage of barometric pressure, is multiplied by the minute volume.

While the normal capnogram is composed of an ascending portion, a plateau, a descending portion, and a baseline, in disease these sharp distinctions are blurred by differences of ventilation and perfusion (Fig. 3). Failure of the airway gas to equilibrate with gas from well-perfused alveoli invalidates P_{ETCO_2} as a reflection of PaCO_2 . Abrupt changes in P_{ETCO_2} may reflect such acute processes as aspiration or pulmonary embolism, especially when VE and breathing pattern remain unchanged.

The capnogram also provides an excellent monitor of breathing rhythm. Close examination of the tracing contour and comparison with earlier waveforms may give helpful indications of circuit leaks, patient ventilator

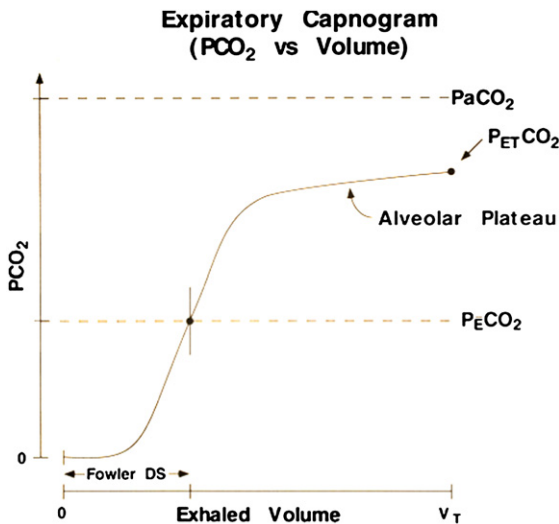


Fig. 2. Information available from an expiratory capnogram plotting PCO_2 concentration against exhaled volume. The slope of the alveolar plateau is a measure of ventilation heterogeneity. End-tidal PCO_2 (P_{ETCO_2}) reflects the concentration of CO_2 within the alveolar units that are last to empty. Although this value may parallel PaCO_2 in normal individuals, it is less reliable in disease. The Fowler deadspace (DS) is a close correlate of anatomic deadspace.

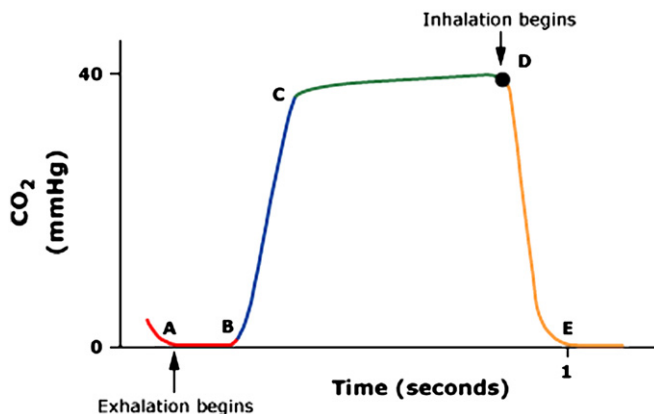


Fig. 3. Expired CO_2 ($P_{\text{E}}\text{CO}_2$) as a function of time. Expired CO_2 tension varies markedly during a breathing cycle in four phases. AB, inhalation; BC, initial expiration phase; CD, expiration plateau; DE, initial inspiration phase.

dyssynchrony, equipment malfunctions, secretion retention, and changes in underlying pathophysiology. In evaluating the $P_{\text{ET}}\text{CO}_2$ it is essential to record and examine the entire capnographic tracing (not only the digital output). Breathing pattern can vary when gas flow is inhomogeneously distributed, as in airflow obstruction. Failure of the tracing to achieve a true plateau can occur because the sampling technique is inappropriate, exhalation is too brief, or ventilation is inhomogeneously distributed. The arterial to end-tidal CO_2 difference is minimized when perfused alveoli are recruited maximally [26]. On this basis, the $(P_{\text{a}}\text{CO}_2 - P_{\text{ET}}\text{CO}_2)$ difference has been suggested as helpful in identifying “best PEEP” [27–29].

Monitoring lung and chest wall mechanics

Mechanics of breathing

During mechanical ventilation the clinician must become familiar with all those properties of the lung and chest wall that determine the ease of chest expansion [30]. Certain of these properties can be assessed only under passive conditions (eg, compliance), others require active breathing effort (eg, maximal inspiratory pressure), while others can be determined with or without active breathing effort (eg, lung’s impedance properties). Finally, to separate static from dynamic variables, points of zero flow within the tidal cycle must be determined.

Pressure-volume relationships

Because the lung is a flexible and passive structure, gas flows to and from the alveoli driven by differences between airway and alveolar pressures. The

total pressure gradient expanding the respiratory system is accounted for in two ways: (1) in driving gas between the airway opening and the alveolus and (2) in expanding the alveoli against the recoil forces of the lung and chest wall. The pressure required for inspiratory flow dissipates against friction, while the elastic pressure that expands the respiratory system is stored temporarily in elastic tissues and is dissipated in driving expiratory flow [31].

The nonelastic impedance to airflow offered by friction and movement of the lung and the chest wall is termed "Resistance." The elastic pressure these structures offer in opposing inflation is termed "Elastance," and its inverse is termed "Compliance." The normal airway resistance of a healthy adult is less than 4.0 cm H₂O per liter per second when breathing spontaneously and rises approximately twofold when orally intubated with an endotracheal tube of standard size and length. The elastance of the lungs (E_L) and the chest wall (E_{CW}) add in series to comprise that of the respiratory system: $E_{RS} = E_L + E_{CW}$; compliances add in parallel. At end-expiration, compliance values for the lung, chest wall, and integrated respiratory system of a spontaneously breathing, healthy adult patient of normal size and weight in the supine position are approximately 200, 150, and 85 mL/cm H₂O, respectively.

Increasing the pressure applied across the normal lungs and chest wall increases lung volume, but the incremental relationship between pressure and volume varies markedly over the vital capacity range. Over a small segment, this relationship can be considered approximately linear over most regions of the pressure-volume curve. Therefore, assuming linearity, the elastic properties of the lung, chest wall, and integrated respiratory system can be described by single values for chord elastance ($\Delta P/\Delta V$) or its inverse, the chord compliance ($\Delta V/\Delta P$).

The same ΔP will result in a different ΔV for two lungs of identical tissue properties but different sizes. Examination of the pressure-volume relationship indicates that chord compliance differs according to the segment over which it is computed. That difference could result from a position shift along the pressure-volume relationship, an alteration of tissue elastic properties, or a variation in the ventilated capacity of the lung.

Respiratory system compliance and elastance

The pressure difference (ΔP) required to expand the lung by a certain volume (ΔV) is the corresponding change in transpulmonary pressure $P_L = (P_{alv} - P_{pl})$, where P_{alv} = alveolar pressure and P_{pl} = pleural pressure. The lung elastance ($E_L = \Delta P_L/\Delta V$) is the pressure per unit of inflation volume required to keep the lung expanded under no flow (static) conditions, and the inverse of elastance is referred to as lung compliance ($C_L = 1/E_L = \Delta V/\Delta P_L$). The slope of the static pressure-volume relationship for the total respiratory system is C_{RS} ($C_{RS} = \Delta V/\Delta P_{alv}$). In ventilator-derived calculations of compliance, ΔV must be measured at the endotracheal tube or expired volume must be adjusted for the volume stored during

pressurized inflation in compressible circuit elements (with disposable external tubing and a low deadspace humidifier, approximately 3 mL of volume are stored per cm H₂O of peak cycling pressure). However, this figure may vary markedly, depending on the peak cycling pressure.

Compliance measurements obtained under passive conditions may have therapeutic and prognostic value for patients with arterial desaturation. When PEEP is applied incrementally, C_L and C_{RS} tend to reach their highest values when lung units are recruited maximally without overstretching. This region also tends to be that associated with minimal ventilatory deadspace and shunt fraction and often coincides with maximal oxygen delivery [32,33]. Different tidal volumes may be associated with different “optimal PEEP” values. Although this guideline does not always apply, it is a good rule to avoid using values of end-expiratory pressure or tidal volume that depress thoracic compliance—unless objective evidence of significantly improved oxygen delivery is available and safe plateau pressure is not exceeded. Severe disease is implied when tidal compliance falls to less than 25 mL/cm H₂O. Maximal depression of C_{RS} often requires 1 to 2 weeks to develop in the setting of acute lung injury [34,35]. Although C_{RS} provides useful information regarding the difficulty of chest expansion, C_{RS} does not necessarily reflect underlying tissue elastance. Ideally, compliance is referenced to a measure of absolute lung volume, such as functional residual capacity (FRC) or total lung capacity (TLC). C_{RS} may differ greatly at the extremes of the vital capacity range, even in the same individual. Although lung and chest wall elastance values add in series ($E_{RS} = E_L + E_{CW}$), their corresponding compliances add in parallel, so that respiratory system compliance bears a complex relationship to the individual compliances of the lung and chest wall:

$$C_{RS} = (C_L \times C_W) / (C_W + C_L).$$

The fraction of expiratory airway pressure (PEEP) transmitted to the pleural space depends on the relative compliances of the lung and chest wall:

$$\Delta P_{pl} = PEEP \times [C_L / (C_L + C_W)].$$

Chest wall compliance

For critically ill patients, chest wall distensibility may be reduced by abdominal distention, pleural effusions, ascites, muscular tone, recent surgery, position, binders, and braces (Fig. 4). For a given lung volume, such reductions cause an increase in P_{PL} . In turn, P_{PL} influences venous return, hemodynamic data, and calculations of chest mechanics based on airway pressure. An appropriate interpretation of tidal airway pressures depends on a valid assessment of intrapleural pressure. Specific values for peak airway pressure and C_{RS} have different prognostic importance and therapeutic

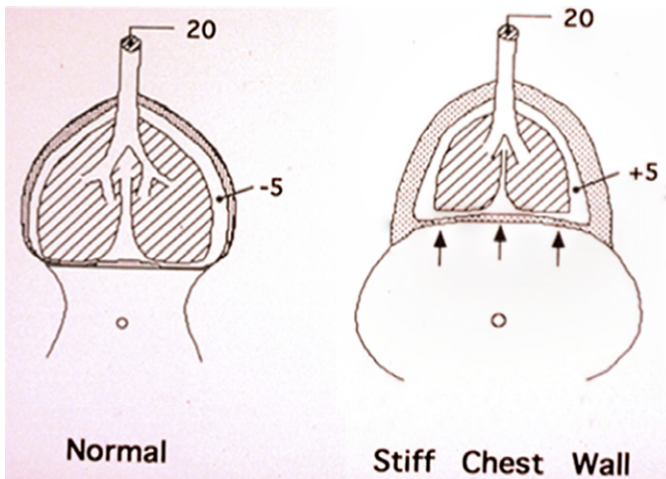


Fig. 4. The effect of PEEP (20 cm H₂O, in this example) on lung volume is influenced by the compliance of the chest wall. Distending force across the lung is 25 cm H₂O with a normal chest wall, but only 15 cm H₂O with a stiff chest wall. A patient with stiff chest wall requires a higher PEEP to achieve the same distending force across the lung.

significance as well, depending on whether the lung or chest wall accounts for the stiffness.

Clinical utility of the pressure-volume curve

In the setting of acute lung injury, perhaps only 20% to 30% of alveoli remain patent, while the others are atelectatic or occluded by lung edema, cellular infiltrate, or inflammatory debris [36]. Moreover, the mechanical properties of the lung differ in dependent and nondependent regions. For a supine patient, atelectasis predominates in dorsal sectors, where lung units tend to collapse under the influence of regionally increased pleural pressure and the weight of the overlying lung [37,38]. In this surfactant-deficient lung, there are tendencies for persisting collapse of dependent alveoli and/or tidal reopening and recollapse of lung units in the middle and dependent zones. The latter process subjects injured tissue to damaging shear forces when high inflation pressures are used [39]. According to current thinking, both persisting collapse of inflamed tissue and the tidal collapse cycle must be avoided. To aid in healing, the objective is to “open the lung and keep it open” without causing overdistention. Nondependent alveoli remain open and relatively compliant but are subject to overdistention by high peak tidal pressures (Fig. 5) [40]. Defining the pressure-volume relationship may help guide the ventilator settings needed to avoid the damaging effect of both tidal collapse and alveolar overdistention [41–43]. The PV curve is a composite of information from myriad lung units, and its contours are shaped by the relative proportion of units at various stages of distension. Many

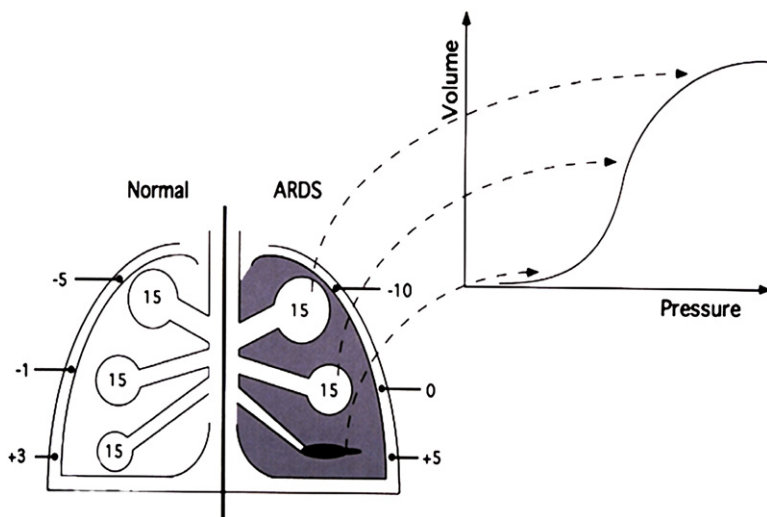


Fig. 5. Dependent alveoli at the base of the lung may remain collapsed at airway pressures that threaten to overdistend those in nondependent regions. To counterbalance this heterogeneity, higher regional PEEP in dependent areas or modified chest wall compliance in nondependent regions would be needed to improve the uniformity of distention and ventilation.

investigators of barotrauma believe that sufficient end-expiratory alveolar pressure, $PEEP_{TOT}$, (ie, the sum of auto-PEEP and extrinsic PEEP) should be maintained to surpass the lower inflection point of the inspiratory PV curve when high end-inspiratory (plateau) pressures are in use [44–48]. The PEEP requirement varies with body size, stage and severity of lung injury, and chest wall compliance. At the same time, peak tidal alveolar pressure should not encroach on the upper deflection zone that signals widespread alveolar overdistention. A few sustained inflations to high static pressure may be necessary to open the lung in the initial stages of acute lung injury and periodic “recruiting breaths” may be needed when very small tidal volumes are used. The relevant pressure here, to achieve near-total recruitment, may be as low as 25 cm H₂O in some patients and as high as 60 cm H₂O in others, influenced heavily by the type and duration of lung injury and by chest wall characteristics.

Construction of the PV curve

There is no simple rule for choosing optimal PEEP that applies to all patients. Not only does the compliance of the lung and chest wall differ among patients, but so does the recruitability of the lung on which optimal PEEP depends [49]. Attempting to construct a PV curve by the traditional super syringe method involves disconnection of the patient from the ventilator, which may cause marked drops in mean and end-expiratory transalveolar pressures. This in turn may cause hypoxemia, bradycardia, arrhythmia,

and/or flooding of the airway with edema fluid. The process that has been followed in recent years is to apply a slow inflation at constant flow (~ 2 L/min) delivered by the ventilator. Such curves may begin from relaxed FRC or PEEP. Construction of an expiratory PV curve has more theoretical appeal as a means of setting PEEP, as its contours are more directly influenced by the expiratory collapse that PEEP is intended to prevent (Fig. 6). Assuming that tidal volume has already been selected, tracking tidal compliance during decrements of PEEP from total lung capacity (proceeding from higher to lower values) has logical appeal for setting PEEP's optimal value.

Calculation of C_{RS} and R_{AW} during mechanical ventilation

Inspiratory resistance

When a mechanical ventilator expands the chest of a passive subject, inspiratory P_{AW} furnishes the entire force accomplishing ventilation. Because the pressure-volume relationships of the lung and chest wall are approximately linear over the tidal volume range and because the increment in the P_{AW} necessary to drive gas flow is nearly unchanging under constant flow conditions, the corresponding P_{AW} waveform resembles a trapezoid during inspiration, a shape composed of a triangle of elastic pressure and a parallelogram of resistive pressure (Fig. 7). The mechanically ventilated respiratory system can be described by inspiratory resistance and compliance, data that in daily clinical practice can be estimated from P_{AW} , during volume cycled, constant flow ventilation with an applied end-inspiratory pause. It should be emphasized, however, that the calculations of C_{RS} and

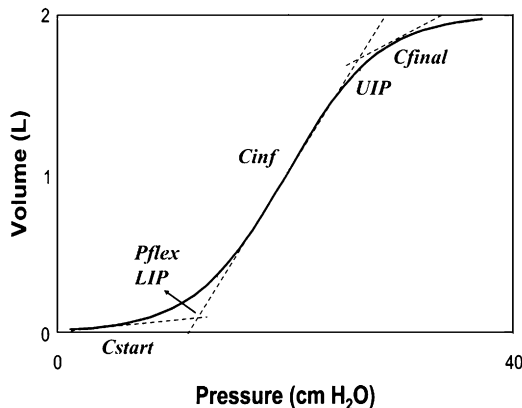


Fig. 6. Pressure-volume curve of the respiratory system. Cstart, starting compliance, computed as the ratio between the first 100 mL inflation and the corresponding pressure; LIP, lower inflection point; Cinf, inflation compliance, computed as the slope of the PV curve during inflation in its most linear portion; UIP, upper inflection point; Cfinal, final compliance. (Data from Rajkumar A, Karmarkar A, Knott J. Pulse oximetry: an overview. *J Perioper Pract* 2006;16(10): 502-4; and Gattinoni L, Eleonora C, Caironi P. Monitoring of pulmonary mechanics in acute respiratory distress syndrome to titrate therapy. *Curr Opin Crit Care* 2005;11(3):252-8.)

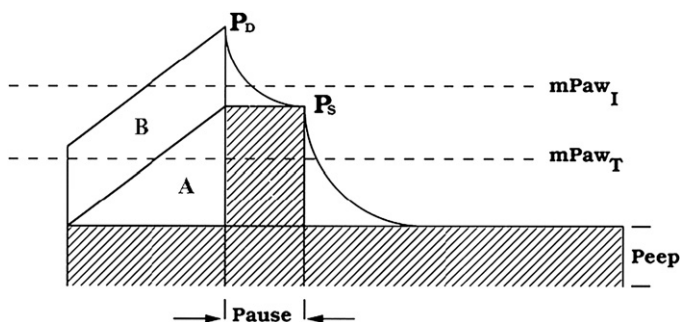


Fig. 7. P_{AW} trapezoid waveform composed of a triangle of elastic pressure and a parallelogram of resistive pressure. P_D represents an end-inspiration airway pressure under dynamic condition. Tidal compliance is the quotient of tidal volume and the difference between static plateau pressure (P_S) (equivalent to alveolar pressure, P_{alv}) and the total PEEP. The slope of the airway pressure tracing at the end-inspiration obtained under constant flow conditions reflects elastance of the respiratory system ($1/C_{RS}$).

resistance from P_{AW} can be made only when inflation is passive. When gas is prevented from exiting the lung at the end of tidal inspiration, P_{AW} falls quickly to a plateau value. If this end-inspiratory “stop-flow,” “plateau,” or “peak static” (P_S) pressure is referenced to the end-expiratory alveolar pressure (total PEEP), the difference determines the component of end-inspiratory pressure necessary to overcome the elastic forces of inflating the chest with the delivered tidal volume. Total PEEP ($PEEP_{TOT}$) is the sum of applied PEEP and auto-PEEP. Effective compliance (C_{eff}) can be computed as follows:

$$C_{eff} = V_{Tc} / (P_S - PEEP_{TOT})$$

where the V_{Tc} is the corrected V_T .

During inflation with a constant flow profile, the P_D (peak dynamic pressure) is the maximal pressure achieved just before the end of gas delivery, which drives gas to the alveolar level at the selected flow rate and expands lungs and chest wall by a full V_T . The difference between P_D and P_S quantifies the gradient driving gas flow (V) at end-inspiration and varies with the resistance of the patient and endotracheal tube as well as with inspiratory gas flow setting. Under conditions of passive inspiration with constant inspiratory flow, the ratio of $(P_D - P_S) / V_{end - insp}$ is the airway resistance (R_{AW}). The ratio of the delivered tidal volume (corrected for the compression volume of the external circuit) to $(P_D - PEEP_{TOT})$ reflects the overall difficulty of chest expansion, if V_T and inspiratory flow settings do not change, during passive inflation. This index had been termed “dynamic characteristic”:

$$DC = V_{Tcorr} / (P_D - PEEP_{TOT}).$$

Because P_D is influenced both by the frictional and elastic properties of the thorax, in a patient receiving the same V_T and inspiratory flow, it may be considered a simple indicator of bronchodilator response under passive conditions. During controlled inflation with constant square wave inspiratory flow and stable airway resistance (R_{AW}), the slope of inspiratory pressure ramp should reflect C_{RS} . However, an estimate of C_{RS} made by this technique is inappropriately low, unless auto-PEEP is taken into account. When there is occult positive end-expiratory pressure (auto-PEEP) at the onset of inspiration, the relevant pressure for chest expansion is $(P_S - PEEP_{TOT})$, not $P_S - PEEP$.

Expiratory resistance

For the same average flow rate, expiratory resistance routinely exceeds inspiratory resistance, even in the normal airway. For the patient connected to a mechanical ventilator, expiratory resistance arises in the endotracheal tube and exhalation valve as well as in the native airway. While the resistance across the exhalation valve and external tubing can be monitored easily, the total expiratory resistance (the quotient of the difference between alveolar pressure and pressure at the airway opening and the expiratory flow) is difficult to measure directly. However, it can be estimated knowing expiratory flow just before an occlusion of the airway opening and the "stop-flow" pressure (as an estimation of alveolar pressure). Alternatively, the expiratory resistance is the quotient of the time constant (the time required to expel 63% of the tidal volume during uniexponential deflation, also equal to the product of Resistance and Compliance) and respiratory system compliance. Modern equipment can provide the requisite display of exhaled volume against time.

Expiratory resistance has important consequences, giving rise to auto-PEEP, dyspnea, and differences between mean airway pressure and the mean alveolar pressure that actually determines average respiratory system distension under passive conditions. Average expiratory flow and expiratory resistance increase as VE rises and the I:E ratio extends, reducing the time available for expiration and boosting average expiratory flow. Except when very mild, the patient must contend with the effects of expiratory resistance by allowing dynamic hyperinflation or by increasing expiratory muscle pressure. New generation ventilators employ techniques to minimize the expiratory resistance of the circuitry.

Depending on its nature, length, diameter, patency, and angulations, the endotracheal tube contributes greatly to R_{AW} . The turbulent flow developing in a narrow or partially occluded tube is the reason for its flow-dependent resistance. If endogenous bronchial resistance is the variable of interest, P_{AW} should be sensed at or beyond the carinal tip of the endotracheal tube. This can be accomplished with an intraluminal catheter or by using a tube specially designed for measuring pressures at this site.

Value of continuously monitoring P_{AW} and flow

Flow tracing

Modern ventilators offer the option of displaying both airway pressure and airflow or montages of one variable against the other. When used in conjunction with a simultaneously recorded airway pressure, the flow tracing is an invaluable aid in determining a number of parameters of clinical interest. A glance at the flow tracing usually is sufficient to determine the inspiratory mode of the ventilator and may yield clues in detecting patient-ventilator asynchrony. Flow must be known to compute airway resistance and the work of breathing, as well to detect auto-PEEP. A linear, biphasic flow profile, rather than a unisexponential one, may give a clear indication of expiration flow limitation. A rippling inspiratory flow tracing indicates secretion retention within the central airways. A proto-expiratory “stutter step” suggests central airway occlusion (Fig. 8) [50]. The “zero flow” points of the airway and esophageal pressure tracings define the dynamic mechanical limits of the respiratory cycle, which are required in computations of mouth occlusion pressure ($P_{0.1}$), minimum airway resistance, and auto-PEEP. The flow tracing is also helpful when

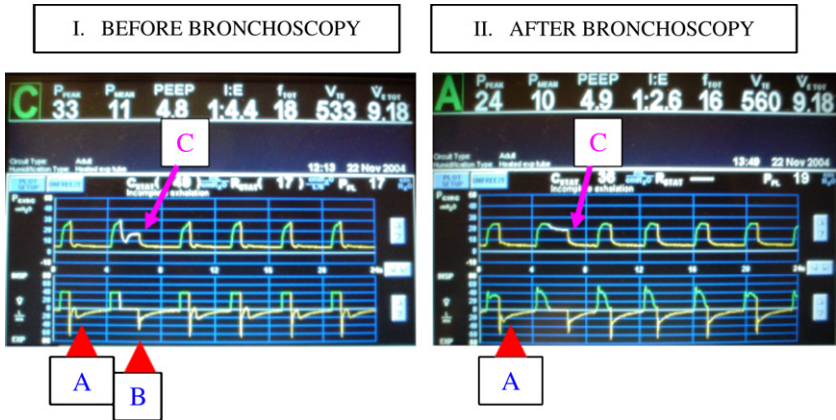


Fig. 8. (I) Before bronchoscopy. Simultaneous airway pressure and flow tracings recorded during mandatory constant flow machine cycles. A single protoexpiratory flow “stutter step” (arrow A) is followed by a unisexponential flow profile on each deflation, except for the one that follows the end-inspiratory pause (arrow B). Note the rising (inverted) plateau on the airway pressure tracing during the pause maneuver (arrow C) that could be accounted for the early decompression of the less-obstructed peripheral airways, followed by contribution of the more severely obstructed lung units. (II) After bronchoscopy. Airway pressure and flow tracings during triggered pressure control ventilation. Note (1) attenuated stutter step of the first exhalation (arrow A) that disappears after the application of the end-inspiratory pause on the next breath; (2) absence of the inverted plateau during the pause (arrow C, compare with panel A). (Adapted from Gattinoni L, Eleonora C, Caironi P. Monitoring of pulmonary mechanics in acute respiratory distress syndrome to titrate therapy. *Curr Opin Crit Care* 2005;11(3):252–8; with permission.)

adjusting the inspiratory period during pressure-controlled ventilation to maximize inspiratory tidal volume and avoiding unintended end-inspiratory pause and excessive auto-PEEP.

Airway pressure tracing

The continuous tracing of P_{AW} provides equally useful information. Apart from enabling estimation of R_{AW} and C_{RS} , the waveform of inspiratory airway pressure traced during a controlled machine cycle provides graphic evidence of the inflation work performed by the ventilator at the particular combination of tidal volume and flow settings in use. When inflation occurs passively during constant flow, the area under the pressure-time curve is proportionate to the work performed by the machine to inflate the chest, and the pressure measured half-way through inspiration (P) is the work per liter of ventilation under those conditions. When average flow and tidal volume are matched to spontaneous values, P is a good estimate of the pressure needed to ventilate the patient during pressure-support ventilation [51,52].

Also, the shape of airway pressure tracing provides information of clinical interest. Using constant inspiratory flow, concavity of the airway pressure ramp reflects patient effort during triggered cycles. An upward inflection of the terminal portion of the inspiratory airway pressure tracing during passive inflation, suggests that the combination of end-expiratory pressure and the specific tidal volume generates pressures that risk overdistention and barotrauma. Conversely, convexity of the P_{AW} tracing indicates that inflation is becoming easier as the breath proceeds. Such a profile can be seen when volume is alternately recruited and derecruited during the breathing cycle, when auto-PEEP is present, or when resistance is highly volume dependent. Last, variations in the peak dynamic pressure of the machine-aided breaths suggest asynchrony between the respiratory rhythms of the patient and ventilator.

Mean airway pressure

The mean airway pressure (mP_{AW}) recorded under passive conditions is the only measurable analog of the mean alveolar pressure and relates intimately to the forces that drive ventilation and hold the lung distended (Fig. 9). The mean airway pressure is the average pressure that distends the alveolus and passive chest wall and therefore correlates with alveolar size and recruitment, as well as with mean intrapleural pressure. It is also the average pressure available to drive expiratory flow. When mean airway pressure (mP_{AW}) is measured without patient effort, it correlates directly with arterial oxygenation in the setting of pulmonary edema and lung injury, with back pressure to venous return, as well as with minute ventilation. Mean airway pressure can be raised by increasing VE, PEEP, or by extending the inspiratory time fraction. It is therefore a crucial variable to monitor when the clinician changes ventilatory parameters.

