Thrombosis in central catheter–associated *Staphylococcus aureus* bacteremia: Always scan the site?*

...as an agent of complicated catheter-related bloodstream infections, *Staphylococcus aureus* is armed to the teeth. The organism utilizes specialized adhesive matrix molecules to bind to fibronectin and other serum components that coat central venous catheters (1, 2). In addition, *S. aureus* uses adhesin–receptor interactions to bind to endothelial cells, and is particularly attracted to areas of catheter-related vascular injury (3–5). Finally, the clumping factor expressed by the organism appears to make it inherently thrombogenic (6).

In this issue of *Critical Care Medicine*, Dr. Crowley and colleagues (7) report a remarkable 71% incidence of associated venous thromboses in a series of patients with catheter-related bacteremia due to *S. aureus*. In addition, they describe how poorly the physical examination is able to distinguish which patients have such thromboses. This report has limitations, including the lack of a control group and the fact that it was underpowered to detect outcome differences in the patients with venous thromboses. In addition, the inclusion in the thrombosis group of an undefined number of patients with only “an abnormal flow pattern present in the vessel”—a relatively nonspecific finding—may have led to an overestimation of the actual thrombosis rate. However, this incidence is made more credible by the fact that such high rates have been reported previously (8–10).

Despite its design limitations, this report may have important clinical implications. The lack of sensitivity and specificity of physical exam findings to detect upper extremity deep-venous thromboses suggests that these findings alone cannot be used to decide which patients warrant ultrasound examination. Ultrasound of the previously catheterized vein, then, should be performed in all patients with catheter-related *S. aureus* bacteremia in whom a positive finding of thrombosis would lead to an alteration in therapy.

The detection of an associated thrombosis in a patient with catheter-related bacteremia may influence both antibiotic and anticoagulant therapy. Because of its propensity to cause endocarditis and other metastatic infections, most patients with catheter-related *S. aureus* bacteremia require 4–6 wks of antibiotic therapy. Because long-term therapy increases the risk both of adverse drug reactions and of superinfections with resistant organisms (particularly if another central venous catheter is needed to deliver parenteral therapy), short-course therapy is preferred by some clinicians. This therapy should be reserved for patients in whom the infected catheter is promptly recognized and removed, bacteremia is cleared rapidly, and there is no evidence of metastatic infection. In addition—because of the high incidence of endocarditis in patients with *S. aureus* bacteremia who lack clinical or transthoracic echocardiographic evidence of such—the Infectious Diseases Society of America’s current guidelines recommend the use of transesophageal echocardiography to rule out occult valvar vegetations before a decision to use short-course therapy in such patients (11, 12). Given the findings of Dr. Crowley and colleagues, ultrasound to rule out thrombosis of the associated vein probably also should be performed before short-course therapy is chosen. When present, such a thrombosis should be assumed to be infected and should preclude short-course therapy.

In terms of anticoagulant therapy, the implications of thrombosis detection in the associated vein of a patient with catheter-related *S. aureus* bacteremia are less clear. Many such thromboses occur in the internal jugular or subclavian rather than in the femoral veins and thus may pose a somewhat lower—although not inconsequential—risk of pulmonary embolism (13, 14). The American College of Chest Physicians recommends full anticoagulation for patients with upper-extremity venous thrombosis (15). Unfortunately, patients with active *S. aureus* bacteremia may be at increased risk for complications of anticoagulation. The risk of cerebral hemorrhage has been reported to be very high in patients with *S. aureus* endocarditis who receive anticoagulation, and this risk may extend to some degree to all patients with ongoing bacteremia (16). If patients with catheter-related *S. aureus* bacteremia and thrombosis are to be anticoagulated, it would be prudent to rule out vegetations by transesophageal echocardiography before such therapy is initiated. Some clinicians may wish to withhold anticoagulation in such patients while there is ongoing evidence of high-grade bacteremia. Studies of anticoagulation in patients with septic venous thrombosis due to *S. aureus* will be needed to guide the clinician in the future.

As full-time availability of bedside ultrasound becomes common and as intensivists become more skilled at and reliant upon its use, we will undoubtedly detect many abnormalities that would have gone unnoticed previously. One challenge we will face will be to know when to act on such findings and when to show restraint.

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A simplified approach to the challenging problem of resuscitation of patients who present in pulseless electrical activity*

The vital statistics from 2004 revealed that cardiovascular disease mortality accounted for 36% of all deaths in the United States (one in every 2.8 deaths; 2,398,000 total deaths). Of these deaths, 325,000 occurred out of hospital or within hospital emergency departments (1). Patients with pulseless electrical activity (PEA) account for approximately 20% of the cardiac arrest victims, but within this cohort survival is very poor (4–5%) (2, 3). PEA includes a broad group of pulseless rhythms, including idioventricular rhythms, ventricular escape rhythms, brady-asystolic rhythms, and pseudoelectromechanical dissociation (4). PEA is broadly considered a state of severe shock, because echocardiogram and pressure catheter studies have shown that mechanical contractions are present but too weak to produce a palpable blood pressure (4–6).

The foundation and hope of resuscitation of a PEA or asystolic cardiac arrest is rapid identification and treatment of potentially reversible causes. A search for these causes should begin almost immediately with onset of the resuscitative effort. The American Heart Association has outlined a simple approach based upon six Hs (hypovolemia, hypoxia, hydrogen ion, hypo- or hyperkalemia, hypoglycemia, and hypothermia) and five Ts (toxins, tamponade, tension pneumothorax, thrombosis [coronary or pulmonary], and trauma). The European Resuscitation Council recommends a similar approach focusing on the Hs (hypoxemia, hypovolemia, hyperkalemia, hypokalemia, hypocalcemia, and hypothermia) and Ts (tension pneumothorax, tamponade, therapeutic or toxic substances, and thromboembolism) (7).

Although guidelines for cardiopulmonary resuscitation from the American Heart Association and International Liaison Committee on Resuscitation are widely implemented and taught, the quality of care provided in both simulated and actual cardiac arrest situations diminishes rapidly after training (8–10). For example, in a case series of 176 patients with out-of-hospital cardiac arrest, chest compressions were not given 48% of the time and the compression depth was often too shallow (9). Similarly, in a study of 67 in-hospital arrests, chest compression rates were less than recommended 28% of the time, the depth was often too shallow, and ventilation rates were often too high (10). In both of these studies, the resuscitation was performed by highly trained medical professionals. Underlying the observations made in these studies are the questions of what can be done to translate clinical guidelines into everyday practice more efficiently and how the information can be retained to allow long-term consistency in the delivery of care.

The review and algorithm proposed by Dr. Desbiens (11) in this issue of Critical Care Medicine tackles both of the questions regarding implementation of guidelines and consistency of care. Although a straightforward mnemonic frames the teaching approach advocated by the American Heart Association to assist in identifying potential causes of PEA arrest, Dr. Desbiens argues that simplifying the approach further may improve retention and performance. The foundation of his approach is from historical arguments made by Dr. Miller (12). He maintained that our span of absolute judgment and immediate memory imposes significant limitations on the amount of information that can be received, processed, and remembered. He argued that through organization of acquired information into several dimensions, or a “sequence of chunks,” the natural limitations can be circumvented in part, or at least minimized (12).

Dr. Desbiens proposes a method to break down the approach to PEA into smaller, more digestible chunks. First, he proposes consideration of one of three mechanisms: severe hypovolemia, obstruction to circulation, and pump failure. To
discern among these mechanisms, he recommends performance of chest compressions with simultaneous assessment of the pulse. If there is no pulse with good chest compressions, then the cause is most likely hypovolemia or obstruction to circulation. Obstruction to circulation then forms a second dimension of learning in that it may be due to tension pneumothorax, massive pulmonary embolism, or cardiac tamponade. If there is a pulse, then the resuscitator should consider cardiac pump failure as the principle cause.

Questions arise regarding those Hs and Ts missing from the simplified approach. Dr. Desbiens provides evidence for each of these based upon detailed literature reviews. For example, hypoglycemia and cardiac arrest yielded only one article. The one available article (his reference 24) that involved patients with advanced heart failure provides little evidence to support hypoglycemia as a mechanism underlying PEA (13). Based upon this review and other similar literature reviews, the majority of the Hs and Ts were left out because of lack of supporting data or low prevalences.

Although the simplified approach is logical and based upon simple concepts, it has not been validated. It is unclear whether this sort of model requiring a higher level of thinking during an arrest—such as performing adequate cardiopulmonary resuscitation, feeling a pulse, and then considering a diagnosis—will lead to improved performance and outcomes when compared with considering basic components of a mnemonic. However, with the current survival rates with PEA, such research needs to be encouraged and tested. Furthermore, the validity of the components of these mnemonics require further study to determine their relative importance in treatment of PEA. Leonardo da Vinci said “simplicity is the ultimate sophistication,” a quote that reinforces the strength of a carefully conceived simplistic approach devoid of unnecessary or potentially unneeded variables. Nonetheless, until this approach is validated in the complex environment of cardiac resuscitation, it remains a hypothesis awaiting an answer. For as Albert Einstein stated, “Everything should be made as simple as possible, but not simpler.”

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Arterial catheters are not risk-free spigots*

In this issue of Critical Care Medicine, Dr. Koh and colleagues (1) demonstrate the same incidence density of arterial catheter and central venous catheter colonization. Since colonization preempts catheter-related bloodstream infection (CR-BSI) (2), the risk of CR-BSI between these intravascular devices should be similar. However, these investigators found a greater than two-fold increased incidence density of CR-BSI with central venous compared with arterial catheters. A larger study of 1,140 central venous and 1,038 arterial catheters, both in situ for an average of approximately 9.5 days, found a CR-BSI incidence of 4.6% and 3.7%, respectively (3). In a review of studies with the best methodology, Maki et al. (4) found that the pooled mean incidence density of CR-BSI of short-term, nonmedicated central venous and arterial catheters is 2.9/1000 catheter-days (95% confidence interval 2.6–3.2) and 1.4/1000 catheter-days (95% confidence interval 0.8–2.0), respectively. It may well be that the risk of CR-BSI from arterial catheters is one half to three fourths that of central venous catheters, but the magnitude of these infections is no small matter. If 6 million arterial catheters are used in the United States each year and the risk of CR-BSI is 0.8% (4), then there are approximately 48,000 arterial catheter-related bloodstream infections yearly. Despite this, arterial catheter infections are not noted in recently published guidelines (5) or in studies using prevention bundles of best practice to reduce CR-BSI (6–8). In addition, many physicians pay little attention to the arterial catheter gently pulsating in the wrist of their patients, covered by the bed sheets but manipulated several times daily for often unnecessary blood draws (9, 10).

*See also p. 397.

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What can be done to reduce the risk posed by arterial catheters? Prevention bundles, similar to those used to reduce central venous CR-BSIs (6–8) but specific to arterial catheters, should be developed, studied to measure their impact, and if beneficial implemented in the standard of practice for arterial catheter insertion. Creating a culture of safety in the hospital is of paramount importance. This should include required education for nurses and physicians regarding proper catheter insertion as well as general concepts of catheter infections and their prevention. Insertion kits and carts should contain all components needed for strict aseptic technique during catheter insertion (6–8). One randomized trial found that maximal barrier precautions did not reduce the risk of arterial CR-BSI (11), but this study was underpowered to definitively address the issue with arterial catheters. For now, the insertion kit should include a gown, gloves, and a large drape to permit a generous sterile field. The kit should also include a mask with eye protection. Although some may argue over the benefit of the latter for prevention of CR-BSI, they are needed to reduce risk of bloodstream pathogen exposure. Further studies are needed to address the need for a hat. Cutaneous antisepsis with alcoholic chlorhexidine should be used. Thereafter, the need for continued arterial catheterization should be discussed and justified on daily rounds so that it is abundantly clear that the device should be removed when no longer required for patient care.

Although much of the focus in guidelines and prevention bundles has been on catheter insertion, more attention is needed regarding maintenance of the device once in place. Catheter hubs should be cleaned with an antiseptic before and after accessing, ideally with an alcoholic chlorhexidine preparation (12) or alcohol. One prospective, randomized trial found that needleless catheter connectors were independently associated with reduced catheter colonization (13); however, mounting evidence suggests that connectors with mechanical valves increase risk of CR-BSI in clinical practice (14–17) and use of these devices should be constrained until further data are published regarding the comparative risk of currently marketed needleless systems. Easy access to all inclusive catheter dressing kits should be the norm to allow nurses to perform dressing changes with strict asepsis. A reduced nurse-to-patient ratio in an intensive care unit independently increases the risk of catheter-related infection (18–20). Thus, intensive care units should have enough nurses per patient per shift so that nurses have the time to properly care for intravascular catheters. Unit-based rates of arterial CR-BSI should be monitored using standard surveillance definitions and reported on a regular basis to the intensive care unit nurse and physician directors and the appropriate hospital administrators. Similarly, consideration should be made for measuring compliance with hospital guidelines regarding aseptic technique for catheter insertion in hospital locations where arterial catheters are placed (e.g., intensive care unit, operating room) and reporting the results to department directors and the hospital administration.

Arterial catheters pose a risk of infectious and noninfectious complications to our patients. We must remain vigilant to minimize unintended consequences of their use. There is every reason to believe that compliance with basic infection control practices for arterial catheter insertion and maintenance, and especially removing these catheters as soon as they are no longer necessary for patient care, will reduce the risk of serious complications.

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Cholinesterase inhibitors improve survival in experimental sepsis: A new way to activate the cholinergic anti-inflammatory pathway

Despite recent advances in intensive care treatment and the discovery of antibiotics, sepsis is the third leading cause of death in the developed world (1).

The body’s first defense against invading pathogens or tissue injury is the innate immune system, but since excessive immune responses can be damaging, an anti-inflammatory mechanism (the so-called cholinergic anti-inflammatory pathway) functions to control the pro-inflammatory response and prevent injury (2, 3). The cholinergic anti-inflammatory pathway is a neural mechanism that suppresses the innate inflammatory response and controls inflammation by inhibiting the release of pro-inflammatory cytokines, such as tumor necrosis factor (TNF-α), and other cytokine-producing cells to dampen inflammation (3, 4). The key endogenous mediator of the cholinergic anti-inflammatory pathway is acetylcholine, the principal neurotransmitter of the vagus nerve, which specifically interacts with α7 cholinergic receptors expressed by macrophages and other cell types to inhibit TNF-α production (4). This hard-wired connection between the nervous and immune systems, considered a critical regulator of inflammation, can be activated via central (brain) cholinergic transmission, via direct stimulation of the vagus nerve, or through the use of cholinergic agonists that specifically activate the macrophage α7 subunit of the acetylcholine receptor, as demonstrated in several previous experimental models (5–7). Data from experimental models have recently been confirmed in preliminary clinical research demonstrating that in a human model of abbreviated inflammation (lipopolysaccharide-induced systemic inflammatory responses in normal subjects), nicotine exposure attenuates the febrile response to lipopolysaccharide and promotes a more prominent anti-inflammatory phenotype (8).

