

Prone position, high-frequency oscillatory ventilation, and Hippocrates in acute respiratory distress syndrome*

The acute respiratory distress syndrome (ARDS) continues to be a frustrating challenge. It is associated with a mortality rate of $\geq 30\%$ (1), and the quality of life of survivors is reduced after discharge (2). We are still lacking effective treatment, possibly in part because our current ARDS definition leads to the enrollment of patients in clinical trials who differ with respect to severity, etiology (e.g., primary vs. secondary), and/or mode of presentation (e.g., diffuse vs. localized ARDS) of lung injury (3). It is likely easier to find an effective treatment for a well-defined entity (e.g., pneumonia) than for the number of loosely related entities currently grouped under the ARDS “umbrella.” The treatment of patients with ARDS currently consists essentially of ventilatory support with positive pressure. Although the key objectives of mechanical ventilation are widely agreed on—restoration/maintenance of adequate gas exchange and implementation of a lung-protective strategy to buy time for lung repair—the best way to achieve this is controversial, particularly in difficult patients. In the presence of refractory hypoxemia, for instance, different rescue strategies have been proposed including inhaled vasodilator (nitric oxide or prostacyclin), a high level of positive end-expiratory pressure (PEEP), recruitment maneuvers, prone positioning (PP), high-frequency oscillatory ventilation (HFOV), or extracorporeal membrane oxygenation. None of these strategies has been proven to improve outcome, and the initial enthusiasm for these techniques has almost invariably been followed by disappointment.

Experimental works have established (4) that a) positive pressure ventilation can induce endothelial and epithelial dysfunction and structural injury; b) the magnitude of the tidal volume relative to the size of the lung that must accommodate the latter is a key determinant of alveolar overdistension and injury (volutrauma) (5); and c) an adequate level of PEEP is needed to protect the lungs from cyclic airway opening and collapse (atelectrauma) and/or also from the strain and stress associated with large tidal excursion (5, 6). We are, however, still debating how to best protect the lungs from ventilator-induced lung injury (VILI). Although the need to avoid excessive tidal volume is now clinically confirmed (7), a recent large multiple-center study failed to confirm the protective effect of PEEP (8). This may have been the combined consequence of enrollment of patients with different forms of lung injury and variable responses to the specific PEEP titration protocol used in this study, as recently pointed out (9).

PP and HFOV have been proposed as alternative strategies to conventional mechanical ventilation and PEEP, particularly in patients doing poorly, given their dual potential to improve gas exchange and prevent the development of VILI. Overall, 70% of patients with acute lung injury/ARDS experience improved $\text{PaO}_2/\text{FiO}_2$ ratio when turned prone (10). In addition, PP appears to be particularly advantageous over PEEP in the *localized* forms of ARDS (11). HFOV's ability to improve blood gas in *selected* adults with difficult to treat ARDS has been reported in uncontrolled series (12). In a recent randomized trial, however, no significant difference in mortality rate and only a transient improvement in gas exchange were observed (13). As reported in the prone trials (10, 14), improved gas exchange does not necessarily translate into better outcome. Indeed, as learned from the ARDSnet trial (7), how a given ventilatory strategy modulates lung stress and injury is a more important determinant

of outcome than gas exchange. It is tempting to speculate that the gas exchange improvement afforded by a given strategy (e.g., PPV, HFOV) should not so much prompt a rapid reduction in the FiO_2 to minimize oxygen toxicity than a change in the ventilatory settings to reduce the mechanical stress and the risk of VILI. Clearly, this needs to be explored.

In regard to VILI, both PP and HFOV have been found to have lung-protective potential in animal models (15–17). In critically patients, neither strategy has so far been proven to improve outcome. Given the low number and limitations of the available randomized trials in adults—to my knowledge one for HFOV (13) and two for PP (10, 14)—the current lack of demonstrated outcome benefit is not a proof that none exists. After all, it took no less than five randomized trials to establish that avoiding excessive tidal volume is important (7), a easier task in this setting than to demonstrate a benefit of a novel approach.

When new ventilatory strategies are compared in a physiologic study, it is clearly not sufficient to look at gas exchange without considering lung injury. In the current issue, Dr. Papazian and colleagues (18) compare the impact of PP, HFOV, and their combination on gas exchange and lung inflammation in patients with ARDS. Their main finding was that PP was associated with better gas exchange and less airway inflammation (lower bronchoalveolar lavage concentration of interleukin-8 and neutrophil count). HFOV did not confer any advantage over conventional ventilation regardless of position. As we currently lack specific and sensitive biomarkers for VILI, one should be cautious in interpreting the significance of the reduction in interleukin-8 and neutrophils with PP. Overall, however, the data are consistent with the lung-protective effect of PP documented in animals (15, 19) and in the *post hoc* analysis of the Italian study (10). The current study also suggests that HFOV may not under any circumstance

*See also p. 2162.