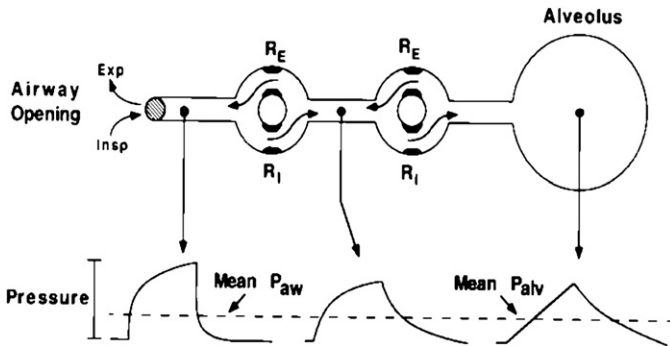


Fig. 9. Relationship of mean airway pressure to mean alveolar pressure. In an airway in which inspiratory (R_I) and expiratory (R_E) resistive pressure losses are equivalent, the mean pressure averaged over the entire ventilatory cycle should be equivalent under identical conditions at every point along the path, including airway opening and alveolus.

The actual relationship between mP_{AW} and mP_{Alv} can be expressed as:

$$MP_{Alv} = mP_{AW} + VE(R_{EX} - R_{IN})$$

where the $R_{EX} - R_{IN}$ is the calculated difference between expiratory and inspiratory resistances [53,54]. This mean pressure difference tends to be positive and may be impressively large in severe airway obstruction, high ventilation requirements, or inverse ratio ventilation.

Auto-PEEP effect

Considerable confusion has arisen regarding the terms “auto-PEEP” or “intrinsic PEEP.” The pressure applied to the airways by the clinician is termed PEEP or “extrinsic PEEP.” The pressure measured when all airflow is stopped is termed “Total PEEP.” “Auto-PEEP” is the difference between total PEEP and extrinsic PEEP (the prefix “auto” derives from the Greek term “self”).

Hyperinflation may occur in the setting of high levels of ventilation when insufficient time elapses between inflation cycles to reestablish the equilibrium (resting) position of the respiratory system. That usually happens in the presence of increased airway resistance and a lengthy exhalation time constant. Auto-PEEP does not necessarily indicate dynamic hyperinflation, unless expiration occurs passively. Even under passive conditions, the extent of dynamic hyperinflation that results from auto-PEEP is a function of respiratory compliance. Auto-PEEP does not necessarily signify airflow obstruction, because it develops any time that VE is high enough and/or the combination of frequency and I/E ratio leaves insufficient expiratory time for decompression to relaxed FRC. Moreover, auto-PEEP varies markedly from one site to another within the obstructed lung (tending to be greatest in the dependent lung regions), and this distribution changes with variations of

body position. The dynamic hyperinflation associated with auto-PEEP may hold adverse consequences for hemodynamics, respiratory muscle function, and lung mechanics. Barotrauma is an obvious risk of serious hyperinflation [55]. Unlike restrictive lung disease, obstructive lung disease allows excellent transmission of the alveolar pressure to the pleural space. Thus, the hemodynamic consequences of the auto-PEEP effect may be more severe than those incurred by a similar level of PEEP intentionally applied to a patient with adult respiratory distress syndrome (ARDS). Immediately after intubation, cardiac output tends to drop as the auto-PEEP impedes venous return during passive inflation. This adverse effect of auto-PEEP is particularly important to keep in mind during cardiopulmonary resuscitation, when gas-trapping secondary to vigorous ventilation further compromises marginally adequate blood flow.

During active breathing efforts, auto-PEEP dramatically increases the work of breathing, presenting an increased threshold load to inspiration, impairs the strength of the inspiration muscles, and depresses the effective triggering sensitivity of the ventilator. For cases in which expiration is *flow limited* during tidal breathing, the addition of low levels of PEEP, less than the original auto-PEEP, replaces auto-PEEP effectively and therefore improves subject comfort and work of breathing, without substantially increasing lung volume or peak cycling pressure (in patients in whom expiration is *not flow limited*, PEEP raises both) [56]. At the bedside, total PEEP can be quantified by occluding the expiratory port of the ventilator at the end of the period allowed for exhalation between mechanical breaths. On modern machines this is an automated function. The auto-PEEP so measured, however, only characterizes the volume-weighted average value of those channels that remain patent at end-expiration.

Variability of auto-PEEP

Pleural pressure follows a gravitational gradient, so transpulmonary pressure and alveolar dimensions are least and the tendency for airway closure greatest in the most dependent regions [57]. Therefore, even if the time constants were otherwise perfectly uniform throughout the lung, there would be a tendency for those units in dependent areas to trap more gas than those located above them.

Minute ventilation is a powerful determinant of auto-PEEP [58]. In a perfectly uniform lung with a single time-constant, variations in f and V_T that do not change minute ventilation have only a modest effect on the observed auto-PEEP. In the diseased lung, however, regional time constants vary widely. While auto-PEEP still remains highly dependent on total ventilation in the great majority of severely obstructed patients, end-expiratory flows from the slowest compartments are so small in some patients that changing the cycling frequency (and therefore the minute ventilation) may have only limited effects on gas trapping. For the same minute ventilation, variations in retained secretions, bronchospasm, apparatus resistance, tissue edema,

body position, and muscle tone alter the deflation time constant and the extent of gas trapping encountered at an unchanging VE.

Methods for determining auto-PEEP

The presence of auto-PEEP should be suspected whenever detectable flow persists to the very end of tidal expiration. Such flow often is audible with a stethoscope positioned over the trachea or if wheezing persists to the very end of the expiratory cycle. This flow can be transduced and displayed graphically on the bedside monitor; however, the magnitude of expiratory flow does not correlate with the magnitude of auto-PEEP. End-expiratory flow for example may result from widespread severe obstruction, or moderate obstructions confined to a smaller subpopulation of alveoli [59]. Finally, auto-PEEP may lurk behind airways that have been sealed completely by mucus plugs.

Because auto-PEEP varies on a breath-by-breath basis during spontaneous breathing, it cannot be quantified precisely under these conditions. If passive conditions are established, an estimate of auto-PEEP can be determined by a variety of methods [60]. Two methods are based on the principle of counterbalancing auto-PEEP, either by end-expiratory occlusion or by the dynamic airway pressure needed to initiate inspiratory flow (Fig. 10). Plateau pressure reflects the degree of dynamic hyperinflation of all open lung units more faithfully than does direct measurement of auto-PEEP itself, which gives an average of the auto-PEEP values from only those units that remain in communication with airway opening. With tidal volume and extrinsic PEEP unchanging, the discrepancy in plateau pressure encountered during an extended expiratory cycle (compared with the ordinary tidal cycles that preceded it) reflects "measurable" auto-PEEP. Two of the most important effects of

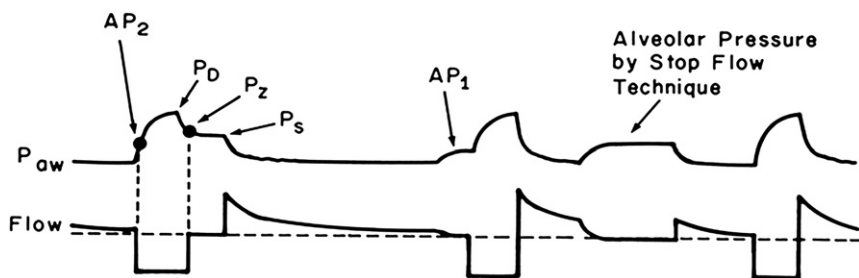


Fig. 10. Simultaneous tracings of airway pressure (P_{AW}) and airflow during controlled volume-cycled ventilation with constant inspiration flow in a patient with airflow obstruction. P_D represents an end-inspiration airway pressure under a dynamic condition, P_Z at the point of flow cessation, and P_S after complete equilibration among all alveolar and airway pressures. Alveolar pressure can be estimated by the stop-flow technique in midexpiration or at end-exhalation (AP_1). Auto-PEEP also can be estimated under dynamic conditions as the airway pressure above the set PEEP value that is needed to counterbalance elastic recoil and stop expiratory airflow (AP_2).

auto-PEEP, those on hemodynamics and work of breathing, are mediated by pleural pressure, which can be measured directly as esophageal pressure (Pes).

Esophageal pressure

Knowledge of intrapleural pressure often facilitates clinical decision making. A thin esophageal catheter (~ 2 mm diameter) inflated with 1 mL of air in the 10-cm-long balloon is inserted through the esophagus into the stomach and then carefully withdrawn to a point just above the position where negative pressure deflections are initially observed during spontaneous inspiration efforts. Because no significant change of transpulmonary pressure can occur without a change in lung volume, good balloon position is indicated by nearly identical deflections of esophageal and airway pressures during an occluded spontaneous breath.

In the upright position, Pes reflects the absolute value of global intrathoracic pressure with acceptable accuracy, but Pes overestimates average resting intrathoracic pressure in the supine position and underestimates it in the prone position. With the patient recumbent, Pes overestimates pleural pressure, but changes in pleural pressure are tracked well. Useful graphics of dynamic pressure-volume and flow-volume enable estimation of force generation during all patient-initiated breaths (spontaneous or assisted) and allow partitioning of transthoracic pressure into its lung and chest wall components during passive inflation. Furthermore, Pes aids in interpreting pulmonary artery and wedge pressures under conditions of vigorous hyperpnea or elevated alveolar pressure (PEEP, auto-PEEP). The Pes can be used to compute the work of breathing across the lung and external circuitry or to calculate the product of developed pressure and the duration of inspiratory effort (pressure-time product). It has been suggested that fluctuations in central venous pressure can serve a similar purpose, but the damped vascular pressure tracing yields a low-range estimate of effort. This underestimation occurs because venous return tends to rise as intrathoracic pressure falls and declines as intrathoracic pressure rises.

Transdiaphragmatic pressure

Transdiaphragmatic pressure (Pdi) is the difference between Pes and the gastric pressure (Pga) [61]. Theoretically generated by a single inspiratory muscle (the diaphragm) Pdi can be used to quantify its effective contractile force. Clinically, the Pdi is rarely used. Occasionally it is measured in conjunction with phrenic nerve stimulation or voluntary efforts to investigate diaphragmatic paralysis.

Abdominal pressure

An increased intra-abdominal pressure (IAP) increases chest wall stiffness. Abnormally high IAP values, as measured by bladder pressure, are

found in many ICU patients. Very high IAP values are associated with restrictive lung physiology and systemic acidosis.

Monitoring breathing efforts

Oxygen consumption of respiratory system

The oxygen consumed by the ventilator pump (VO_2R) estimates respiratory muscular effort at its most basic level: cellular metabolism. Although difficult to measure, the VO_2R theoretically accounts for all factors that tax the respiratory muscles, ie, the external workload (W) and the efficiency (e) of the conversion between cellular energy and useful work ($\text{VO}_2\text{R} = W/e$). Two patients with different chest configurations, patterns of muscle activation, or degrees of coordination between the muscles of inspiration and expiration may perform identical external work (W) but consume vastly different amounts of O_2 in the process. Because VO_2R cannot be measured directly, total body oxygen consumption (VO_2) is tracked as ventilatory stresses are imposed or relieved, perturbing the respiratory system. Unfortunately, VO_2 is difficult to measure in unstable patients, so that other measures of respiratory muscle effort usually are sought.

Direct measures of external mechanical output

External work of breathing

Work of breathing is a global measure of respiratory pump activity and reflects the imposed respiratory load. The mechanical work of breathing and breathing effort are not synonymous terms. If breathing is inefficient, great effort can be expended without developing forceful pressures or accomplishing measurable external work. Mechanical work is accomplished when a pressure gradient (P) moves the lung or relaxed chest wall through a volume change. At any volume (V) above relaxed FRC, pressure resulting from a flow (V) dissipates against frictional and elastic forces in the following way:

$$P = R_{\text{AW}}(V) + V/\text{Crs}$$

Average developed pressure (P) for the tidal inflation (V_{T}) during the inspiratory period (t_i) can be approximated as follows:

$$P = R_{\text{AW}}(V_{\text{T}}/t_i) + V_{\text{T}}/2C_{\text{RS}} + \text{auto-PEEP}$$

and is numerically equivalent to the work per liter of ventilation, while work per tidal breath (W_b) can be quantified as the product of P and V_{T} . Thus, if R_{AW} , C_{RS} , t_i , and V_{T} are known for the spontaneously breathing subject, the external work rate for inspiration can be computed easily. Exhalation normally proceeds passively, dissipating elastic energy stored during the inspiratory half cycle.

Bronchospasm, retained secretions, and mucosal edema are the primary reversible factors that increase R_{AW} . Lung edema and infiltration, high lung volumes, pleural effusions, abdominal distention, and supine posture reduce C_{RS} . In the clinical setting, such computations serve to estimate the pressure support level needed to achieve most ventilatory needs. When the ventilator performs the entire workload for a passive patient, total inflation pressure (P) is simply P_{AW} , that is approximated by the inflation pressure at midcycle (when inflation is achieved with a constant-flow waveform). With pressures and volumes expressed in their customary units, a convenient work unit is the joule or watt-second, $1 \text{ J} = 10 \text{ cm H}_2\text{O} \times 1 \text{ L}$. Total inspiratory mechanical work per minute is the product of P and minute ventilation or $\dot{V}_b$ and f , the breathing frequency.

To accurately estimate the work rate of spontaneous breathing, flow delivery during passive inflation must approximate the mean inspiratory flow rate of spontaneous breathing, the tidal volume delivered must be similar, and no inflation effort must occur. Unfortunately, such preconditions often cannot be accomplished without deep sedation or paralysis.

Influence of auto-PEEP on work of breathing

Auto-PEEP imposes a threshold load on inspiration. The patient must supply a pressure sufficient to counterbalance auto-PEEP before central airway pressure falls sufficiently to trigger the ventilator or initiate a pressure-supported breath. The threshold load imposed by auto-PEEP effectively reduces the triggering sensitivity of the machine to a value equal to the sum of auto-PEEP and the set trigger sensitivity value. When expiration is flow limited during tidal breathing, low levels of continuous positive airway pressure (CPAP) or PEEP can help restore triggering sensitivity and reduce the work of breathing. Moreover, during pressure-support ventilation, PEEP that counterbalances auto-PEEP leaves a greater proportion of the inspiratory pressure available to power inflation, often resulting in an increased tidal volume for the same value of pressure-support. Although low-level PEEP also tends to improve the distribution of ventilation, PEEP should not be used if it causes the peak dynamic cycling pressure to rise significantly.

Work measurements

Although the work of breathing can be estimated using the equation of motion, an esophageal balloon is required to directly measure work during spontaneous, machine-assisted, or pressure-supported breathing. During spontaneous breathing cycles, the fluctuations in P_{es} reflect patient efforts to overcome the impedance of the lung and external circuit. Inspiratory inflections of the P_{AW} waveform quantify the pressure needed to suck gas through the inspiratory circuit to the point of pressure measurement. While care must be taken to include any component attributable to auto-PEEP, it must be understood that surreptitious or overt expiratory efforts may contribute to the "inspiratory" work calculation. Inspiratory work can be

quantified by electronically integrating the product of P_{es} and the flow or by measuring the area within a plot of P_{es} against inspired volume. The work done in expanding the chest wall cannot be directly measured during active breathing. To exclude the resistance of the endotracheal tube, P_{AW} must be sampled between the tube tip and the carina, a site at which much deeper pressure fluctuations may be seen during inspiration. The resistance of standard endotracheal tube often exceeds 10 cm H₂O/L/sec and is commonly offset during inspiration by pressure support.

During patient-initiated but machine-assisted breathing cycles, it is often assumed that patient work becomes negligible. Indeed, the ventilator is fully capable of performing the entire work of breathing if the patient were to cease effort immediately after triggering inspiration. However, relaxation does not occur abruptly once the machine cycle begins. Instead, patient effort continues in direct proportion to the intensity of respiratory drive. When the ventilator requirement or sense of dyspnea is high (eg, when the ventilator is poorly adjusted with respect to sensitivity, peak inspiratory flow rate, inspiration duration, or tidal volume), exertion levels may approach those of unsupported breathing [62]. Interestingly, resistance and compliance do not influence the work of breathing during triggered cycles, provided that the machine fully satisfies the patient's peak inspiratory flow demand ($\approx 4 \times V_E$) [58]. However, if the patient's flow demand exceeds the delivery rate, the patient works against the resistance of the endotracheal tube and the ventilatory circuitry, as well as against the innate impedance characteristics of the chest. Clues to patient exertion during triggered machine cycles are provided by the airway pressure tracing, as already described. Peak dynamic pressure itself may not be much different from expected, in as much as inspiratory effort slackens near the end of inflation. During Pressure-Support Cycles, inspiratory airway pressure is maintained nearly constant by the machine at the pre-set level. Therefore, patient effort can be gauged directly only from a P_{es} tracing.

Pressure-time product

Isometric components of muscle tension that consume oxygen without contributing to volume change fail to register as externally measured work, accounting in large part for the lack of agreement between force generation and W_b . A pressure-time product ($PTP = P \times t_i$) parallels effort and VO_2R more closely than W_b because it includes the isometric component of muscle pressure and is less influenced by the afterload to contraction. When average inspiratory pressure (P , as computed earlier) is referenced to the maximal isometric pressure that can be generated at FRC (P_{max}) and inspiratory time (t_i) is expressed as a fraction of total cycle length ($ttot$), a useful effort index is derived:

$$\text{Pressure-time index (PTI)} = P/P_{max} \times t_i/t_{tot}$$

Values of PTI that exceed 0.15 identify highly stressful breathing workloads that may not be sustainable [63,64].

Monitoring ventilatory drive and breathing pattern

Importance of assessing ventilatory drive

Considering that ventilatory drive is a primary correlate of dyspnea and the ability to ventilate, it is remarkable that so little clinical attention has been paid previously to drive measurement. Heightened ventilatory drive increases work expenditure during triggered machine cycles and often signals pain, sepsis, and important perturbations of the cardiopulmonary system. During machine-assisted breathing, ventilatory drive plays a more important role in determining the energy expenditure of the patient than any other indicator of ventilatory mechanics. Derangements in ventilatory drive also may furnish clues regarding the ability of the patient to wean from ventilatory support. Several recent clinical studies demonstrate that most patients who failed to wean from mechanical ventilation have elevated drives to breathe and limited ability of drive to respond to increases in ventilatory loads (eg, increased PaCO_2) [65,66].

Ventilatory drive indices

Several methods can be used to index drive. When respiratory mechanics and strength reserves are normal, minute ventilation directly parallels the output of the ventilatory control center. Unfortunately, such preconditions are seldom met in the clinical setting. Minute ventilation can be viewed as the product of mean inspiratory flow rate (the quotient of tidal volume and inspiratory time, V_T/t_i) and the inspiratory time fraction or duty cycle (t_i/t_{tot}):

$$V_E = V_T/t_i \times t_i/t_{\text{tot}}$$

Both components yield useful and largely ignored clinical information. Mean inspiratory flow (V_T/t_i) provides a valid index of drive but its value also depends on the mechanical properties of the ventilatory system. The pressure generated against an airway surreptitiously occluded 100 msec after the onset of inspiratory effort (the $P_{0.1}$) is measured before the occlusion is recognized consciously, so that the corresponding outflow from the respiratory center is representative of the unimpeded cycles that preceded it. As an isometric measurement, the $P_{0.1}$ is influenced by muscle strength and lung volume but does not depend on respiratory mechanics.

Breathing pattern, frequency, and duty cycle

The breathing pattern also offers valuable information. When muscular strength is limited, patients tend to meet V_E requirements by increasing frequency (f) without raising V_T . Although smaller breaths require less effort, the cost of rapid, shallow breathing may be increased deadspace ventilation and the need for a higher V_E to eliminate CO_2 . Thus, although work per breath (W_b) is controlled by limiting tidal volume, total work (the product

of f and W_b) per minute tends to increase when f exceeds some optimal value. A very high and continuously rising frequency (to rates >30 breaths/minute) is generally accepted as a sign of ventilatory muscle decompensation and impending fatigue. It should be noted, however, that some patients increase f to a stable value of more than 35 breaths/minute and remain compensated, especially when VE rises proportionally to the rise in breathing frequency, or the patient has inherent restrictive physiology.

In recent years, considerable attention has focused on the f/V_T ratio, or rapid shallow rebreathing, index, a simply computed bedside parameter that seems to indicate the ability or inability of mechanically ventilated patients to breathe without mechanical assistance [67–70]. Discontinuation of ventilator support is unlikely to prove successful if (f/V_T) exceeds approximately 105 breaths/minute liters within the first minute of a brief trial of fully spontaneous breathing. Although hardly infallible, this simple guide does seem to have clinical utility.

As the ventilatory muscles fatigue, the duty cycle (t_i/t_{tot}), the fraction of each breathing cycle spent in inspiration, also changes. When there is a breathing stress, the t_i/t_{tot} of spontaneous breathing normally increases from about 0.35 to a value of 0.40 to 0.50. At the limits of compensation, the t_i/t_{tot} fails to increase with further stress and may actually decline.

At times of maximal effort, noteworthy alterations may be observed in the pattern of activation and coordination of the ventilatory muscle groups. Although normally passive, expiratory muscles may be called into play whenever the inspiratory muscles face a burden that is stressful in relation to their capability (eg, during expiratory flow obstruction, when the patient is anxious, when machine-controlled inspiration duration is excessive, and at high level of VE). Visible use of the accessory muscles, especially the sternocleidomastoid group, may also signal the approach to the limits of the ventilatory compensation.

Asynchrony between the peak excursions of the chest and abdominal compartments and paradoxical inward movement of the abdomen on inspiration are two indicators of diaphragmatic dysfunction or fatigue [71]. These motions also reflect the normal response of a compensated system to stress. Asynchrony between the excursions of rib cage and abdomen may be a stage in the development of full-blown abdominal paradox.

Inductance (impedance) plethysmography provides a noninvasive means of monitoring f , V_T , t_i/t_{tot} , and respiratory muscle coordination. With this technique, loose elastic bands encircle the chest and abdomen. Changes in compartmental volume create proportional changes in the cross-sectional areas of the electrical inductance loops. Fluctuations of compartmental motion can be summed to estimate overall tidal volume changes. The ratio of maximal compartmental amplitude to tidal volume (the MCA/V_T ratio) correlates with ventilatory distress and provides tangible evidence of mechanical inefficiency. Impedance plethysmography can also be used as an apnea detector in nonintubated patients and may prove helpful in

monitoring volume changes during pressure-cycled modes of ventilation (eg, pressure support, pressure control).

Monitoring strength and muscle reserve

Strength measures

The two most common measures of respiratory muscle strength are the vital capacity (VC) and the maximal inspiratory pressure (MIP) generated against an occluded airway. Without full patient cooperation, it is questionable that any measure of strength can reflect the full capability for pressure development.

Vital capacity

In cooperative patients, VC tends to be well preserved relative to MIP because small applied pressures achieve relatively large volume changes. Vital capacity generally should be measured upright rather than supine, because certain conditions, such as diaphragmatic paralysis, may demonstrate a positional reduction of more than 30%. A routine measurement of VC involves a single forceful effort from residual volume to total lung capacity. However, many weak patients fail to sustain inspiratory effort long enough to achieve their potential maximum. Others simply refuse or cannot fully cooperate with the testing. Thus, for critically ill patients, the VC has proven to be a disappointing and unreliable measure of strength. A one-way valve can be used to achieve a “stacked vital capacity” even when patients do not cooperate fully with testing. An involuntary deep breath may also be induced by stimulating cough and a crude estimate of inspiratory capacity obtained from the recorded exhaled volume.

Maximal inspiratory pressure

The maximal inspiratory pressure (MIP) is an isometric pressure optimally measured in a totally occluded airway after 20 seconds or 10 breathing efforts. A one-way valve directed toward expiration can ensure that inspiration efforts begin from a lung volume low enough to achieve maximal mechanical advantage. The P_{AW} during the MIP maneuver should be measured continuously, either with a needle gauge or by a pressure transducer linked to recording apparatus. Ideally, the MIP effort is sustained for at least 1 second. It should be kept in mind that the validity of MIP in uncooperative patients depends on the strength of ventilatory drive. In a fully cooperative patient the intensity of a voluntary effort is likely to exceed that elicited by simple airway occlusion unless the stimulus is both sustained and strong [72,73].

Measures of endurance

Endurance is the ability of a muscle to sustain effort, determined by the balance between the supply and demand of muscular energy. Two simple indices

of ventilatory power reserve—the ratio of V_E requirement to maximal voluntary ventilation (MVV) and the V_T/V_C ratio— have long been used to predict the outcome of machine withdrawal. On empirical grounds, it has been suggested that ratios higher than 50% portend weaning failure. Interestingly, newer laboratory data confirm that only about 50% to 60% of the MVV can be sustained longer than 15 minutes without ventilatory fatigue [69].

Pressure-time index

Measured accurately, the MIP can be used in conjunction with P to judge endurance and the likelihood of weaning success. In the laboratory setting, a diaphragmatic P/Pmax ratio higher than 40% (with $t_i/t_{tot} = 0.40$) or a pressure-time index ($PTI = P/P_{max} \times t_i/t_{tot}$) greater than 0.15 predicts the inability to indefinitely sustain a target workload. No confirmatory data are available yet for the specific clinical setting of the weaning trial.

Sequential measurements of drive

A practical indication of declining power reserve may also be provided by a comparison of drive indices (such as the $P_{0.1}$) measured sequentially during the stress period. Patients who fail to increase ventilatory drive in response to increased $PaCO_2$ are prone to alveolar hypoventilation and weaning failure. In the future, monitoring the response of such indices as $P_{0.1}$ to an imposed stress or CO_2 loading may provide valuable clinical indications of breathing reserve.

Patient-ventilator interaction

Specific problems: patient–endotracheal tube–ventilator circuit

Smooth interaction between the patient and the ventilator may be interrupted by malfunctioning of the ventilator system, worsening of cardiopulmonary mechanics, or by factors completely unrelated to ventilation. Malfunctions of the ventilator system prevent adequate ventilation or oxygenation and usually present as altered states of consciousness, changes in vital signs, or unexplained deterioration in blood gases. When a crisis develops suddenly during mechanical ventilation, the patient should be ventilated manually to distinguish if the problem is related to the patient or to the ventilator. The difference between exhaled and set tidal volume is crucial data. Checking the airway pressure profile and comparing the peak dynamic (P_D) and static (P_S) pressure against previous values also provides essential information. A large disparity between P_D and P_S suggests a resistance problem in the tube or airways. Failure to generate or hold pressure during circuit occlusion indicates a system leak.

An important distinction must be made between massive atelectasis and tension pneumothorax. Note that a pneumothorax without tension may not elevate peak pressure or reduce tidal volume noticeably. Nonpulmonary causes of discomfort (distention of the bladder, pain, and so forth) should

not be overlooked. When agitation develops, hypoxemia frequently occurs, increasing both the drive to breathe and dyspnea. Increasing the FiO_2 often relieves hypoxemia and can undo the self-reinforcing process of agitation. In fact, increasing FiO_2 is a good first option whenever desaturation accompanies agitation.

Modern ventilators are equipped with audible alarms that sense excessive or inadequate system pressure, failure to exhale a set minimum of tidal volume, or disconnection of the patient from the machine. Endotracheal tubes often kink, block with secretions, or become constricted by the teeth of a biting patient [74–76]. Tubes that are poorly placed or secured may migrate into the larynx, main bronchus, or rest on the carina, producing cough and bronchospasm.

Poor coordination between breathing rhythms of patient and ventilator

Shortly after mechanical ventilation begins, attempts to “fight the ventilator” are the rule in alert, awake and mildly obtunded patients [77–79]. In conventional ventilation, the triggering variable may be pressure or flow [80–82]. Patient-ventilator asynchrony during the triggering process is expressed in several forms: absence of inspiratory muscle contraction (autotriggering), delay between the beginning of inspiratory effort and ventilatory triggering (excessive triggering delay), and inability of the patient’s inspiratory effort to trigger the ventilator (ineffective efforts). Autotriggering may result from random noise or presence of leaks or water in the circuit, and cardiogenic oscillations. Autotriggering usually occurs in patients with low inspiratory drive, low breathing frequency, relatively high stroke volume, and no dynamic hyperinflation [83,84]. Autotriggering is minimized by increasing the threshold of flow or pressure triggering, augmenting the patient respiratory drive, and elimination of the leaks or water in the circuit.