In this issue of Critical Care Medicine, Dr. Hofer and colleagues (9) demonstrate that pharmacologic cholinesterase inhibition with physostigmine or neostigmine improves survival in murine experimental sepsis consistent with activation of the cholinergic anti-inflammatory pathway (10). In particular, treatment with physostigmine significantly reduced lethality as efficiently as direct stimulation of the cholinergic anti-inflammatory pathway with nicotine. Administration of cholinesterase inhibitors significantly down-regulated the binding activity of nuclear factor-κB and reduced the concentrations of circulating pro-inflammatory cytokines (TNF-α, interleukin-1β, and interleukin-6) and pulmonary neutrophil invasion. Animals treated with the peripheral cholinesterase inhibitor neostigmine showed no difference compared with physostigmine-treated animals. Hypotension, considered an important marker of septicemia, was significantly more decreased in control animals than physostigmine-treated animals 24 hrs after cecal ligation and puncture.

Treated animals survived significantly longer than controls receiving the solvent, and after survival, there were no further dropouts within an observation period of 1 wk, indicating a true resolution of sepsis. Nevertheless, when treatment was delayed beyond 6 hrs, no significant trend to a reduction in mortality could be achieved.

These data are quite different from previous studies by Akinci et al. (11), which failed to demonstrate effects of neostigmine in an animal model of endotoxin induced septic shock. Nevertheless, both studies evidenced that mortality was increased when higher doses of cholinesterase inhibitors were administered.

In addition, the failure to reduce mortality if the treatment is delayed contradicts the results from other findings (12) demonstrating that nicotine treatment could be delayed for 24 hrs after sepsis in a similar experimental model. But this difference might be at least in part explained by the use of antibiotics, which were not administered in the Dr. Hofer and colleagues’ (9) experiment.

Could the results of Dr. Hofer and colleagues (9) be of interest for clinical use? Cholinesterase inhibitors are already being used clinically in anesthesia, analgesia, and intensive care and for the treatment of several diseases in other medical specialties. Systemic treatment with the cholinesterase inhibitor physostigmine and peripheral neostigmine can activate the cholinergic anti-inflammatory pathway. Therefore, peripheral stimulation of cholinergic receptors is sufficient to confer protection against experimental sepsis: It means that the additional central component of cholinesterase inhibition by physostigmine is not needed to achieve the observed activation of the anti-inflammatory pathway (9).

As pointed out above, cholinesterase inhibition significantly improves survival if administered directly after induction of sepsis, but when treatment was delayed no trend to a reduction in mortality could be achieved. This point appears to be relevant since therapeutic interventions are required within a short time following induction of sepsis, and it could be considered a weakness of the study. Patients are often observed and treated hours or days after instauration of a septic condition, and therefore treatment with cholinesterase inhibition with phys-

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*See also p. 404.

Key Words: cholinergic anti-inflammatory pathway; cholinesterase inhibitors; neostigmine; nicotine; physostigmine; sepsis

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Subglottic secretions and Sutton’s law: A simple and effective approach*

Ventilator-associated pneumonia (VAP) continues to be an important cause of morbidity and mortality in critically ill patients. VAP develops in approximately 10% to 25% of patients undergoing mechanical ventilation. The mean incidence of VAP ranges from 4 to 16 episodes per 1000 ventilator days, depending on the type of intensive care unit (ICU) and the diagnostic and prevention methods used. VAP usually develops if the bacterial inoculums are sufficiently large, if the microorganism is particularly virulent, or if the host’s defenses break down (1, 2).

The primary route of infection of the lungs is through microaspiration of organisms that have colonized the oropharyngeal tract (or to lesser extent the gastrointestinal tract). A high proportion of severely ill patients aspirate routinely. Although frequently regarded as partially protective, the presence of an endotracheal tube permits the aspiration of oropharyngeal material or bacteria of gastrointestinal origin. In the mechanically ventilated patient, leakage of previously colonized oropharyngeal secretions through the endotracheal cuff is a common route of infection. Subglottic secretions accumulate above the endotracheal cuff may progress to the lower respiratory tract by descending along the channels within the folds of the cuff wall (3). For the high-volume, low-pressure endotracheal tube cuffs (HVLP) currently in use, pressures should be monitored to avoid cuff leak and minimize the risk of ischemic airway complications (4).

Pharmacologic and nonpharmacologic methods have been used as preventive measures to reduce VAP. Most of the nonpharmacologic methods attempt to reduce the incidence of aspiration of colonized oropharyngeal secretions through the endotracheal cuff. A persistent endotracheal cuff pressure <20 cm H₂O has been shown to increase the risk for developing VAP, and consequently periodic monitoring of intracuff pressure has been recommended to prevent VAP (5). Continuous or intermittent subglottic suctioning, which decreases the risk of aspiration of secretions that pool around the endotracheal cuff, has been shown to prevent VAP (6–9). A meta-analysis concluded that subglottic secretion drainage was effective in preventing VAP in patients expected to require >72 hrs of mechanical ventilation (10). Another nonpharmacologic strategy to prevent the aspiration of subglottic secretions into the lower respiratory tract is to impede channel formation within

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Key Words: ventilator-associated pneumonia; mechanical ventilation; endotracheal tube; subglottic secretions; positive end-expiratory pressure; endotracheal tube cuff pressure monitoring

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the folds of the endotracheal cuff. Recently, HVLP endotracheal tubes with polyurethane cuffs have been introduced; the membranes of these cuffs are much thinner than those of the polyvinyl chloride cuffs used in conventional HVLP endotracheal tubes and prevent the formation of folds within the cuff, thereby preventing fluid and air leakage (11, 12). A recent randomized clinical study in mechanically ventilated patients (13) compared the incidence of VAP using a conventional HVLP endotracheal tube without subglottic secretion drainage vs. an endotracheal tube with polyurethane cuff and subglottic secretion drainage. Early- and late-onset VAP were significantly reduced (22.1% vs. 7.9%) with the endotracheal tube with polyurethane cuff and subglottic secretion drainage.

In this issue of Critical Care Medicine, Dr. Lucangelo and colleagues (14) compare the leakage around two endotracheal tubes with HVLP cuffs but different cuff composition (polyvinyl chloride vs. polyurethane) and shape (oval-like vs. cylindrical) in the clinical scenario and in the laboratory. Interestingly, better sealing and less aspiration were observed with the endotracheal tube with the cylindrical polyurethane cuff (SealGuard) compared with the endotracheal tube with the oval-like polyvinyl chloride cuff (HiLo). Application of 5 cm H2O positive-end expiratory pressure (PEEP) exerted a counterbalance pressure that was effective in delaying the passage of subglottic secretions around both types of endotracheal tube cuffs in patients as well as in the laboratory. However, the SealGuard avoided the leakage around the cuff to a greater extent. Images from different bronchoscopies in patients and pictures taken at the bench illustrate these findings remarkably. However, the findings of this study cannot be extrapolated to all patients receiving mechanical ventilation for two reasons. First, the authors excluded patients with chronic obstructive lung disease, active pneumonia, obesity, or elevated intraabdominal pressure. Second, patients were sedated and paralyzed; therefore, it remains to be determined whether PEEP would have a similar protective effect against leakage around the endotracheal tube in mechanically ventilated patients breathing actively at different inspiratory loads.

Despite decades of debate, PEEP is currently indicated to ameliorate shunting in patients with acute lung injury or acute respiratory distress syndrome. Furthermore, using small amounts (<5 cm H2O) of PEEP to decrease incomplete exhalation and improve patient-ventilator interaction is considered beneficial for actively breathing patients with expiratory flow limitation (15). A recent multicenter randomized controlled trial showed that application of a PEEP level of 5–8 cm H2O in nonhypoxemic patients had no effect on mortality but significantly reduced the incidence of ventilator-associated pneumonia (16). Among other possible causes, the blocking effect of PEEP on leakage of subglottic secretions around the cuff must be taken into consideration.

When asked why he continued to rob banks after being caught several times, the notorious bank robber Willy Sutton replied, “Because that is where the money is.” In medicine, Sutton’s law—“Go where the money is.”—implies that our main efforts should be aimed at the most likely target. If the main step in the pathophysiology of VAP is the aspiration of contaminated oropharyngeal secretions, preventive measures should be directed at avoiding this step. In this case, the simplest approach is the most effective one.

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Dear SIRS, can MEDS help you predict patient outcome now, really?*

After many years of unsuccessful clinical trials investigating novel therapies, the management of severe sepsis in this century was suddenly revolutionized with several therapeutic approaches (1). Similarly, the definitions for sepsis were also re-examined with the hope of initiating treatment based on a clinical suspicion rather than confirmed culture positivity (2). The use of the systemic inflammatory response syndrome (SIRS) as part of the definitions also has been de-emphasized because of its high sensitivity and lack of specificity (3). The new definition of sepsis now includes “infection, documented or suspected, and some of the signs and symptoms of an inflammatory response” (2).

Meanwhile, the clinical use of SIRS continues as a crucial component of disease recognition for the initiation of early goal-directed therapy (EGDT) and severe sepsis bundles in many hospitals around the world (4, 5). A patient with SIRS, a suspected infection, and lactate ≥4 mmol/L or systolic blood pressure <90 mm Hg after a fluid bolus should receive hemodynamic monitoring to target optimal central venous pressure, mean arterial pressure, and central venous oxygen saturation, with fluid resuscitation, transfusion, vasopressor and/or inotropic support, in addition to early broad-spectrum antibiotics. With 43% to 76% of severe sepsis patients presenting initially to the emergency department (ED) (6–8), timely identification of the appropriate patients for this level of intensive therapy becomes paramount in this setting. A common barrier to implementation of EGDT and the severe sepsis bundles is clinician reluctance in obtaining a lactate level as part of patient identification. For example, we often claim that a patient having a cough, febrile with tachycardia, does not need a lactate level if the patient appears “stable.” Barriers such as this arise possibly from clinicians’ fear of acknowledging that these patients actually have significant risk for poor outcome. It appears that we cannot handle the truth about our under-recognition of severe sepsis. Furthermore, not many hospitals have the facility for an expedited turnaround time for lactate measurements. Thus, an alternative method for quickly predicting outcome in a patient with signs and symptoms of sepsis in the ED seems prudent.

Dr. Shapiro and colleagues (9) developed and internally validated a mortality prediction score, Mortality in Emergency Department Sepsis (MEDS), for patients presenting to the ED with SIRS and a suspected infection as defined by the physician obtaining a blood culture. The score also was shown to be predictive of 1-yr mortality by the same group of investigators (10). Other investigators have noted that MEDS may be better than other scoring systems such as Acute Physiological and Chronic Health Evaluation II (11) or biomarkers such as procalcitonin and C-reactive protein (12). In this issue of Critical Care Medicine, Dr. Sankoff and colleagues (13) performed a multicenter prospective external validation study of MEDS. Four centers participated in the study, enrolling patients within 2 hrs of presentation to the ED who met criteria for SIRS and were admitted to the hospital. The sample size was relatively small, including 385 patients, compared with the original single-center study (9). Only 165 patients met criteria for sepsis with a source of infection. Among these patients, 4% met criteria for severe sepsis and another 10% for septic shock. The mortality groups in this study were similar to those in the original study. The receiver operating characteristics area under the curve was 0.88. The authors then recalibrated the MEDS score using their patient population and showed that the area under the curve for the receiver operating characteristics curve for the recalibrated score was 0.84. This result was troublesome, because we would expect the recalibrated score to perform better in their own risk-adjusted population, but yet it performed worse than the original MEDS score. The authors also found that both the original and recalibrated MEDS scores underestimated actual mortality. This was not surprising, because MEDS was derived from a patient population having a mortality of 5.3% compared with this study’s patient mortality of 8.6%.

An interesting finding of this study was the comparison between MEDS and lactate level. Lactate was obtained in 46% of patients, having a mortality of 11%. Survivors and nonsurvivors had statistically significant different median lactate levels, 2.3 vs. 4.3 mmol/L, respectively. The area under the curve for the receiver operating characteristics curve for lactate level was 0.78, lower than the original and recalibrated MEDS scores. This result challenges existing data advocating a baseline lactate level measured in the ED as a prognosticator for 3-day and in-hospital mortality (14, 15). However, because elevated lactate as a cause of tissue hypoperfusion in sepsis is debatable (16), serial measurements of lactate may be more predictive of outcome than initial lactate (17, 18). Thus, we do not know how MEDS will compare to lactate clearance, or whether mortality prediction will be improved with the combination of MEDS and lactate.

Current physiologic scoring systems in the intensive care setting commonly require the worse physiological variables after 24 hrs of admission. MEDS includes variables that are easily obtainable in the ED, and thus will facilitate the identification of high-risk patients beyond the use of SIRS and infection. The authors suggest that this will allow for initiation of more aggressive therapy, such as EGDT. However, caution is in order regarding the use of MEDS to risk-stratify patients for EGDT, because the septic shock patients who would qualify for EGDT comprise a small percentage in the current study (10%) (13) and in the original study (2.5%) (9). We do not know how many severe sepsis patients had lactate ≥4 mmol/L in both studies. Furthermore, physiologic scoring systems generally were developed to examine the severity of illness over a population of patients, but we tend to misuse them as indicators for therapy, such as the use of the Acute Physiological and Chronic Health Evaluation II scoring system to identify severe sepsis patients for drotrecogin alfalfa (activated) administration. Regardless, a more useful analysis of MEDS would allow a clinician to identify the patient with infection, SIRS, and hypotension refractory to fluids or lactate ≥4 mmol/L with seemingly normal vital signs who will later die, and thus requires immediate at-
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Reversing oversedation in the intensive care unit: The role of pharmacists in energizing guideline efforts and overcoming protocol fatigue*

I am troubled when I make rounds in the critical care units today because of the grotesque and inhuman scenarios that I so frequently encounter . . . what I see these days are paralyzed, sedated patients, lying without motion, appearing to be dead, except for monitors that tell me otherwise.—Thomas L. Petty, MD, 1998

This shocking observation was made by Dr. Petty in an editorial (1) that accompanied one of the first investigations to find that oversedation using continuous infusions could hinder care, lengthen stay, and worsen outcomes in the sickest of patients, those requiring mechanical ventilation (2). Dr. Petty, for our younger readers, was among the first scientists to recognize the acute respiratory distress syndrome in 1967 (3) and to advocate the use of positive end-expiratory pressure for its management in 1971 (4). By virtue of his decades of caring for patients in respiratory distress, his mortifying observation that we maintain patients in states of suspended animation was then, and is still today, hard to refute. Dr. Petty went on to address why this might be:

Why have we regressed to these practices? I am afraid that the conspiracy between the requirements of high acuity care and available pharmacologic therapy has led to the present situation. It is a fact that the awake and alert patient who is anxious or depressed requires a great amount of interaction with the healthcare team.
Our enthusiasm to relieve pain and suffering by aggressively providing analgesia and anxiolysis has been counterproductive by unnecessarily prolonging intensive care stays that aggravate the very pain and anxiety we wish to relieve in our patients. Moreover, as hinted at by Dr. Petty, the sedated patient is easier to care for than the awake and potentially agitated patient, so that bedside providers may oversedate patients. This was proven true by Weinert and Calvin (5), who showed in a large overview of sedative patterns at the University of Minnesota that in the nearly one third of patients who were unarousable, only 2.6% of the nursing assessments considered these patients to be oversedated. Clinical practice guidelines on sedation and analgesia that were jointly issued in 2002 by the American College of Critical Care Medicine and by the American Society of Health-System Pharmacists stressed the importance of monitoring sedation and tapering sedative use (6, 7). However, a tenet of the use of protocols and guidelines is measuring care providers’ compliance in their application (8).