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be the ideal lung-protective strategy despite a) allowing maintenance of adequate gas exchange and a high end-expiratory lung volume while using extremely small tidal volumes; and b) being combined with recruitment maneuvers to help HFOV to develop its full protective effect (20). Most patients had primary ARDS due to pneumonia and were thus less likely to recruit (9, 11). This could also explain the gas exchange advantage of PP over HFOV, as already demonstrated against PEEP in this setting (11). In the PP, everything else being equal, the homogeneous vertical distribution of perfusion (21) may alone help improve oxygenation even in the absence of a net gain in lung volume. In contrast, with no or minimal recruitment, the high mean airway pressure strategy associated (HFOV) tendency to redirect blood flow to the dependent atelectatic and/or to consolidated regions may help explain the absence of gas exchange improvement and the lack of lung protective effect (16) seen here.

A great deal of our knowledge regarding HFOV was acquired in small animals and infants (22) with large potential for lung recruitment and administered through small endotracheal tubes. In adult patients ventilated through larger endotracheal tubes and with low recruitment potential (e.g., primary ARDS), the lung-protective profile of HFOV may be offset by larger transmission at high frequency of the high proximal airway pressure and its variation. Generally in adult patients, and particularly in those with low potential for recruitment, we clearly need further studies before this mode of ventilation can be widely recommended. One should also be prudent when judging a mode of ventilation: Clearly the devil is in the settings. After all, the impact of assist-control ventilation on outcome is dependent on the choice of the tidal volume! It is also possible that in a group of patients with highly recruitable lungs, different if not opposite results may have been observed with HFOV.

We should encourage physiologic investigation along the line of Dr. Papazian's group to deepen our understanding of how to optimally apply new ventilatory strategies under different physiologic conditions. It is unlikely that a specific mode and settings will work for all conditions. Secondly, we need to stop lumping together all patients with shunt physiology under the "ARDS" label to enroll

them into clinical studies that do not take into account important and relevant differences between them. We should reconsider the ideal grouping for patients with acute respiratory failure, to increase our chance of designing better clinic studies and ultimately make a difference for these patients. Otherwise, we may run the risk of prematurely burying new approaches such as PP and HFOV. Decades after first description of ARDS and multiple outcome studies, it is ironic to consider that the only proven established "treatment" for ARDS is nothing else but an intensive care unit variant of the Hippocrates' oath: First, do not deliver excessive tidal volumes. It is high time to move to the next stage.

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Predicting mortality: How fast can you go?*

The main goal of treating critically ill patients is to offer them a possible benefit that they would desire (1). Often, early aggressive therapy aims at buying sufficient time to see if the disease responds favorably so that overall changes of a possible benefit increase (2). Failure to respond to first-line therapy should urge the clinician to reevaluate the correctness of the initial diagnosis, assess the adequacy of this first-line treatment, and if necessary increase treatment modalities. However, when life-saving technology and organ support appear to delay inevitable death rather than prolong meaningful life, we should be prepared to withdraw these technologies (3). Timing in this is essential, not only to limit the duration of inappropriate care but also to have maximal assurance that there is no meaningful change of benefit for the patient.

Ideally, the parameters and variables used to assess the patient should thus have a low intra- and interinvestigator variability. Two approaches are frequently used in critical care. First is a static approach in which one or more parameters are used to characterize patients with an increased chance of dying in the intensive care unit. One-time measurements of easily obtainable variables with low bias have repeatedly been associated with extremely high mortality rates (4, 5). A frequently used approach in severity of disease scoring systems (e.g., Acute Physiology and Chronic Health Evaluation) is to collect several variables over a period of time (usually the first 24 hrs of admission) and to take into account the most abnormal values. The use of these instruments is limited by significant inter- and intraobserver variability (6) and the duration of data collection. In addition, these assessments do not seem to be superior to the clinical judgment by either nurses or doctors (7, 8).

Second, a dynamic approach in which one or more variables or parameters are evaluated over time has been shown to adequately identify patients with high mortality risk (5, 9). Similar findings have been reported for more complicated scoring systems (2). These evaluations are also limited by the time needed to collect the data; in most cases a period of 24–48 hrs has been used.

Another dynamic approach that has been used is to assess the hemodynamic response of a patient to a short-time infusion of a vasoactive drug. Failure of the circulation to respond to an infusion of dobutamine has thus been associated with an extremely high mortality rate (10), although differences between similar diagnostic groups exist (11). In the latter studies, results were available within the hour.