Excessive triggering delay and ineffective efforts to trigger the ventilator are related to the machine’s functioning, as well as the characteristics of the respiratory system. The main patient-related factors are dynamic hyperinflation, low respiratory drive, and weak inspiratory muscles. The most important ventilator factors are related to events during the pressure delivery and termination phases, such as the maximum pressure setting and expiratory asynchrony in the form of delayed opening of the exhalation valve. The strategies for decreasing the triggering delay and the number of ineffective efforts are measures that decrease the magnitude of dynamic hyperinflation, cessation of supplemental flows (eg, continuously aerosolized prostacyclin), application of external end-expiratory pressure, decrease of the pressure and the flow thresholds for triggering, and the use of new-generation ventilators with more responsive triggers.

Patient-ventilator asynchrony during the pressure delivery and cycle off phases is due to dissociation between the patient’s respiratory effort and ventilator response in terms of timing (uncoupling between the end of

mechanical and neural inspiration), and inadequate or excessive assist. In addition, with pressure-support, the pressure rise time may influence the synchronization between the patient and the ventilator.

Imaging of function and structural heterogeneity—the future

To this point in the history of mechanical ventilation, the primary database from which monitored information derives has been limited to global measures of pressure and flow sampled from the airway opening. Yet it is now understood that the diseased lung, whether obstructed or acutely injured, is composed of heterogeneous subunits with behaviors and risk susceptibilities that vary considerably site to site. Poised to be introduced to clinical practice are several methodologies designed to monitor regional anatomy and function and thereby help regulate therapy and modify risk. Foremost among these are

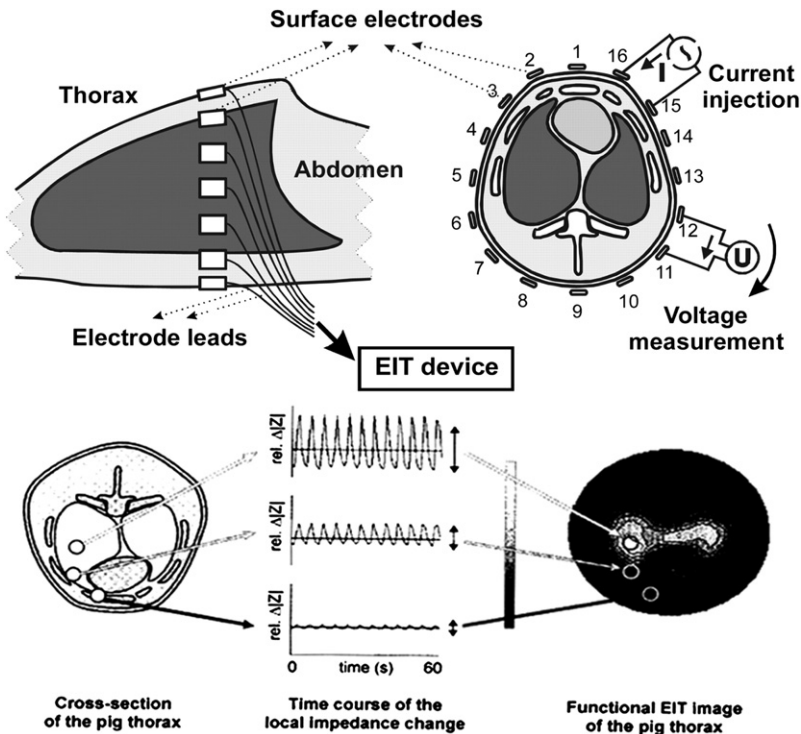


Fig. 11. Electrical impedance tomography (EIT) device for monitoring regional lung ventilation, based on the measurement of electrical voltages at the surface of the chest, resulting from repeated applications of small electrical currents to the body and transformed the collected data on two dimensional images of the distribution of electrical impedance in the chest. (*Adapted from* Frerichs I, Hahn G, Schroder T, et al. Electrical impedance tomography in monitoring experimental lung injury. *Intensive Care Med* 1998;24(8):829–36; and Frerich I, Hinz J, Herrmann P, et al. Detection of local lung air content by electrical impedance tomography compared with electron beam CT. *J Appl Physiol* 2002;93(2):660–6; with permission.)

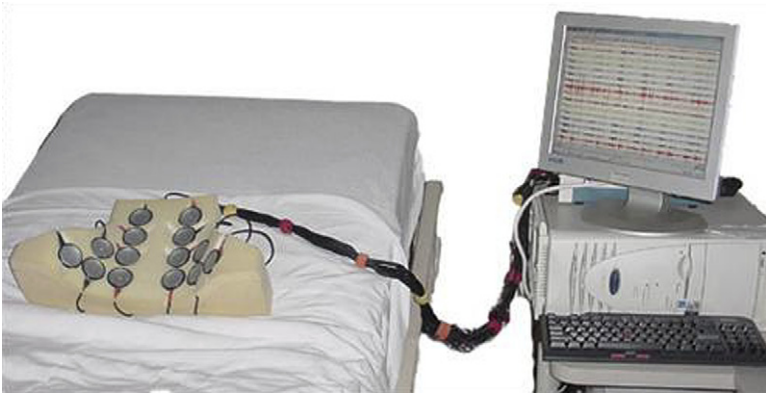


Fig. 12. Acoustic monitoring and mapping device on which 14 microphones are incorporated into a soft foam pad, while two more microphones are used to record tracheal and heart sounds, respectively. (Courtesy of R. Murphy, MD, Boston, MA.)

electrical impedance tomography (EIT), acoustic monitoring, and pulmonary ultrasound (Figs. 11 and 12) [85–95]. Although little clinical experience has yet been accumulated, it seems clear from an expanding base of experimental and observational studies that these “real time imaging” methodologies have the potential to elevate respiratory monitoring of the critically ill onto a new plane of management better aligned with our understanding of underlying pathophysiology and treatment goals.

Summary

Many options are currently available for monitoring respiratory function in the critically ill patient. Most are obtained with little intrusion into the patterns of ongoing care. Yet, the information secured is often of vital importance in bedside decision making. To use it effectively, the clinician must take an integrative approach based on mastery of the underlying physiology and familiarity with the principles upon which these technologies are based.

Further readings

- Marini JJ, Wheeler AP. Respiratory monitoring. In: Critical care medicine: the essentials. 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 78–106.
- Marini JJ, Truitt J. Monitoring the respiratory system. In: Hall JB, Schmidt G, Wood LDH, editors. Principles of critical care. 2nd edition. New York; 1998. p. 131–54.
- Nahum A. Use of pressure and flow waveforms to monitor mechanically ventilated patients. In: Yearbook of intensive care and emergency medicine. Berlin: Springer; 1995. p. 89–114.

References

- [1] Marini JJ. What derived variables should be monitored during mechanical ventilation? *Respir Care* 1992;37(9):1097–107.

- [2] Slutsky AS. Mechanical ventilation. American College of Chest Physicians' Consensus Conference. *Chest* 1993;104(6):1833–59.
- [3] Fernandez M, Burns K, Calhaun B, et al. Evaluation of a new pulse oximeter sensor. *Am J Crit Care* 2007;16(2):146–52.
- [4] van Oostrom JH, Melker RJ. Comparative testing of pulse oximeter probes. *Anesth Analg* 2004;98(5):1354–8.
- [5] Jurban A. Pulse oximetry. *Intensive Care Med* 2004;30(11):2017–20.
- [6] Hinkelbein J, Genzwuerker HV, Fielder F. Detection of a systolic pressure threshold for reliable readings in pulse oximetry. *Resuscitation* 2005;64:315.
- [7] Cannesson M, Attouf Y, Rosamel P, et al. Respiratory variations in pulse oximetry plethysmographic waveform amplitude to predict fluid responsiveness in the operating room. *Anesthesiology* 2007;44(4):273–9.
- [8] van de Louw A, Cracco C, Cerf C, et al. Accuracy of pulse oximetry in the intensive care unit. *Intensive Care Med* 2001;27:1606.
- [9] Rajkumar A, Karmarkar A, Knott J. Pulse oximetry: an overview. *J Perioper Pract* 2006;16(10):502–4.
- [10] Bolliger D, Steiner LA, Kasper J, et al. The accuracy of non-invasive carbon dioxide monitoring: a clinical evaluation of two transcutaneous systems. *Anaesthesia* 2007;62(4):394–9.
- [11] Senn O, Clarenbach CF, Kaplan V, et al. Monitoring carbon dioxide tension and arterial oxygen saturation by a single earlobe sensor in patients with critical illness or sleep apnea. *Chest* 2005;128(3):1291–6.
- [12] Gutierrez G, Wulf-Gutierrez ME, Reines HD. Monitoring oxygen transport and tissue oxygenation. *Curr Opin Anaesthesiol* 2004;17(2):107–17.
- [13] Marx G, Reinhart K. Venous oximetry. *Curr Opin Crit Care* 2006;12(3):263–8.
- [14] Caille V, Squara P. Oxygen uptake-to-delivery relationship: a way to assess adequate flow. *Crit Care* 2006;(10 Suppl 3):54.
- [15] Boden AG, Harris MC, Parkes MJ. Apneic threshold for CO₂ in the anesthetized rat: fundamental properties under steady-state conditions. *J Appl Physiol* 1998;85(3):898–907.
- [16] Lindholm P, Lundgren CE. Alveolar gas composition before and after maximal breath-holds in competitive divers. *Undersea Hyperb Med* 2006;33(6):463–7.
- [17] Hinkson CR, Benson MS, Stephens LM, et al. The effects of apparatus dead space on PaCO₂ in patients receiving lung-protective ventilation. *Respir Care* 2006;51(10):1140–4.
- [18] Kiiski R, Kaitainen S, Karppi R, et al. Physiological effects of reduced tidal volume at constant minute ventilation and inspiratory flow rate in acute respiratory distress syndrome. *Intensive Care Med* 1996;22(3):192–8.
- [19] Reutershan J, Schmitt A, Dietz K, et al. Alveolar recruitment during prone position: time matters. *Clin Sci (Lond)* 2006;110(6):655–63.
- [20] Schmalisch G, Proquitt H, et al. The effect of changing ventilator settings on indices of ventilation inhomogeneity in small ventilated lungs. *BMC Pulm Med* 2006;18(6):20.
- [21] Beydon L, Uttman L, Rawal R, et al. Effects of positive end-expiratory pressure on dead space and its partitions in acute lung injury. *Intensive Care Med* 2002;28(9):1239–45.
- [22] Kallet RH, Katz JA. Respiratory system mechanics in acute respiratory distress syndrome. *Respir Care Clin N Am* 2003;9(3):297–319.
- [23] Koutsoukou A, Bekos V, Sotiropoulou C, et al. Effects of positive and expiratory pressure on gas exchange and expiratory flow limitation in adult respiratory distress syndrome. *Crit Care Med* 2002;30(9):1941–9.
- [24] Whalen FX, Cajic O, Thompson GB, et al. The effects of alveolar recruitment maneuver and positive end-expiratory pressure on arterial oxygenation during laparoscopic bariatric surgery. *Anesth Analg* 2006;102(1):298–305.
- [25] Carvalho AR, Jandre FC, Pino AV, et al. Effects of descending positive end-expiratory pressure on lung mechanics and aeration in healthy anaesthetized piglets. *Crit Care* 2006;10(4):R122.

- [26] Schreiter D, Reske A, Stichert B, et al. Alveolar recruitment in combination with sufficient positive end-expiratory pressure increases oxygenation and lung aeration in patients with severe chest trauma. *Crit Care Med* 2004;32(4):968–75.
- [27] Morley TF, Giaimo J, Maroszan E, et al. Use of capnography for assessment of the adequacy of alveolar ventilation during weaning from mechanical ventilation. *Am Rev Respir Dis* 1993;148(2):339–44.
- [28] Sakamoto H, Kubota C, Misumi K. Relationship between arterial and end-tidal carbon dioxide pressures during controlled ventilation in porcine neonates. *Exp Anim* 1996;45(2): 195–8.
- [29] Kerr ME, Zempsky J, Sereika S, et al. Relationship between arterial carbon dioxide and end-tidal carbon dioxide in mechanically ventilated adults with severe head trauma. *Crit Care Med* 1996;24(5):785–90.
- [30] Chase JG, Yuta T, Mulligan KJ, et al. A novel mechanical lung model of pulmonary diseases to assist with teaching and training. *BMC Pulm Med* 2006;6:21.
- [31] Kacmarek RM, Hess DR. Airway pressure, flow and volume waveforms, and lung mechanics during mechanical ventilation. Philadelphia: Mosby; 1993.
- [32] Suter PM, Fairley B, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. *N Engl J Med* 1975;292(6):284–9.
- [33] Levy MM. Pathophysiology of oxygen delivery in respiratory failure. *Chest* 2005;128 (5 Suppl 2):5475–535.
- [34] Penuelas O, Aramburu JA, Frutos-Vivar F, et al. Pathology of acute lung injury and acute respiratory distress syndrome: a clinical-pathological correlation. *Clin Chest Med* 2006; 27(4):571–8.
- [35] Villar J, Perez-Mendez L, Kacmarek RM. Current definitions of acute lung injury and acute respiratory distress syndrome do not reflect their true severity and outcome. *Intensive Care Med* 1999;25(9):930–5.
- [36] Castro CY. ARDS and diffuse alveolar damage: a pathologist's perspective. *Semin Thorac Cardiovasc Surg* 2006;18(1):13–9.
- [37] Puybasset L, Gusman P, Muller JC, et al. Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure. CT scan ARDS Study Group. Adult respiratory distress syndrome. *Intensive Care Med* 2006;26(9):1215–27.
- [38] Gattinoni L, Caironi P, Valenza F, et al. The role of CT-scan studies for the diagnosis and therapy of acute respiratory distress syndrome. *Clin Chest Med* 2006;27(4):559–70.
- [39] Gillette MA, Hess DR. Ventilator-induced lung injury and the evolution of the lung-protective strategies in acute respiratory distress syndrome. *Respir Care* 2001;46(2): 130–48.
- [40] Terragni PP, Rosboch G, Tealdi A, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2007; 175(2):160–6.
- [41] Lucangelo U, Bernabe F, Blanch L. Lung mechanics at the bedside: make it simple. *Curr Opin Crit Care* 2007;13(1):64–72.
- [42] Lucangelo U, Bernabe F, Blanch L. Respiratory mechanics derived from signals in the ventilator circuit. *Respir Care* 2005;50(1):55–65 [discussion: 7].
- [43] Marini JJ. Advances in the understanding of acute respiratory distress syndrome: summarizing a decade of progress. *Curr Opin Crit Care* 2004;10(4):265–71.
- [44] Brower RG, Morris A, MacIntyre N, et al. Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. *Crit Care Med* 2003;31(11):2592–7.
- [45] Gattinoni L, Eleonora C, Caironi P. Monitoring of pulmonary mechanics in acute respiratory distress syndrome to titrate therapy. *Curr Opin Crit Care* 2005;11(3):252–8.
- [46] Marini JJ, Gattinoni L. Ventilatory management of acute respiratory distress syndrome: a consensus of two. *Critical Care Med* 2004;32(1):250–5.

- [47] Nunes S, Uusaro A, Takala J. Pressure-volume relationships in acute lung injury: methodological and clinical implications. *Acta Anaesthesiol Scand* 2004;48(3):278–86.
- [48] Albaiceta GM, Taboada F, Parra D, et al. Tomographic study of the inflection points of the pressure-volume curve in acute lung injury. *Am J Respir Crit Care Med* 2004;170(10):1066–72.
- [49] Matamis D, Lemaire F, Harf A, et al. Total respiratory pressure-volume curves in the adult respiratory distress syndrome. *Chest* 1984;86(1):58–66.
- [50] Zamanian M, Marini JJ. Pressure-flow signatures of central-airway mucus plugging. *Crit Care Med* 2006;34(1):223–6.
- [51] Abubakar KM, Keszler M. Patient-ventilator interactions in new modes of patient-triggered ventilation. *Pediatr Pulmonol* 2001;32(1):71–5.
- [52] Sarkar S, Donn SM. In support of pressure support. *Clin Perinatol* 2007;34(1):117–28.
- [53] Marini JJ, Ravenscraft SA. Mean airway pressure: physiologic determinations and clinical importance—Part 1: physiologic determinants and measurements. *Crit Care Med* 1992;20(10):1461–72.
- [54] Marini JJ, Ravenscraft SA. Mean airway pressure: physiologic determinations and clinical importance—Part 2: Clinical implications. *Crit Care Med* 1992;20(11):1604–16.
- [55] Grasso S, Terragni P, Mascia L, et al. Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. *Crit Care Med* 2004;32(4):1018–27.
- [56] Takeuchi M, Goddon S, Dolhnikoff M, et al. Set positive end-expiratory pressure during protective ventilation affects lung injury. *Anesthesiology* 2002;97(3):682–92.
- [57] Marini JJ, Crooke PS 3rd. A general mathematical model for respiratory dynamic relevant to the clinical setting. *Am Rev Respir Dis* 1993;74(2):922–33.
- [58] Marini JJ. Critical care medicine: the essentials. 3rd edition. chapter 5. Lippincott, Williams & Wilkins; 2006.
- [59] Dhand R. Ventilator graphics and respiratory mechanics in the patient with obstructive lung disease. *Respir Care* 2005;50(2):246–61 [discussion: 59–61].
- [60] Blanch L, Bernabe F, Lucangelo U. Measurement of air trapping, intrinsic positive end-expiratory pressure, and dynamic hyperinflation in mechanically ventilated patients. *Respir Care* 2005;50(1):110–23 [discussion: 23–4].
- [61] Sharshar T, Desmarais G, Louis B, et al. Transdiaphragmatic pressure control of airway pressure support in healthy subjects. *Am J Respir Crit Care Med* 2003;168(7):760–9.
- [62] Tassaux D, Gannier M, Battisti A, et al. Impact of expiratory trigger setting on delayed cycling and inspiratory muscle workload. *Am J Respir Crit Care Med* 2005;172(10):1283–9.
- [63] Collett PW, Perry C, Engel LA. Pressure-time product, flow and oxygen cost of resistive breathing in humans. *J Appl Physiol* 1985;58(4):1263–72.
- [64] Gonzalez C, Servera E, Celli B, et al. A simple noninvasive pressure-time index at the mouth to measure respiratory load during acute exacerbation of COPD. A comparison with normal volunteers. *Respir Med* 2003;97(4):415–20.
- [65] Hernandez G, Fernandez R, Luzon E, et al. The early phase of the minute ventilation recovery curve predicts extubation failure better than the minute ventilation recovery time. *Chest* 2007;131(5):1315–1322.
- [66] Martinez A, Seymour C, Nam M. Minute ventilation recovery time: a predictor of extubation outcome. *Chest* 2003;123(4):1214–21.
- [67] Wysocki M, Cracco C, Teixeira A, et al. Reduced breathing variability as a predictor of unsuccessful patient separation from mechanical ventilation. *Crit Care Med* 2006;34(8):2076–83.
- [68] Chao DC, Scheinhorn DJ. Determining the best threshold of rapid shallow breathing index in a therapist-implemented patient-specific weaning protocol. *Respir Care* 2007;52(2):159–65.
- [69] Manthous CA, Schmidt GA, Hall IB. Liberation from mechanical ventilation: a decade of progress. *Chest* 1998;114(3):886–901.

- [70] Yang KL, Tobin ML. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med* 1991;324(21):1445–50.
- [71] Talmor D, Sarge T, O'Donnell CR, et al. Esophageal and transpulmonary pressures in acute respiratory failure. *Crit Care Med* 2006;34(5):1389–94.
- [72] Syabbalo N. Assessment of respiratory muscle function and strength. *Postgrad Med J* 1998;74(870):208–15.
- [73] Truitt JD, Marini JJ. Validation of a technique to assess maximal inspiratory pressure in poorly cooperative patients. *Chest* 1992;102:1216–9.
- [74] Freitag L, Long WM, Kim CS, et al. Removal of excessive bronchial secretions by asymmetric high-frequency oscillations. *J Appl Physiol* 1989;67(2):614–9.
- [75] Trawoger R, Kolobow T, Cereda M, et al. Clearance of mucus from endotracheal tubes during intratracheal pulmonary ventilation. *Anesthesiology* 1997;86(6):1367–74.
- [76] Kim CS, Iglesias AJ, Sackner MA. Mucus clearance by two-phase gas-liquid flow mechanism: asymmetric periodic flow model. *J Appl Physiol* 1987;62(3):959–71.
- [77] Racca F, Squadrone V, Ranieri VM. Patient-ventilator interaction during the triggering phase. *Respir Care Clin N Am* 2005;11(2):225–45.
- [78] Sassoon CS, Foster GT. Patient-ventilator asynchrony. *Curr Opin Crit Care* 2001;7(1):28–33.
- [79] Tobin MJ, Jubran A, Laghi F. Patient-ventilator interaction. *Am J Respir Crit Care Med* 2001;163(5):1059–63.
- [80] Georgopoulos D, Prinianakis G, Kondili E. Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. *Intensive Care Med* 2006;32(1):34–47.
- [81] Kondili E, Georgopoulos D. New and future developments to improve patient-ventilator interaction. *Respir Care Clin N Am* 2005;11(2):319–39.
- [82] Kondili E, Xirouchaki N, Georgopoulos D. Modulation and treatment of patient-ventilator dyssynchrony. *Curr Opin Crit Care* 2007;13(1):84–9.
- [83] Imanaka H, Nishimura M, Takeuchi M, et al. Auto triggering caused by cardiogenic oscillation during flow-triggered mechanical ventilation. *Crit Care Med* 2000;28(2):402–7.
- [84] Hill LL, Pearl RG. Flow triggering, pressure triggering and auto-triggering during mechanical ventilation. *Crit Care Med* 2000;28(2):579–81.
- [85] Frerichs I, Hahn G, Schroder T, et al. Electrical impedance tomography in monitoring experimental lung injury. *Intensive Care Med* 1998;24(8):829–36.
- [86] Frerichs I. Electrical impedance tomography (EIT) in applications related to lung and ventilation: a review of experimental and clinical activities. *Physiol Meas* 2000;21(2):R1–21.
- [87] Frerichs I, Hinz J, Herrmann P, et al. Detection of local lung air content by electrical impedance tomography compared with electron beam CT. *J Appl Physiol* 2002;93(2):660–6.
- [88] Murphy RL, Vyshedskiy A, Power-Charnitsky VA, et al. Automated lung sound analysis in patients with pneumonia. *Respir Care* 2004;49(12):1490–7.
- [89] Paciej R, Vyshedskiy A, Shane J, et al. Transpulmonary speed of sound input into the supraclavicular space. *J Appl Physiol* 2003;94(2):604–11.
- [90] Vyshedskiy A, Bezares F, Paciej R, et al. Transmission of crackles in patients with interstitial pulmonary fibrosis, congestive heart failure, and pneumonia. *Chest* 2005;128(3):1468–74.
- [91] Lichtenstein D, Meziere G, Biderman P, et al. An ultrasound sign of alveolar-interstitial syndrome. *Am J Respir Crit Care Med* 1997;156(5):1640–6.
- [92] Lichtenstein D, Goldstein I, Mourgeon E, et al. Comparative diagnostic performances of auscultation, chest radiography and the ultrasonography in acute respiratory distress syndrome. *Anesthesiology* 2004;100:9–15.
- [93] Vignon P, Chastagner C, Berkane V, et al. Quantitative assessment of pleural effusion in critically ill patients by means of ultrasonography. *Crit Care Med* 2005;33(8):1757–63.
- [94] Picano E, Frassi F, Argicola E, et al. Ultrasound lung comets: a clinically useful sign of extravascular lung water. *J Am Soc Echocardiogr* 2006;19(3):356–63.
- [95] Alptekin B, Tran DT, Lisbon A, et al. Bedside ultrasonography in the differential diagnosis of pulmonary pathologies in the intensive care unit. *J Clin Anesth* 2006;18(70):534–6.

Liberation from Mechanical Ventilation: What Monitoring Matters?

Jonathan M. Siner, MD^{a,*},
Constantine A. Manthous, MD^b

^a*Section of Pulmonary and Critical Care Medicine, Department of Internal Medicine,
Yale University School of Medicine, P.O. Box 208057, New Haven, CT 06520-8057, USA*

^b*Yale University School of Medicine & Bridgeport Hospital, West Tower 6, 267 Grant Street,
Bridgeport, CT 06610, USA*

We are unaware of a monitoring technique that, in itself, has been shown to improve outcomes of patients during weaning from mechanical ventilation. However, it does not follow that monitoring physiologic parameters is unnecessary or inappropriate. Some physiologic signs of distress—extreme tachypnea, tachycardia, acute onset of pain, hypoxemia—are unacceptable, and to conduct studies demonstrating efficacy of monitoring for these would be unethical. For example, a patient who breathes 50 labored breaths per minute during a spontaneous breathing trial (SBT) will not be extubated to demonstrate that he or she requires reintubation at a very high rate. Common sense tells us that humans will fatigue, rapidly, if subjected to prolonged tachypnea. On the other hand, the precise threshold of tachypnea that is unsustainable is not known, and likely varies substantially from patient to patient. The ideal value for most patients may reside somewhere between 25 and 35 per minute depending on the patient and the progress and nature of his or her acute/chronic diseases. But to suggest that there is one threshold that demarcates success and failure for all patients with varying respiratory loads and neuromuscular capacity is counterintuitive and antiphiologic. Again, that doesn't make respiratory rate during an SBT a useless piece of information, but rather one of many monitored factors to consider in the context of each patient's specific conditions.

Weaning is not physics. It would be ideal to know with certainty the earliest moment when a patient has recovered sufficiently to breathe indefinitely without the ventilator and endotracheal tube so as to avoid both the

* Corresponding author.

E-mail address: jonathan.siner@yale.edu (J.M. Siner).

complications of prolonged invasive ventilation [1] and the risks of failed extubation [2,3]. However, because the number of variables that affect weaning outcomes are vast, the process of liberating patients from ventilators and then removing their endotracheal tubes will always be art guided but not predicted entirely by science. Most experts on this subject accept that to do the most good for the most patients, some extubation failures are not only acceptable but expected. The exact rate of extubation failure that correlates with serving the greatest number of patients is not known. However, most weanologists (or weaners, as you like) believe that if the extubation failure rate is 15% to 20%, the remaining 80% to 85% have likely been served well by aggressive earlier extubation than would be the case if clinicians had delayed. The optimal trade-off associated with conducting SBTs and trials of extubation on the first possible day to minimize ventilator complications versus the *possibly* higher mortality associated with reintubation (ie, cause-effect has not been proven) has no scientifically right answer [3].

Monitoring of physiologic variables gauges repair of the cardiorespiratory system and tolerance of the patient to breathe without the ventilator and endotracheal tube. Whereas a multitude of variables have been examined [4–7], in this review we will concentrate mainly on how to use monitored variables that are commonly and easily measured at bedsides of critically ill patients. Although neither simple nor sophisticated methods are proven efficacious, we believe there is an abundance of useful information hidden in simple physiologic variables that can be applied to sharpen the art of weaning.

Terminology

For the purpose of this article we will often distinguish between respiratory failure and airway incompetence. Respiratory failure comes in two pure forms: hypoxemic and hypercapnic [8]. Hypoxemic failure results when patients develop hypoxemia resulting from shunt (ie, flooding or collapsing of distal airspaces), to the point where they desaturate even while inspiring high concentrations (eg, 100%) oxygen. Hypercapnic respiratory failure results from insufficient neuromuscular capacity to meet the loads (resistance, elastance, and minute ventilation) of breathing and generally manifests as rapid shallow breathing that precedes frank hypercapnia and respiratory acidosis/arrest. In the real world, these two “forms” commingle so patients with pneumonia and hypoxemia also have increased lung stiffness and minute ventilation requirements. Many patients experience varying degrees of both mechanisms. Notwithstanding, patients who require mechanical ventilation, as distinguished from the necessity for an artificial airway, are treated for their underlying diatheses and each day, to minimize complications [1], clinicians seek to determine patients’ readiness to breathe: (a) without the ventilator, and (b) without

the artificial airway. In this review, we will use the term “weaning” to mean liberation from the ventilator *and* endotracheal extubation since most studies have examined factors that contribute to failure and success of these combined treatments. In reality, the factors that determine successful liberation from the ventilator and those that determine successful removal of the artificial airway are probably intimately intertwined. For example, a patient with severe brain injury but no airway protective reflexes and abundant secretions might be able to breathe without the machine, but requires an artificial airway to allow caregivers to suction/remove secretions. Other patients with brain injury and incompetent airways may fail SBTs *because* of their neurologic abnormalities. Similarly, patients who pass an SBT and then undergo a trial of extubation (TOE) may fail because of airway incompetence (ie, they are aspirating but not *yet* breathing rapidly and shallowly or developing worsening hypoxemia) *or* because of primary respiratory failure (ie, hypoxemia due to developing shunt as with atelectasis or pulmonary edema, or rapid shallow breathing as occurs with increments in respiratory load). Airway incompetence and true respiratory failure are often codependent. Patients with airway incompetence experience increased respiratory resistance from retained secretions, atelectasis (causing increased elastance **AND** hypoxemia) when secretions plug and prevent aeration of distal airspaces, and, often, increased distress causing hyperventilation. Conversely, patients with rapid shallow breathing are prone to dependent atelectasis that promotes hypoxemia and escalating increments of respiratory elastance. The goal in any patient with respiratory failure or endotracheal intubation because of airway incompetence is to define how the system has broken and to actuate repairs as quickly as possible to reduce complications of mechanical ventilation [1].