Clinical guidelines and protocols, based on best available evidence and usually developed through multidisciplinary consensus, are increasingly being used in the intensive care unit (ICU) to guide the management of a number of different conditions, such as pneumonia, hyperglycemia, nutrition, and sedation (9). Despite the proven benefits of protocol implementation in the ICU, a number of factors have been shown to affect clinician adherence to guidelines, including their underlying knowledge and attitudes, the incentive for them to change practice, and the organizational culture in which they practice (10). Use of protocols may dissipate over time due to such factors as a change in ICU personnel, a lack of reinforcement, or the implementation of additional protocols in other therapeutic areas that may shift the focus on the ICU caregiver away from the protocol and potentially lead to “protocol fatigue” (11). Proposed strategies to improve guideline adherence include the presence of effective leaders to promote guidelines adoption, education that is individualized to each profession involved in ICU patient care and repeated regularly, and the use of audits and feedback (12).

Sedation protocols have been shown to reduce the duration of mechanical ventilation, length of ICU stay, incidence of ventilator-associated pneumonia, and sedation costs (13, 14). Despite recommendations in the Society of Critical Care Medicine sedation guidelines (7) that protocols be used to manage sedation in the ICU, survey data suggest they are not widely used (15). The potential barriers to the use of sedation protocols are numerous and include a tendency for physicians to prescribe sedation outside of protocol recommendations because they are not familiar with the protocol, because they feel that the protocol does not apply to their own patients or that the use of a protocol will result in oversedation, and because there is a lack of nursing acceptance of the use of protocols (16).

While the role of critical care pharmacists in improving the outcome of patients in the ICU is well established, their role in boosting ICU protocol efforts has only recently been documented (17, 18). In this issue of Critical Care Medicine, Dr. Marshall and colleagues (19) provide strong evidence that the applied efforts of critical care pharmacists are a useful strategy by which to boost compliance with ICU sedation guidelines. In this before-after study, implementation of a daily intervention by ICU pharmacists at an academic medical center that focused on promoting adherence to new institutional sedation guidelines in medical ICU patients receiving continuous sedation led to a decrease in the mean duration of mechanical ventilation of nearly 7 days (338 ± 348 hrs vs. 178 ± 178 hrs, p < .001), which translated into a substantial decrease in both ICU and hospital length of stay. Strengths of this study include the fact that the guidelines were developed through multidisciplinary consensus, that the pre- and postintervention patient groups were well matched, and that ICU caregivers received substantial education concerning the sedation protocol before its implementation.

While the authors demonstrate a strong association between greater compliance with institutional sedation guidelines and improved patient outcomes, the exact mechanism for the substantial decrease in the duration of mechanical ventilation and length of stay that was observed in this study remains unclear. Was it related to the choice of the sedative and anxiolytic agents prescribed, the improved titration of sedation to an established Sedation Agitation Scale sedation goal, the use of an every 4 hrs down titration strategy when patients were deemed to be oversedated, or an improved ability for clinicians to identify and treat delirium? While the number of patients prescribed propofol and benzodiazepines and the average amount of each agent used were equal between groups, the amount of fentanyl that was prescribed between groups was not. The nearly four times greater use of fentanyl in the pre-intervention group may have accounted in part for the greater duration of mechanical ventilation that was observed in this cohort. The retrospective nature of the data collection for the pre-intervention group makes an evaluation of adequacy of sedation challenging given recent evidence suggesting that patients are frequently not documented to be oversedated despite being deemed unarousable on careful clinical exam (5). It is therefore possible that the pre-intervention cohort of patients may have been documented as being adequately sedated but in fact may have been oversedated and thus more difficult to liberate from mechanical ventilation.

Daily interruption of sedation, although not yet widely practiced in ICUs because of the substantial time required for nurses to monitor patients when sedation is stopped and the fact that only one controlled study supports its use, has been shown to lead to a substantial decrease in the duration of mechanical ventilation (20). While one might expect the incorporation of an active sedation down-titration strategy in the protocol to account for the substantial decrease in mechanical ventilation that was observed, the method used to decrease sedation infusions in the study has not been prospectively evaluated in a controlled fashion and constituted only 18% of the pharmacist interventions. Last, given the fact that routine delirium screening was not conducted during the study, the association of delirium with a longer duration of mechanical ventilation is unclear whether interventions focused on reversing delirium played a role in the ability to extubate patients in the postintervention cohort sooner (21).

Although not evaluated in this study, the economic impact of pharmacists enforcing the sedation protocol is likely to be substantial. Given a daily cost of ICU care that exceeds $2,500 at most centers, the average reduction of >3 days in ICU length of stay realized after protocol implementation would conservatively approximate $7,500 per patient. The potential cost savings for the 78 patients in whom the protocol was used over this 3-month study period would be $585,000. In addition, the decreased need for tracheostomies in the postintervention cohort would also be expected to yield additional cost savings. The
Is continuous really continuous?*

The assessment of cardiac output (CO) is a cornerstone in the monitoring of critically ill patients. During the past years, a number of new techniques have been used in clinical practice besides the established pulmonary thermodilution technique (CO\textsubscript{p}) via a pulmonary artery catheter (PAC) (1).

The available devices can be subdivided into invasive (transpulmonary thermodilution, lithium dilution) and noninvasive techniques (Doppler, transthoracic echocardiography, bioimpedance) and intermittent vs. continuous techniques. Regarding invasive techniques, the transpulmonary thermodilution technique combined with continuous arterial pulse contour analysis has gained increasing popularity for several reasons. First, the accuracy and validity of the transpulmonary thermodilution technique are comparable to pulmonary thermodilution (2). Second, the technique requires only an arterial catheter (A. femoralis, A. axillaris) instead of pulmonary arterial cannulation. Third, the technique can be combined with continuous pulse contour analysis (C\textsubscript{p}CO) enabling on-line measurement of CO (3), stroke volumes, and stroke volume variation (4). PACs equipped with a heating fil-

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*See also p. 434.

Key Words: cardiac output; arterial pulse contour; intermittent thermodilution

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ament are likewise able to continuously measure cardiac output (CCO-PAC) (5). While CCO-PAC demonstrated a good correlation to intermittent CO$_r$ even when used over longer time periods (6), the time constant of the CCO device is known to be slow, resulting in a lack of accuracy in situations of rapidly changing hemodynamics (7). On the other hand, the accuracy of arterial pulse contour analysis critically depends on vascular tone, and therefore a calibration with another technique is mandatory to compensate for changes in arterial compliance and resistance. Initially, pulse contour analysis was combined with intermittent pulmonary artery thermodilution; however, this did not help to achieve minor invasiveness. Since it has been demonstrated that pulse contour analysis can be calibrated by intermittent transpulmonary thermodilution, a PAC is no longer necessary when the clinician is interested merely in CO measurements. Still, a number of studies showed controversial results with respect to the minimal recalibration interval of a pulse contour device in the presence of acute changes of vascular tone, which are common in patients with both sepsis and cardiac failure (8, 9).

In the current issue of Critical Care Medicine, Dr. Hamzaoui and colleagues (10) report on the effect of changes in vascular tone on the agreement between pulse contour (CI$_{PC}$) and transpulmonary thermodilution cardiac index (CI$_T$). The authors performed a careful retrospective analysis of 59 patients equipped with a combined transpulmonary thermodilution/pulse contour device (PICCO, Pulsion Medical Systems, Germany). The authors determined the reproducibility of CI$_{PC}$ and CI$_T$ and, more important, assessed the reliability of pulse contour analysis in dependence of the time interval elapsing from the previous calibration. Last, the authors assessed the agreement between CI$_T$ and CI$_{PC}$ measurements obtained in patients experiencing a change in systemic vascular resistance (SVR) $>15\%$ compared with those with changes in SVR $<15\%$. This latter analysis was performed to study the effects of changes in vascular tone, which are a clinically important determinant of cardiovascular function and potentially influence the accuracy of CI$_{PC}$ measurements, which are inherently based on the analysis of vascular compliance and resistance.

The authors found a fair overall agreement between CI$_T$ and CI$_{PC}$ measurements, which was not affected in patients in whom SVR changed $>15\%$.

On the other hand, the accuracy of CI$_{PC}$ measurements apparently declined depending on the time interval elapsing from the previous calibration. At time intervals $>1$ hr of recalibration, the percentage error of CI$_{PC}$ measurements exceeded the generally accepted cutoff value of 30$\%$ (11), both in the overall population and in patients with SVR changes $>15\%$. This finding is concerning because it implies that recalibrations should be performed more frequently than is the case in current clinical practice. While cardiac surgical patients are in cardiac anesthesia, clinicians have learned to frequently recalibrate the CI$_{PC}$ systems, in particular in the presence of profound changes in SVR (e.g., after weaning from cardiopulmonary bypass) (9); clinical routine in the majority of intensive care units has been to recalibrate only every 4–8 hrs, as suggested mainly by observations in cardiac surgical patients in which no decrease in accuracy was found even after periods of up to 44 hrs without recalibration (8).

The data of Dr. Hamzaoui and colleagues (10) are even more intriguing, since by using a retrospective analysis, the authors used a vulnerable statistical design. As the authors state themselves, recalibration was performed at the discretion of the attending physician, either systematically or at times of hemodynamic deterioration and/or during important therapeutic changes. Most probably, recalibrations took place more frequently in hemodynamically unstable patients than in stable patients. It is logically consistent that hemodynamically unstable patients were unintentionally excluded from the observations on longer calibration-free intervals. On the background of the presented data, one has to expect that limits of agreement between CI$_{PC}$ and CI$_T$ would have even increased when hemodynamically unstable patients were included (in whom disagreement between the two methods seems to be more probable from a theoretical point of view than in stable patients). Moreover, the cutoff value of a 15$\%$ change in SVR is rather small, as only slight changes in mean arterial pressure and cardiac index occurred in the patient population.

The results of the retrospective study by Dr. Hamzaoui and colleagues (10) encourage more frequent recalibrations of the arterial pulse contour analysis by intermittent thermodilution as commonly performed. However, slight changes in vascular tone apparently are devoid of major effects on the agreement between CI$_T$ and CI$_{PC}$ measurements. Due to the methodological limitations of a retrospective study, a prospective trial is needed to determine the accuracy and validity of cardiac index measurement in patients with profound changes in vascular tone. This trial should be performed under strictly controlled clinical conditions to enable discrimination between patient-related and technology-related factors, both of which potentially influence the results.

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Noninvasive ventilation, a thing of beauty!*

*A thing of beauty is . . . a sleep
Full of sweet dreams, and health, and quiet breathing.—Endymion, John Keats, 1818

In Greek mythology, Endymion, a handsome youth passionately loved by Selene (the moon) was placed into a perpetual sleep by either Selene or Zeus, because Selene could not bear to have him die.

Prolonged positive pressure ventilation via endotracheal tube, developed during the 1950s poliomyelitis epidemic, was quickly adopted by general intensive care, and in 1958 66 patients with respiratory failure were provided with induced “quiet breathing” by endotracheal intubation and “life support” ventilation in the Massachusetts General Hospital (1). Despite their loved ones’ worst fears, most did not die. Since then, millions of intensive care patients worldwide have received some form of artificial ventilation, while thousands of trials have studied the mode, style, and other variations of ventilation practice in the quest to improve outcome. Some innovations were adopted, while others were rejected, often with little scientific support for either alternative. Noninvasive ventilation (NIV) was first described by Dr. Barach and colleagues in the 1930s (2), administered ad hoc by mask to critically ill patients in the 1980s, and extensively studied in randomized controlled trials in the 1990s. It has become accepted practice in many settings in the new millennium (3–6).

In this issue of Critical Care Medicine, Dr. Schettino and colleagues (7), also from the Massachusetts General Hospital, describe their clinical experience of NIV in the clinical setting. When subjected to the rigors of examination by controlled randomized trials, many ideas that were adopted with initial enthusiasm fail to deliver perceived benefits and are abandoned, or prove to be impractical, unattractive, or inconvenient and fade to obscurity. NIV has done none of these. The ability of NIV to influence intubation rates, morbidity, and death in a wide range of patients with acute respiratory failure under research conditions has been well documented, and the use of NIV is on the increase (6).

Suspicious of the Hawthorne phenomenon, many seasoned or cynical clinicians harbor doubts that the effects obtained under research conditions would translate into clinical efficacy (8). We should be reassured that, in at least some patient groups, NIV in a general clinical setting produces comparable results to the earlier clinical trials.

NIV is not a simple “plug and play” therapy. The Massachusetts General Hospital has an outstanding reputation, and its staff is populated by some of the world’s leading experts in their field. Their success with NIV may have been enhanced by the enthusiastic intervention of motivated clinicians and their considerable experience with the technique. Importantly, the staff, all educated in NIV themselves, undertook an instruction program with each patient, then proceeded with a gentle introduction of ventilatory support.