In theory, monitoring could be useful to:

1. Predict outcomes.
2. Guide decisions about when to initiate, continue, or discontinue SBTs or TOEs.
3. Monitor and repair physiologic variables that contribute to ventilator dependence.

Monitoring to predict outcomes

A huge literature examines the utility of monitoring techniques to predict weaning outcomes. There is no use in reproducing the comprehensive evidence-based review of the many physiologic parameters because *none* faithfully predicts with sufficient accuracy who will be successfully liberated/extubated [4,6,7,9]. A consensus of experts analyzed the available data and concluded that no “weaning parameter” should be used to preclude

patients who were otherwise stable (from a cardiopulmonary perspective) from performing an SBT [4,6,7]. Since extubation failure is associated with excess mortality, it can be argued that predicting outcome is important [2,3]. However, if no monitored parameter predicts extubation outcomes well, and the reference standard for identifying readiness for a TOE is a successful SBT [9], measuring/monitoring “weaning parameters” is only likely to delay SBTs or preclude SBTs in patients who might otherwise be successfully extubated. Routinely requiring f/V_t (respiratory rate/tidal volume) $< 105/\text{min/L}$ to begin SBTs prolongs weaning. In 304 patients enrolled to perform SBTs after achieving hemodynamic stability and $\text{PaO}_2/\text{FiO}_2 \geq 150$, weaning time was shorter (2 versus 3 days) compared with those who performed SBTs after achieving the same criteria plus $f/V_t \leq 105/\text{min/L}$ [10]. Until a near-perfect predictor of extubation outcome is identified, which is unlikely to happen, SBTs are the de facto litmus test for determining readiness to breathe without a ventilator (see Meade and colleagues [4]

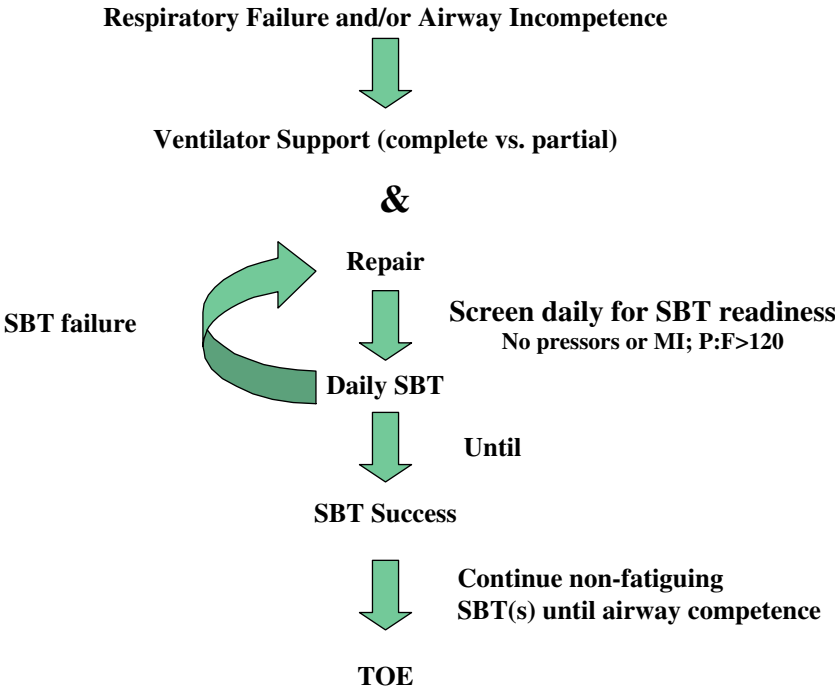


Fig. 1. Algorithm implied by ACCP evidence-based panel [9]. The text suggests a number of studies that might provide evidence to refine this algorithm (which could then be used as the control arm for future studies). SBT, spontaneous breathing trial; TOE, trial of extubation; P:F, $\text{PaO}_2/\text{FiO}_2$. Evidence has suggested that SBTs of T-piece or pressure support $\leq 7 \text{ cmH}_2\text{O}$ [24] are equivalent and that the duration of the first SBT need not be longer than 30 minutes [23]. Airway competence is determined by ability of the patient to cough and follow simple commands, and amount of endotracheal secretions [56].

and Fig. 1). Weaning parameters should not be used to preclude hemodynamically stable, sufficiently oxygenated patients from performing SBTs.

Monitoring to guide decisions about SBTs

Monitoring of cardiopulmonary and laboratory parameters is used routinely to guide weaning management decisions. The algorithm in Fig. 1 describes “best” weaning practice based on available data (April 2007). Monitoring is required for each step of the process. Unfortunately, the discriminative utility of commonly monitored variables (eg, heart rate, respiratory rate, blood pressure, oxygenation) has not been well studied. A multitude of physiologic parameters and derived variables have been examined during weaning. We could not hope to cover all here, but rather will expend most of our effort describing the utility of monitored parameters that are most commonly available. When appropriate, we will also suggest study designs that may be performed in the future to help clarify how monitoring might be used to positively impact patients’ outcomes. We specifically use the verb “clarify” versus “answer” definitively because, considered pathophysiologically, no single threshold is likely to demarcate perfectly success and failure in every patient.

Step 1: Identifying patients who are candidates for SBTs

Hemodynamic parameters

Nearly all studies and reviews published to date have suggested patients should be “hemodynamically stable” before weaning [4–6,9]. Accordingly, measures of hemodynamic stability including blood pressure and absence of cardiac ischemia have been those most often cited as prerequisites for studies and clinical guidelines.

Blood pressure: Are patients who require vasoactive medications candidates for SBTs? Shock is expected to increase the work of breathing (increased CO₂ production associated with lactic acidosis) while the respiratory muscles are not receiving adequate substrate. During septic shock, for example, more than 20% of oxygen consumption can be associated with the work of breathing [11]. If shock cannot be reversed rapidly, and work of breathing is excessive (eg, >30/min), it is *theoretically* reasonable to assume the work of breathing for the patient by initiating mechanical ventilation to allow a limited oxygen delivery to other shocked organs. Many patients with shock develop airway incompetence that requires endotracheal intubation for airway protection, and positive pressure ventilation follows whether or not it is required. Nonetheless, most clinicians have treated patients with hemodynamic instability requiring pressors, whose airway competence, work of breathing, and oxygenation *did not* require mechanical ventilation; NOT all patients who have shock require endotracheal intubation and positive pressure ventilation. Nearly all studies published to date examining

patients' outcomes during weaning have excluded patients with hypotension or who required substantial vasoactive medications.

We could find only one published abstract [12] suggesting that the rate of reintubation was 19% following extubation of patients recovering from septic shock who received decreasing doses of norepinephrine (up to a mean of 0.52 $\mu\text{g/kg/min}$). There was no control group, but this observed rate is not substantially different from that observed in a multitude of published studies of patients weaned on no vasoactive medications. This report has yet to be published in final form, but if verified, it challenges the conventional wisdom that weaning should not commence until cessation of vasopressors. Until studies are conducted and published in final form, clinicians should exercise caution in performing SBTs and TOEs in patients with shock. *If* the trajectory of illness is one of rapid improvement *and* patients are on modest and rapidly decreasing doses of vasoactive medications, SBTs might be conducted with great care, after considering the relative risks (worsened cardiopulmonary status) and benefits (earlier extubation).

Study needed to clarify. Randomize patients recovering from shock to the current evidence-based algorithm (see Fig. 1) or to current algorithm modified to initiate SBTs while on low (and decreasing) doses of vasopressors.

Myocardial ischemia: Are patients with evolving or threatening myocardial infarction or ischemia candidates for weaning? Excess catecholamines [13] and cardiac ischemia associated with weaning may exacerbate myocardial ischemia [14]. Weaning failure was observed more commonly in patients with ischemic changes on electrocardiograms [14], so an argument can be made that it is not appropriate to commence weaning in patients with already active ischemia. Clinically silent ischemia, however, occurs commonly in critically ill patients [15], and there are no data to prove that it *causes* weaning failure or definitely harms patients. When ischemia is symptomatic or already detected, it makes little sense not to treat it. The study needed to answer this question (ie, randomizing those with detected ischemia and/or evolving infarction to weaning or deferral until no ischemia), will never be performed for ethical reasons. Nonetheless, myocardial ischemia should be considered as a possible cause of persistent weaning failure in otherwise asymptomatic patients with coronary disease risk factors. Many bedside ICU monitors possess real-time ST-segment monitoring capability. Ischemic ST-segment changes (eg, observed during monitoring of I anterior, I inferior, and I lateral lead) can be confirmed with 12-lead ECGs. Appropriate medical or interventional therapies can be pursued until SBTs are successful. Accordingly, electrocardiographic monitoring may be useful in highly selected circumstances to diagnose unsuspected ischemia that may promote weaning failure.

The optimal timing for SBTs following a documented myocardial infarction (MI) has never been studied. Most patients with acute MI do not

require endotracheal intubation and mechanical ventilation, but those who do are most often in shock or suffering severe left ventricular dysfunction precipitating congestive heart failure. This particularly ill subset begins SBTs when myocardial ischemia and/or infarction are treated as evidenced by normalization of the electrocardiogram and decreasing cardiac enzymes. In this manner, monitoring of electrocardiograms and cardiac enzymes, coupled with resolution of pulmonary edema to sufficient oxygenation ($\text{PaO}_2/\text{FiO}_2 > 120$), guides when to begin SBTs safely. Careful monitoring for patients' symptoms and/or ST-segment changes either by bedside 3-lead monitors or 12-lead electrocardiogram is suggested. While greater caution and preemptive medical management may be warranted, asymptomatic ST-changes have *not* been shown to predict extubation failure during recovery following acute MI.

Study needed to clarify. Randomize patients recovering from myocardial ischemia/infarction to the current evidence-based algorithm (see Fig. 1) or to the same algorithm modified to initiate SBTs only after no chest pain, decreasing cardiac enzymes, and quiescent electrocardiogram.

Heart rate: Is there any maximal or minimal heart rate threshold for performing SBTs? Studies that have examined weaning outcomes were not designed to test whether heart rate during full ventilatory support affected weaning outcomes. Nonetheless, there are common sense rules that are the standard of care and are unlikely to be tested prospectively. SBTs are not performed on patients with (1) bradycardia requiring pacemaker placement (eg, complete heart block), (2) sinus tachycardia $> 140/\text{min}$, or (3) sustained tachyarrhythmia. Nearly all clinicians are likely to agree that these three situations are potentially life threatening and the augmentation of catecholamines during weaning and/or risks of cardiac arrest outweigh potential benefits associated with earlier extubation.

Whether it is appropriate to perform SBTs on patients whose fully ventilated heart rate is 100 to 140/min is unknown. Published studies have used varying heart rate thresholds to commence SBTs, but nearly all have studied patients with heart rates $< 140/\text{min}$ [16,17]. Tachycardia is a clinical sign of catecholamine excess and/or electrical excitability of the heart. Accordingly, weaning, which often augments catecholamines, is only likely to exacerbate tachycardias with associated risks of hypotension and heart failure. One author (C.A.M.) must admit that he rarely if ever begins SBTs until a patient's heart rate during full support is less than 110/min, reasoning, without data, that sinus tachycardia connotes stress that will only be exacerbated with weaning. However, in some patients that stress could be distress associated with the patient-ventilator interaction; so to wait until complete resolution of tachycardia may unnecessarily extend the duration of mechanical ventilation.

Study needed to clarify. Randomize patients with tachycardia (100 to 140/min) to the current evidence-based algorithm (see Fig. 1) or to the

same algorithm modified to initiate SBTs when resting, fully supported heart rate is $<100/\text{min}$.

Respiratory parameters

The landmark study on weaning parameters, published by Yang and Tobin [18], examined whether a number of respiratory parameters measured during 1 to 2 minutes of unsupported breathing, including respiratory rate, tidal volume, minute volume, respiratory mechanics, oxygenation, and f/V_t , predicted weaning outcomes. Since not all patients were extubated (ie, failure was defined as either failed SBT or failed TOE), this study suffers from the ethical conundrum faced by all weaning studies, which is the inability to test TOE in those who failed the SBT. It is not unreasonable to assume that the majority would have continued to fail unassisted breathing even without the endotracheal tube. In this landmark study, no variable identified with sufficient reliability (eg, specificity $>90\%$) patients who would be successful. Three variables predicted failure very well: tidal volume <325 mL (negative predictive value [NPV] = 94%), negative inspired pressure >-15 cmH₂O (NPV = 100%), $f/V_t > 105/\text{min}/\text{L}$ (NPV = 95%). These variables and thresholds were also most often associated with statistically significant odds of failure in a meta-analysis of the Health Services/Technology Assessment Text (HSTAT) used in the American College of Chest Physicians' Guidelines [4,6]. The f/V_t was most consistently and powerfully predictive of both SBT and extubation outcomes. More sophisticated measures of respiratory mechanics (eg, respiratory compliance, resistance, and integrated indices) are less reliably associated with weaning outcomes.

While the data do not substantiate the use of respiratory mechanics to gate SBTs in *all comers*, subcohorts have not been well studied. Common sense should permit caveats. For example, a patient with severe status asthmaticus and airway resistance of 50 cmH₂O/L/s might remain hemodynamically stable, with $\text{PaO}_2/\text{FiO}_2 > 120$ and thus otherwise qualify for an SBT (see Fig. 1). To subject such a patient, with life-threatening asthma, to awakening and an SBT risks promoting greater bronchospasm with little chance of successful extubation. The bronchospasm that caused respiratory failure has not remitted. Some may suggest that integrated indices have statistically significant predictive utility (eg, the CROP [compliance, rate, oxygenation, pressure-max] and $\text{P}_{0.1}/\text{P}_{\text{imax}}$ [pressure-at-0.1 s/pressure-max]), but these have been studied in a smaller number of studies. Accordingly, clinicians should only circumvent the algorithm of Fig. 1, which amounts to daily SBTs for patients who are hemodynamically stable and with $\text{PaO}_2/\text{FiO}_2 > 120$, in similar exceptional cases.

Rare caveats aside, no respiratory parameter or threshold, within the ethical envelope examined in most studies, absolutely predicts failure in all patients. However, the HSTAT analysis suggests that the optimal threshold value separating weaning successes from failures measured during a brief

trial (1 to 2 minutes) of unassisted breathing is between 30 and 38 breaths per minute. Tidal volume of <325 mL was also significantly predictive of failure. The integrated “rapid shallow breathing index,” f/V_t , was a more powerful predictor than either component alone. Irrespective, the recent study by Tanios and colleagues [10] demonstrates convincingly that when the f/V_t is monitored and used to initiate SBTs, outcomes are not better than when patients simply begin SBTs when they are hemodynamically stable and adequately oxygenated. It is obvious why this is so: because every patient is different, with widely varying acute and chronic diseases that define their ability to sustain unassisted respirations.

Indices of oxygenation have been less well studied. Yang and Tobin [18] indexed oxygenation by the PaO_2/PAO_2 (threshold of 0.35), but it did not reliably identify success versus failure. Many large studies that have examined weaning from mechanical ventilation did not include patients with $PaO_2/FiO_2 < 200$ [16,17]. Nonetheless, Khamiees and colleagues [19] demonstrated that in the small number of patients who were otherwise improving clinically with PaO_2/FiO_2 of 120 to 200, rates of extubation failure were not different than patients with $PaO_2/FiO_2 > 200$ (10.5% versus 19.8%, $P = .35$). There are very few other data to support that $PaO_2/FiO_2 = 120$ to 200 is unsafe or associated with an inordinately high failure rate simply because very few studies have begun weaning at the 120 threshold. In the absence of good data, the ACCP Guidelines panel offered “adequate oxygenation” to begin SBTs as $PaO_2/FiO_2 = 150$ to 200.

Study needed to clarify. Randomize patients with $PaO_2/FiO_2 = 120$ to 200 to the current evidence-based algorithm (see Fig. 1) or to same algorithm modified to initiate SBTs when $PaO_2/FiO_2 \geq 200$.

Is there a body temperature above which SBTs should not be performed? Some large weaning trials (eg, Esteban and colleagues [16], Brochard and colleagues [20]) have precluded patients from commencing SBTs until their body temperature was $<38^\circ$ or 38.5°C . It should be noted that two thirds of patients in these studies were successfully extubated on the first day of SBTs suggesting that they had been delayed inordinately in beginning their SBTs by overly stringent criteria. The central message of the past decade’s weaning research is that clinicians created many plausible but unproven prerequisites for commencing SBTs, thus binding patients unnecessarily to ventilators. And since unnecessarily prolonged ventilation promotes unnecessary complications, physicians’ unsubstantiated practices contributed to patient harm. There are no data suggesting that body temperature in itself (ie, not accompanied by other signs of sepsis) precludes successful weaning. In fact, in a study we conducted of septic patients on their first day of weaning, 26% (6 of 23) of those with maximal temperatures $>38.3^\circ\text{C}$ in the

previous 24 hours were successfully extubated [21]. Accordingly, hyperthermia by itself should not be used to preclude SBTs testing for readiness.

Study needed to clarify. Randomize patients with fever ($> 38^{\circ}\text{C}$) to the current evidence-based algorithm (see Fig. 1) or to the same algorithm modified to initiate SBTs when temperature $< 38^{\circ}\text{C}$.

Is there a hemoglobin below which SBTs should not be performed? The same argument applies to studies that required a particular hemoglobin (Hgb) concentration before commencing SBTs. Although data supporting that anemia negatively impacts weaning outcomes are sparse, we found that patients with $\text{Hgb} \leq 10 \text{ g/dL}$ were five times as likely to fail to wean successfully compared with those $> 10 \text{ g/dL}$ [19]. This finding has not been confirmed, and in light of strong data to suggest that transfusion to $\text{Hgb} = 10 \text{ g/dL}$ arbitrarily does NOT improve general clinical outcomes [22], it is not appropriate to gate SBTs based on circulating hemoglobin concentration.

Study needed to clarify. Randomize patients with anemia ($\text{Hgb} < 8 \text{ g/dL}$) to the current evidence-based algorithm (see Fig. 1) or to the same algorithm modified to initiate SBTs when $\text{Hgb} > 8 \text{ g/dL}$.

Step 2: Monitoring during SBTs

Nearly every study that has examined weaning outcomes has included time-honored, common sense, but unproven thresholds designating failure of SBTs. If SBTs are stopped, based on medical ethics and physicians' fear of causing harm, when respiratory rates exceed 35 per minute, tachycardia ($> \text{a } 20\% \text{ increase or an absolute rate } > 140/\text{min}$), hypertension ($> 180, < 90 \text{ mm Hg}$) we cannot know whether some small fraction of such "failures" would have been successful if extubated. Since SBT failure (the dependent variable) is being defined by tachycardia and tachypnea in many studies, there is codependence of variables; ideally tachycardia and tachypnea should be entirely independent variables to assess whether they predict outcomes. But in theory, outside-the-envelope values could result from causes other than true task failure. A minority of such patients may reach these thresholds because of anxiety and/or mechanical exigencies of the SBT (eg, "sticky demand valve," discomfort with the specific inspiratory flow regime of pressure support) and not as a result of true respiratory failure. We have seen numerous examples, usually of patients with severe restrictive disease, fail pressure support trials of up to $20 \text{ cmH}_2\text{O}$, but pass a subsequent T-piece on the same day without difficulty.

Some studies have demonstrated associations of monitored variables with extubation outcomes within what most would deem *ethically acceptable envelopes*, but most have NOT studied trends/changes over the course of the SBT. Physiologic variables measured during a minute or two of

unassisted breathing to *predict* readiness [4] have not been as well studied over the course of the SBT to predict extubation outcomes. When patients develop subjective distress that is not allayed with bedside coaching, sustained hypertension, tachycardia, or tachypnea during SBTs, the trial is abandoned *BEFORE* the patient fatigues and/or experiences cardiorespiratory collapse associated with acidemia and/or hypoxemia in the late stages of failure. However, many patients make it to the end of the SBT without reaching edges of the ethical envelope—with lesser increments in these physiologic parameters. If their airway competence is monitored and considered sufficient for a TOE, then extubated breathing tests their ability to sustain unassisted ventilation, oxygenation, and airway protection. Extubation failure can occur because of recurrent respiratory failure and/or airway incompetence, but it is NOT well known whether subtle changes in monitored variables during SBTs predict reliably patients at increased risk of postextubation respiratory failure.

Hemodynamic parameters

Can heart rate and blood pressure be used reliably to designate SBT failure?

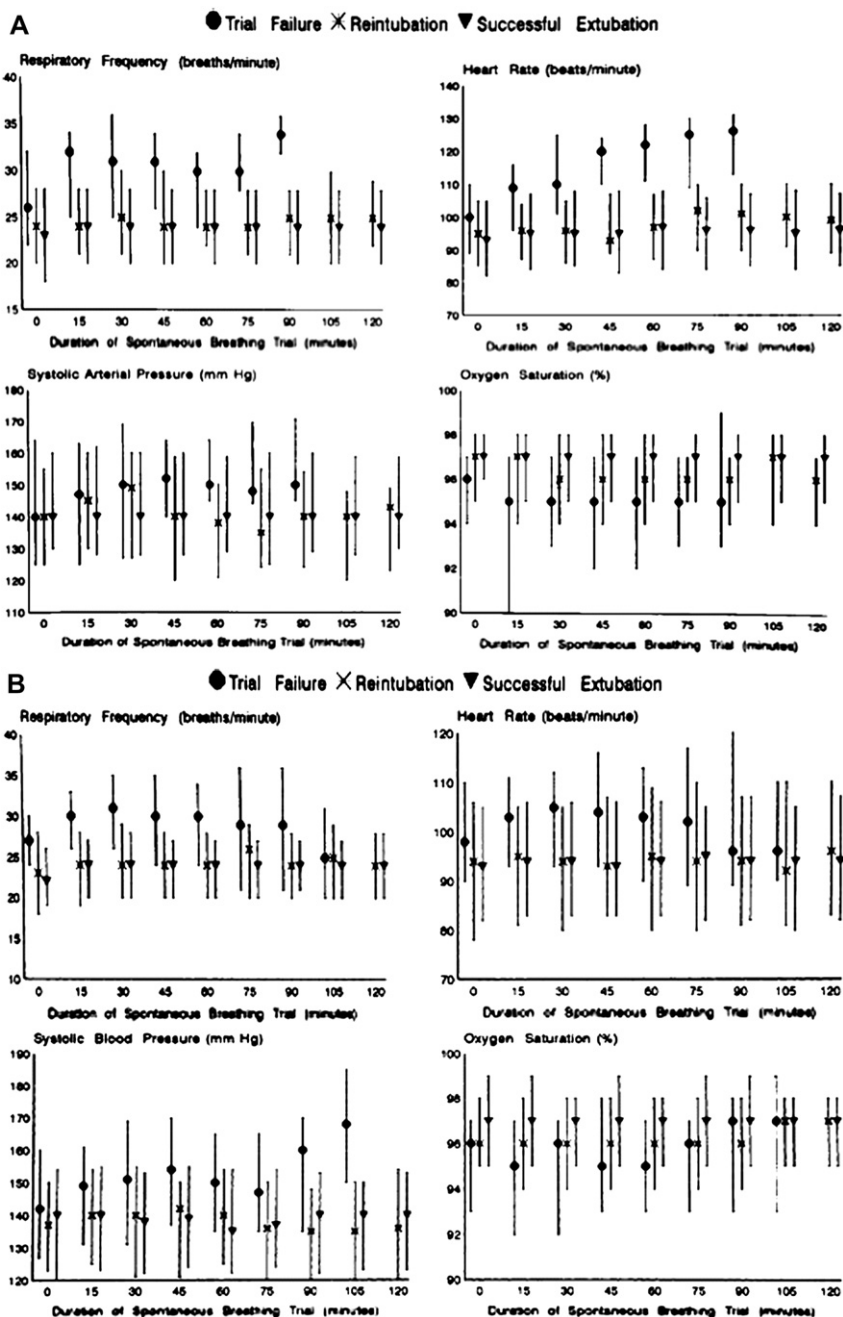
There are not sufficient data to answer this question. Sinus tachycardia and tachyarrhythmias designate stress and, theoretically, a higher risk of extubation failure. A higher heart rate has been noted in patients who fail SBTs compared with those who are successful (Fig. 2) [23,24], but that may be because excess tachycardia ($> 140/\text{min}$) was a criterion for SBT failure. It is not known whether:

1. Specific heart rates (and rhythms) highly predict extubation failure,
2. Specific increments of heart rate or blood pressure during the SBT highly predict extubation failure,
3. Specific reductions in heart rate variability predict extubation failure [25]

As mentioned above, clinical studies must not require patients' parameters to exceed acceptable ethical envelopes. However, researchers could "sneak up" on these questions by designing studies that first established whether there were strong associations of threshold values or patterns of response with extubation outcomes and then testing by prospectively extubating groups at the differing thresholds/patterns but remaining within the ethical envelope of values. Since extubation may or may not have occurred previously in the more stressed group (ie, no data to guide definitively), true equipoise is possible. For example:

Studies needed to clarify.

1. Randomize patients with heart rates of 100 to 140/min during otherwise successful SBTs and competent airway to be extubated when heart rate is $< 140/\text{min}$ versus $< 100/\text{min}$.
2. Randomize patients with increments of heart rate or systolic blood pressure of 20 to 40 during otherwise successful SBTs and competent airway



to be extubated when SBT heart rate or blood pressure increment is 20 to 40 versus <20 .

3. Randomize patients who have otherwise passed SBTs per algorithm and whose airway is competent, but whose heart rate variability is low to extubation versus waiting until increased SBT heart rate variability.

Because there are so many variables that likely impact the outcomes of TOEs, we will never find a perfect tool. However, to date, the discriminative value of commonly monitored physiologic parameters during SBTs is unknown. We simply observe “norms” established by common sense, and the insufficient available evidence. Common sense is most often right, but medical history is littered with ideas that seemed like common sense but were discounted when tested scientifically. And interestingly, two studies by Esteban and colleagues [23,24] suggest that heart rate and blood pressure during SBTs do not discriminate extubation success from failure in patients who pass the SBT.

Can other hemodynamic parameters be used to improve SBT outcomes? The total cardiovascular response during weaning has been investigated using pulmonary artery catheterization (PAC). An initial investigation suggested that patients who pass an SBT have increased cardiac output and stable mixed venous oxygenation (SvO_2) and those who fail have a decreased SvO_2 as a result of increased peripheral O_2 -extraction but unchanged cardiac output [26]. Interestingly, none of the patients in this study significantly demonstrated augmented oxygen consumption (VO_2) during weaning. A more recent study suggested that patients whose SvO_2 decreased, as a result of increased consumption, were more likely to have an inadequate cardiovascular response to the oxygen cost of breathing. These patients were more likely to fail and some had an increase in their arterial lactate supportive of insufficient oxygen delivery to meet demands of weaning [27]. Pulmonary artery catheterization is impractical and of unproven benefit. However, using noninvasive Fick rebreathing inference of cardiac output, Frazier and colleagues [28] showed that patients who successfully weaned had



Fig. 2. Physiologic variables, monitored during SBTs, of patients who experienced SBT failure, SBT success but TOE failure, and successful extubation. Values are listed as medians with 25th and 75th percentiles. (A, B) Comparison of physiologic variables during spontaneous breathing trials. Patients with SBT failure had higher respiratory frequency, heart rate, and systolic blood pressure with lower oxygen saturation compared with those who passed their SBTs. (A) (*Reproduced from* Esteban A, Alia I, Tobin MJ, et al. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish Lung Failure Collaborative Group. *Am J Respir Crit Care Med* 1999;159(2):512–8; with permission.) (B) (*Reproduced from* Esteban A, Alia I, Gordo F, et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. The Spanish Lung Failure Collaborative Group. *Am J Respir Crit Care Med* 1997;156(2 Pt 1):459–65; with permission.)

significantly increased stroke volume during SBTs, whereas those who failed did not. Despite differing results, the data to date suggest that successful weaning is marked by stable or increased cardiac output and that failure to augment cardiac output during SBTs is associated with ventilator dependence. Although these data are interesting and physiologically plausible, they are as yet of no practical utility in improving weaning outcomes.