The Massachusetts General Hospital care model includes the primary clinician supported by the expert respiratory therapist, with general ward or intensive care nurses providing the immediate care. The presence of a respiratory therapist is not ubiquitous, and in other health systems nursing staff, physiotherapists, respiratory physicians, and intensive care specialists have been utilized as the primary resource for an NIV service (6, 9–12). A thorough understanding of the available equipment’s performance characteristics is essential (13). However, the success of an NIV service is more likely to be dependent upon access to timely, high quality advice and the interaction between the patient and clinicians, rather than simple adherence to a prescribed system or acquiring elaborate equipment. Whatever service has evolved, it appears the emphasis upon training, education, communication, and increasing experience breeds success (10, 11, 14). Unfortunately, the cost-effectiveness of NIV may be translated in some environments to an opportunity for budget reductions, at the expense of high-quality service. Sufficient staff training and appropriately resourced service are essential if the results enjoyed by the Massachusetts General Hospital are to be reproduced (11).

Not all of the patients seem to derive the expected benefits of NIV. Perhaps it should not surprise us that those with hypoxic respiratory failure appeared to gain least benefit, nor that outcomes were worse than those in the trials (3, 7).

With NIV, relief from hypoxemia is achieved through a raised mean alveolar pressure, a reduction in tidal derecruit-


*See also p. 441.

Key Words: noninvasive positive pressure ventilation; respiratory failure; chronic obstructive pulmonary disease; cardiogenic pulmonary edema; hypoxic respiratory failure

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ment of alveoli, and/or provision of high oxygen concentrations through a relatively closed system. With invasive ventilation, reduction in alveolar pressure below positive end-expiratory pressure occurs relatively rarely. However, a less than perfect seal of the NIV mask may produce both air entrainment during inspiration and an airway pressure below the “closing” pressure more frequently than during invasive ventilation (13). While the effects of air entrainment can be rapidly corrected by adjusting the mask, or increasing oxygen concentrations, the lowered pressure may result in small airway collapse or alveoli derecruitment. Once collapsed, these structures require much higher pressures to reopen them. Persistent leaks may result in tidal derecruitment, as would time without NIV treatment. Maintaining the patency of the small airways and alveoli ducts using near continuous NIV, while possibly achievable in clinical trials, may be impossible in clinical practice. Thus, the outcomes of these hypoxemic patients using NIV may be sensitive to the Hawthorne phenomena. Of course, NIV usually will temporarily reverse hypoxia, and is a useful tool for permitting orderly assessment and intubation preparation, even if the final outcome is intubation.

Patients suffering from nonhypoxic respiratory failure, where NIV assists with the work of breathing rather than oxygenation, are less sensitive to short periods of lowered support. Mask leaks and removal, when tolerated, do not precipitate subtle and difficult to reverse effects, and thus do not result in long-term disadvantages when lapses in NIV application occur. Thus, the clinical experience mirrors the results from controlled trials.

As Dr. Schettino and colleagues have demonstrated, in the hands of trained, competent, and appropriately supported staff, many patients in a standard clinical setting may enjoy the benefit and beauty of quiet breathing with NIV, without the insult of intubation and invasive ventilation. Now, we just need to work on the sweet dreams and health!

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Optimizing patient–ventilator interaction: How we sync about it?*

Patients suffering from acute hypoxic or hypercapnic respiratory failure are placed on mechanical ventilation to improve gas exchange, reduce (or eliminate) work of breathing, and allow recovery of the respiratory muscles. The most effective way to achieve this goal is by proper synchronization between the patient and the ventilator (1, 2). Patient–ventilator triggering asynchrony (TA) refers to a patient failing to initiate the inspiratory phase on a ventilator in an assist mode, resulting in wasted inspiratory effort; this phenomenon can be identified by careful observation of the ventilator waveforms. Ideally, the patient should demonstrate minimum effort to trigger the ventilator, measured as the change in airway pressure (Paw) between patient effort and gas flow delivery (3). Factors either related to the patient’s condition (respiratory muscle weakness, decreased respiratory drive, and the presence of intrinsic positive end-expiratory pressure) or ventilator setting may increase the work required to trigger (2, 4, 5). Patient-related factors include abnormal respiratory drive or abnormal lung mechanics. On the ventilator side, improper setting of sensing devices, inspiratory flow rate, or level or mode of support can lead to various types of asynchrony. The interaction between the two is more important than the presence of a single factor (1). For example, patient agitation or anxiety can lead to patient–ventilator asynchrony, and on the contrary, asynchrony can result in patient agitation. Therefore, recognizing patient–ventilator asynchrony and optimizing patient–ventilator interaction are essential to achieve appropriate ventilatory support. The presence of TA may unnecessarily prolong mechanical ventilation by hindering the capacity to recognize patient readiness for

*See also p. 455.

Key Words: patient–ventilator interaction; ineffective triggering

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liberation. Failure to account for untriggered breaths may result in underestimation of the true respiratory rate while measuring frequency/tidal volume ratio or during spontaneous weaning trial when the respiratory rate is used to detect a failed trial. This underestimation may explain why lower frequency/tidal volume value (below the traditional threshold of 100 breaths-min\(^{-1}\)) seems to improve predictive accuracy in chronic obstructive pulmonary disease (6, 7). There is also increasing recognition that patient–ventilator asynchrony may portend a poor prognosis and is associated with prolonged mechanical ventilation (5, 8). Chao et al. (8) found that only three of 19 patients (16%) with patient ventilator trigger asynchrony were successfully weaned compared with 56% of patients without asynchrony. Interventions such as adjusting trigger sensitivity, changing to flow triggering and increasing external positive end-expiratory pressure were unsuccessful in eliminating trigger asynchrony.

In the current issue of Critical Care Medicine, Dr. Chen and colleagues (9) propose a novel approach to detecting ineffective triggering in the expiratory phase (ITE). They integrated the waveform flow and pressure deflection in a computer algorithm and utilized a Visual C++ language program to identify ITEs. The authors used an a priori criteria and validated the waveform visual assessment by esophageal balloon monitoring. The working definition of ITE was a decrease in esophageal pressure of >1 cm H\(_2\)O that failed to open the inspiratory valve. The software identified the expiratory phase, detected and calculated the maximum airway flow and pressure deflection, and an algorithm was used to verify the wasted inspiratory efforts. The focus on the study was to detect the wasted efforts in the expiratory phase, in which there is no active ventilator pump. The study found that 58% of their patients had ITE, and the authors validated their method with both sensitivity and specificity exceeding 90%. The algorithm demonstrated a similar level of detecting ITE as fellows blinded to the purpose of the study who analyzed the waveform after removing the esophageal balloon. The authors did a commendable job analyzing and validating their algorithm for detecting single and multiple ITEs while controlling for the ventilator triggering method. They observed larger deflections in the single ITEs with pressure triggering in comparison with flow triggering, as noted in previous studies. Although the protocol was designed for minimal pressure of 0.01 cm H\(_2\)O and flow value of 0.1 L/min, the optimum values determined by the receiver operating characteristics curve were 0.45 cm H\(_2\)O and 5.45 L/min, respectively. The algorithm was less robust in detecting multiple events. In this study, the authors provided a noninvasive tool to record ITE during daily ventilatory care. The algorithm, however, has a few deficiencies that render it not ready for prime-time introduction. The algorithm only detects one type of patient–ventilator interaction and has limited capacity to recognize other types of trigger-related asynchrony (posttrigger delay, autocycling, or double triggering). Should it be implanted in a ventilator in its current form, there would more sources for misclassification and possibility to misguide clinicians. In addition, the presence of artifacts in the waveform arising from airway secretion, water in the ventilator tubing, or cardiac pulsation may reduce the specificity of the algorithm. With increasing databases and further refinement of the algorithm, a better correlation would be present. In addition, this method is not validated for spontaneously breathing patients, such patients during their weaning trial on pressure assist. Another shortcoming is that the optimum level of flow and pressures to detect trigger asynchrony may vary from one patient to the next and also in the same patient, depending on the change in lung mechanics, level of sedation, and the extent of ventilatory support; therefore, the reliability of this method alone without visual assessment of the ventilator waveform may be problematic.

The concept of utilizing software to automatically recognize asynchrony has been previously explored. Mulqueeny et al. (10) proposed a similar “real-time” method to detect ineffective triggering, and others suggested the possibility to automatically optimize patient–ventilator interaction by either utilizing a signal generated by the equation of motion (11) or automatic adjustment of trigger sensitivity (12, 13).

The study by Dr. Chen and colleagues (9) presents a continuous effort to produce an innovative computerized method that can be integrated in a ventilator for real-time identification of asynchrony. The benefit and clinical application of this method are uncertain: how close to real time should we be monitoring asynchrony in daily ventilatory care? More importantly, what (and how much) effort should we invest in eliminating TA once identified? Failure to trigger may result from increased intrinsic positive end-expiratory pressure, increased airways resistance, increased elastance, decreased respiratory drive, respiratory muscle weakness or fatigue, or improper settings for triggering (14). Therefore, to eliminate TA, we should aim to correct these processes in addition to using optimal trigger sensitivity settings (e.g., switching from pressure trigger to flow trigger during assist control ventilation may reduce the work of breathing). It is unclear whether we can always safely and effectively eliminate TA and if that would translate into tangible clinical benefits and improve outcome. Chao et al. (8) demonstrated that some strategies directed at eliminating TA may result in imposing a fatigue load on the respiratory muscles. There is a possibility that the presence of TA may be a marker of diseased respiratory control or severely deconditioned respiratory muscles instead of a phenomenon that should be corrected. This may explain its association with poor outcome and prolonged mechanical ventilation. Automatic detection of wasted efforts might be useful during weaning trials. A method that accounts for untriggered breathing effort is the assessment of weaning—by using the total respiratory efforts, triggered and untriggered, to determine the value of frequency/tidal volume ratio or the outcome of a spontaneous breathing trial. This may avoid underestimation of the true respiratory effort and potentially improve the predictive values of those variables. New closed-loop modes of mechanical ventilation designed to improve triggering and ventilation interaction provide more comfort by decreasing respiratory drive during the triggering phase (15–17). Although the physiologic basis for these modes are sound, well-designed clinical investigation to demonstrate their benefit and efficacy is lacking. Awaiting further studies to demonstrate the benefit of eliminating TA, an algorithm, such as presented by Dr. Chen and colleagues (9), would alert clinicians to the potential importance of optimizing patient–ventilator synchrony.

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identifying effective treatment is the first step in improving patient outcome. However, the impact that any intervention has in a patient population depends on how consistently it is administered. Deviation from the indications or the correct application of a single treatment plan can independently cause variable and negative outcomes regardless of how effective the treatment potentially can be. Consequently, the way that any treatment is applied can have as much impact as invention in modifying outcomes in patient populations. This explains the avid interest in developing clinical methodology that creates a uniform approach to the diagnosis and treatment of specific disease states. Evidence-based protocols, guidelines, and recommendations are the product of this line of inquiry.

The same reasoning used to defend the implementation of uniform treatment plans also applies to the process of formulating a prognosis. Patient autonomy is now recognized as an essential element in any clinical care plan (1). Within the context of western culture, physicians are obligated to provide patients with reasonably accurate information about their prognoses. While there are a number of studies that measure life expectancy for specific diseases, physicians often filter this information through their personal experience (2). This naturally causes variation in prognostic accuracy among physicians that is then relayed to the patients (3). Very little is known about the factors that actually influence the decision-making process and how these modify the use of treatment protocols or estimates of prognosis. In this issue of Critical Care Medicine, Dr. Quartin and colleagues (4) try to tackle the problem of prognostic variability.

This study joins a small collection of publications that attempt to dissect the decision-making process to identify enduring subjective elements that derail the application of otherwise effective processes such as protocol use or making a prognosis (5). In their study, Dr. Quartin and colleagues test how three factors influence a physician’s estimate of short- and long-term prognoses. These factors were a) the context in which a case is presented (the presence of more than one disease process); b) the order in which the physician encounters additional health problems; and c) framing questions about survival in a positive or negative manner (4). All three factors previously have been shown to influence medical decision-making when deliberating other issues such as patient treatment plans (5–7). Thus, the authors had sound evidence for choosing their test variables. Dr. Quartin and colleagues created imaginary clinical scenarios to test decision-making. They presented the study participants with one of two cases and then mixed and matched these with an additional one of two case scenarios to assess decision-making. They presented the results using a standard survey tool, providing the participants with a limited number of possible answers. This approach requires the participants to choose from a very small repertoire of possibilities. Based upon the findings, the investigators concluded something that is already well known: A group of physicians will make different decisions when given identical information, but they argue that our understanding is improved by identifying these three factors as a cause of variable physician responses.

Within the limitations of the study design, these are valid and important findings. However, the study design substantially veers from reality given that the process of formulating a prognosis is much more complex than the model used by Dr.

Can we really randomize the thought process?*

*See also p. 462.

Key Words: sepsis; septic shock; intensive care units; comorbidity; physician-patient relations; decision-making

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Quartin and colleagues implies. Making a prognosis requires physicians to weigh the importance of a patient’s underlying disease and comorbid disease, and the types of treatment available. Physicians must use the limited amount of available objective information to proceed through a complex analysis of the interaction between these variables. It is impossible to control all of the variables except for those few being tested in the study design. The investigators attempted to control for the effect of other variables by instructing the participants to ignore additional information that was purposefully provided. Because physicians are trained to be inclusive, why would they ignore additional patient information? Rather, the study was designed to intentionally “trip” the participant while walking down the decisional pathway.

The investigators also omitted an important point: They cannot control for a lack of evidence that is endemic in their own clinical scenarios. This pertains to the deficit of evidence on outcomes in patients with more than one disease. History has proven that a lack of evidence is a void that is usually filled with personal impression. This may well be what the investigators uncovered in their study cohort. The reader will then naturally ask if the findings of the study are really due to three simple variables, or if these variables are really markers for other more complex factors that the study design did not have the power to isolate.

It is quite easy to find an Achilles’ heel in any study that examines how people think. This is particularly true when the analysis focuses upon the process of medical decision-making. Omissions always can be found in the study design or analysis of this type of research, because the process under investigation is inherently complex and there are no all-inclusive analytic tools or designs (8). Medical research is built from evidence, and the apparent gaps in studies that focus upon decisional processes may make some readers uncomfortable. However, these gaps can be tolerated as long as they are made obvious to the reader. The information that emerges from these studies helps the medical community to understand the pitfalls in their own decision-making. After all, even if physicians had more outcome evidence, they would probably still differ in their decisions. The unproductive variability can only be contained by adding structure to the method that physicians use to make decisions. The latter requires a thorough understanding of the process itself. Studies such as the one by Dr. Quartin and colleagues are the bold starting points for developing a more sophisticated methodologic approach to understanding how physicians make decisions.

The rapid response team paradox: Why doesn’t anyone call for help?*

The medical emergency team (MET) or rapid response team (RRT) system is a system of care for clinically unstable patients in the general ward areas of hospitals. When observations at a patient’s bedside breach predetermined levels of abnormality or the bedside nursing staff is worried about a patient’s condition, they can call a resuscitation team to attend the patient (1). The assumption for this system of care is that resuscitation of unstable patients is more likely to succeed if commenced as soon as possible after clinical instability is discovered, and in particular before the patient has a cardiac arrest. For obvious ethical reasons, this assumption has never been tested. However, numerous studies describe poor patient outcomes not only from in-hospital cardiac arrests (2, 3) but also from unplanned intensive care unit admissions from general wards (4, 5). Furthermore, a significant body of research documents that these events are often preceded by significant periods of documented clinical instability (2, 6–9).

Despite this rationale for MET/RRT systems and their endorsement by the Institute for Health Care Improvement in the United States (10) and the Quality Council in Australia (11), the data to support their effectiveness are equivocal. In 2002, our group reported a 50% case mix-adjusted reduction in our hospital cardiac arrest incidence from 1996 to 1999 with the implementation of a MET system (1). Three other studies have since reported similar findings with MET implementation (12–14). We have followed up on our initial results with data from the last 6 yrs, during which we have demonstrated a 24% annual reduction in cardiac arrest incidence in our hospital.
However, these studies have been criticized because we used a historical control before-and-after methodology (16, 17). On the other hand, the only large randomized prospective study of MET implementation, the MERIT study (18), did not demonstrate a significant reduction in a composite outcome that combined the incidence of cardiac arrest, unexpected death, and unplanned intensive care unit admission (5.86 vs. 5.31, \( p = .64 \)).

A clue regarding the discrepancy in results between the historical control single-center studies (1, 12–15) and the MERIT study is given in Table 2 of the MERIT study (18). This table shows that in a large number of instances where the composite outcome occurred, the patient had MET call criteria. Yet medical/nursing staff did not call the MET. For patients in the MET hospitals who had a cardiac arrest and demonstrated MET calling criteria >15 mins before the cardiac arrest, the MET team was not called in 30% of instances. Likewise, for unplanned intensive care unit admission and unexpected hospital death, the incidence of failure to call the MET was 51% and 50%, respectively. Thus, the MERIT study could not measure MET effectiveness simply because the randomized intervention often was not received by the patient. These findings then raise an obvious question: Why did the bedside clinical staff not activate the MET? In a voluntary survey of staff in the 12 MET intervention hospitals in the MERIT study, MET utilization was related to staff understanding of the MET system and a general positive perception of the individual’s hospital to accept change (19).

In this issue of Critical Care Medicine, Mr. Downey and colleagues (20) further describe this phenomenon. These authors started with the hypothesis that delay in activating the MET should be more common and longer in patients with an acute change in conscious state (defined as a sudden decrease in Glasgow Coma Scale score of \( \geq 2 \) points or the development of delirium) than in patients with acute cardiac arrhythmia (defined as heart rate <40 or \( >120 \) beats/min). The authors then measured that delay (defined as MET activation time >30 mins from the time of documentation of the trigger observation) in these two groups. More important, impact of that delay on 30-day mortality was assessed. This study was done as a retrospective analysis of two cohorts of 100 patients in a single university teaching hospital with a MET system in place since 2000. There was a trend to increased delay in the conscious state group in both incidence (35% vs. 24%) and duration (16 vs. 13 hrs), but this difference was not statistically significant (\( p = .09 \)). The authors then pooled the two groups to find that 59 of the 200 MET calls were delayed (29.5%). The 30-day mortality rate for patients who had MET call delay was 37% vs. 22% for patients who were attended by the MET within 30 mins of a documented deterioration (\( p = .025 \)). All of these differences were the same when patients with not-for-resuscitation orders were excluded. The fact that in this study, patients who received prompt MET intervention did better than patients who received standard care, at least for a period of time, by default supports the MET system of care.

Despite these findings, the question raised by the MERIT study remains the same: Why did nobody call for help? This is even the case in a hospital with a mature MET system that has in-service, educational, and audit support and that has demonstrated international leadership in MET implementation (12, 20). Sadly, our hospital has experienced the same phenomenon (21). Interestingly, the Austin hospital group previously reported the results of a survey of their own hospital ward nursing staff, which reveals that when confronted with a patient who fulfilled MET call criteria, these staff would still call the parent clinical unit rather than activate the MET (22). In other words, despite the plethora of in-service education and audit that the Austin hospital has devoted to MET implementation, a significant minority of staff would still rely on the traditional hierarchical referral model of care instead of calling the MET.

These findings lead us to the rather awkward conclusion that we as critical care physicians have a better understanding of the management and pathophysiology of defined clinical syndromes of critical illness, such as sepsis and myocardial ischemia, than we do of the way that clinical care is delivered to critically ill patients in the wards of our own hospitals. It would similarly be easy to conclude that our colleagues in the general ward areas, more often than not junior and inexperienced, are inappropriately managing such cases. However, invariably when one performs a root cause analysis of such cases, we uncover the phenomenon of “clinical futile cycles.” Clinical futile cycles occur when a lot of clinical activity (all of it with good intention) is directed at the patient, but little of this activity relieves the dire circumstances of the patient (15). Frequent examples of this include the surgical team seeking a cardiology consult for the overtly septic postoperative patient because of the narrow complex tachycardia of 150 beats/min or obtaining advanced imaging to make a diagnosis in the severely hypoxic patient. All such clinical activities have merit, but they are invariably time consuming and can delay appropriate resuscitation.

What conclusions can we draw from the evolving literature on METs and RRTs? First, as critical care physicians, we need to understand more about the pathophysiology of critical illness in our own hospitals. More specifically, we need to discover and then dissolve the barriers that prevent staff from calling for appropriate and timely help for their patients. We also need to understand more clearly the relationship between resuscitation status and the use of teams, such as the MET (23). Second, regardless of one’s view regarding the value or otherwise of METs and RRTs, we need to decide who should resuscitate critically ill hospital patients. As specialists trained in resuscitation and management of critically ill patients, we should not wash our hands of critically ill general ward patients. At the very least, we should guide, educate, and support our colleagues in the general wards. It would be totally unacceptable for a cardiac surgeon to perform orthopedic surgery or a hematologist to attend a patient with severe asthma. Similarly, critical illness should be managed by specialists with training in that area. Third, the health information communication technology industry needs to demonstrate much greater innovation in developing new solutions that provide real-time patient information to healthcare providers, including patient alerts and alert logic that ensure appropriate and timely clinical responses. Fourth, education and training of all staff in the management of the complex critically ill ward patient need to be a priority. In particular, we need a greater focus on team training, skill development, and communication. Finally, we need to consider the perspective of our patients. “Right care, right now” should be a patient right.

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Critical role of p38 mitogen protein kinase in sepsis*

Within the context of critical care events, such as trauma, hemorrhagic shock, sepsis, and many other inflammatory conditions, p38 mitogen-activated protein kinase (MAPK) signaling has become an important regulatory protein (1, 2). Whether p38 MAPK activation is a significant component of septic lung injury through the signaling steps that regulate CXC chemokine-induced leukocyte recruitment is the main concern of Dr. Asaduzzaman and colleagues (3), as published in this issue of Critical Care Medicine.

Ischemic or septic injury activates chemokines, which stimulate leukocyte adhesion and extravasation with continuation of leukocyte migration (1–3). This is a simple and at the same time complex process. It is enlightening to recognize that p38 MAPK can regulate lipopolysaccharide-associated increased secretion of tumor necrosis factor-α and chemokine response from macrophages (4). Furthermore, the control of adhesion molecules of the intercellular adhesion molecule-1 type can be dependent on the effect of this specific MAPK (5). Many references point toward the multifaceted role of p38 MAPK in specific and generalized pathologic inflammatory conditions.

The p38 MAPK was discovered in 1994 as scientists determined the specific chemical characteristics of this important molecule (1). p38 MAPK belongs to a family of serine/threonine protein kinases with four different isoforms, of which the α is the most studied. As time advanced, substrates, homologs, cell processes, and many other details surrounding this molecule were described. Studies of p38 MAPK in sepsis, ischemia, and reperfusion have provided new information about the mechanisms of the particular pathology in question and the role of this compound. Several inhibitors of p38 MAPK have been discovered as well, mostly related to the pyridinylimidazole structure.

In 2001, Song et al. (6) studied for the first time the contribution of p38 MAPK activation to immune dysfunction in polymicrobial sepsis. The state of sepsis was induced by cecal ligation and puncture (CLP) in C3H/HeN male mice. The animals were given 100 mg/kg body weight of a p38 MAPK inhibitor (SB 203580) at 12 hrs post-CLP. The inhibition of p38 MAPK suppressed interleukin-10 levels as well as interleu-
kin-10 and interleukin-4 gene expression. Most important, delayed \textit{in vivo} p38 MAPK inhibition improved survival after CLP. Improved survival is a notable practical implication of this experiment.

A year later, in 2002, Song et al. (7) advanced their previous findings by introducing the concept that nitric oxide from inducible nitric oxide synthase (iNOS) regulated part of p38 MAPK activity in sepsis-induced dysfunction of C57BL/6 mice. Using iNOS knockout (iNOS \(-/-\)) 24 hrs after CLP, the authors found that p38 MAPK phosphorylation was inhibited in splenic cells taken from septic mice. In 2006, Guo et al. (8) demonstrated divergent signaling pathways in phagocytes during sepsis. When using the same CLP model in mice, those authors found increased CXC chemokine production, impaired signaling in neutrophils, and enhanced signaling in alveolar macrophages. The activation of p38 and p42/p44 MAPKs occurred in sham neutrophils but not in CLP neutrophils, whereas MAPK phosphorylation was evident in sham and CLP alveolar macrophages. Even though the environment was one of chemokine induction and neutrophil accumulation in lung sepsis, the signaling pathways were not consistently expressed under the conditions analyzed.

Dr. Asaduzzaman and colleagues (3) used a second-generation p38 MAPK inhibitor (SB 239063) to mitigate lung injury associated with polymicrobial sepsis in a CLP model in C57BL/6 mice. The administration of the p38 MAPK inhibitor occurred immediately before CLP induction. At 4 mg/kg of the inhibitor, the histology response, neutrophil infiltration, chemokine levels, and p38 MAPK activity were significantly suppressed. When the authors used another p38 MAPK inhibitor, SKF 86002, the results were similar to those obtained with SB 239063.

Despite the convincing data presented by Dr. Asaduzzaman and colleagues (3), some areas need to be resolved before further consideration for application in the clinical arena, especially the optimal time of administration that needs to be studied at different times after CLP injury. An increased characterization of the signaling response, including other MAPKs, such as extracellular signal-regulated protein kinases and c-Jun NH2-terminal protein kinases, and other major pathways, would be of great interest. Survival of septic animals after p38 MAPK inhibition is worth evaluating. Sepsis, as we know by the plethora of previous studies, is a complex and humbling problem that needs complete definition before improved management can occur in clinical consideration. In this case, with the studies of Lee et al. (1), Song et al. (6, 7), Guo et al. (8), Yan et al. (5), Schnyder-Candrian et al. (4), and other researchers, the work of Dr. Asaduzzaman and his group should receive more attention in the context of sepsis response.

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REFERENCES


To cope with oxygen: A long and still tumultuous story for life*

Since the earliest origin, life has had a confrontational relationship with oxygen. Oxygen, which is among the strongest oxidizing agents, can damage all biological molecules due to its high oxidizing potential. However, the same property renders oxygen the best final electron acceptor in the respiratory chain pathway, which allows a highly sustained rate of adenosine triphosphate synthesis from the redox energy delivered by the nutrient oxidation. The increase of oxygen’s partial pressure in the terrestrial atmosphere, which resulted from the successful evolution of photosynthetic organisms, paralleled its toxicity. It is believed that the accumulation of oxygen was responsible for the largest life extinction on earth, so-called “holocaust by oxygen” by the Nobel Prize winner Christian de Duve (1). As a result, living organisms had to develop powerful antioxidant strategies to survive, both despite and thanks to oxygen. Evolutionary selection of cytochrome c oxidase activity, followed by a complete respiratory chain in mitochondrion ancestors, permitted organisms not only to reduce oxygen back to water, preventing any further accumulation, but also to produce considerable amounts of adenosine triphosphate. Hence, an intimate and subtle compromise between pro- and antioxidant strategies is a prerequisite for life, under physiologic and pathophysiological conditions.

The use of oxygen as a therapeutic agent also involves this ambiguity.

*See also p. 495.

Key Words: hyperoxia; oxidative stress; sepsis; apoptosis; tissue perfusion

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Whereas oxygen is considered a major lifesaving agent by some (2), it is also regarded as potentially harmful (3). However, both positions share a similar feature: relatively poor scientific demonstration, at least in adult patients (4). In a very interesting experimental study, published in this issue of Critical Care Medicine, Dr. Barth and coworkers (5) demonstrated that several variables regarded as clinically relevant were improved in septic pigs that were exposed to hyperoxic atmosphere (pure oxygen). In this work, it was shown clearly that 24 hrs of hyperoxic mechanical ventilation may not be regarded as deleterious to lung mechanics or pulmonary gas exchange. Such a result is contrasted with other literature observations which indicated that pure oxygen is harmful for the lung (6). The second main conclusion by Dr. Barth and coworkers suggests a redistribution of blood flow in hyperoxia, favoring the splanchnic bed, as already suggested in hyperbaric conditions (7), and probably also the kidney, this being accompanied by improved renal function, pH, base excess, and redox state (lactate-pyruvate) abnormalities induced by the severe septic conditions. The third main conclusion points to the significant decrease in cellular apoptotic events in both lung and liver, a finding that is contrasted with other data from the literature (5, 8). Few other effects presented in this article appeared of potential interest, such as the increase in the respiratory quotient ($V_{\text{CO}_2}/V_{\text{O}_2}$) and glucose oxidation and the lack of effect on inflammatory and antioxidant status.

Oxygen toxicity varies largely according to age (4), species (9), and genetic characteristics (10). In addition, metabolic and inflammatory status is significant; thus, the severe septic state of the animals studied here probably influences the effects of hyperoxia in comparison with healthy physiologic conditions. Indeed, coexisting inflammatory response and oxidative stress may interfere with the response to hyperoxia by modulating the fine-tuning between pro- and antioxidant pathways. Cellular toxicity of hyperoxia is well established (11), leading to cell apoptosis (8) via cytochrome c release in the cytoplasm in relation to mitochondrial permeability transition, since this phenomenon is prevented by cyclosporin A (12). The complex relationship between inflammation and oxygen toxicity is illustrated by the fact that interleukin-13 gene deletion is accompanied by an increased mortality (13), while interleukin-11 induction is able to induce a 100% survival to pure oxygen exposure, a condition consistently leading to death in this model (14).