Gastric intramural pH (gastric tonometry) has been promoted as providing information about the adequacy of vital organ perfusion [29]. Patients with low gastric pH (elevated mucosal PCO_2) at baseline were at much higher risk of weaning failure. Comparison of gastric-arterial PCO_2 to the f/Vt showed comparable sensitivity and specificity in predicting successful extubation in some but not all studies but its use remains experimental [30–32].

Although serial measurements of troponin I do not appear to provide additional information regarding weaning outcomes, brain natriuretic peptide (BNP) may hold some promise [12]. Patients with elevated BNP levels before weaning had higher rates of weaning failure and those who had developed significant left ventricular dysfunction had significantly increased levels above their baseline after SBT [33,34]. It remains to be determined whether BNP levels can be used to enhance outcomes, perhaps to signal the need for diuresis of vulnerable patients who fail initial SBTs (see below).

Discontinuation from mechanical ventilation (ie, SBT) presents many challenges to the cardiovascular system including increased afterload, increased preload, and increased work of breathing (WOB) [35]. Evidence of active cardiac ischemia may be present even in patients who are not actively weaning although the true incidence likely depends on the ICU population being evaluated [36,37]. Ischemia is associated with risk of failure during SBT, however its contribution to causing failure probably depends on the patient population [36–38]. Although routine ST-monitoring, available at no extra cost on many newer-generation bedside monitors, of all patients for ischemia is not warranted, it may have a role for identifying and treating patients with coronary disease and new ischemia during failed SBTs.

Respiratory parameters

Because patients with respiratory rates higher than 35 per minute during SBTs are deemed failures in most clinical trials, the TOE failure rate following extubation of patients breathing above this ethical envelope is unknown. Some studies have demonstrated higher respiratory rates in patients with SBT failure (see Fig. 2) [23,24] but with the caveat that failure occurred by definition at higher respiratory rates ($>35/\text{min}$). Based on available data, the appropriate threshold demarcating extubation success and failure is likely to be between 28 and 38 per minute depending on the patient. The patient-specific acute and chronic diseases and pace of improvement all likely contribute to what observed respiratory rate during the SBT is likely

to yield a successful TOE. For example, if the patient is otherwise young and healthy and the trajectory of illness is rapidly improving, a higher threshold respiratory rate may be more acceptable because with more time, respiratory loads will decrease and neuromuscular capacity will increase. For more chronically ill, debilitated patients whose respiratory loads are high and unlikely to decrease much more, an extubation threshold of closer to 28 to 30 per minute may be more prudent. To assert a single threshold applicable to all patients denies the unique pathophysiology of each patient. Esteban's studies [23,24] also demonstrated no significant difference of respiratory frequency in extubation successes versus failures at the end of successful SBTs. Although an observational study suggests that 30 per minute is too low a threshold (yielding excessive false negatives) for trauma patients subjected to a room air SBT [39], it is not clear these findings can be generalized to chronically ill medical patients.

The same can be said of tidal volume during SBTs. Most studies have allowed clinicians to terminate SBTs or reintubate based on "clinical criteria" that include shallow breathing. Ultimately, prolonged shallow breathing is most often a sign of insufficient capacity to meet loads and will eventuate in atelectasis that further stiffens (loads) the system and promotes hypoxemia, and trial failure. Persistent tidal volumes less than 325 mL in adults are not favorable for long-term success [6,9] except perhaps in very small adults or children. Fewer studies have indexed tidal volumes for body mass; it may be just slightly less useful than the f/V_t .

The f/V_t has been the most reliable, albeit integrated, monitored value associated with extubation outcomes. Although this index was originally validated for predicting outcomes measured after only 1 to 2 minutes of unassisted breathing, there are some data to suggest that changes in f/V_t during SBTs may yield greater discriminative value. It is physiologically plausible that the f/V_t will change in some patients during trials. First, at the beginning of SBTs some patients may still have hangover effects of sedatives that are known to cause rapid shallow breathing [40]. Second, some patients may experience dynamic hyperinflation during SBTs [41], for which rapid shallow breathing is more energetically efficient preceding full-blown muscle fatigue/failure. In patients with significant neuromuscular weakness, fatigue may ensue even without changes in dynamic respiratory loads. We demonstrated that the predictive utility of the f/V_t after 30 minutes of an SBT was markedly better than measured in the first 2 minutes of the SBT (area under receiver operator curve = 92% versus 74%) [42]. Others have reported similar observations [43]. It is worth mentioning that in our study only 1 of 100 patients was successfully extubated with initial $f/V_t > 125/\text{min/L}$ [42]. More recently, Frutos-Vivar and colleagues [44] demonstrated that the f/V_t measured at the end of SBTs is associated with improved outcomes. However, relatively few patients had $f/V_t > 100/\text{min/L}$ and there was no value of f/V_t in this or any other study that well (eg, with $>90\%$ certainty) demarcated successes and failures. And so we have yet to learn

how to use even this most promising monitored parameter to improve patients' outcomes [10].

Variability of tidal volumes during SBTs has also been associated with outcomes (ie, low variability is associated with weaning failure) [45,46], although even less is known about predictive utility of this monitored variable. Similarly, very little is known about changes in the $\text{PaO}_2/\text{FiO}_2$ ratio during SBTs, although patients who fail have lower oxygen saturation during trials (see Fig. 2) [23,24]. One might hypothesize that significant decrements during a trial (usually due to atelectasis or pulmonary edema) may mark the beginning of a process that will eventually "catch up" with the patient following extubation. But we are aware of no study that examined the effect on outcomes of changing $\text{PaO}_2/\text{FiO}_2$ during SBTs.

Studies needed to clarify.

1. Randomize patients with respiratory rates of 30 to 35 per minute during otherwise successful SBTs and competent airway to be extubated when SBT respiratory rate is less than 35 per minute versus less than 30 per minute.
2. Randomize patients with V_t of 250 to 300 mL during otherwise successful SBTs and competent airway to be extubated when $V_t = 250\text{--}325$ mL versus $V_t > 325$ mL.
3. Randomize patients with $f/V_t = 105\text{--}125/\text{min}/\text{L}$ during otherwise successful SBTs and competent airway to be extubated when $f/V_t = 105\text{--}125/\text{min}/\text{L}$ versus $f/V_t < 105/\text{min}/\text{L}$.
4. Randomize patients with low respiratory variability during otherwise successful SBTs and competent airway to be extubated versus delaying extubation until SBT respiratory variability increases.
5. Randomize patients with $\text{PaO}_2/\text{FiO}_2$ decrement greater than 20 (but ratio remains > 120) during otherwise successful SBTs and competent airway to be extubated versus waiting until decrement is less than 20 during SBT. (An alternative would be to randomize those with a change of O_2 -saturation on a fixed concentration of inspired oxygen.)

Miscellaneous respiratory variables. Arterial blood gases (ABGs) are used routinely to assess precisely oxygenation and CO_2 elimination during weaning yet surprisingly little is known about their appropriate role during SBTs. Beyond routine bedside monitoring (of heart rate, respiratory rate, blood pressure and subjective parameters), ABGs affect decision making infrequently and may not necessarily lead to a correct decision [47].

End-tidal CO_2 (EtCO_2 ; capnography) can be monitored continuously and is used commonly by anesthesiologists to confirm correct tube placement during endotracheal intubation. It can also be helpful in monitoring dead space in mechanically ventilated patients. Unfortunately, it may be insufficiently sensitive to detect episodes of hypercapnia [48]. Some data suggest poor sensitivity detecting less than 10 mm Hg increments of

PaCO₂, but greater sensitivity for increases of 10 mm Hg or more [49]. But accuracy is reduced in patients with parenchymal lung disease, which comprise a majority of medically ill patients [49]. False positives (ie, increments of EtCO₂ without significant increments in PaCO₂) may also contribute to unnecessary ABGs [50]. Accordingly, there is no proven role for capnography for weaning.

Minute ventilation recovery time has been proposed as a novel method of predicting extubation outcomes. Minute ventilation is measured just before SBTs; the minute ventilation recovery time is the time to return to the pre-SBT value following an SBT. This variable is thought to reflect respiratory reserve and initial studies suggest it may be more predictive than f/V_t or PaCO₂ [51,52].

Step 3: Identifying patients who have passed SBT who are candidates for a trial of extubation (TOE)

Once a patient has “passed” an SBT, again determined by the parameters monitored and described above, clinicians must determine whether patients require the endotracheal tube. “Airway competence” infers sufficient airway reflexes (eg, cough, gag) to (1) prevent secretions from above the glottis from dripping continually into the trachea, and (2) clear secretions that have dripped down from above or been produced below the glottis to above the glottis so they can be swallowed or suctioned. Upper and lower airway reflexes are a complex symphony of neurologic inputs to coordinate muscles that gag, cough, and swallow. In addition, intact sensory pathways are required—excessive secretions either rattling above the glottis or in the trachea are sensed and coughed to above the glottis and swallowed. Global neurologic condition may also be germane, so that patients who do not sense their secretions can be instructed to cough, or to sigh and combat atelectasis on command. The amount of airway secretions is the final important variable, since excessive or tenacious secretions may overwhelm competent airways. All of these factors can be monitored and quantified [19,53–56]. Some data suggest that decisions based on monitored variables might impact outcomes. Our work suggested that the post-test probability of extubation failure was nearly 50% in patients who had passed an SBT but who had two of three negative prognostic signs: excessive secretions (>2.5 mL/H), weak cough (≤ 60 L/min), or gross neurologic dysfunction (Fig. 3) [56]. However, to date, no prospective study has demonstrated that use of airway or neurologic monitored variables to guide extubation decisions affects outcomes.

Study needed to clarify

Randomize patients who have passed SBTs per algorithm to extubation only after satisfying quantitative airway and/or neurologic criteria or as per best judgment of bedside staff.

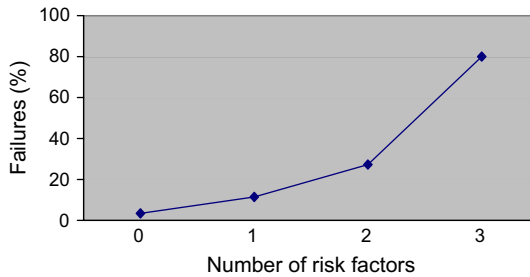


Fig. 3. Cumulative modifiable risks and risk of extubation failure [56]. Risk factors included inability to perform all four simple tasks, cough peak flow ≤ 60 L/min and secretions ≥ 2.5 mL/H. The accumulation of risks was additive. (*Adapted from* Salam A, Tilluckdharry L, Amoateng-Adjepong Y, et al. Neurologic status, cough, secretions and extubation outcomes. *Intensive Care Med* 2004;30(7):1334–9; with permission.)

Although the scientific purist might prefer to see the prospective randomized studies described above to help clarify physiologic values to demarcate weaning success and failure, the assumption is that heterogeneous patients will act similarly. Owing to the multitude of variables that contribute to weaning success versus failure, we doubt that even the best studies can identify perfect tools to improve weaning outcomes. Refine weaning? Perhaps. Perfect it? Unlikely. How much better can we get? Thanks to the contributions of leaders like Andres Esteban, Scott Epstein, Martin Tobin, and Wes Ely, we may have harvested our biggest scientific gains and future studies will yield diminishing marginal returns.

Monitoring to aid in effecting repairs to expedite successful liberation

Perhaps the most neglected area in weaning research is how to identify components of the cardiopulmonary system that have initiated or led to continued need of mechanical ventilation. One important study by Smyrniotis and colleagues [57] examined the efficacy of a combined intervention to define readiness through daily interrogation (with SBTs) and an algorithmic approach to identifying and repairing reversible causes of respiratory failure. Mortality was nearly lower (28% versus 32%; $P = .06$) despite higher APACHE II scores. ICU length of stay decreased markedly (from 30.5 to 20.3 days), patient ventilator-days decreased (23.9 to 17.5 days) and over \$3 million was saved. The high mortality, length of stay, and duration of ventilation relative to other hospitals makes this study difficult to generalize. Nonetheless, the study suggests that outcomes are improved with daily systematic attention to reversible processes contributing to respiratory failure. Since such a strategy depends entirely on monitored variables, the following should be measured every day a patient remains on a ventilator to persevere at identifying and repairing patients' diatheses until they can breathe without the ventilator and endotracheal tube. While only the above-cited study

can be used to justify this approach, it is patient-focused [8] and has little or no additional cost.

Assessment of ventilation: neuromuscular capacity versus loads

Total work of breathing consists of resistive and elastic pressure components. So $P_{tot} = P_{peak} = P_r + P_e$, where $P_r = \text{Flow} \times \text{Resistance}$ and $P_e = \text{Elastance} \times \text{Volume}$. Accordingly, during quiet volume-cycled breathing, stiffness and resistance of breathing can be computed. Most new ventilators can measure/compute these values without manipulation. However, they can be performed manually by measuring with constant flow of 60 L/min (1 L/s) so $P_{peak} (\text{peak pressure}) - P_{plat} (\text{plateau pressure}) = R_{aw} (\text{airways resistance})$ (since flow is 1 L/s), and compliance = tidal volume/ $P_{plat} - \text{PEEP}$ (= 1/elastance). Normal airway resistance in patients with size 7- to 8-mm endotracheal tubes is less than 15 cmH₂O/L/s and normal respiratory compliance around 50 mL/cmH₂O. Minute ventilation, the third respiratory load, is normally around 5 to 6 L/min. So every day a patient remains on the ventilator clinicians should seek to quantify and treat reversible causes of increased load. Increased resistance can be reduced by removing excessive secretions and administering aerosolized bronchodilators. Systemic corticosteroids can be used in patients with acute exacerbations of obstructive lung disease and/or when resistance remains high despite aerosolized medications. Reversible causes of system hyperelastance include pulmonary edema, pneumonia, dynamic hyperinflation due to high resistance (each of which cause increased lung elastance), and large effusions or ascites (each of which cause increased chest wall elastance). The third load of breathing is minute ventilation—not a mechanical load in itself, but a higher minute ventilation requires more mechanical work. Increased minute ventilation occurs when CO₂ production is excessive as in systemic inflammatory response syndromes/sepsis, withdrawal syndromes and overfeeding, or when dead space is increased as in alveolar hypertension, hypovolemia, pulmonary embolus, or emphysema.

Neuromuscular weakness can be identified and quantified by measuring a maximal inspired pressure (should be < -30 cmH₂O). Reasons for weakness include neurologic problems that are usually syndromic (eg, excessive sedatives, amyotrophic lateral sclerosis, polio, Guillain Barre, myasthenia) or, more commonly, because of muscle dysfunction. Chronic overloading of the muscles (monitor ventilator-induced fatigue with waveforms; see paragraph on patient-ventilator interactions), sepsis (monitor with white cell counts and fever curves), oversedation [58], corticosteroids, magnesium and phosphorus depletion, malnutrition (monitor pre-albumin), and deconditioning frequently contribute to prolonged ventilator dependence. Neuromuscular disease associated with severe inflammation/sepsis/corticosteroids may also contribute to respiratory muscle weakness. Phrenic nerve dysfunction and unilateral diaphragmatic dysfunction may also complicate cardiac surgery.

Box 1. Reversible contributors to ventilator dependence—prioritized, roughly, in order of importance/frequency as impediments to weaning success

Improve Neuromuscular Capacity

- Treat sepsis*
- Reduce sedatives and narcotics to least needed to awaken rapidly without agitation (consider using ultra-short-acting agents in anticipation of SBTs)
- Avoid exhausting breathing trials (stop trials or add more support if frequency persistently >35/min)
- Eliminate *excess* work of breathing during fully supported breathing (preferably by using ventilator mode and settings – flow characteristics, tidal volume – that promote synchrony/comfort)
- Nutritional support without overfeeding (aim to achieve a normal prealbumin)
- Identify and treat cardiac ischemia in vulnerable patients (eg, SBT failure with new wheezing)
- Replace K^+ , Mg^{2+} , PO_4^{3-} to normal
- Limit use of neuromuscular blocking drugs to only if absolutely necessary (eg, ARDS with high PEEP or life-threatening status asthmaticus)
- Consider stopping aminoglycosides and reducing corticosteroids
- Consider rare causes including:
Neurologic disease/occult seizures
Hypothyroidism
Critical illness myopathy/polyneuropathy

Reduce Respiratory Load

Resistance

- Bronchodilators
- Remove excess airway secretions
- Corticosteroids only if aerosolized bronchodilators fail to reduce Raw <20 cmH₂O
- Treatment of upper airway obstruction due to edema (eg, corticosteroids)

Elastance

- Treat pulmonary edema (proactively retrieve excess salt/water with diuretics)
- Treat pneumonia
- Reduce intrinsic PEEP with bronchodilators and corticosteroids if necessary

- Drain large pleural effusions
- Decompress abdominal distention and drain large ascites
- Evacuate pneumothoraces

Minute volume

- Treat sepsis*
- Antipyretics
- Correct metabolic acidosis
- Resuscitate shock and hypovolemia
- Reduce intrinsic PEEP (contributing to dead space) with bronchodilators
- Maintain least PEEP possible
- Identify and treat pulmonary embolism
- Avoid overfeeding

Improve Oxygenation

- Attention to fluid balance and retrieval of fluid in recovery phase of illness
- Identify and treat pneumonias *early*
- Identify and treat atelectasis (with sighs, tidal volumes sufficient to recruit without overdistending; eg, tidal volume yielding $P_{plat} = 20\text{--}25\text{ cmH}_2\text{O}$; or intermittent positive pressure breathing when atelectasis complicates extubation)
- Identify and treat cardiac ischemia if contributing to SBT failure

* Note that sepsis occurs on both sides of the capacity-load imbalance and is the most serious and common impediment to weaning success. Sepsis potentially reduces neuromuscular capacity (regression of weaning progress may precede fever, tachycardia, or leukocytosis) and increases loads through fever and hypermetabolism. Since sepsis is among the most common serious diatheses causing or complicating critical illness, it should be identified early, through low index of suspicion, and treated empirically pending results of microbiologic work-up.

It is also important to note that the patient-ventilator interaction may adversely affect the patient on a number of levels. First, excessive sedation administered to facilitate ventilation may inadvertently prolong ventilator dependence [58], so monitoring the Ramsay or Richmond agitation sedation scale (RASS) scores to provide the least sedative needed to maintain patient-ventilator synchrony is essential. Daily awakenings are absolutely necessary when constant infusions are used. We use intermittent bolus sedation titrated to RASS of 0 in most of our patients to avoid overdosing. We also suggest anticipating when a patient is going to begin SBTs and exchange sedation to ultra-short-acting medications (eg, propofol) to obviate the hangover effect that can occur with benzodiazepines.

Those unfamiliar with patient-ventilator interactions often view the ventilator as de facto rest. Unfortunately, the ventilator can “whip” the patient even in “rest” (eg, assist control) mode. Coughing and “bucking” breaths (eg, patient attempts to inhale during ventilator exhalation phase) can be detected simply by observing the patient at the bedside. More subtle signs of ventilator-induced work of breathing may include large negative deflections of intrathoracic pressure (on venous pressure monitors) during assisted inspirations or abnormal pressure-volume loops in the ventilator mechanics display [59]. Intrinsic PEEP that occurs commonly in patients with obstructive lung disease may cause excessive work of breathing through “trigger asynchrony” and can be detected crudely by observing the patient for inspiratory efforts not sensed by the ventilator (attempted breath against closed inspiratory valve). Kress and colleagues [60] identified an elegant physical examination technique for identification of intrinsic PEEP. Intrinsic PEEP is sometimes detected on flow-time curves on ventilator displays (ie, expiratory flow continues at initiation of subsequent breaths), which can then be quantified using expiratory hold maneuvers in appropriately relaxed patients.

The goal is to quantify loads and reasons for neuromuscular dysfunction daily, and to systematically repair what is broken until the patient can breathe without the ventilator. Rapid shallow breathing during an SBT is the sign of capacity-load imbalance and requires meticulous measurements of load and capacity, and systematic review for reversible contributors to ventilator dependence.

Assessment of oxygenation

It is appropriate to monitor the $\text{PaO}_2/\text{FiO}_2$ daily to detect changes (good or bad) that may require therapeutic responses. For example, a drop in the $\text{PaO}_2/\text{FiO}_2$ with a new focal lung infiltrate and fever often points to pneumonia, whereas diffuse infiltrates most often suggest pulmonary edema (cardiogenic or noncardiogenic). Increasing evidence suggests that fluid balance may impact duration of respiratory failure [44,61,62]. Monitoring daily and cumulative inputs and outputs may help clinicians to appreciate patients' potential for developing pulmonary edema during SBT. Cardiogenic pulmonary edema is a common reason for failure [2,3] and occurs because during SBTs venous return increases as mean systemic pressure increases and right atrial pressure decreases. Both authors aggressively seek to retrieve salt/water that has been administered during the resuscitation phase of illness—diuresing patients during the recovery phase as tolerated by the kidneys (signaled by increasing blood urea nitrogen). This approach has not been scientifically validated, but is predicated upon common sense and recent data [60,63].

Airway competence

Common causes of increased airway secretions include pneumonia and tracheobronchitis for purulent secretions and cardiogenic pulmonary edema

for watery, sometimes lightly blood-tinged secretions. Weak cough may be caused by neurologic injury (eg, stroke), medications (eg, sedatives, opioids), or infections. Inability to follow simple commands most often results from neurologic injury or medications.

This list of common causes of reversible contributors to respiratory failure (Box 1) and airway incompetence is not exhaustive; however, it emphasizes the point that in any given patient, a multitude of factors contribute to ventilator dependence. Nearly all of these factors can be monitored either with laboratories, ventilator measurements, or radiographs. Indeed there are not sufficient data to prove that attention to these details will hasten recovery from respiratory failure. However, common sense and the study by Smyrniotis and colleagues [57] suggest that systematic, vigorous repair and daily interrogation of readiness is most likely to expedite successful liberation. Most of these reversible factors are measured routinely in most ICUs and/or are relatively easy and inexpensive to obtain. In the absence of data, common sense should be enough justification to adopt such a strategy.

Summary

The reader may be struck by the “low-tech” nature of this review. Fancy gadgetry and monitoring may defer attention from the patient to numbers. Since no higher-tech monitoring has ever been shown to expedite patients’ liberation from mechanical ventilation, we believe in focusing on the patient. After all, the patient, not the ventilator, is broken [64]. To the extent that we have not even fully learned how to take advantage of the most elemental aspects of monitoring to enhance patients’ outcomes, a minimalist approach to monitoring is probably most appropriate until we learn how to use what we’ve got or studies demonstrate a “magic bullet.” To be transfixed by fancy, high-tech monitors misses the point. It behooves us to maintain our focus and energies on reversing the pathophysiologic processes that bind patients to the ventilator. And when they are sufficiently reversed, patients, who after all have breathed for decades without assistance, will most often be successfully liberated. While future research suggested in this article may help refine decision making, there will never be a perfect test or monitored variable that predicts with certainty outcomes of TOEs. Nevertheless, bedside clinicians can apply data as it becomes available to seek the unreachable holy grail of weaning: to simultaneously minimize the duration of mechanical ventilation and achieve TOE success rates approaching 100%. Two decades of scholarship have validated the view of weaning, nay “liberation,” introduced by Hall and Wood [64]. Institutionalization of those findings in the form of hospital protocols and national standards of care for ventilator management will certainly save lives and reduce complications. While the panoply of variables that contribute to determining outcomes will prevent realization of a perfect monitored variable, clinical science is the best hope of improving our decision making and enhancing the outcomes of our patients.

References

- [1] Mutlu GM, Factor P. Complications of mechanical ventilation. *Respir Care Clin N Am* 2000;6(2):213–52, [v].
- [2] Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest* 1997;112(1):186–92.
- [3] Epstein SK. Endotracheal extubation. *Respir Care Clin N Am* 2000;6(2):321–60, [vi].
- [4] Meade M, Guyatt G, Cook D, et al. Predicting success in weaning from mechanical ventilation. *Chest* 2001;120(Suppl 6):400S–24S.
- [5] Meade M, Guyatt G, Sinuff T, et al. Trials comparing alternative weaning modes and discontinuation assessments. *Chest* 2001;120(Suppl 6):425S–37S.
- [6] Meade M, Guyatt G, Griffith L, et al. Criteria for weaning from mechanical ventilation. *AHRQ HSTAT: National Library of Medicine*; 2007.
- [7] Epstein SK. Weaning parameters. *Respir Care Clin N Am* 2000;6(2):253–301, [v–vi].
- [8] Raju P, Manthous CA. The pathogenesis of respiratory failure: an overview. *Respir Care Clin N Am* 2000;6(2):195–212, [v].
- [9] MacIntyre NR, Cook DJ, Ely EW Jr, et al. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest* 2001;120(Suppl 6):375S–95S.
- [10] Tanios MA, Nevins ML, Hendra KP, et al. A randomized, controlled trial of the role of weaning predictors in clinical decision making. *Crit Care Med* 2006;34(10):2530–5.
- [11] Manthous CA, Hall JB, Kushner R, et al. The effect of mechanical ventilation on oxygen consumption in critically ill patients. *Am J Respir Crit Care Med* 1995;151(1):210–4.
- [12] Da Silva N, Teixeira C, Tonietto T, et al. Norepinephrine use at the time of extubation was not associated with weaning failure from mechanical ventilation in septic patients. *Critical Care* 2006;10(Suppl 1):46.
- [13] Lemaire F, Teboul JL, Cinotti L, et al. Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. *Anesthesiology* 1988;69(2):171–9.
- [14] Srivastava S, Chatila W, Amoateng-Adjepong Y, et al. Myocardial ischemia and weaning failure in patients with coronary artery disease: an update. *Crit Care Med* 1999;27(10):2109–12.
- [15] Kress JP, Vinayak AG, Levitt J, et al. Daily sedative interruption in mechanically ventilated patients at risk for coronary artery disease. *Crit Care Med* 2007;35(2):365–71.
- [16] Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *N Engl J Med* 1995;332(6):345–50.
- [17] Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med* 1996;335(25):1864–9.
- [18] Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med* 1991;324(21):1445–50.
- [19] Khamies M, Raju P, DeGirolamo A, et al. Predictors of extubation outcome in patients who have successfully completed a spontaneous breathing trial. *Chest* 2001;120(4):1262–70.
- [20] Brochard L, Rauss A, Benito S, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1994;150(4):896–903.
- [21] Amoateng-Adjepong Y, Jacob BK, Ahmad M, et al. The effect of sepsis on breathing pattern and weaning outcomes in patients recovering from respiratory failure. *Chest* 1997;112(2):472–7.
- [22] Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;340(6):409–17.