The kinetic aspect is another major variable to be considered. Indeed, whereas most works evidencing a harmful effect in vivo involved long exposure, in the work by Dr. Barth and coworkers (5), septic pigs were exposed to pure oxygen for 24 hrs only, and surprisingly none of the inflammatory and oxidative stress variables were affected by hyperoxia. However, inflammation and oxidative stress induced by the septic state were clearly evidenced in the two groups. This is especially important, since a biphasic effect has been reported. In a classic study investigating oxygen toxicity on flies, Sohal et al. (15) reported that long-term exposure to pure oxygen was responsible for a dramatic decrease in life span, while shorter and intermittent exposure (3 days) to the same hyperoxic atmosphere resulted in a substantial and significant increase in life span. The preconditioning effect reported for hyperoxia might be related to a similar mechanism (16). Hence, the actual power of the antioxidant-scavenging path is probably re-sized permanently according to appropriate signals. Several results point to the level of intracellular reactive oxygen species as the signal and the trigger for antioxidant enzyme regulation at the transcriptional level (17), hydrogen peroxide being a putative candidate (18).

The use of hyperoxia as a therapeutic agent is still a very challenging issue. Indeed, its effect on inflammatory response and oxidative stress appears to be highly dependent on many different variables related to the physio/pathophysiological environment. According to the experimental work proposed by Dr. Barth and coworkers (5), interesting and clinically relevant effects could be expected from the use of hyperoxia. However, long-term studies are warranted to confirm such a potentially important therapeutic perspective.

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REFERENCES
Maldistribution of interalveolar perfusion—one early step in the pathogenesis of lung injury?*

The lungs of critically ill patients are at a constant threat of diverse inflammatory reactions. Indeed, critically ill patients may develop acute lung injury (ALI) or its more severe form, acute respiratory distress syndrome (ARDS), which can be the result of either a pulmonary insult such as pneumonia or an indirect insult such as sepsis from an extrapulmonary source (1, 2). Although the mechanisms of sepsis-induced ALI/ARDS are indefinite, we know it is characterized by an exaggerated inflammatory and procoagulant response with activation of endothelial cells and influx of neutrophils.

In an abdominal sepsis model in rats, Dr. Conhaim and colleagues (3) explored the effect of sepsis on the distribution of interalveolar perfusion. The investigators hypothesized the effects of sepsis on the lung may be the consequence of early disturbances in interalveolar perfusion. Sepsis was induced by placing gelatin capsules containing Escherichia coli and Bacteroides fragilis into the abdomens of rats. Empty capsules were placed into the abdomens of control rats. After 24 hrs, fluorescent latex particles were infused intravenously. Confocal microscopy was used to prepare maps of latex particle trapping patterns in air-dried lungs. Sepsis caused pulmonary inflammation, as indicated by cell counts in histological images that were three-fold higher in septic lungs than in controls. Also, lung lavage showed seven-fold higher amounts of plasma in the lungs of septic rats than in nonseptic animals. Imaging showed that perfusion was markedly disturbed at both regional and alveolar levels in septic lungs compared with those of controls. Analysis of latex particle trapping patterns revealed statistically more clustering down to tissue volumes less than that of ten alveoli in septic lungs compared with controls. Thus, perfusion was significantly more inhomogeneous in septic lungs than in controls. Of interest, this sepsis-induced maldistribution of interalveolar perfusion resembled earlier findings in lungs of rats that were hemorrhaged (4, 5).

A strength of this study is that the investigators did not use the common lipopolysaccharide model of sepsis, which can be criticized for its lack of clinical relevance. Second, by using bacteria-containing gelatin capsules, the septic challenge may have been more uniform than in the more common cecal ligation plus puncture model, in which the inoculum may vary from one animal to the other. However, the results may not be generalizable to all forms of ALI/ARDS. Certainly, differences in the pathogenesis may exist between direct forms of ALI/ARDS (e.g., pneumonia, the most frequent cause of ALI/ARDS [1, 2]) and the presently studied indirect insult. Another weakness of this study is the lack of other pulmonary challenges frequently involved in critically ill patients, such as mechanical ventilation. Mechanical ventilation may aggravate pulmonary inflammation (also known as ventilator-induced lung injury), causing substantial additional morbidity and mortality (6–9). Mechanical ventilation frequently is mandatory in septic patients. Therefore, adding mechanical ventilation to the model would improve clinical significance. Also, general treatment measures were lacking in the study protocol, such as antimicrobial therapy and fluid resuscitation. It can be questioned whether these additional therapeutic strategies would have altered the findings in this study.

Nevertheless, the study by Dr. Conhaim and colleagues (3) gives important insights into early changes in the lungs with sepsis. Interestingly, disturbed alveolar perfusion distribution was found while arterial blood gas values recorded from septic animals showed no significant changes in P0₂ values compared with controls; i.e., these changes were present very early in the pathogenesis of sepsis-induced ALI. Accordingly, it can be hypothesized that disturbed alveolar perfusion distribution is one first step in the pathogenesis of ALI. However, it may not be the only change found early with development of lung injury. Clinical studies in patients at risk for ALI/ARDS, but not yet suffering from the clinical manifestations, have shown that they already have changes in pulmonary inflammation and coagulation (10).

The explanation for the disturbance of alveolar perfusion in sepsis is challenging. The concomitant influx of neutrophils may point to a cellular-mediated mechanism of malperfusion. This may not be the sole explanation, as the authors have previously found perfusion maldistribution in lungs perfused with a cell-free solution. Hypoxic vasoconstriction by arterial smooth muscle is unlikely, because malperfusion occurred in very small lung tissue volumes. Whether endothelial cells contribute to vasoconstriction early in the course of ALI remains to be determined. Although arterial oxygen tension was normal, endothelial modulation of vascular tone may be an early event. An explanation that the authors offer for the disturbed alveolar perfusion distribution is the formation of microthrombi. Systemic coagulopathy is intrinsic to sepsis (11); in addition, thrombus formation has been shown to be associated with ALI in animal studies following complement activation and ischemia-reperfusion injury. Obstruction of microvessels by microthrombi would explain the perfusion maldistribution as recorded in the present study, even when gas exchange is still unaffected. Indeed, with the improvement of imaging techniques, pulmonary embolism in the absence of clinical symptoms has been described (12). Of note, pulmonary fibrin deposition is an important feature of ALI/ARDS. The mechanisms that contribute to pulmonary coagulopathy are localized tissue factor-mediated thrombin generation and depression of bronchoalveolar urokinase plasminogen activator–mediated fibrinolysis, caused by the increase of plasminogen activator inhibitors. Some studies also suggest that pulmonary coagulopathy is a feature of ventilator-induced lung injury. Theoretical considerations suggest that anticoagulant therapy may influence the early finding of disturbed alveolar perfusion distribution. Therefore, future studies should explore this possibility while applying one of the several anticoagulant strategies pres-

*See also p. 511.

Key Words: acute lung injury; sepsis; coagulopathy; alveolar perfusion

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Pathophysiology of tissue acidosis in septic shock: Blocked microcirculation or impaired cellular respiration?

Tissue acidosis is the biological hallmark of cellular energetic failure, which may result in organ dysfunction and ultimately death, and it originates from deficient oxygen and substrate supply or impaired cellular respiration. Although the pathophysiological mechanisms of tissue acidosis are fairly well-defined during aortic cross-clamping and hemorrhagic shock (i.e., typical clinical examples of the former) and carbon monoxide and cyanide poisoning (i.e., classic clinical representatives of the latter), the respective roles of a disturbed microcirculation and impaired mitochondrial function for septic shock–related tissue dysoxia are still a matter of debate. In fact, ample literature is available, both in experimental animals and in patients, that either of these two phenomena is directly related to tissue acidosis or organ dysfunction in septic shock. More than 10 yrs ago, Faruqhar et al. (1) demonstrated that intestinal villous capillary density decreased in resuscitated rodent cecal ligation and perforation–induced septic shock, and in endotoxic pigs, we showed that the progressive increase in the ileal mucosal-arterial PCO2 gap and, subsequently, the portal venous lactate/pyruvate ratios were associated with impaired villous microcirculation, despite aggressive resuscitation that had allowed maintaining a hyperdynamic circulatory state with supranormal regional microcirculatory blood flow (2). Ellis et al. (3) finally reported that a maldistribution of microvascular blood flow caused impaired cellular oxygen extraction. Patient data confirmed these experimental findings: in landmark studies using orthogonal polarization spectrophotometry imaging, De Backer et al. (4) demonstrated that microvascular blood flow is altered in patients with sepsis, and that, if persistent, these alterations are associated with organ failure and lethal outcome (5, 6). In addition, regional microcirculatory blood flow was shown to be the main determinant of tissue CO2 tension, a marker of tissue acidosis (7).

Finally, based on the concept that excess nitric oxide (NO) is crucial to maintain microvascular perfusion under these conditions (8), Spronk et al. (9) showed that nitroglycerin could at least partially restore the impaired capillary blood flow. The role of NO in this context, however, is equivocal: selective inhibition of the inducible NO synthase (iNOS) (10) and infusion of the NO donor SIN-1 (11) comparably improved both microvascular blood flow and tissue acidosis. Furthermore, investigating iNOS inhibitors suggested that impaired cellular respiration also contributes to the sepsis-related tissue acidosis: similar to the oxygen radical scavenger tempol (12), the iNOS blocker L-NIL virtually normalized the intestinal mucosal-arterial PCO2 gap during porcine bacteremia (12, 13), whereas intestinal microvascular blood flow was only partially restored (12, 13). Moreover, in endotoxic pigs, the iNOS inhibition–related attenuation of tissue acidosis was associated without any effect on intestinal microcirculation, as assessed by orthogonal polarization spectrophotometry imaging together with combined laser-Doppler flowmetry and remission spectrophotometry (14). Finally, murine normotensive, hyperdynamic cecal ligation and

**Pathophysiology of tissue acidosis in septic shock: Blocked microcirculation or impaired cellular respiration?**

*See also p. 535.*

Key Words: endotoxin; sheep; CO2 tonometry; orthogonal polarization spectrophotometry; respiratory quotient; substrate utilization

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perforation–induced septic shock resulted in impaired hepatic metabolic capacity, despite well-maintained liver microcirculation (15), and both pharmacologic and genetic iNOS blockade attenuated this metabolic deficit without change in regional microcirculatory perfusion (16). Such a predominant role of impaired mitochondrial respiration as a cause of tissue acidosis was already described by Vandermeer et al. (17) in endotoxic pigs, and data from rats with cecal ligation and perfusion sepsis (18) and in patients (19) demonstrated a close relationship between the degree of mitochondrial dysfunction and organ failure. Oxidative and nitrosative stress are referred to assume major importance in this context (20).

In the present issue of Critical Care Medicine, Dr. Dubin and colleagues (21) add another piece to the puzzle of the pathophysiologic mechanism of tissue acidosis. In an ovine model of endotoxic shock, the authors used orthogonal polarization spectrophotometry imaging to quantify the intestinal mucosal and serosal microvascular perfusion together with tissue CO₂ tonometry. The authors have the merit of combining these analyses with the investigation of the sublingual microcirculation, which was already referred to as the beginning of a “new era of hemodynamic monitoring” (22). The authors also have to be complimented for studying both the initial, hypotensive, and hypodynamic shock phase and the effect of fluid resuscitation, which resulted in normotensive and hyperdynamic hemodynamics, and for having meticulously analyzed systemic and regional oxygen and CO₂ exchange. How does the study compare with the existing literature? The authors confirm previous findings that 1) intestinal microcirculatory blood flow is not directly related to tissue CO₂ tonometry (23), that 2) fluid resuscitation alone does not allow restoring the intestinal mucosal perfusion (2), that 3) the tissue acidosis was directly related to the degree of microcirculatory disturbance (7), and that 4) sublingual microcirculation may fail to track the intestinal microcirculatory blood flow (24). Consequently, which conclusions can be drawn concerning the above-mentioned debate on the respective role of disturbed microcirculatory perfusion and impaired mitochondrial respiration in the pathogenesis of cellular energetic failure and subsequent tissue acidosis? At first glance, the findings by Dr. Dubin and colleagues (21) are fairly straightforward: the severity of the impaired intestinal villous microcirculation completely allowed explaining the degree of tissue CO₂ accumulation, and thus, any contribution of disturbed cell respiration was unlikely. Definitive conclusions, however, should be cautioned: the authors used a short-term model that lasted for only 150 mins after the initial endotoxin bolus. During this period, activation of mediators referred to interfere with mitochondrial respiration (e.g., NO) is most unlikely: other authors reported that, for example, blood nitrate levels, a surrogate for NO production, only increased as late as 3 hrs after the start of continuous intravenous endotoxin in sheep (25, 26). Furthermore, the marked depression of mitochondrial function in rodent cecal ligation and perforation–induced septic shock was only present at 24 hrs after induction of peritonitis (18). Finally, the attenuation of tissue acidosis, which resulted from selective iNOS inhibition and oxygen radical scavenging in bacteremic or endotoxic swine, was only present at 3–12 hrs after the start of the respective treatment (10, 12–14). Thus, it is tempting to speculate that an impaired microvascular perfusion is a hallmark of early endotoxic or septic shock, whereas mitochondrial dysfunction comes into existence in the late phase. This rational well agrees with the improved outcome concomitant with less disturbed sublingual microcirculation in patients with septic shock who underwent early goal-directed therapy (6).

In addition to the investigation of the intestinal microcirculatory perfusion, Dr. Dubin and colleagues (21) analyzed the systemic and regional oxygen and CO₂ exchange. Interestingly, within the limits of the validity of calculated CO₂ content values (27), the authors show that endotoxin alone, without fluid resuscitation, 1) markedly reduced both regional oxygen uptake and CO₂ production, which was 2) associated with a fall of the regional respiratory quotient from approximately 1 to 0.7. The fall of oxygen uptake paralleled that of the mesenteric blood flow, indicating regional oxygen uptake/supply dependency, such as it was previously shown for the hepatosplanchinic region in patients with sepsis (28). Furthermore, the decreased respiratory quotient indicates a preferential use of fatty acids rather than carbohydrates as a fuel for energy metabolism. It is well established that predominant glucose oxidation allows increasing the yield of adenosine triphosphate production under conditions of limited oxygen supply (29). One may speculate, hence, whether such an increased fatty acid utilization might mirror an endotoxin-induced failure of metabolic adaptation during the early, hypodynamic phase of endotoxic shock.

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cute subdural hematoma (SDH) is a frequent consequence (12% to 29%) of traumatic brain injury (TBI). The currently recommended treatment options for SDH are described in “The Guidelines for Treatment of Traumatic Brain Injury” (1). According to the guidelines, the indication for surgical evacuation is an SDH with >10 mm thickness or a midline shift greater than 5 mm. In patients with large SDH, surgical evacuation should be performed as soon as possible, regardless of the patient’s Glasgow Coma Scale score. The use of nonoperative treatment as a first line in TBI has also been described. Hypertonic saline (HS) has been studied in patients with elevated intracranial pressure (ICP) with different etiologies, such as TBI (2–5), elective brain surgery (6), subarachnoid hemorrhage (7), and even liver failure (8). During the preparation of the current medical guidelines for severe adult TBI, it was surprising and also somewhat frustrating to realize that even though there are many publications indicating the benefit of HS, neither class one nor class two evidence exists to support its use in adult head trauma (2).

The proposed mechanisms of action for HS are osmotic, hemodynamic, vasoregulatory, neurochemical, and immunologic. By increasing serum sodium and serum osmolality, HS creates an osmotic gradient that pulls water from the intracellular and interstitial compartments of the brain and reduces cerebral edema and ICP (9). HS has also been shown to enhance regional cerebral blood flow (CBF) (10, 11) via reduction of vascular resistance and through decreased edema in the vascular endothelium of injured tissues (12). Treatment with HS increases mean arterial blood pressure, a major determinant of outcome from TBI, which may normalize resting membrane potentials and cell volumes by restoring normal intracellular electrolyte balances to injured cells. Acute brain injury is associated with an acute inflammatory response, white blood cell activation, and pial arteriolar vasodilation (13). HS with dextran has also been proposed to reduce cerebral injury by limiting secondary pathologic events after TBI through reduced adhesion of polymorphonuclear cells to microvasculature and attenuated pial dilation (14).

In their thoughtful experimental study titled “Effects of hypertonic/hyperoncotic treatment and surgical evacuation of acute subdural hematoma in rats” (15), the authors create an acute SDH in rats and study the effect of treatment via a craniectomy with evacuation of the SDH compared with a bolus infusion of 7.2% saline/6% hydroxyethyl starch (HHS). The authors studied a number of different variables, including acute changes of CBF, ICP, and cerebral perfusion pres-
pressure over the first hour after the injury. The authors also present data on neurologic function and neuronal cell death 11 days after injury. Their main results indicate that experimental acute SDH leads to an acute increase of ICP that is treated effectively with HHS. However, there was no significant difference between surgical evacuation of the hematoma alone and surgery in combination with HHS treatment after 11 days. Even more surprisingly, the combination of early HHS infusion combined with surgical evacuation of the hematoma did not appear to be superior to either treatment alone. As the reader will understand, these results are highly provocative to surgeons who have spent countless nights trying to get these patients to the operating room for a rapid and effective surgical evacuation. In our opinion, this conflict can be resolved by pointing out several features in their study: first, the trauma model used resulted in a transient and significant increase in ICP, but it is unclear (and in our opinion unlikely) that this effect on ICP was sustained beyond the first hour; and second, treatment with HHS was initiated 30 mins before surgical evacuation and resulted in an effective reduction in ICP during a phase when the brain is most vulnerable. The authors conclude that treatment with HHS is effective in their acute SDH animal model but that should also be studied in more severe TBI models for applicability in the clinical setting.

Currently, the guideline recommendation is to administer mannitol to patients with clinical signs of cerebral herniation, such as dilated pupils, or as part of ICP therapy when ICP monitoring is in place (2). Due to the lack of well-designed clinical trials, there is no recommendation supporting the use of HS or HHS in adult severe TBI. The ultra-early use of a hyperosmotic agent as an adjunct to surgical evacuation is certainly intriguing and has inspired many bright minds in our field with sometimes tragic consequences. In 2001, Cruz et al. seemed to clinically validate what many experts suspected—that mannitol helps in the first few hours after SDH when the risk of secondary ischemic damage is greatest (16). Unfortunately, the results in this publication have recently been criticized and appear to have been based on fictitious data. Nevertheless, there is a tremendous interest in finding an intervention that will buy time for these patients in the ambulance or on the way to the operating room and Dr. Jussen’s data paves a path for future studies.

No only timing should be addressed but posing questions such as: HS or mannitol treatment? Bolus or continuous treatment? What are the complications of HS treatment? Further investigation into the mechanisms of action is also needed. Even though the data presented by Mr. Jussen and colleagues (14) appear to be derived in a nonideal trauma model, they indicate where the future may lie, and animal and clinical studies should be planned accordingly. Clinical studies should be planned with the guideline criteria in mind that require a homogeneous TBI population of adequate number and with adequate follow-up, in order to be included in the process of evidence-based evaluation (see inclusion/exclusion criteria in Ref. 17). If planned and conducted accordingly and in relevant trauma models, these studies will be an important part of the future evidence-based management in TBI.

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Severe acute respiratory distress syndrome (ARDS) is characterized by respiratory failure and need for mechanical ventilation. In clinical practice, the more severe the disease, the more difficult it is to maintain an adequate level of gas exchange. In the most severe cases, recruitment maneuvers and high positive end-expiratory pressure (PEEP) levels are necessary (1), as are adjuncts to mechanical ventilation (2, 3). Protective ventilation is recommended in ARDS lungs to avoid ventilator-induced lung injury (4–6). To limit mechanical ventilation damage, it is essential not to disconnect the ventilator several times a day, except in cases of excessive tracheal secretions.

Maggiore et al. (7) showed that suctioning-induced lung derecruitment in acute lung injury can be prevented by performing recruitment maneuvers during suctioning and can be minimized by avoiding disconnection from mechanical ventilation. They showed that the changes in alveolar recruitment were correlated with changes in lung volume (p = 0.88, p < 0.001) and compliance (p = 0.9, p < 0.001) and that changes in oxygenation paralleled lung volume.

Caramez et al. (8) evaluated the respiratory and hemodynamic effects of open suctioning (OS) vs. closed suctioning (CS) during pressure-controlled (PC) and volume-controlled (VC) ventilation, using a lung-protective ventilation strategy in an animal model of ARDS. PaCO2/FIO2 was lower after OS than after CS/VC or CS/PC. There was no postsuctioning difference in oxygenation between CS/VC and CS/PC. PaCO2 recorded 10 mins after suctioning was greater than the presuctioning value in all groups. Intrapulmonary shunt fraction increased between baseline and 10 mins postsuctioning with OS and CS/VC but did not significantly increase with CS/PC. There were no significant changes in hemodynamics presuctioning vs. postsuctioning with OS, CS/VC, or CS/PC.

In this issue of Critical Care Medicine, Dr. Caramez and colleagues (9) analyzed the effects of baseline PaCO2 and the duration of suctioning on gas exchange in a lung lavage model. Seven female Dorset sheep experienced four experimental conditions in random order (PaCO2 of 40 and 80 mm Hg and duration of suctioning 10 and 30 secs). Before each of the four experimental conditions, animals underwent lung recruitment with continuous positive airway pressure 40 cm H2O for 40 secs to normalize volume history, followed by ventilation for 15 mins, where FIO2 and PEEP were set based on the ARDSnet FIO2/PEEP criteria. There was no difference in the increment of PaCO2 based on baseline PaCO2 (40 vs. 80 mm Hg), although there was a trend for severe elevations under conditions of baseline hypercapnia (p = .06). This was mainly due to marked CO2 elevations in a subgroup of this restricted number of studied animals. So in hypercapnia conditions, some animals worsened after suctioning, an issue that needs further investigation. Dr. Caramez and colleagues (9) changed PEEP levels and FIO2 according to the ARDSnet criteria before each experimental condition, arguing that their goal was to assess the impact of suctioning during clinically relevant mechanical ventilator settings (i.e., based on the ARDSnet approach, which is the current gold standard). Nevertheless, changes in PEEP and FIO2 before the protocol could have changed the deadspace—cardiac output and PaCO2 being possible confounding factors. This reminds us that the goal of an experimental laboratory study is to have a good question and a protocol able to answer that question.

Therefore, the key message of the study by Dr. Caramez and colleagues (9) is that baseline PaCO2 had no consistent effect on the CO2 elevation experienced after suctioning in this lavage lung model. However, because these elevations were highly variable, clinicians should be aware of the possibility of marked deterioration in gas exchange in some patients who undergo even brief suctioning, particularly the most severely ill patients ventilating with low PEEP levels, as PEEP did influence the recovery of PaO2 following suctioning. So, in everyday critical care of ARDS patients, one should try not to disconnect the ventilator several times a day, unless excessive tracheal secretions are present. In ARDS patients, if the clinician notices tidal volume loss while keeping the same pressure control ventilation or oxygen desaturation, it is time to perform a recruitment maneuver and increase PEEP (1, 10).

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N-Acetylcysteine as the magic bullet: Too good to be true*

Should N-acetylcysteine (NAC) be used in the treatment of severe sepsis? Answer: No, grade C. Recommendation: NAC should not be used in severe sepsis until new data are available, focusing in particular on very early therapy” (1). This is a quote from an evidence-based practice guideline from 2001. In a more recent meta-analysis, pooling the results of 3,272 patients showed no effect on early mortality. In a more recent quote from an evidence-based practice guideline from 2001, they also reported that pretreatment and posttreatment with NAC reduced the inflammatory response, but may also worsen outcome if commenced in a later phase of the disease, as a result of the impaired granulocyte-dependent bacterial killing that requires oxygen free radicals (3–5). This idea was followed through in a high-risk surgical patient population, but prophylactic NAC treatment failed to prevent postoperative organ dysfunction (6).

Although the results of clinical studies are conflicting and practice guidelines and reviews do not recommend the routine use of NAC in critically ill patients (7), animal experiments still produce results in favor of NAC. The latest study of one of the most active research groups in this field is published in this issue of Critical Care Medicine by Dr. Liu and colleagues (8). Recently they also reported that pretreatment and posttreatment with NAC reduced the inflammatory response in endotoxin-induced septic shock and ameliorated organ damage (9, 10). In a similar endotoxin-induced ALI model, they found that NAC improved the lipopolysaccharide-induced hypoten-sion and leukocytopenia. It also reduced the extent of ALI, as evidenced by reductions in lung weight changes, exhaled nitric oxide, and lung pathology. In addition, NAC diminished the lipopolysaccharide-induced increases in nitrate/nitrite, tumor necrosis factor-α and interleukin-1β (11).

In the current experiment on isolated rat lung, fat embolism was caused by the infusion of corn oil in water. In the treatment group, lungs were perfused with 150 mg/kg NAC 10 mins after the induction of fat embolism. The corn oil mixture exerted its desired effect as pulmonary hypertension and the capillary filtration coefficient increased significantly. It also caused ALI, as indicated by enhanced production of cytokines in the lung perfusate, and increased lung weight, lung weight gain, exhaled nitric oxide, and protein concentration in the bronchoalveolar lavage. Posttreatment with NAC resulted in a remarkable improvement in every investigated variable, biochemical and hemodynamic alike.

It is yet another well-designed, well-thought-through, and well-executed experimental study with convincing results. How come that promising animal experiments cannot be confirmed in the clinical scenario? Is it surprising? Surely not. ALI, regardless of its cause, is more complicated in real life than just an intra-venous injection of lipopolysaccharide or corn oil infusion. Other factors, such as shock, blood loss, hypoxia, tissue damage, and infection, can occur in parallel or soon after one and the other, each serious enough to turn physiology upside down before help can arrive. In an isolated lung model, these cannot be taken into consideration. The authors are obviously aware of that, as their comments on the clinical adaptation of their results are very modest.

Another usual problem with laboratory experiments investigating therapeutic effects in acute illnesses is timing. The authors did their best to delay NAC administration and give it in a posttreatment fashion, but it is unlikely that even 10 mins is long enough to mimic a real-life situation in which NAC may be given even after 24 hrs of the initiating insult (4).

On the other hand, there is some evidence that NAC in the given dose is not without harm either, as it may cause myocardial depression (12). Different NAC-administration regimens have been tried, with most studies applying the 150 mg/kg loading dose, which surprisingly, has never been challenged since it was recommended for paracetamol overdose (13), despite that paracetamol-caused liver damage was prevented just as effectively at the lowest and at the highest plasma concentrations of NAC (14). Therefore, one cannot exclude that including the heart in the experiment by Dr. Liu and colleagues (8) would have influenced the results less in favor of NAC due to myocardial depression.

Nevertheless, Dr. Liu and colleagues (8) gave us another convincing study that inflammatory markers, especially free radicals, do play an important role not just in sepsis, but also in mechanical injury, such as fat embolism, which caused ALI too. Therefore, carrying on with future studies in this field is well justified. Whether NAC would be the magic bullet seems too good to be true at present.

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n this issue of Critical Care Medicine, Dr. Renkens and colleagues (1) present a series of experiments characterizing the effects of sterile inflammation on subsequent host defense directed at *Pseudomonas aeruginosa* lung infection. As such, this is a two-hit (2) experimental model where intramuscular turpentine oil injection (first hit) is followed by intranasal inoculation of 10^7 colony-forming units of *P. aeruginosa* 24 hrs later (second hit). At a macro level, the mice that received turpentine oil injection all died within 48 hrs of lung inoculation. In contrast, the mice that received saline injection survived 72 hrs after lung inoculation with *P. aeruginosa*. The decreased survival of the mice subjected to turpentine oil-induced inflammation was accompanied by reduced histologic evidence of lung inflammation, decreased bacterial clearance and numbers of pulmonary neutrophils, and attenuated lung macrophage tumor necrosis factor-α response to *in vitro* stimulation with *P. aeruginosa* endotoxin. Finally, to begin to address a possible mechanism, it was observed that the adhesion molecule CD11b (Mac-1) on neutrophils was significantly decreased in turpentine oil-pretreated mice compared with saline-pretreated animals and that administration of a blocking CD11b antibody to nonturpentine oil-pretreated mice led to significantly decreased myeloperoxidase activity (presumably reflecting decreased neutrophil numbers) and increased bacterial growth in the lung.