- [23] Esteban A, Alia I, Tobin MJ, et al, Spanish Lung Failure Collaborative Group. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. *Am J Respir Crit Care Med* 1999;159(2):512–8.
- [24] Esteban A, Alia I, Gordo F, et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. The Spanish Lung Failure Collaborative Group. *Am J Respir Crit Care Med* 1997;156(2 Pt 1):459–65.
- [25] Shen HN, Lin LY, Chen KY, et al. Changes of heart rate variability during ventilator weaning. *Chest* 2003;123(4):1222–8.
- [26] Jubran A, Mathru M, Dries D, et al. Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof. *Am J Respir Crit Care Med* 1998;158(6):1763–9.
- [27] Zakyntinos S, Routsi C, Vassilakopoulos T, et al. Differential cardiovascular responses during weaning failure: effects on tissue oxygenation and lactate. *Intensive Care Med* 2005;31(12):1634–42.
- [28] Frazier SK, Stone KS, Moser D, et al. Hemodynamic changes during discontinuation of mechanical ventilation in medical intensive care unit patients. *Am J Crit Care* 2006;15(6):580–93 [quiz: 594].
- [29] Mohsenifar Z, Hay A, Hay J, et al. Gastric intramural pH as a predictor of success or failure in weaning patients from mechanical ventilation. *Ann Intern Med* 1993;119(8):794–8.
- [30] Uusaro A, Chittock DR, Russell JA, et al. Stress test and gastric-arterial PCO₂ measurement improve prediction of successful extubation. *Crit Care Med* 2000;28(7):2313–9.
- [31] Maldonado A, Bauer TT, Ferrer M, et al. Capnometric recirculation gas tonometry and weaning from mechanical ventilation. *Am J Respir Crit Care Med* 2000;161(1):171–6.
- [32] Hurtado FJ, Beron M, Olivera W, et al. Gastric intramucosal pH and intraluminal PCO₂ during weaning from mechanical ventilation. *Crit Care Med* 2001;29(1):70–6.
- [33] Grasso S, Leone A, De Michele M, et al. Use of N-terminal pro-brain natriuretic peptide to detect acute cardiac dysfunction during weaning failure in difficult-to-wean patients with chronic obstructive pulmonary disease. *Crit Care Med* 2007;35(1):96–105.
- [34] Mekontso-Dessap A, de Prost N, Girou E, et al. B-type natriuretic peptide and weaning from mechanical ventilation. *Intensive Care Med* 2006;32(10):1529–36.
- [35] Pinsky MR. Cardiovascular issues in respiratory care. *Chest* 2005;128(5 Suppl 2):592S–7S.
- [36] Chatila W, Ani S, Guaglianone D, et al. Cardiac ischemia during weaning from mechanical ventilation. *Chest* 1996;109(6):1577–83.
- [37] Hurford WE, Favorito F. Association of myocardial ischemia with failure to wean from mechanical ventilation. *Crit Care Med* 1995;23(9):1475–80.
- [38] Frazier SK, Brom H, Widener J, et al. Prevalence of myocardial ischemia during mechanical ventilation and weaning and its effects on weaning success. *Heart Lung* 2006;35(6):363–73.
- [39] DeHaven CB, Kirton OC, Morgan JP, et al. Breathing measurement reduces false-negative classification of tachypneic preextubation trial failures. *Crit Care Med* 1996;24(6):976–80.
- [40] Khamiees M, Amoateng-Adjepong Y, Manthous CA. Propofol infusion is associated with a higher rapid shallow breathing index in patients preparing to wean from mechanical ventilation. *Respir Care* 2002;47(2):150–3.
- [41] Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1997;155(3):906–15.
- [42] Chatila W, Jacob B, Guaglianone D, et al. The unassisted respiratory rate-tidal volume ratio accurately predicts weaning outcome. *Am J Med* 1996;101(1):61–7.
- [43] Kuo PH, Wu HD, Lu BY, et al. Predictive value of rapid shallow breathing index measured at initiation and termination of a 2-hour spontaneous breathing trial for weaning outcome in ICU patients. *J Formos Med Assoc* 2006;105(5):390–8.
- [44] Frutos-Vivar F, Ferguson ND, Esteban A, et al. Risk factors for extubation failure in patients following a successful spontaneous breathing trial. *Chest* 2006;130(6):1664–71.

- [45] Wysocki M, Cracco C, Teixeira A, et al. Reduced breathing variability as a predictor of unsuccessful patient separation from mechanical ventilation. *Crit Care Med* 2006;34(8):2076–83.
- [46] Bien MY, Hseu SS, Yien HW, et al. Breathing pattern variability: a weaning predictor in postoperative patients recovering from systemic inflammatory response syndrome. *Intensive Care Med* 2004;30(2):241–7.
- [47] Salam A, Smina M, Gada P, et al. The effect of arterial blood gas values on extubation decisions. *Respir Care* 2003;48(11):1033–7.
- [48] Niehoff J, DelGuercio C, LaMorte W, et al. Efficacy of pulse oximetry and capnometry in postoperative ventilatory weaning. *Crit Care Med* 1988;16(7):701–5.
- [49] Morley TF, Giaimo J, Maroszan E, et al. Use of capnography for assessment of the adequacy of alveolar ventilation during weaning from mechanical ventilation. *Am Rev Respir Dis* 1993;148(2):339–44.
- [50] Saura P, Blanch L, Lucangelo U, et al. Use of capnography to detect hypercapnic episodes during weaning from mechanical ventilation. *Intensive Care Med* 1996;22(5):374–81.
- [51] Seymour CW, Christie JD, Gaughan CA, et al. Evaluation of a new method for measurement of minute ventilation recovery time. *Respir Care* 2006;51(2):133–9.
- [52] Martinez A, Seymour C, Nam M. Minute ventilation recovery time: a predictor of extubation outcome. *Chest* 2003;123(4):1214–21.
- [53] Smina M, Salam A, Khamiees M, et al. Cough peak flows and extubation outcomes. *Chest* 2003;124(1):262–8.
- [54] Coplin WM, Pierson DJ, Cooley KD, et al. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. *Am J Respir Crit Care Med* 2000;161(5):1530–6.
- [55] Namen AM, Ely EW, Tatter SB, et al. Predictors of successful extubation in neurosurgical patients. *Am J Respir Crit Care Med* 2001;163(3 Pt 1):658–64.
- [56] Salam A, Tilluckdharry L, Amoateng-Adjepong Y, et al. Neurologic status, cough, secretions and extubation outcomes. *Intensive Care Med* 2004;30(7):1334–9.
- [57] Smyrniotis NA, Connolly A, Wilson MM, et al. Effects of a multifaceted, multidisciplinary, hospital-wide quality improvement program on weaning from mechanical ventilation. *Crit Care Med* 2002;30(6):1224–30.
- [58] Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000;342(20):1471–7.
- [59] MacIntyre NR. Respiratory mechanics in the patient who is weaning from the ventilator. *Respir Care* 2005;50(2):275–86 [discussion: 284–6].
- [60] Kress JP, O'Connor MF, Schmidt GA. Clinical examination reliably detects intrinsic positive end-expiratory pressure in critically ill, mechanically ventilated patients. *Am J Respir Crit Care Med* 1999;159(1):290–4.
- [61] Upadaya A, Tilluckdharry L, Muralidharan V, et al. Fluid balance and weaning outcomes. *Intensive Care Med* 2005;31(12):1643–7.
- [62] Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354(24):2564–75.
- [63] Bardoczky GI, d'Hollander AA, Cappello M, et al. Interrupted expiratory flow on automatically constructed flow-volume curves may determine the presence of intrinsic positive end-expiratory pressure during one-lung ventilation. *Anesth Analg* 1998;86(4):880–4.
- [64] Hall JB, Wood LD. Liberation of the patient from mechanical ventilation. *JAMA* 1987;257(12):1621–8.

Severity of Illness and Organ Failure Assessment in Adult Intensive Care Units

Bekele Afessa, MD^{a,*}, Ognjen Gajic, MD^a,
Mark T. Keegan, MB, MRCPI^b

^a*Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine,
200 First Street, SW, Rochester, MN 55905, USA*

^b*Department of Anesthesia, Mayo Clinic College of Medicine, 200 First Street, SW,
Rochester, MN 55905, USA*

The cost of providing critical care services increased from \$19.1 billion to \$55.5 billion in the United States between 1985 and 2000 [1]. Federal, state, and private health care insurers, professional organizations, and accreditation agencies have started focusing on the quality of care provided to patients. Some states compare hospitals by publishing adverse events, often without adjustment for hospital size or patients' severity of illness. As a result of these pressures, it has become obsolete to practice medicine without implementing process improvement measures and assessing clinical outcome. However, performance measurements and the assessment of clinical outcome require appropriate risk adjustment. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has proposed severity adjusted mortality rate as a specific measure that should be recorded [2]. Aside from external pressures, monitoring and improvement of quality is important to clinicians. The creation of a data collection and reporting system, using prognostic models, helps to provide accurate baseline data and to document improvement [3]. In addition to their use for performance improvement, the ICU prognostic models have been used to measure the severity of illness and demonstrate equivalency of groups in trials of critically ill patients for over 2 decades.

The first ICU model of disease severity, the Therapeutic Intervention Scoring System (TISS), was proposed in 1974 [4]. During the past 25 years,

B.A. was supported by Mayo Clinic Critical Care Research fund and Department of Medicine, Quality QUEST.

* Corresponding author.

E-mail address: afessa.bekele@mayo.edu (B. Afessa).

several physiologic-based ICU prognostic models have emerged. Most of the prognostic models focus on hospital mortality. In addition to the outcome prediction models, there are several models that assess selected organ functions. The main adult ICU severity-of-illness models are Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), and Mortality Probability Model (MPM) (Table 1). The main adult organ failure models are the Multiple System Organ Failure (MSOF) score [5,6], Multiple Organ Dysfunction Score (MODS) [7], Sequential Organ Failure Assessment (SOFA) score [8], and Logistic Organ Dysfunction Score (LODS) (see Table 1) [9]. SOFA is the most widely used organ failure model. Recent reviews have addressed the older severity-of-illness and the various organ failure models [10,11]. This review will focus on the most important and most recent adult severity-of-illness models and SOFA. We will not discuss the science of artificial neural networks since it is rarely used in clinical trials, clinically, or for benchmarking.

Severity-of-illness models

Model creation

Development of a prognostic model requires the identification of reliable predictive variables, precise definition of predictor and outcome variables, collection of data on the predictive and outcome variables, analysis of the relationship between the predictor and outcome variables, and validation of this relationship in a new independent database [12]. Predictor variables

Table 1
The main adult severity-of-illness and organ dysfunction assessment models

Model	Purpose
APACHE	Prediction of: • ICU and hospital mortality • ICU and hospital length of stay • Duration of mechanical ventilation • Risk of needing an active treatment during ICU stay • Probability of pulmonary artery catheter use • Potential transfer from ICU
SAPS	Prediction of hospital mortality
MPM	Prediction of hospital mortality
SOFA [8]	Assessment of organ dysfunction
MODS [7]	Assessment of organ dysfunction
LODS [9]	Assessment of organ dysfunction
MSOF [5,6]	Assessment of organ dysfunction

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; LODS, Logistic Organ Dysfunction Score; MODS, Multiple Organ Dysfunction Syndrome; MSOF, Multiple System Organ Failure; MPM, Mortality Probability Model; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

entered in a model should be routinely available, reliable, and independent of ICU intervention to eliminate treatment effect.

The predictor variables in the adult ICU prediction models are selected and scored subjectively by expert consensus or objectively using statistical methods. The predictor variables consist of age, comorbidities, physiological abnormalities, acute diagnoses, and lead-time bias. In addition to short-term mortality, the APACHE III model has included length of ICU and hospital stay, duration of mechanical ventilation, and need for active treatment as outcome measures [13–15]. To be generalizable, the development of an ICU prognostic model requires a large database compiled from representative ICUs. The models should include the main prognostically important predictor variables that should be tested for their independent contributions and interactions. If the validation sets originate from the same population as the development sets, the results may not be reproducible in other populations.

Model performance

Outcome prediction models need to be subjected to the same scrutiny as drugs and technology before they are used in decisions that impact health care delivery and individual patient care. A mortality prognostic model must differentiate between survivors and nonsurvivors, and be well calibrated (accurate throughout all risk ranges) and reliable (provide identical and reproducible estimates for an individual patient independent of the observer) [16]. It also has to be dynamic, reflecting the change in treatment and case mix over time. The performance of the ICU prognostic models is usually assessed by the area under the receiver operating characteristic curve (AUC) for discrimination and Hosmer-Lemeshow [12] statistic for calibration. Some advocate the addition of R^2 as part of model evaluation. The AUC is the measure of how well a model differentiates between groups, for example survivors from nonsurvivors (Table 2). Calibration refers to the correlation between the predicted and actual outcome for the entire range of risk and it is assessed by the Hosmer-Lemeshow [17] H or C goodness-of-fit statistic. This is usually done by grouping patients into

Table 2
Discrimination levels based on the AUC

AUC	Level of discrimination
1.00	Perfect
0.90–0.99	Excellent
0.80–0.89	Very good
0.70–0.79	Good
0.60–0.69	Moderate
<0.60	Poor

Abbreviation: AUC, Area under the receiver-operating characteristic curve.

10 deciles of risks. The calibration is considered good if the Hosmer-Lemeshow statistic P value is greater than .05 and the C or H statistic is close to the degrees of freedom (usually 8). The Hosmer-Lemeshow [18] statistic is affected by sample size. The P value will be small in very large samples and the opposite in small samples leading to inappropriate estimation of the calibration [19]. R^2 represents the proportion of outcome variance explained by the model. Most models have R^2 of 0.045 to 0.388 [12]. The upper limit of R^2 is 1.

Customization

Because of changes in case-mix, the performances of prognostic models deteriorate over time. To counterbalance the deterioration, models are often subjected to customization by creating a new equation (level 1) or changing the weights of the constituent variables (level 2) [20,21]. At times, the addition of new predictor variables may be needed during customization [22,23].

Specific models

The ICU prognostic models are divided into four generations (Table 3).

First generation: APACHE I

The development of APACHE I was based on 805 patients from 2 medical centers in the United States [24]. The APACHE I model consisted of 34 physiologic variables and preadmission health status. The variables were selected and assigned scores by an expert clinician panel. Missing values were considered normal. The most abnormal value for each variable in the first 32 hours after ICU admission was used for scoring. Since the APACHE I approach to mortality prediction was new at that time, it was not subjected to the currently accepted discrimination and calibration metrics.

Second generation

APACHE II. APACHE II was developed on data from 5815 patients in 13 hospitals from the United States [25]. The model consisted of 12 physiologic measurements, age, previous health status, and ICU admission diagnosis. The 12 physiologic variables were heart rate, mean arterial blood pressure,

Table 3
The four generations of the ICU severity prognostic models

First generation	Second generation	Third generation	Fourth generation
APACHE I [24]	APACHE II [25]	APACHE III [28]	APACHE IV [36]
	SAPS I [26]	SAPS II [30]	SAPS III [34,35]
	MPM I [27]	MPM II [31]	MPM III [33]

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; MPM, Mortality Probability Model; SAPS, Simplified Acute Physiology Score.

temperature, respiratory rate, alveolar to arterial oxygen tension gradient, hematocrit, white blood cell count, creatinine, sodium, potassium, pH/bicarbonate, and Glasgow Coma Scale (GCS) score. The collection time limit was reduced to 24 hours after ICU admission. The total APACHE II scores range from 0 to 71. Different weights were given for postoperative admission diagnoses and adjustment was made for emergency surgery. The AUC of APACHE II was 0.863. No goodness-of-fit testing was reported.

SAPS I. SAPS I was developed on data from 679 patients admitted to eight ICUs in France [26]. The model included age and 13 physiologic variables. The 13 physiologic variables were heart rate, systolic blood pressure, temperature, respiratory rate/mechanical ventilation, urine output, blood urea nitrogen, hematocrit, white blood cell count, glucose, potassium, sodium, bicarbonate, and GCS score. The model was based on the most abnormal physiologic values in the first 24 hours after ICU admission. The AUC of SAPS I was 0.85. No goodness-of-fit testing was reported.

MPM I. The MPM I model was created from a small number of easily available variables [27]. The development model was derived from data of 755 patients from the ICU of a single medical center. MPM I assigned weights to the predictor variables based on statistical techniques, rather than expert opinions [27]. MPM I had two models: MPM₀ I, based on data obtained at ICU admission, and MPM₂₄ I, based on data obtained within 24 hours of ICU admission. MPM₀ I included seven predictor variables: age, systolic blood pressure, level of consciousness, type of admission, cancer, infection, and number of organ system failures. The variables included in the MPM₂₄ I were age, type of admission, level of consciousness, infection, inspired oxygen fraction, shock, and number of organ system failures. None of the seven MPM₀ I variables was treatment dependent. The discrimination and calibration of the model were good.

Third generation

APACHE III. APACHE III was developed from a database of 17,440 patients from 66 hospitals, 26 of them randomly selected to represent hospitals in the United States with more than 200 beds [28]. The model included age, chronic health conditions, acute physiology score, admission diagnosis category, and patients' location before ICU admission, as a measure of lead-time bias. Seventeen physiologic variables were included in the APACHE III model: heart rate, mean arterial pressure, respiratory rate, temperature, GCS, urine output, hematocrit, white blood cell count, glucose, sodium, creatinine, blood urea nitrogen, albumin, bilirubin, arterial pH, arterial oxygenation, and arterial carbon dioxide tension. The Acute Physiology Score (APS) was calculated based on the most abnormal values of the physiologic variables in the first 24 hours of the patient's ICU stay. The chronic health conditions included AIDS, lymphoma, hepatic failure, metastatic

cancer, leukemia/multiple myeloma, cirrhosis, and immunosuppression. If a patient had multiple chronic conditions, the one with the worst score was used. The APACHE III score is the sum of APS, age score and chronic health condition score, and ranges from 0 to 299. Seventy-eight major disease categories were assigned weights by multivariate logistic regression analysis. The AUC of APACHE III was 0.90. The overall explanatory power of APACHE III for hospital mortality as measured by R^2 was 0.41. The calibration was not reported in the original study but appeared to be poor when tested in an independent data set [29]. The APACHE investigators also developed a real-time ICU database and scoring system that could be deployed in individual institutions and interfaced with existing ICU information systems. Despite its excellent performance and potential for use, APACHE III was narrowly disseminated because the logistic regression coefficients and equations were proprietary and unavailable for the public unless with permission for research. APACHE III has been externally validated in various populations with results showing consistently good discrimination but mixed calibration.

SAPS II. SAPS II was developed on a data set of 13,152 patients from 137 ICUs in 12 countries [30]. Seventeen variables were entered to create the SAPS II model: 12 physiologic variables, age, type of admission (scheduled surgical, unscheduled surgical, or medical) and three underlying disease variables (AIDS, metastatic cancer, and hematologic malignancy). The physiologic variables used the worst values of the first 24 hours in the ICU. The weights for each variable were estimated using multiple logistic regression analysis. The AUC of SAPS II was 0.88 for the development data set, and 0.86 for the validation set. The calibration was good. Subsequent studies with SAPS II showed good discrimination but poor calibration unless customized.

MPM II. The training and development sets of MPM₀ II included 12,610 and 6514 patients, respectively, from 12 countries [31]. Fifteen variables were used in the admission model, MPM₀ II: physiology (Coma/stupor, heart rate, systolic blood pressure), chronic diagnosis (chronic renal insufficiency, cirrhosis, metastatic cancer), acute diagnoses (acute renal failure, cardiac dysrhythmia, cerebrovascular accident, gastrointestinal bleeding, intracranial mass effect), and other (age, cardiopulmonary resuscitation before ICU admission, medical or unscheduled surgery admission, mechanical ventilation). The 13 variables entered in the 24-hour model, MPM₂₄ II: variables at admission (age, cirrhosis, intracranial mass effect, metastatic cancer, and medical or unscheduled surgery admission) and at 24-hour assessments (coma/stupor, creatinine, confirmed infection, mechanical ventilation, arterial oxygen tension, prothrombin time, urine output, and use of vasoactive drugs). The MPM₂₄ II model was developed on data from 10,357 patients still in the ICU at 24 hours. The AUC and calibration of

MPM₀ II and MPM₂₄ II were good. Well-performing models based on data collected at 48 hours, MPM₄₈ II, and 72 hours of ICU admission, MPM₇₂ II, have been subsequently developed for predicting mortality [32].

Fourth generation

A review of studies from several countries evaluating the performances of the old generation adult ICU prediction models has shown an overall good discrimination but poor calibration [11]. Customization was attempted to maintain good performance of the models over time. However, the initial improvement in the performance of the older models with customization was not maintained since the older models no longer reflected current case mix, practice patterns, and treatment necessitating the development of the fourth-generation models [33–36]. All three fourth-generation prognostic models excluded readmissions in their development and assumed values to be normal when not measured or obtained.

APACHE IV. APACHE IV was developed from data collected on 110,558 patients in 104 ICUs of 45 nonrandomly selected hospitals in the United States (Table 4) [36]. Exclusion criteria include age under 16 years, ICU length of stay less than 4 hours or more than 365 days, burn, transfer from another ICU, and admission after transplant (except kidney and liver). The study patients were randomly split into development (60%) and validation (40%) subsets. Among the fourth-generation models, APACHE IV included the largest number of variables (Tables 4 and 5). The APS variables and the seven chronic conditions of APACHE IV were the same as those of APACHE III. The number of ICU admission diagnostic categories was increased from 78 in APACHE III to 116 (see Table 5). Similar to APACHE III, the APS of APACHE IV is based on the worst values obtained within 24 hours of ICU admission and ranges from 0 to 252. However, the data were subjected to a more robust statistical analysis with added spline terms to develop a model with a superior performance. Unlike APACHE III, age, APS, and chronic health were each given a separate coefficient to calculate the probability of death in APACHE IV. The discrimination of APACHE IV was very good with good calibration (see Table 4). APACHE IV used a different data set for calculating the probability of death of patients admitted to the ICU following coronary artery bypass graft. For patients admitted for acute myocardial infarction, a variable for thrombolysis therapy was added. The explanatory powers of the APACHE IV model were due to acute physiology (65.6%), age (9.4%), chronic health conditions (5.0%), admission variables (2.9%), ICU admission diagnosis (16.5%), and mechanical ventilation (0.8%).

SAPS III. SAPS III was developed from data of 16,784 patients in 303 ICUs from five continents (see Table 4) [34,35]. The hospitals volunteered to participate in the model development. Patients under age of 16 years

Table 4
Study characteristics and performance of the fourth-generation prognostic models

Characteristics	SAPS III [34,35]	APACHE IV [36]	MPM ₀ III [33]
Study population	16,784	110,558	124,855
Study period	14 Oct–15 Dec 2002	1 Jan 2002–31 Dec 2003	Oct 2001–Mar 2004
Number of ICUs	303	104	135
Number of hospitals	281	45	98
Geographic regions	35 countries, 5 continents	USA	USA
Time of data collection	±1 h of ICU admission	24 h of ICU admission	Within 1 h of ICU admission
Variables in the model	20	142	16
Missing data	1 per patient		
Reliability	Excellent		
AUC	0.848	0.880	0.823
H-L C statistic	14.29	16.90	11.62
H-L P value	.16	.08	.31
SMR	1.000	0.997	1.018

Abbreviations: AUC, Area under the receiver-operating characteristic curve; H-L, Hosmer-Lemeshow; SMR, Standardized mortality ratio.

were excluded. For cross validation, the model-building process was run five times, using 80% of randomly selected data for development and the remaining 20% for validation. The SAPS III model includes fewer variables than APACHE IV (see [Tables 4 and 5](#)). The model was based on data obtained within 1 hour of a patient’s admission to the ICU. SAPS III was subjected to a robust statistical analysis. Unlike APACHE IV, the explanatory powers of the SAPS III model were mostly attributable to the patients’ characteristics before ICU admission (50.0%) and the circumstances of ICU

Table 5
Variables included in the fourth-generation prognostic models

Predictive variables	SAPS III [34,35]	APACHE IV [36]	MPM ₀ III [33]
Age	Yes	Yes	Yes
Length of hospital stay before ICU admission	Yes	Yes	No
ICU admission source	3	8	No
Type of ICU admission	Yes	Yes	Yes
Chronic comorbidities	6	7	3
Cardiopulmonary resuscitation before ICU admission	No	No	Yes
Resuscitation status	No	No	Yes
Surgical status at ICU admission	Yes	Yes	No
Anatomical site of surgery	5	No	No
Reasons for ICU admission/Acute diagnosis	10	116	5
Acute infection at ICU admission	Yes	No	No
Mechanical ventilation	Yes	Yes	Yes
Vasoactive drug therapy before ICU admission	Yes	No	No
Clinical physiologic variables	4	6	3
Laboratory physiologic variables	6	10	0

admission (22.5%) and less dependent on the physiological abnormalities at ICU admission (27.5%).

MPM₀ III. MPM₀ III was developed from data of patients from the United States (see Table 4) [33]. The study patients were randomly split into development (60%) and validation (40%) subsets. Patients with cardiac surgery, acute myocardial infarction, burns, and those younger than 18 years were excluded. Only five acute diagnoses and three physiologic variables were included in the model (see Table 5). MPM₀ III was based on data obtained within 1 hour of ICU admission. MPM is the only fourth-generation model that includes “Do-Not-Resuscitate” status as a predictor variable. The discrimination of MPM₀ III was very good with good calibration (see Table 4).

Fourth-generation model comparisons. With the availability of three recently updated prognostic models, users have to make choices. Although the performances of all three models appear to be good, there are differences. Data for SAPS III were collected as part of a research project specifically designed to develop the model. The data for APACHE IV and MPM₀ III were obtained from ICUs that had bought the APACHE or Project Impact Critical Care systems (both owned by Cerner Corporation, Kansas City, MO) as part of their efforts for performance improvement. Since institutions that participated in the development of these models were not randomly selected and were likely to have more interest in research and performance improvement, the findings may not apply to other ICUs [37].

MPM₀ III and SAPS III are based on data obtained within 1 hour of ICU admission. Thus, they can be used to assess severity of illness before ICU interventions take place. They avoid contamination of data by patients who are allowed to deteriorate after ICU admission. All three fourth-generation models consider missing data as normal. Limiting data to those obtained within 1 hour of ICU admission may not adversely affect the performance of MPM₀ III since the variables included in the model are easily available and do not require special laboratory testing. However, the unavailability of some physiologic data may compromise the performance of SAPS III [38]. Because of the multiplicity of data to be collected, missing data have the highest impact on the performance of APACHE IV and lowest on MPM₀ III.

The predictors of MPM₀ III include age and 15 easily available binary variables (see Table 4). Only five acute diagnoses are included in the MPM₀ III model. The SAPS III model includes 20 variables (see Table 4), 6 of which require laboratory testing (see Table 5). APACHE IV consists of 142 predictor variables, 10 of them requiring laboratory testing. Vital signs, urine output, and GCS are almost always measured in critically ill patients. However, there is no standardized laboratory testing in most individual ICUs, let alone nationally or internationally. The lack of standardization may adversely affect the performance of ICUs that do not

routinely perform certain laboratory tests and may also compromise the performance of the prognostic models. Although the characteristics of MPM₀ III may help to minimize errors that may arise from the misclassification of the diagnosis and missing or incorrect data entry, the exclusion of prognostically important variables from the model may downgrade its performance.

Several ICUs use computer interfaces with their laboratory and bedside monitor systems to extract data. Others still enter data manually. SAPS III was calibrated for manual acquisition of data. The performance of ICUs as measured by the severity models and the performance of the prognostic models in predicting outcome are likely to be compromised by the lack of uniformity in data acquisition.

All patients included in the development of APACHE IV and MPM III were from the United States. In contrast, patients from five continents were included in the development of SAPS III, although most were from Europe. With its customized models, SAPS III appears to be a good candidate for an international benchmark; however, the number of patients included from some of the countries is small and the results may not be generalizable.

All three fourth-generation models need external validation in independent datasets. All three models are free of charge, which may help their use for research, health care delivery, and performance measure. However, APACHE IV is the most complex and may require software support. MPM₀ III is the least complex.

Knowledge about the probability of clinical outcome has the potential to help administrators, clinicians, and patients and their families select treatment options taking into account costs and potential benefits. However, the use of the prognostic models for such purposes requires caution. There are several factors that influence outcome and yet are not included in the prognostic models. Some of these factors such as patients' preferences for life support and response to disease, the surrounding environment, and effect of treatment are not easy to evaluate [11]. Despite their limitations, the predictive models have potential uses at the national, hospital, physician, and patient levels [12].

Benchmarking

Independent of physicians' resistance, health care professionals and institutions are going to be evaluated based on performance. Some have already started ranking ICUs based on their performances derived from administrative data [39]. Severity adjusted mortality rates are increasingly used to assess the quality of care provided by hospitals and physicians. Compared with the severity models derived from administrative data, the ICU adult prognostic models are better tools for risk adjustment in quality assessment. The fourth-generation models are well positioned for use as ICU benchmarks. Since mortality is the most objective measure, and not prone to

error, standardized mortality ratio (SMR) is widely used to evaluate performance. SMR is the ratio of the observed to predicted mortality. The SMR should be reported with its 95% confidence intervals (CI) [40]. If the 95% CI of the SMR includes 1, the performance is considered average. If the 95% CI does not include 1, SMRs less than 1 and more than 1 are considered to show good and poor performances, respectively.

Benchmarking helps to identify variations in clinical outcome and changes in practice patterns over time [41]. The appropriate application of benchmarking at the national and community levels may provide reliable information to insurers, health care providers, and patients. However, it requires support and pressure by state and federal governments, businesses, and hospitals and embracing by health care providers. Since case mix influences SMR [42], the performance of a prognostic model needs to be validated before its application for benchmarking in a specific group. Benchmarking provides opportunities to improve performance based on the findings from good and bad performers [43,44].