Dr. Renkens and colleagues (1) suggest that these finding are due to the exuberant acute phase response induced by turpentine oil injection. The classic acute phase response is limited to a number of hepatic proteins invoked by cytokines like tumor necrosis factor-α, interleukin (IL)-1β, and especially IL-6 after inflammatory or injury stress (3, 4). Although there is generally an association in this study between the elevations of acute phase reactants, as assessed by serum amyloid A, serum amyloid P, and complement component 3 as well as IL-6, no experimental evidence is presented demonstrating a causal relationship between these proteins and the multiple observed differences between mice administered turpentine oil vs. saline. The authors likely focused on the acute phase response because an earlier similarly designed study using pulmonary infection with *Acinetobacter baumannii* (5) showed that intraperitoneal administration of recombiant human serum amyloid A reduced lung inflammatory responses 24 hrs later, as also observed in the present study in response to turpentine oil administration.

However, in addition to the implication of the acute phase response as proposed by Dr. Renkens and colleagues (1), several other conceptual frameworks for the impairment of host defense induced by turpentine oil administration may be suggested. One of these is tolerance (6, 7), the attenuation of a response to a stimulus subsequent to an initial exposure. The flip side of tolerance is priming (8, 9), the augmentation of a response to a stimulus subsequent to an initial exposure. Although there is a complex, mine-riddled literature on both tolerance and priming, a general impression is that priming occurs earlier after the initial stimulus and is more robust in neutrophils (8, 9), while tolerance occurs later after the initial stimulus and is more robust in monocytes and macrophages (6, 7, 10, 11). An extensively studied type of tolerance is endotoxin tolerance, in which an exposure to endotoxin induces a subsequent lack of responsiveness to a second challenge with endotoxin (6, 7, 10, 11). But the name is a misnomer given that a considerable lack of specificity exists, in that after initial endotoxin exposure, tolerance can be demonstrated to a variety of secondary stimuli, including cytokines, Gram-positive toxins, and other cell wall components (6, 7). Finally,
a reciprocal relationship also exists where the initial exposure is to something other than endotoxin but tolerance is demonstrated on subsequent exposure to endotoxin (6, 7, 11). This latter phenomenon may play a role in the results of the current study.

But how can turpentine oil have such effects? This substance is a mixture of wood-derived organic molecules, presumably devoid of pathogen-associated molecular patterns (PAMPs), that is, immune-activating, microorganism-derived components (toxins, cell wall components, nucleic acids, etc.), and thus is not able to bind and activate innate immune system pattern recognition receptors, such as Toll-like receptors, nucleotide oligomerization domain (NOD)-like receptors, and retinoic acid-inducible protein (RIG)-like helicases. A likely possibility lies in the irritant and tissue-damaging qualities of turpentine oil. It is now known that tissue injury is associated with the induction or release of endogenous damage-associated molecular patterns (DAMPs), which in some cases can activate the same pattern recognition receptors as bona fide PAMPs (12). Some examples of DAMPs include defensins, heat shock proteins (12), high-mobility group box 1 protein (13), S100 calgranulins (14), uric acid crystals, calcium pyrophosphate dehydrate crystals, and decreased intracellular potassium concentrations (15, 16). One receptor complex that can respond to both PAMPs and DAMPs is the so-called NALP3 or cryopyrin inflammasome (16). When activated by an appropriate PAMP or DAMP, the output of the NALP3 inflammasome is IL-1 converting enzyme (caspase-1) leading to increased IL-1 production. Interestingly, Moldawer and colleagues (17) previously demonstrated that turpentine oil inflammation in mice was associated with a greater increase in IL-1β than tumor necrosis factor-α levels, perhaps suggesting that turpentine oil is inducing DAMPs that activate the NALP3 inflammasome.

Hormonally mediated immunosuppression is another possible mechanism that may be in play in the impaired inflammatory response observed by Dr. Renkens and colleagues (1). The authors address a possible β-adrenergic immunosuppressive effect by using pharmacologic attenuation with either propranolol or 6-hydroxy-dopamine. Neither of these agents affected the impaired host defenses observed with turpentine oil pretreatment. Curiously, the role of glucocorticoid hormones was not evaluated. Corticosterone, the major glucocorticoid in rodents, is elevated after turpentine oil-induced inflammation (18) and synergizes with IL-1 and IL-6 in promoting the acute phase response (3, 4). It also has, do other glucocorticoids, well-established pleiotropic immunosuppressive actions. Although adrenaledenonitomized rodents are sick due to death of both glucocorticoid and mineralocorticoids and thus are probably not suitable subjects for a stressful two-hit study, treatment of rodents with the progestin/glucocorticoid receptor blocker RU486 might be a viable approach to assess the role of glucocorticoid hormones in this model (20).

Dr. Renkens and colleagues (1) have found in a murine model that a first hit of sterile, localized inflammation (turpentine oil injection) causes a slump in host defense in the lung 24 hrs later, most likely due to defective recruitment of neutrophils to this tissue. Whether this slump is specific to the pulmonary compartment has not been determined. Nor do we know, at times other than 24 hrs after the first hit, if a rally in host defense can be observed.

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Neuroprotective properties of xenon and helium in an \textit{in vitro} model of traumatic brain injury: One small step or one big jump?*

Traumatic brain injury (TBI) is a significant source of morbidity and mortality throughout the world (1). Accordingly, an effective treatment would fill a major clinical need.

Promising strategies to minimize secondary brain injury after TBI have met with very limited clinical success. To date, all compounds investigated produced adverse side effects and provided intrinsic neuroprotection and therapeutic concentrations (2), or they were ineffective when translated into the clinical setting.

The “inert” gas xenon is an antagonist of the N-methyl-D-aspartate-type glutamate receptor but also blocks AMPA and kainate receptors in cortical neurons. On this basis, xenon seems to be rather non-specific as a channel blocker, and this may contribute to its analgesic and anesthetic potency (3, 4). In addition to having anesthetic and analgesic effects, xenon has been shown to exert substantial organoprotective properties, especially in the brain and the heart (5), and to be an effective neuroprotectant in a variety of \textit{in vitro} and \textit{in vivo} models of neuronal injury (6–8).

Helium, often used in association with oxygen (Heliox), has shown a number of potential medical applications in critically ill patients (9) and in pediatric intensive care units (10). In this regard, in a rat model of cerebral focal ischemia, although hyperoxia reduced the infarct volume, helium addition further reduced the infarct volume and improved 24-hr neurologic deficits, suggesting a potential benefit from helium therapy (11). However, it is unknown whether these “inert gases” can provide neuroprotection following experimental TBI.

In this issue of \textit{Critical Care Medicine}, Dr. Coburn and colleagues (12) attempted to examine neuroprotective properties of xenon and helium in an \textit{in vitro} model of TBI. In this study, brain slices were subjected to a focal mechanical trauma in the presence and absence of these inert gases, at normal and elevated pressures, and under both normothermic and hypothermic conditions. The authors concluded that helium and xenon are surprisingly effective as neuroprotectants in this \textit{in vitro} TBI model, especially in a hyperbaric chamber in addition to 1 atm of air. Whereas the beneficial effects of helium could be accounted for entirely in terms of the effect of pressure \textit{per se}, in the case of xenon, the neuroprotection was due to a combination of the positive effects of pressure and beneficial pharmacologic gas properties. In addition, both gases were effective at normobaric pressures when they replaced nitrogen in a gas mixture, and adding moderate hypothermia to xenon treatment demonstrated only marginal additional benefit.

Although these positive results were obtained in a simple brain-slice model, the study findings are sufficiently interesting to sustain future investigations in animal models and successive potential consideration as a clinical treatment in humans. These attractive features also have potential clinical implications for the critical care practitioner.

Xenon presents several advantages since it can be rapidly introduced into the brain, has a favorable hemodynamic profile, with little or no toxicity, and is not metabolized (13). In addition, if xenon proves to be an effective treatment for head injury at elevated pressures, its administration using a hyperbaric chamber is not inconceivable. Moreover, xenon neuroprotection is still observed if treatment is delayed by 3 hrs following injury. This point appears to be relevant since therapeutic interventions are required within a few hours following injury (12). As pointed out by the Dr. Coburn and colleagues (12), providing treatment within this narrow window of time may represent a formidable challenge.

However, there are some weaknesses in this study, the most important being the model chosen, the so-called organotypic slices (hippocampal brain slices investigated after 2 wks in culture). Such a model excludes the presence of all the injury pathways that follow ischemia and/or hypoxia and changes resulting from systemic parameter variation. Nevertheless, the model used maintains heterogeneous populations of cells whose synaptic contacts reflect, at least to some extent, the \textit{in vivo} state (14) and therefore represents a compromise between models that use dissociated cell cultures and those that use intact animals (15).

Future investigations in animals and clinical trials will confirm whether these “noble gases” have neuroprotective properties in attenuating cerebral damage in the clinical setting and may thus be useful tools in TBI.

Despite the gap between biomedical investigations and clinical applications, the findings of Dr. Coburn and collaborators (12) suggest new and fascinating perspectives and lend hope for reducing the consequence of head trauma, thus providing a potential, large jump toward neuroprotective therapy.

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A tantalizing question: Ferrari or Rolls Royce? A meta-analysis on the ideal renal replacement modality for acute kidney injury at the intensive care unit*

ike Tantalus, some of us are “tantalized” to prove superiority of one of the renal replacement techniques (RRT) in the intensive care unit (ICU) intermittent hemodialysis (IHD) or continuous RRT (CRRT). This problem parallels the question of which is the best car: Ferrari or Rolls Royce? The answer is: it depends on your preference and the conditions in which you want to use it. It might even seem that for most circumstances, a more simple car might be as good, or even better: the question of which car is the best cannot be answered without nuance.

In this issue of *Critical Care Medicine*, Dr. Bagshaw and colleagues (1) present a meta-analysis on RRT in the ICU. Their major conclusion is that no difference in outcome can be found between IHD and CRRT. This is no surprise, as each individual study included in the meta-analysis came to this conclusion (2, 3). The comforting inference would be that each unit or physician can safely go ahead using the technique they are best acquainted with (4). Instead, the authors underscore a need for further evidence, suggesting another randomized controlled trial comparing IHD vs. CRRT, pointing to the limitations of the available studies. To our opinion, there is no need for such an additional study: a Ferrari cannot transport five people at once, a Rolls is not built for racing on a circuit, and neither is appropriate for everyday use. More people will be interested in the question: “which car serves me best in everyday conditions?” Most likely, this will be a less fancy car, with great flexibility, maybe a break or an SUV. CRRT has changed substantially over time from a low-efficient, simple treatment to a high-volume, high-efficiency therapy using sophisticated and dedicated machinery, whereas IHD in the ICU is now performed as a daily and more extended, flexible treatment (5). Both modalities have become more and more alike, leading to the concept of “slow low-efficient daily dialysis” (SLEDD) (5–8) as a kind of hybrid compromise. In SLEDD, the treatment is performed using a modified dialysis monitor, and the treatment conditions (duration, blood and dialysate flow, mix of convection and diffusion, filter choice) are adapted daily to the needs of the patient. The major advantages of this approach are the flexibility of the system and the reduced costs as compared with CRRT (9). The weaknesses of both IHD and CRRT become clear from the “limitations” Dr. Bagshaw and colleagues (1) attribute to the different randomized controlled trials included in the meta-analysis: patient randomization was not optimal (10, 11), the treatments performed were not adequate according to the levels proposed in the Ronco study (12), or treatment specifications were changed during the course of the study (3). Whereas all these violate the rigorous analysis of the question of which is best, they at the same time indicate that the obtained answers reflect daily practice. Uehlinger et al. (11) could not randomize one out of three patients due to logistic reasons because the modality the patient was randomized to was not available. This is an illustration of real life in most ICUs: one day there are a substantial number of patients needing RRT, next day, there is only one. Machines that can perform only in the ICU and only in a continuous mode hamper logistics in these conditions. A more flexible solution would be to use machines allowing both short, more intensive treatments (so that more than one patient can be dialysed during a day) and slow, long, extended daily dialysis (SLEDD) treatments when needed. In the Hemodiaife study (3), treatment time in the IHD arm was prolonged up to 5.2 ± 0.1 hours during the course of the study, whereas in the CRRT, doses remained below the recommended 35 mL·min⁻¹·kg⁻¹. It is clear from subanalyses that this change improved outcome of IHD. More important, it demonstrates that adaptations (e.g., enhancing dose) are more easily obtained in IHD/SLEDD than in CRRT, for which

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*See also p. 610.

Key Words: meta-analysis; acute kidney injury; renal replacement therapy; intensive care unit; slow low-efficient daily dialysis unit; continuous venovenous hemofiltration

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such adaptations always increase cost substantially. Adequacy standards are often not obtained in ICUs (13), due to reasons differing from circuit downtime (because of clotting, technical investigations, or surgery) to financial (expensive replacement solutions) or logistic (nursing time) reasons. Again, SLEDD offers a valuable compromise, as ultrapure dialysate is delivered here on line, reducing costs, with easy to handle machines, with the installation and breakdown done by a dialysis nurse, and the supervision of the alarms during the treatment done by the ICU nurse (9). To avoid the cost of a water treatment system in the ICU, a batch system can be used (14). The treatment duration and the intensity can be adapted to the tolerance of the patient, but all using one single machine. As such, these all are no reasons to develop another randomized controlled trial, comparing IHD and CRRT, because they just reflect how the treatments are performed in daily life. A new randomized controlled trial should thus not compare “IHD vs. CRRT” but “SLEDD to CRRT.” As SLEDD, however, allows a continuous range of treatment modes, it may become difficult, if not impossible, to “randomize” this in a fixed protocol. It would be irrational to believe that a single, fixed treatment regimen might be suitable for all patients in all circumstances and at every ICU. The most flexible treatment regimen is probably the most optimal one for most of us.

The availability of different options for RRT, and the observation that, overall, all treatments are equal, allows us to provide tailor-made treatment: the best modality can be chosen depending on local expertise and the individual clinical scenario. If RRT is only a rare event in the ICU in your unit, or there is no nephrologic backup, CRRT is an acceptable option. With larger ICU units, investing in a separate water treatment system and a dialysis monitor, enabling the performance of SLEDD, or a batch system like Genius, might be a more sensible and economical solution to perform state-of-the-art, adequate treatment.

Despite several technical innovations, it is still not clear whether the outcome of patients with acute kidney injury needing RRT has improved over the years (15–18). Many important questions remain unanswered, like timing of start of RRT, or how to evaluate adequacy in the ICU-RRT setting. We should not be like Tantalus, asking the same already answered question all over again, but we should move on, trying to answer more pertinent questions, and use our time and money to study more innovative aspects of dialysis in the ICU.

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