The use of adult ICU models for benchmarking should be limited to regions in which they have been shown to perform well. The fourth-generation models are based on data obtained 3 to 6 years ago. From the past 3 decades of experience with the adult ICU prognostic models, we have learned that their performances deteriorate over time. For appropriate benchmarking, the performances of the models need to be evaluated periodically and updated when needed.

Although the ICU prognostic models have focused on mortality, there are other important outcome measures that can be used for benchmarking. The APACHE prognostic system has models for predicting ICU length of stay [13,45] and duration of mechanical ventilation [14]. The APACHE III database also provides accessories to track low-risk monitor admissions and readmissions [44,46].

Performance improvement

Performance improvement requires data collection for measuring outcome, adjusted for confounding variables. A well-performing prognostic model helps to make meaningful comparisons of a hospital's current performance with its past. This will allow hospitals to identify their weaknesses and initiate interventions aimed at quality improvement and allow patients and third party payers to choose health care providers based on performance. Institutions that use the ICU prognostic models may have the advantage of meeting the JCAHO requirements for accreditation. The ICU severity models may also serve as tools for evaluation of the impact of new therapies as well as organizational and process of care changes [43,44,46].

The APACHE Critical Care series and Project Impact have taken the prognostic models to a higher level by adding accessories to track

readmission, sentinel event, TISS, reimbursement, and resource consumption [47]. They provide standard and customized reports of outcome regularly. Based on data from the APACHE III database, Zimmerman and colleagues [44] have highlighted the policies and practices of ICUs with low mortality rate and efficient resource use. Defining good performance by low SMR, short adjusted ICU length of stay, and low ICU admission rate for low-risk monitoring, they described the structural characteristics and process of care in ICUs with good performance.

Resource use

In theory, accurate estimation of severity of illness can facilitate appropriate allocation of scarce ICU resources. Unsalvageable patients and patients who require simple monitoring can be discharged from the ICU. However, current models are far from perfect to support such decisions and have not been validated for these purposes. Using APACHE III data, Seneff and colleagues [14] reported an accurate prediction of the average duration of mechanical ventilation for groups of ICU patients using an equation developed using multivariate regression techniques. If validation shows good performance, such predictions may be useful for resource allocation. Using demographic, physiologic, and treatment information obtained during the first 24 hours in the ICU and over the first 7 ICU days of the APACHE III database, Zimmerman and colleagues [15] identified low-risk patients who were unlikely to require active ICU treatment. Such capability can be used to assess ICU resource use and develop strategies for providing care in intermediate care units at a reduced cost. Even in the best performing ICUs, 10% to 38% of the admissions are for low-risk monitoring [44].

Clinical decision support

Although most prognostic models perform well at a population level, their poor calibration on an individual level has prevented their use at the bedside. Probabilities of hospital mortality provide meaningful information to physicians when discussing patient prognosis with patients and their families; however, use of probabilities should not be employed for making treatment decisions in individual patients [48]. Even severity-of-illness models demonstrating good agreement for describing patients in the aggregate do not perform as well for individual patients. Currently, most patients and their families rely on prognostic information given to them by the physicians to make decisions. However, because of the biases of subjective estimates, a physician's ability to correctly predict mortality is highly variable [49]. Overconfident physicians tend to underestimate mortality, whereas those who lack self-confidence tend to overestimate mortality [50]. Assessment of futility is another important potential application for the use of severity-of-illness systems. Trends in the severity of illness provide important

prognostic information [51]. In patients with high risk of death at ICU admission, lack of improvement in predicted mortality indicates poor prognosis [52,53]. Whether the addition of the probability of death derived from the prognostic models improves the clinicians' estimates awaits future studies. In the mean time, the probabilities derived from the prognostic models should be used as "the drunken man uses the lamppost, for support rather than illumination" in making clinical decision [54].

With the scarcity of ICU beds in many hospitals, avoiding unnecessary ICU admission and transferring patients who do not need ICU care are important. The ICU prognostic models have the potential to be used for decision support for these purposes. MPM₀ III and SAPS III have the potential to be used as decision support for ICU admission triage since most of their predictor variables are available at admission. Patients who are unlikely to require active ICU intervention can be identified and early transfer arranged. The Critical Care Series of the APACHE III clinical support system provides the risk of requiring specific critical care interventions, potential transfer from the ICU, and TISS score for individual patients [47]; however, the real impact of this clinical support system on clinical outcome has not been well described.

Limitations

There are several limitations inherent in the ICU prognostic models [55]. Biases and errors in case mix, errors in collecting and entering data, and flaws in model development and validation weaken the performance of prognostic models. A prognostic model accurately predicts mortality only if the case mix is similar to the one used in its development. There are several factors, including lead-time bias, pre-ICU location, acute diagnosis, physiologic reserve and patients' preferences for life support, that influence mortality. Most of these prognostically important variables are not included in some of the latest prognostic models. Although the models are unlikely to include all predictor variables, a balance needs to be struck between model simplicity and performance. Most importantly, long-term survival and quality of life, issues that may be more important than simple mortality, are not forecast by the prediction models.

Summary

We have reviewed some of the most commonly used severity-of-illness models for adult ICUs. Similar models exist for the pediatric populations and specific conditions, and many of the issues discussed here are also applicable to those models. Although we have outlined the potential uses of the newer models and their improved performance, their acceptance by health care providers and their impact on health care delivery and clinical outcome have yet to be realized.

The unavailability of a structured data acquisition system and the proprietary nature of APACHE III have been the main barriers for the dissemination of the ICU prognostic models. With the increased application of clinical information systems for data acquisition and decision support and the availability of all the fourth-generation prognostic models, including APACHE IV, in the public domain, these barriers have been reduced. If studies show the benefits of prognostic models in improving patient outcome and health care delivery, the time may come to use them for various purposes including for daily patient care. The ICU prognostic models may also help us to further understand the link between ICU severity of illness and long-term morbidity and mortality. More than a decade ago, the Rand group highlighted the importance of addressing the cost and feasibility of implementing predictive systems in hospitals and the extent to which the predictor and outcome variables included in the model are resistant to manipulation [12]. These issues are still pertinent and need to be addressed.

Organ failure models

Introduction/creation

Multiple organ failure is a major cause of morbidity and mortality in the ICU. The main treatment plans of critically ill patients depend on supporting failing organs. Initial and sequential assessments of the failing organs provide information about the patients' prognoses as well as the effectiveness of treatment. Several models have been developed to assess the degree of organ dysfunction [10]. Most organ failure assessment systems assign values to six organ systems: respiratory, cardiovascular, renal, hematology, hepatic, and central nervous system. These values can be dichotomous or continuous. Although the organ failure systems assess the same organs, the scorings are based on different cut points. The gastrointestinal and endocrine/metabolic systems are important in the critically ill; however, their functions have not been incorporated into scoring systems because of the complexity and difficulty of measuring them.

Organ dysfunction assessment models

One of the earliest organ failure assessment tools, MSOF, used dichotomous variables (Table 6) [5]. However, since organ failure is a process rather than an event, recent assessment tools use continuous scales [7–9]. The three currently used main organ failure scoring systems are MODS, SOFA, and LODS (Table 7) [7–9]. Most of the variables included in these systems are easily available and usually obtained regularly in the critically ill. SOFA (Table 8) and MODS assign scores ranging from 0 to 4, based on severity. MODS and SOFA scores were developed subjectively as a result of

Table 6
Multiple system organ failure [5,6]

Organ failure	Criteria
Cardiovascular	Heart rate $\geq 54/\text{min}$ Mean arterial pressure ≤ 49 mm Hg or systolic blood pressure < 60 mm Hg Ventricular tachycardia or fibrillation PH ≤ 7.24 with PaCO ₂ ≤ 49 mm Hg
Respiratory	Respiratory rate $\leq 5/\text{min}$ or $\geq 49/\text{min}$ PaCO ₂ ≥ 50 mm Hg Alveolar to arterial oxygen tension gradient ≥ 350 mm Hg Dependent on ventilator or CPAP on second day of OSF
Renal	Urine output $\leq 479/\text{mL}/24$ hours or ≤ 159 mL/8 hours Blood urea nitrogen ≥ 100 mg/dL Creatinine ≥ 3.5 mg/dL
Hematologic	White blood cell count $\leq 1000/\text{mm}^3$ Platelets $\leq 20,000/\text{mm}^3$ Hematocrit $\leq 20\%$
Neurologic	Glasgow coma score ≤ 6 (in the absence of sedation)

Abbreviations: CPAP, continuous positive airway pressure; OSF, organ system failure; PaCO₂, arterial CO₂ tension.

consensus and literature review. In contrast, LODS was derived from objective data subjected to robust statistical analysis [9]. LODS assigns scores to each organ based on their impacts on mortality, not on arbitrarily selected cut points. MODS differs from LODS and SOFA, by its use of

Table 7
Variables included in the calculation of the organ failure scores

Organ	Variable	SOFA [8]	LODS [9]	MODS [7]
Respiratory	PaO ₂ /FIO ₂	Yes	Yes	Yes
	MV	Yes	Yes	
Hematology	Platelets	Yes	Yes	Yes
	WBC		Yes	
Liver	Bilirubin	Yes	Yes	Yes
	Prothrombin time		Yes	
Cardiovascular	Mean arterial pressure	Yes		
	Systolic blood pressure		Yes	
	Heart rate		Yes	
	PAR			Yes
	Dopamine	Yes		
	Dobutamine	Yes		
	Epinephrine	Yes		
	Norepinephrine	Yes		
CNS	Glasgow coma score	Yes	Yes	Yes
Renal	Creatinine	Yes	Yes	Yes
	Blood urea nitrogen		Yes	
	Urine output	Yes	Yes	

Abbreviations: CNS, central nervous system; LODS, Logistic Organ Dysfunction System; MODS, Multiple Organ Dysfunction Score; MV, mechanical ventilation; PAR, pressure-adjusted heart rate; SOFA, Sequential Organ Failure Assessment; WBC, white blood cells.

Table 8
Sequential Organ Failure Assessment (SOFA) score [8]

Organ failure	Variable	Score 0	Score 1	Score 2	Score 3	Score 4
Respiratory	PaO ₂ /FIO ₂ , mm Hg	≥ 400	< 400	< 300	< 200 on MV	< 100 on MV
Hematology	Platelets, 10 ⁹ /L	≥ 150	< 150	< 100	< 50	< 20
Liver	Bilirubin, mg/dL	< 1.2	1.2–1.9	2.0–5.9	6.0–11.9	> 12.0
Cardiovascular	Mean arterial blood pressure, mm Hg	≥ 70	< 70			
	Dopamine, µg/kg ⁻¹ ·min ⁻¹			≤ 5	> 5	> 15
	Dobutamine, µg/kg ⁻¹ ·min ⁻¹			Any dose		
	Epinephrine, µg/kg ⁻¹ ·min ⁻¹				≤ 0.1	> 0.1
	Norepinephrine, µg/kg ⁻¹ ·min ⁻¹				≤ 0.1	> 0.1
Central nervous system	Glasgow coma score	15	13–14	10 – 12	6 – 9	< 6
Renal	Creatinine, mg/dL	< 1.2	1.2–1.9	2.0–3.4	3.5–4.9	≥ 5.0
	Urine output, mL/day	≥ 500			< 500	< 200

Abbreviation: MV, mechanical ventilation.

pressure-adjusted heart rate to measure cardiovascular dysfunction [7–9]. Pressure-adjusted heart rate is calculated as central venous pressure $\times$ heart rate/mean blood pressure. Assessment of cardiovascular function using the MODS criteria is not possible in patients without central venous catheters [56].

The main purpose of the organ failure scores is to describe the sequence of complications, not to predict mortality. However, the organ failure scores can accurately discriminate survivors from nonsurvivors. In the original study performed in a surgical ICU, the first and subsequent ICU days' MODS correlated well with mortality, with the AUC exceeding 0.90 [7]. Initial and trends in SOFA scores correlate well with mortality [57,58]. When analyzing trends in the daily SOFA score during the first 96 hours, regardless of the initial score, the mortality rate was at least 50% when the score increased, 27% to 35% when it remained unchanged, and less than 27% when it decreased [57].

There is paucity of data comparing the performance of the organ failure assessment systems in a common patient population. A study comparing SOFA and MODS did not find statistically significant differences between them in discriminating survivors from nonsurvivors [59].

Use

Because the organ dysfunction measures may be obtained daily, they give a complete understanding of the patient's entire ICU course as opposed to just the initial 24-hour period [60]. The trend in the daily organ failure scores can be used to demonstrate the effects of various therapeutic interventions in clinical practice as well as clinical trials. Daily scores also help to capture the intensity of resource use and may help us gain a better understanding of what truly ICU-acquired organ dysfunction is. However, unlike the severity models, the organ failure assessment systems have not been studied in large samples.

Summary

The organ failure assessment systems are based on easily obtainable variables, with the exception of pressure-adjusted heart rate in MODS. They can be measured daily and have the potential to be used in assessing patients' clinical course and for clinical trials; however, these potential roles have not yet been supported by data. Future studies are needed to better define these roles as well as to compare the performance of the organ failure assessment systems in a large sample size. MODS, SOFA, and LODS are limited to six organs. Despite the complexity and difficulties, some researchers have tried to define gastrointestinal failure with some success [61]. Future organ failure assessment systems need to incorporate gastrointestinal and endocrine organ dysfunctions.

References

- [1] Halpern NA, Pastores SM, Greenstein RJ. Critical care medicine in the United States 1985–2000: an analysis of bed numbers, use, and costs. *Crit Care Med* 2004;32(6): 1254–9.
- [2] ICU measure overview. Available at: <http://www.jcaho.org/pms/core+measures/Oficucore-measureoverview.pdf>. Accessed March 3, 2005.
- [3] Curtis JR, Cook DJ, Wall RJ, et al. Intensive care unit quality improvement: a “how-to” guide for the interdisciplinary team. *Crit Care Med* 2006;34(1):211–8.
- [4] Cullen DJ, Civetta JM, Briggs BA, et al. Therapeutic intervention scoring system: a method for quantitative comparison of patient care. *Crit Care Med* 1974;2(2):57–60.
- [5] Knaus WA, Draper EA, Wagner DP, et al. Prognosis in acute organ-system failure. *Ann Surg* 1985;202(6):685–93.
- [6] Knaus WA, Wagner DP. Multiple systems organ failure: epidemiology and prognosis. *Crit Care Clin* 1989;5(2):221–32.
- [7] Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995;23(10):1638–52.
- [8] Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European society of intensive care medicine. *Intensive Care Med* 1996;22(7): 707–10.
- [9] Le Gall JR, Klar J, Lemeshow S, et al. The logistic organ dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU scoring group. *JAMA* 1996;276(10): 802–10.
- [10] Le Gall JR. The use of severity scores in the intensive care unit. *Intensive Care Med* 2005; 31(12):1618–23.
- [11] Ohno-Machado L, Resnic FS, Matheny ME. Prognosis in critical care. *Annu Rev Biomed Eng* 2006;8:567–99.
- [12] Hadron DC, Keeler EB, Rogers WH, et al, editors. Assessing the performance of mortality models (monograph on the Internet). Santa Monica (CA): Rand Corporation; 1993. Available at: http://www.rand.org/pubs/monograph_reports/MR181/.
- [13] Knaus WA, Wagner DP, Zimmerman JE, et al. Variations in mortality and length of stay in intensive care units. *Ann Intern Med* 1993;118(10):753–61.
- [14] Seneff MG, Zimmerman JE, Knaus WA, et al. Predicting the duration of mechanical ventilation. The importance of disease and patient characteristics. *Chest* 1996;110(2): 469–79.
- [15] Zimmerman JE, Wagner DP, Knaus WA, et al. The use of risk predictions to identify candidates for intermediate care units. Implications for intensive care utilization and cost. *Chest* 1995;108(2):490–9.
- [16] Watts CM, Knaus WA. The case for using objective scoring systems to predict intensive care unit outcome. *Crit Care Clin* 1994;10(1):73–89.
- [17] Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol* 1982;115(1):92–106.
- [18] Ridley S. Severity of illness scoring systems and performance appraisal. *Anaesthesia* 1998; 53(12):1185–94.
- [19] Zhu BP, Lemeshow S, Hosmer DW, et al. Factors affecting the performance of the models in the mortality probability model II system and strategies of customization: a simulation study. *Crit Care Med* 1996;24(1):57–63.
- [20] Beck DH, Smith GB, Pappachan JV. The effects of two methods for customising the original SAPS II model for intensive care patients from South England. *Anaesthesia* 2002;57(8): 785–93.
- [21] Moreno R, Apolone G. Impact of different customization strategies in the performance of a general severity score. *Crit Care Med* 1997;25(12):2001–8.

- [22] Le Gall JR, Neumann A, Hemery F, et al. Mortality prediction using SAPS II: an update for French intensive care units. *Crit Care* 2005;9(6):R645–52.
- [23] Rivera-Fernandez R, Vazquez-Mata G, Bravo M, et al. The APACHE III prognostic system: customized mortality predictions for Spanish ICU patients. *Intensive Care Med* 1998;24(6):574–81.
- [24] Knaus WA, Zimmerman JE, Wagner DP, et al. APACHE-Acute Physiology and Chronic Health Evaluation: a physiologically based classification system. *Crit Care Med* 1981;9(8):591–7.
- [25] Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13(10):818–29.
- [26] Le Gall JR, Loirat P, Alperovitch A, et al. A simplified acute physiology score for ICU patients. *Crit Care Med* 1984;12(11):975–7.
- [27] Lemeshow S, Teres D, Pastides H, et al. A method for predicting survival and mortality of ICU patients using objectively derived weights. *Crit Care Med* 1985;13(7):519–25.
- [28] Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991;100(6):1619–36.
- [29] Zimmerman JE, Wagner DP, Draper EA, et al. Evaluation of Acute Physiology and Chronic Health Evaluation III predictions of hospital mortality in an independent database. *Crit Care Med* 1998;26(8):1317–26.
- [30] Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993;270(24):2957–63.
- [31] Lemeshow S, Teres D, Klar J, et al. Mortality probability models (MPM II) based on an international cohort of intensive care unit patients. *JAMA* 1993;270(20):2478–86.
- [32] Lemeshow S, Klar J, Teres D, et al. Mortality probability models for patients in the intensive care unit for 48 or 72 hours: a prospective, multicenter study. *Crit Care Med* 1994;22(9):1351–8.
- [33] Higgins TL, Teres D, Copes W, et al. Assessing contemporary intensive care unit outcome: an updated mortality probability admission model (MPM0-III). *Crit Care Med* 2007;35: [Published on line January 23, 2007 ahead of print].
- [34] Metnitz PG, Moreno RP, Almeida E, et al. SAPS 3—from evaluation of the patient to evaluation of the intensive care unit. Part 1: objectives, methods and cohort description. *Intensive Care Med* 2005;31(10):1336–44.
- [35] Moreno RP, Metnitz PG, Almeida E, et al. SAPS 3—from evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med* 2005;31(10):1345–55.
- [36] Zimmerman JE, Kramer AA, McNair DS, et al. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med* 2006;34(5):1297–310.
- [37] Afessa B. Benchmark for intensive care unit length of stay: one step forward, several more to go. *Crit Care Med* 2006;34(10):2674–6.
- [38] Afessa B, Keegan MT, Gajic O, et al. The influence of missing components of the acute physiology score of APACHE III on the measurement of ICU performance. *Intensive Care Med* 2005;31(11):1537–43.
- [39] 100 Top Hospitals™: ICU Benchmarks for Success—2000. Available at: http://www.100tophospitals.com/Media/releases/nr010206_icu.htm. Accessed February 3, 2007.
- [40] Hosmer DW, Lemeshow S. Confidence interval estimates of an index of quality performance based on logistic regression models. *Stat Med* 1995;14(19):2161–72.
- [41] Sirio CA, Shephardson LB, Rotondi AJ, et al. Community-wide assessment of intensive care outcomes using a physiologically based prognostic measure: implications for critical care delivery from Cleveland health quality choice. *Chest* 1999;115(3):793–801.
- [42] Glance LG, Osler T, Shinozaki T. Effect of varying the case mix on the standardized mortality ratio and W statistic: a simulation study. *Chest* 2000;117(4):1112–7.

- [43] DePorter J. UHC operations improvement: adult ICU benchmarking project summary. University Healthsystem Consortium. *Best Pract Benchmarking Healthc* 1997;2(4): 147–53.
- [44] Zimmerman JE, Alzola C, Von Rueden KT. The use of benchmarking to identify top performing critical care units: a preliminary assessment of their policies and practices. *J Crit Care* 2003;18(2):76–86.
- [45] Zimmerman JE, Kramer AA, McNair DS, et al. Intensive care unit length of stay: benchmarking based on acute physiology and chronic health evaluation (APACHE) IV. *Crit Care Med* 2006;34(10):2517–29.
- [46] Afessa B, Keegan MT, Hubmayr RD, et al. Evaluating the performance of an institution using an intensive care unit benchmark. *Mayo Clin Proc* 2005;80(2):174–80.
- [47] Sakallaris BR, Jastremski CA, Von Rueden KT. Clinical decision support systems for outcome measurement and management. *AACN Clin Issues* 2000;11(3):351–62.
- [48] Teres D, Lemeshow S. Why severity models should be used with caution. *Crit Care Clin* 1994;10(1):93–110.
- [49] Sinuff T, Adhikari NK, Cook DJ, et al. Mortality predictions in the intensive care unit: comparing physicians with scoring systems. *Crit Care Med* 2006;34(3):878–85.
- [50] Poses RM, McClish DK, Bekes C, et al. Ego bias, reverse ego bias, and physicians' prognostic. *Crit Care Med* 1991;19(12):1533–9.
- [51] Chang RW, Jacobs S, Lee B. Predicting outcome among intensive care unit patients using computerised trend analysis of daily APACHE II scores corrected for organ system failure. *Intensive Care Med* 1988;14(5):558–66.
- [52] Afessa B, Keegan MT, Mohammad Z, et al. Identifying potentially ineffective care in the severely critically ill patients on the third ICU day. *Chest* 2004;126(6):1905–9.
- [53] Flegler BM, Jackson DK, Turnbull J, et al. Identifying potentially ineffective care in a community hospital. *Crit Care Med* 2002;30(8):1803–7.
- [54] TPN and APACHE. *Lancet* 1986;1(8496):1478.
- [55] Cowen JS, Kelley MA. Errors and bias in using predictive scoring systems. *Crit Care Clin* 1994;10(1):53–72.
- [56] Vincent JL. Organ dysfunction in patients with severe sepsis. *Surg Infect (Larchmt)* 2006; 7(Suppl 2):S69–72.
- [57] Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001;286(14):1754–8.
- [58] Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on “sepsis-related problems” of the European society of intensive care medicine. *Crit Care Med* 1998;26(11):1793–800.
- [59] Peres BD, Melot C, Lopes FF, et al. The multiple organ dysfunction score (MODS) versus the sequential organ failure assessment (SOFA) score in outcome prediction. *Intensive Care Med* 2002;28(11):1619–24.
- [60] Herridge MS. Prognostication and intensive care unit outcome: the evolving role of scoring systems. *Clin Chest Med* 2003;24(4):751–62.
- [61] Reintam A, Parm P, Redlich U, et al. Gastrointestinal failure in intensive care: a retrospective clinical study in three different intensive care units in Germany and Estonia. *BMC Gastroenterol* 2006;6:19.

Monitoring Patient Safety

Sean M. Berenholtz, MD, MHS*,
Peter J. Pronovost, MD, PhD

Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, 1909 Thames Street, 2nd floor, Baltimore, MD 21231, USA

The Institute of Medicine's (IOM) report estimating 44,000 to 98,000 annual deaths from medical errors prompted a considerable amount of effort to monitor and improve patient safety [1,2]. Despite this effort, many say we lack empiric evidence to demonstrate large-scale improvements in quality of care [3–5]. Also, many organizations struggle to confidently answer important questions: are patients safer now as a result of their efforts; and if so, how do we know?

A comprehensive approach to evaluate an organization's progress with patient safety efforts has not been clearly articulated, and existing efforts to monitor safety are likely inadequate. Federal agencies, organizations and some institutions have developed performance measures to evaluate quality and safety of care. However, most of these measures either lack validity (eg, overall hospital mortality) or target specific patient populations (eg, congestive heart failure), preventing generalizability of results to the entire organization [6–8]. As a result, current publicly reported performance measures will not likely be sufficient for providers to evaluate progress in patient safety since, in many hospitals, these measures apply to less than 10% of a hospital's discharges [9].

In this article we describe a framework that health care organizations can use to monitor patient safety, and present an example of how the safety scorecard from this framework is used to monitor patient safety at the Johns Hopkins Hospital (JHH) and in over 150 ICUs in Michigan, New Jersey, and Rhode Island.

This work is supported in part by Grant No. K23HL70058-01 from the National Heart, Lung and Blood Institute; and by Grant No. 1UC1HS14246 from the Agency for Healthcare Research and Quality.

* Corresponding author.

E-mail address: sberenho@jhmi.edu (S.M. Berenholtz).

A framework to monitor patient safety

Prior efforts to monitor safety have predominately focused on outcome measures, including in-hospital mortality [10]. To facilitate comparison of performance across ICUs, a significant amount of effort has been devoted to developing sophisticated risk adjustment models. These models were rigorously developed, but to date, have significant limitations that may inhibit broad implementation [11,12]. In addition, mortality rate alone, although important, provides an incomplete picture of patient safety.

Donabedian's model [13] for measuring quality provides a useful framework for monitoring safety. In this model, *structure* (how care is organized) plus *process* (what we do) influences patient *outcomes* (the results achieved). We adapted this model to patient safety by adding a fourth element, *culture* (collective attitudes and beliefs of caregivers), based on emerging evidence that local culture is linked to a variety of important clinical outcomes [14]. Indeed, the Joint Commission for Accreditation of Healthcare Organizations (JCAHO) plans to require yearly assessments of organizational culture as part of their 2008 leadership standards (www.jointcommission.org).

Although the attributes of performance measures are well developed, they should be scientifically sound (valid and reliable), feasible, important, and usable. Challenges remain in implementing performance measures to evaluate safety [15–18].

In evaluating patient safety it is important to clarify what can and cannot be measured as a valid rate. To be a valid rate, the numerator (event or harm) and denominator (population at risk for the event or harm) must be clearly defined and measured with minimal bias. This requires a standardized surveillance system to accurately identify and measure both the numerator and denominator of the rate [19]. Standardized surveillance systems are not widely used to evaluate delivery of clinical care.

Most safety parameters, such as information from patient safety reporting systems, are difficult or impossible to capture in the form of a valid rate. Such safety parameters remain useful, but should not be interpreted as a rate. For example, medical errors that result in significant patient harm are important as a numerical count (numerator), but they are not valid rates since the denominator is ambiguous and we cannot account for reporting biases. Establishing safety indicators that can be measured as a valid rate is a critical first step in monitoring and improving safety.

In our framework to monitor patient safety (Table 1) [20], we stratify measures into two categories. One category uses valid rate-based measures to evaluate the following: how often we harm patients (*outcome* measure), and how often we use evidence-based medicine (*process* measure). The second category captures indicators that are essential to patient safety, but not measurable as valid rates. This category addresses: how we know that we learned from mistakes (*structural* measure), and how well we have created

Table 1
Patient safety scorecard framework for the ICU

Domain	Definition	Examples for the ICU
How often do we harm patients? (<i>Outcome measure</i>)	Measures of health care–acquired infections	Central line associated blood stream infections (CLA-BSI)
How often do we use evidence-based medicine? (<i>Process measure</i>)	Percentage of patients who receive evidence-based interventions	Elevate the head of bed, use stress ulcer and deep venous thrombosis prophylaxis in mechanically ventilated patients
How do we know we learned from our mistakes? (<i>Structural measure</i>)	Percentage of months per year the ICU learns from mistakes	Monitor percentage of months per year in which the ICU creates a shared story
How well have we created a culture of safety? (Survey of staff attitudes)	Annual assessment of safety culture at the unit level	Teamwork and safety climate score

a culture of safety. Safety culture is measured using the Safety Attitudes Questionnaire [21,22]. Each type of measure will be discussed below.

How often do we harm patients?

Although patients, providers, and policymakers generally seek outcomes when considering performance measures, it is difficult to develop scientifically sound and feasible outcome measures [6,23–25]. While it would be ideal to track a wide variety of safety outcomes (eg, medication errors, incidence of deep venous thrombosis), we currently have few valid measures of harm. The most robust measures we do have are health care–acquired infections, particularly central line–associated blood stream infections (CLA-BSI). These infections can be validly measured and most can be prevented with focused interventions [26,27].

Other measures of harm (outcomes) may be biased and should be used cautiously. For example, most deep venous thromboses (DVT) and postoperative myocardial infarctions are silent. If clinically identified rates of these postoperative complications are monitored without a standardized method of screening, both would be subject to surveillance bias [28,29]. When trauma surgeons at our hospital implemented standardized surveillance, for example, rates of DVT increased 10-fold, changing our performance from being one of the best to one of the worst in the state. As a result, physicians who conduct increased screening for these complications could be falsely labeled “low quality” providers given their “unexpectedly high” rates. Thus, monitoring most measures of harm as rates may be biased in the absence of standardized surveillance systems.

The ability to measure health care–acquired infection rates (eg, CLA-BSI) highlights the importance of standardized surveillance systems and definitions to capture harms that are to a large extent preventable [30]. For example, the Centers for Disease Control and Prevention provides standard definitions for CLA-BSI, and most hospitals have epidemiology and infection control departments to independently monitor, report, and reduce infections [31]. Nevertheless, implementing standardized surveillance requires resources; payers and policymakers will have to decide whether the benefits of measurement outweigh the costs. For example, it would be costly and probably unrealistic to monitor rates of DVT in all postoperative patients using an ultrasound or venogram. However, it may be feasible to monitor myocardial infarctions in all postoperative patients with troponins.

How often do we do what we should?

Despite our best efforts, some patients will develop complications. This may result from patient factors or inadequate processes of care. As such, we should try to ensure that patients reliably receive evidence-based interventions that improve outcomes and prevent harm, and seek out new effective interventions [32].

There is a growing body of evidence-based interventions to guide our practice in critical care. For example, several interventions or processes of care have demonstrated reductions in morbidity, mortality, and costs of care associated with mechanical ventilation, including head of bed (HOB) elevation [33], peptic ulcer disease prophylaxis (PUD) [34], DVT prophylaxis [35], adjusting sedation such that patients can follow commands once a day [36], and daily assessment of ability to extubate [37]. Increasing adherence with the ventilator bundle, or group of interventions in which each has independently demonstrated improved outcomes for specific patient populations, has consistently resulted in improved patient outcomes [38]. Three of these interventions, elevating the head of the bed ≥ 30 degrees, PUD prophylaxis, and DVT prophylaxis have been selected by JCAHO for inclusion in the initial core set of ICU quality measures. Further research is needed to develop and validate additional care bundles for ICU patients.

Given the relative paucity of process measures, it will be important to consider structural (organization of care) elements. The science of linking structural elements to patient safety outcomes is immature, but more advanced than outcome and process measurement. In critical care, structural measures of patient safety might include the presence of intensivists, nurse-to-patient ratios [39], pharmacist presence during ICU rounds [40], and use of the comprehensive unit-based safety program [41]. In addition, the presence of computerized physician order entry [42] may represent another potential structural measure, although recent studies have raised concerns about the effectiveness of this intervention [43,44]. Nevertheless, changes in organizational structure are often slow to implement, in part

because of perceived costs, and a shortage of qualified providers [45]. Continued research is needed to identify effective ways of organizing care (including organizational-level interventions), to ensure patients reliably benefit from those interventions.

How often do we learn from defects?

Most safety issues should not be expressed as rates but rather events, sometimes described as defects that should not happen again. Establishing patient safety reporting systems recommended by the IOM and promoted by a new federal law are a common method to identify patient safety defects [46,47]. As we previously discussed, trending of incident reports from patient safety reporting systems as rates are likely a biased measure of whether safety is improving [48–51]. Consider the following scenario. If the number of reported incidents per 1000 discharges dropped from 100 last year to 70 this year, and the hospital now receives fewer incident reports or fewer reports compared with their peers, is the hospital safer? We simply don't know this answer. Since incident reports are submitted voluntarily, and studies show that only a tiny, nonrandom fraction of incidents is submitted [1,48,52], these incidents cannot serve as a valid numerator in an error rate equation. While decreased reporting volume could represent fewer incidents, it is equally plausible that staff are too busy, or devalue reporting since the information they submit rarely leads to meaningful changes.

Health care organizations may be better served by monitoring how often they learned from mistakes identified through reporting systems rather than evaluating rates constructed from these reports. To learn from incidents, caregivers must investigate what happened and why, what they will do to reduce the probability that the event will recur, and how they know the intervention was effective [53,54].

Hospitals need a method to evaluate whether they are learning from defects, especially those that result in or could have caused significant harm. There are many sources to identify defects, including patient safety reporting systems, morbidity and mortality conferences, sentinel events, liability claims, and perhaps most powerfully, asking staff how they think the next patient will be harmed [41]. In most institutions, making defects transparent will catalyze efforts to reduce the risk of another patient being harmed. How will we know whether these efforts were effective? In general, the science of evaluating interventions is underdeveloped, not standardized, and relatively inefficient. Nevertheless, our understanding of this science is improving and we believe that further efforts to determine whether insights from errors lead to meaningful interventions is a useful measure of an organization's safety.

Hospitals can determine whether they have learned from defects by evaluating the extent to which they implemented interventions to prevent the event from recurring. For example, let's assume a hospital had a sentinel event involving inappropriate programming of a medication pump to

deliver insulin that resulted in a neurologic complication from hypoglycemia. The hospital conducted a root cause analysis (RCA) and recommended several interventions in an effort to minimize the chance that the mistake will happen again in the future [55].

The RCA revealed that the bedside nurse was very busy and not familiar with the new medication pump. Thus, the RCA team recommended staff education about the risks associated with insulin administration and how to program the new medication pump, and an independent check by another provider for all dose adjustments.

We classify these interventions from strongest, that is most likely to reduce the probability that the mistake will reoccur, to weakest, that is least likely to prevent the mistake. Types of interventions, from strongest to weakest, include eliminating or preventing the mistake, making the mistake visible, mitigating the hazard should a mistake occur, and reeducating or creating a policy in the absence of any stronger features. Unfortunately, weak interventions predominate and are often the same traditional solutions offered in a new package. In addition, efforts to improve patient safety are often superficial, an inch deep and mile wide; we need efforts that are an inch wide and a mile deep.

How do we know whether the recommended interventions reduced the probability of another complication related to pump programming errors? To answer this question, we need a structural measure since this defect may be too rare to monitor as a rate. In general, there are three indicators to evaluate whether the risk for harm is reduced. We can measure the presence of a program or policy, staff's knowledge of the program or policy, or appropriate use of the program or policy. If the program or policy involves communication among multiple caregivers, the only way to capture if the intervention is used appropriately is to observe team behavior.

Which of these indicators, if any, should be measured and how should it be done? There is no clearly correct indicator. What is measured should be influenced by the risks, including the costs and benefits. In general, measuring the appropriate use of a policy or program will be the most valid, yet also the most resource-intensive strategy. If the policy or program has a high probability of eliminating the mistake, measuring the presence of the program may be sufficient. For example, after a mistake involving transvenous pacing that resulted primarily from a failure to package required equipment together, the JHH created a kit of requisite pacing equipment. Presence of this "pacing kit" essentially prevented the mistake from recurring. Therefore, to monitor the effectiveness of this intervention, it was appropriate to measure the presence, not the use, of these kits. Conversely, if the intervention has a lower probability of preventing the mistake (eg, educating staff to prevent medication errors) it would be better to measure whether the intervention was used—in this case, the use of an independent double-check. For common mistakes, standardized measurement tools should be developed.

For years, hospitals believed safety lived at the policy level; a belief reinforced by the accreditation process, which emphasized the presence of policies rather than actions or attitudes. Based on this belief, after an event happened, policies were written and little-to-no effort applied to evaluate whether the policy was understood and used. The tracer methodology, now used by JCAHO, attempts to move measurement close to the patient—a welcomed change. Hospitals must commit resources to make these changes and to undertake the subsequent measurement process.

Have we created a safe culture?

Given that much of the efforts to measure safety have focused on the context of care (such as teamwork and communication), measuring this context (often called “safety culture”) may inform our efforts to assess patient safety. Failures in communication are the most common contributing factor to sentinel events and errors [51] (www.jointcommission.org). There are validated tools to measure safety culture, often by evaluating caregivers’ perceptions of teamwork and safety climate. The most commonly used and rigorously validated tool is the Safety Attitudes Questionnaire (SAQ) [21,22,56]. Higher SAQ scores are associated with lower rates of nurse turnover, CLA-BSIs, decubitus ulcers, and in-hospital mortality (B. Sexton, PhD, personal communication, 2007).

By measuring safety culture, providers and institutions can obtain valid, feasible measures of teamwork and communication. Indeed, emerging evidence supports the hypothesis that these measures relate to safety outcomes. We believe that evidence will increasingly demonstrate that improvements in safety culture will be reflected in improvements in patient safety.

Applying the safety scorecard

The framework to monitor patient safety is presently being applied at JHH and in over 150 ICUs in the states of Michigan, New Jersey, and Rhode Island [57]. The safety scorecard is a product of this framework. Table 2 illustrates the safety scorecard for three ICUs at JHH. To evaluate harm, we measured CLA-BSI rates. To evaluate how often we do what we should, we evaluate compliance with the ventilator bundle. This bundle includes rates of head of bed elevation, rates of stress ulcer and deep venous thrombosis prophylaxis, appropriate sedation, and evaluation of ability to extubate, as described elsewhere [58]. We have also developed a perioperative scorecard to measure rates of surgical site infections, rates of hypothermia, and providing timely antibiotics to prevent surgical site infections. Additional process measures are under development.

To understand the nonrate measures, our stated goal is that departments learn from at least one defect per quarter in a year. A department has

Table 2
Example of ICU patient safety scorecard

Domain	Score			
	Unit A	Unit B	Unit C	Overall
How often do we harm patients? (<i>No. blood stream infections/1000 catheter days</i>)	4	1	1	2
How often do we use evidence-based medicine? (<i>% patients receiving ventilator bundle</i>)	88	96	94	93
How often do we learn from defects? (<i>% months unit learned from a defect</i>)	100	100	100	100
How well have we created a culture of safety? (<i>No. of units in which 60% of staff report positive teamwork and safety climate and the average score [%] in each ICU</i>)	52 ^a	65 ^a	89 ^a	1/3 (33) ^b
	55 ^a	84 ^a	82 ^a	2/3 (67) ^b
Safety Climate				
Teamwork Climate				

^a % reporting good climate (eg, agree slightly or agree strongly).
^b % ICUs reporting >80% agreement.

successfully learned from a defect if it can produce a written summary of what happened, why it happened, what department staff did about it, and how they know they reduced the risk of harm [54]. Culture and teamwork scores are presented as the percentage of patient care areas within a department or hospital in which 80% (our target score) of staff report positive safety and teamwork climate.

At JHH, we aggregate patient care area-level measures up to department-level measures, department-level measures to hospital-level measures, and hospital-level measures to health system measures (see Table 2). Overall, evidence-based interventions in the ventilator bundle are used more than 90% of the time and 100% of units learned from one defect per quarter. In addition, 33% of units reported good safety climate (eg, one of three ICUs had >80% agreement) and 67% good teamwork climate (eg, two of three ICUs had >80% agreement).

Limitations of the safety scorecard

The patient safety framework that we describe is a work in progress with several limitations. First, the framework may not be comprehensive enough

to address all aspects of patient safety. Nevertheless, caregivers and administrators have found it meaningful and manageable. We do not explicitly distinguish between safety and quality measures, although the level of importance in highlighting this distinction remains unclear. Second, the overall scorecard includes aggregate measures and may be less meaningful for senior hospital leaders than individual measures. However, as the number of individual measures increases, they become difficult to comprehend; our goal is to develop measures that are meaningful to the caregivers using the data to improve. In addition, senior and departmental leaders can access the raw data that underlie these aggregate measures. Third, we have limited structure, process, and outcome measures. We are very early in our efforts to determine which in the growing list of measures to evaluate. For now, we are trying to balance measures that are scientifically sound and feasible to collect. Fourth, measures of whether we have learned from mistakes are particularly underdeveloped and not validated. National measures could be developed for common mistakes. Finally, evidence for the validity of cultural measures as proxies for improved safety is still emerging.

What might teams do to monitor safety?

The first step in developing a safety scorecard to monitor safety in the ICU is to convene a multidisciplinary panel. Potential stakeholders who should be involved include senior and departmental leaders, physicians, nurses, and representatives from departments of performance improvement/quality assurance, hospital epidemiology, and information systems.

The second step is to gain consensus about measures that should be included on the safety scorecard. We previously discussed potential measures for three of the questions on the scorecard. How often do we harm patients? How do we know we learned from mistakes? How well have we created a culture of safety? Several criteria must be considered when choosing measures to answer how often we use evidence-based medicine [59].

First, ensure that the area or outcome to be improved is important to the intended audience. In ICU care for example, providers should focus on structural or process measures that likely have a significant impact on patient morbidity, mortality, and/or costs of care.

Second, select measures with evidence demonstrating a strong association between the process or structure, and the outcome. When evaluating the strength of the evidence, providers should consider the type and number of studies available to guide practice. Randomized clinical trials (RCT) provide the strongest level of evidence, or the least risk of bias, while observational studies and consensus groups provide significantly weaker evidence (www.cebm.jr2.ox.ac.uk). Also, multiple studies or a meta-analysis of well-done RCTs provide stronger evidence than single studies. The strength of the evidence behind the measure will determine the likelihood that improvement in the quality measure will produce consistent and credible

improvements in quality of care [10,60]. For example, it is unclear that providing hospitals data on mortality, without data on how to reduce mortality, will lead to decreased death rates and improved quality of care. Evidence-based therapies in critical care are a recent occurrence. For example, we now have evidence that ventilator strategies [61], tight glucose control [62], and the use of activated protein C [63] are associated with decreased hospital mortality, and that length of stay can be reduced by daily interruption in sedative-drug infusions [36]. These process measures represent appropriate areas for future measures of ICU quality.

Third, evaluate whether variability in performance exists, either within an ICU or across ICUs. This variability represents a potential opportunity for improvement [60,64]. Indeed, providers may not want to focus on improving rates of CLA-BSI if this rate is already low in a particular ICU. The fourth criterion is to choose a measure in which providers or managers will be able to impact performance. For example, elevating the head of the bed is an evidence-based intervention that improves care in ventilated patients, and a practice that can be measured and improved. It would be illogical to focus on a measure over which providers have no control.

When selecting measures of safety, we need to consider not only the clinical rationale of collecting the data, but also the business rationale; necessitating knowledge of the costs of data collection and potential cost savings from improving performance. As such, we may not want to focus on measuring performance if the cost of collecting the data exceeds the potential benefit from the improvement. This is particularly problematic in critical care where sophisticated risk adjustment methods may require physiologic data that may be burdensome to collect in hospitals without automated data collection.

Finally, people, not data, improve patient care. It is imperative that quality measures are meaningful, scientifically sound, generalizable, and interpretable [60]. To accomplish this, measures must be designed and implemented with the same rigor applied in clinical research.

Is our safety scorecard valid?

We have limited ability to evaluate the validity of a safety scorecard, or determine if an organization has made valid inferences about its quality of care. To help develop such tools, we modified the approach used in evidence-based medicine to evaluate the quality of published literature (Box 1) [65]. Although we recognize that this tool will evolve, it is designed to help organizations develop and evaluate their safety scorecard by answering three questions:

1. Are the measures important?
2. Are the measures valid?
3. Can I use this scorecard in my organization?

Box 1. Worksheet to evaluate a safety scorecard*Are the measures important?*

1. Do the measures fit a strategic priority for the organization?
2. Who will use the data for each measure to improve quality, and do they believe each measure evaluates an important aspect of quality?

Are the measures valid?

1. Is the measure supported by empiric evidence or expert opinion?
2. Are explicit patient inclusion and exclusion criteria provided for each measure?
3. Are explicit definitions provided for events (numerator) and for those at risk for events (denominator)?
4. Is a standardized surveillance system and data collection form in place?
5. Are estimates of performance or changes in performance presented with an estimate of precision (confidence intervals)?

Can I use this scorecard in my organization?

1. Do we have an infrastructure to collect the data?
2. What does it cost to collect the data, and do the benefits likely outweigh the costs?
3. Where do the measures fit on our list of organizational priorities?
4. Are potential limitations and biases of performance on measures acknowledged?

This worksheet can help leaders of organizations address important issues and overcome common barriers encountered in efforts to monitor and improve patient safety.

Barriers to monitoring safety

There are a number of barriers to implementing a safety-monitoring program that must be overcome. First, hospitals need to dedicate resources to develop measures of safety, and collect and manage data. In our experience, providers are busy and have limited time for added responsibilities. They need protected time with dedicated staff and other resources. Second, payers must determine the costs and benefits of measuring additional patient safety indicators; then, commit the resources and coordinate their efforts with individual health care institutions and providers. Different stakeholders (insurers, regulators, and accreditors) want different measures, which

imposes a significant burden on health care organizations and limits the ability to benchmark performance. Third, the current number of valid safety-related process and structural measures is small. Few individual health care organizations have the resources to develop valid measures. Rather, regulators, accreditors, researchers, and professional societies should jointly develop and make measures and data collection tools widely available. Fourth, standards for constructing and reporting safety measures should be developed and widely promulgated. Fifth, the science for measuring safety must advance. Given its present immaturity, the framework we present should be considered a work in progress. A sixth barrier is limited information technology. We should strive to automate data collection and data management.

One approach to reduce the costs of measurement would be to randomly evaluate the prevalence of a measure over a given period. If such efforts were coordinated, we could obtain national estimates of specific safety measures, moving us significantly closer to answering whether patients are safer at a national level. We also need to increase the number of people who know how to rigorously measure and evaluate quality of care. In our experience, weekend or week-long courses will not provide the required level of expertise. Rather, to build this capacity will require master's or doctoral level training in quality measurement methods. Such programs could be modeled after programs proven successful in training clinical researchers; both authors are graduates of such a program (Graduate Training Program in Clinical Investigation, The Johns Hopkins Bloomberg School of Public Health; <http://www.jhsph.edu/gtpci>).

Summary

The opportunity to improve patient safety is significant and the pressure to improve it increasing. Nevertheless, nearly all of health care currently lacks the ability to track progress despite considerable efforts to improve patient safety. As a result, few organizations can confidently say that patients are safer as a result of their efforts. In this article, we present a framework to monitor patient safety that combines valid rate-based measures to evaluate outcomes and processes of care, and non-rate-based measures to evaluate structure and context of care.

Acknowledgments

We thank Christine G. Holzmüller for her assistance in editing the manuscript. Dr. Berenholtz reports receiving consulting fees from DocuSys, and holds equity ownership in DocuSys. Dr. Pronovost reports receiving consulting fees from CriticalMed and DocuSys, and holds equity ownership in DocuSys and VISICU, Inc.

References

- [1] Kohn L, Corrigan J, Donaldson M, editors. *To err is human: building a safer health system*, Report from the Committee on Quality of Health Care in America, Institute of Medicine. Washington, DC: National Academy Press; 1999.
- [2] Institute of Medicine. *Crossing the quality chasm: a new health system for the 21st century*. Washington, DC: National Academy Press; 2001.
- [3] Brennan T, Gawande A, Thomas E, et al. Accidental deaths, saved lives, and improved quality. *N Engl J Med* 2005;353(13):1405–9.
- [4] Leape LL, Berwick DM. Five years after *To Err Is Human*: what have we learned? *JAMA* 2005;293(19):2384–90.
- [5] Wachter R. The end of the beginning: patient safety five years after “*To Err Is Human*”. *Health Aff (Millwood)* 2004; Suppl Web Exclusives (W4):534–45.
- [6] Lilford R, Mohammed M, Spiegelhalter D, et al. Use and misuse of process and outcome data in managing performance of acute medical care: avoiding institutional stigma. *Lancet* 2004;363(9415):1147–54.
- [7] Hayward R, Hofer T. Estimating hospital deaths due to medical errors; preventability is in the eye of the reviewer. *JAMA* 2004;286(4):415–20.
- [8] Thomas J, Hofer T. Accuracy of risk-adjusted mortality rate as a measure of hospital quality of care. *Med Care* 1999;37(1):83–92.
- [9] Jha A, Li Z, Orav E, et al. Care in U.S. hospitals—the Hospital Quality Alliance program. *N Engl J Med* 2005;353(3):265–74.
- [10] Brook RH, McGlynn EA, Cleary PD. Quality of health care. Part 2: measuring quality of care. *N Engl J Med* 1996;335(13):966–70.
- [11] Zimmerman JE, Draper E, Wagner D. Comparing ICU populations: background and current methods. In: Sibbald WJ, Bion J, editors. *Evaluating critical care: using health services research to improve quality*. New York: Springer; 2000. p. 121–39.
- [12] Clermont G, Angus DC, DiRusso SM, et al. Predicting hospital mortality for patients in the intensive care unit: a comparison of artificial neural networks with logistic regression models. *Crit Care Med* 2001;29(2):291–6.
- [13] Donabedian A. Evaluating the quality of medical care. *Milbank Mem Fund Q* 1966;44: 166–206.
- [14] Pronovost PJ, Berenholtz SM, Goeschel CA, et al. Creating high reliability in healthcare organizations. *Health Serv Res* 2006;41(4):1599–617.
- [15] Arispe I, Holmes J, Moy E. Measurement challenges in developing the National Healthcare Quality Report and the National Healthcare Disparities Report. *Med Care* 2005;43(3): I17–23.
- [16] Kelley E, Moy E, Stryer D, et al. The national healthcare quality and disparities reports: an overview. *Med Care* 2005;43(Suppl 3):13–8.
- [17] Zhan C, Miller MR. Excess length of stay, charges, and mortality attributable to medical injuries during hospitalization. *JAMA* 2003;290(14):1868–74.
- [18] McGlynn EA. An evidence-based national quality measurement and reporting system. *Med Care* 2003;41(Suppl 1):18–15.
- [19] Gordis L. *Epidemiology*. Philadelphia: Saunders; 2004.
- [20] Pronovost PJ, Holzmüller CG, Sexton JB, et al. How will we know if patients are safer? An organization-wide approach to measuring and improving patient safety. *Crit Care Med* 2006;34(7):1988–95.
- [21] Sexton JB, Thomas E. *Measurement: assessing a safety culture. Achieving safe and reliable healthcare strategies and solutions*. Chicago: Health Administration Press; 2004. p. 115–27.
- [22] Sexton JB, Helmreich RL. Using language in the cockpit: relationships with workload and performance. In: Dietrich R, editor. *Communication in High Risk Environments*. Humboldt Universität zu Berlin, Germany; 2003. p. 57–73.

- [23] Lilford R, Mohammed M, Brauholtz D, et al. The measurement of active errors: methodological issues. *Qual Saf Health Care* 2004;12(Suppl II):ii8–12.
- [24] Pronovost PJ, Thompson DA, Holzmueller CG, et al. Defining and measuring patient safety. *Crit Care Clin* 2005;21(1):1–19, vii.
- [25] Pronovost PJ, Nolan T, Zeger S, et al. How can clinicians measure safety and quality in acute care? *Lancet* 2004;363(9414):1061–7.
- [26] Berenholtz SM, Pronovost PJ, Lipsett PA, et al. Eliminating catheter-related bloodstream infections in the intensive care unit. *Crit Care Med* 2004;32(10):2014–20.
- [27] Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006;355(26):2725–32.
- [28] Martinez E, Pronovost P, Kim L, et al. Sensitivity of routine intensive care unit surveillance for detecting myocardial ischemia. *Crit Care Med* 2003;31(9):2302–8.
- [29] Kim Y, Oh S, Kim J. Incidence and natural history of deep-vein thrombosis after total hip arthroplasty. A prospective and randomized clinical study. *J Bone Joint Surg Br* 2003;85:661–5.
- [30] Needham D, Dowdy D, Mendez-Tellez P, et al. Studying outcomes of intensive care unit survivors: measuring exposures and outcomes. *Intensive Care Med* 2005;31(9):1153–60.
- [31] Gerberding J. Hospital-onset infections: a patient safety issue. *Ann Intern Med* 2002;137(8):665–70.
- [32] Woolf S. Patient safety is not enough: targeting quality improvements to optimize the health of the population. *Ann Intern Med* 2004;140:33–6.
- [33] Drakulovic M, Torres A, Bauer T, et al. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet* 1999;354(9193):1851–8.
- [34] Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med* 1998;338(12):791–7.
- [35] Attia J, Ray JG, Cook DJ, et al. Deep vein thrombosis and its prevention in critically ill adults. *Arch Intern Med* 2001;161(10):1268–79.
- [36] Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000;342(20):1471–7.
- [37] Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med* 1996;335(25):1864–9.
- [38] Resar R, Pronovost P, Haraden C, et al. Using a bundle approach to improve ventilator care processes and reduce ventilator-associated pneumonia. *Jt Comm J Qual Patient Saf* 2005;31(5):243–8.
- [39] Needleman J, Buerhaus P, Mattke S, et al. Nurse-staffing levels and the quality of care in hospitals. *N Engl J Med* 2002;346(22):1715–22.
- [40] Leape LL, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *JAMA* 1999;282(3):267–70.
- [41] Pronovost P, Weast B, Rosenstein B, et al. Implementing and validating a comprehensive unit-based safety program. *Journal of Patient Safety* 2005;1(1):33–40.
- [42] Bates DW, Teich JM, Lee J, et al. The impact of computerized physician order entry on medication error prevention. *JAMA* 1999;6(4):313–21.
- [43] Koppel R, Metley J, Cohen A, et al. Role of Computerized physician order entry systems in facilitating medication errors. *JAMA* 2005;293(10):1197–203.
- [44] Han Y, Carcillo J, Venkataraman S, et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. *Pediatrics* 2005;116:1506–12.
- [45] Angus DC, Kelley MA, Schmitz RJ, et al. Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? *JAMA* 2000;284(21):2762–70.

- [46] Institute of Medicine. Patient safety: achieving a new standard of care. Washington, DC: National Academies Press; 2004.
- [47] Patient Safety and Quality Improvement Act of 2005, Public Law 109-41.
- [48] Barach P, Small SD. Reporting and preventing medical mishaps: lessons from non-medical near miss reporting systems. *BMJ* 2000;320(7237):759-63.
- [49] Holzmüller CG, Pronovost PJ, Dickman F, et al. Creating the web-based intensive care unit safety reporting system. *JAMA* 2005;12(2):130-9.
- [50] Lubomski L, Pronovost PJ, Thompson D, et al. Building a better incident reporting system: perspectives from a multisite project. *J Clin Outcomes Mgmt* 2004;11(5):275-80.
- [51] Needham D, Sinopoli D, Thompson D, et al. A system factors analysis of "line, tube, and drain" incidents in the intensive care unit. *Crit Care Med* 2005;33(8):1701-7.
- [52] Cullen D, Bates D, Small S, et al. The incident reporting system does not detect adverse drug events: a problem for quality improvement. *Jt Comm J Qual Improv* 1995;21:541-8.
- [53] Vincent C. Understanding and responding to adverse events. *New Eng J Med* 2003;348(11):1051-6.
- [54] Pronovost PJ, Holzmüller CG, Martinez E, et al. A practical tool to learn from defects in patient care. *Jt Comm J Qual Saf* 2006;32(2):102-8.
- [55] Ammerman M. The root cause analysis handbook. Portland (OR): Productivity Inc; 1998.
- [56] Colla J, Bracken A, Kinney L, et al. Measuring patient safety climate: a review of surveys. *Qual Saf Health Care* 2005;14:364-6.
- [57] Pronovost PJ, Goeschel C. Improving ICU care: it takes a team. *Healthc Exec* 2005;20(2):14-22.
- [58] Berenholtz SM, Milanovich S, Faircloth A, et al. Improving care for the ventilated patient. *Jt Comm J Qual Saf* 2004;30(4):195-204.
- [59] Rubin H, Pronovost P, Diette G. The advantages and disadvantages of process-based measures of health care quality. *Int J Qual Health Care* 2001;13(6):469-74.
- [60] McGlynn EA. Choosing and evaluating clinical performance measures. *Jt Comm J Qual Improv* 1998;24(9):470-9.
- [61] Berenholtz SM, Dorman T, Ngo K, et al. Qualitative review of intensive care unit quality indicators. *J Crit Care* 2002;17(1):1-12.
- [62] Van Den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345(19):1359-67.
- [63] Bernard G, Vincent J, Laterre P, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344(10):699-709.
- [64] McGlynn EA, Asch SM. Developing a clinical performance measure. *Am J Prev Med* 1998;14(Suppl 3):14-21.
- [65] Guyatt G, Sackett D, Cook D. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? *JAMA* 1993;270(21):2598-601.