In this issue of *Critical Care Medicine*, Dr. Levy and colleagues (12) report a multiple-center study in which they assessed the differences in prognosis in patients with septic shock. In this study, a clinically relevant intervention was chosen: Infusion of dopamine in patients with septic shock when fluid resuscitation failed to restore mean arterial pressure to >70 mm Hg. When dopamine up to 20 µg/kg/min failed to increase mean arterial pressure to >70 mm Hg, treatment was switched to norepinephrine or epinephrine. Whereas the overall mortality rate of these patients (54%) was not very different from other studies (13), the patients who responded to dopamine had a mortality rate of 16% whereas the patients who did not respond to dopamine had a mortality rate of 78%. The interesting aspect of this study is that already after 30 mins of vasopressor therapy, this group of patients could be identified, as the increases in dopamine were protocol driven. This finding can have several implications for clinical practice and research. First, the identification of patients with a poor prognosis early in the process of resuscitation could help the clinician to guide additional hemodynamic diagnostics. Second, therapy could be optimized by implementation of new strategies (steroids, activated protein C, etc. (14). Third, this rapid identification

could help to stratify patients in the design of clinical trials. Fourth, it could help to characterize a group of patients in whom benefit from treatment may be limited and disproportional to the resources used. However, in this respect we should recognize some limitations of the study by Dr. Levy and colleagues. First, fluid resuscitation was not standardized so that hypovolemia in some patients could have been present, although this study design thus more or less reflects real life and efficiency rather than efficacy of the protocol used. Second, some baseline imbalances between the responders and nonresponders to dopamine (underlying liver disease and immunosuppression as well as rapidly fatal disease in nonsurviving patients) may have influenced the results. Nevertheless, nonresponders to vasopressor therapy in septic shock have universally been associated with very high mortality rates (15–17). Therefore, standardized dosing of vasopressor therapy might rapidly identify patients who especially need our attention as researchers but even more as intensivists.

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Multifactorial aspects to explain variations of control group mortality rates of randomized controlled trials*

To improve standardization of intensive care unit (ICU) research protocols, standard sepsis definitions have been introduced (1, 2). However, recent clinical trials found substantial differences in populations studied, hindering comparison of results. One approach to analyze differences in patient populations and magnitude of illness between trials is to compare control group mortality keeping in mind that mortality in controls is influenced not only by entry criteria but also by differences in care and data collection during the trial. To determine the impact of entry criteria on baseline mortality risk and number of eligible patients, Dr. Peelen and colleagues (3) projected entry criteria from nine selected randomized controlled clinical trials (RCTs) on severe sepsis published between 1999 and 2003 to a large national database of >70,000 Dutch ICU patients (3). The results from this investigation are presented in this issue of *Critical Care Medicine*. The authors show that RCTs selected for analysis and all designed to specifically investigate patients with severe sepsis report substantially dif-

ferent mortality rates of patients in the control groups. Heterogeneity in mortality rate within the control groups had been assessed by inverse variance testing showing a high significance ($p < .0001$). Although sepsis patients in the trials all had different mortality rates, applying the same definitions of sepsis to the Dutch registry yielded rather similar rates. Therefore, the authors conclude that differences in outcome of control patients in individual trials may be attributed to factors that vary between trials, for example, regional differences in case mix and/or quality of care, rather than to differences in entry criteria.

A number of the reported RCTs were multinational in scope, attempting to randomize regional variability. Vice versa, ICUs participating in a national registry might be more similar in terms of structure and care provided. Differences in case mix are probably a better explanation for the differences observed. Selection bias is a common problem of clinical trials. Due to restrictive inclusion criteria, the majority of clinical trials include only a few individuals, who usually have a better prognosis than non-participants. A second important problem is referral bias. Clinical trial sites are usually academic centers, at which the more complicated cases are treated. This effect may subsequently lead to the inclusion of patients into clinical trials that are sicker than the average patients being treated in a lower level hospital. Therefore, it appears not surprising to detect differences be-

tween trial populations and average ICU populations as observed in the present comparison.

Recruitment bias is another important issue that needs to be considered. A detailed description of the recruitment process including information on how many of potentially eligible patients were actually recruited into individual trials and on how recruited ones differed from their nonrecruited counterparts should nowadays be a standard when reporting RCTs (4). In many multiple-center trials, trial physicians are not entirely adopting the trial's eligibility criteria; rather they are focusing on certain subgroups that fit to these criteria. The observed differences in Acute Physiology and Chronic Health Evaluation (APACHE) II scores seem to support this hypothesis of selective recruitment in some trials. Some of the differences in APACHE II scores are quite high and therefore might easily explain the differences in mortality rates. Especially in large trials, like PROWESS (5) and OPTIMIST (6), differences between the APACHE II scores are considerably large: 25 in the trials vs. 22 in the registry (3).

Another important source for variability in mortality rates among control groups is sample size. Although the authors did not analyze studies with <30 patients in the control groups, the highest reported control mortality was reported in studies with the smallest control groups (groups G, H, and I in study 3). This suggests that smaller sample sizes of these studies may easily be

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associated with sampling errors in the population.

There are quite some limitations to the study by Dr. Peelen and colleagues (3). Mortality in the RCTs was defined as 28-day mortality. In contrast, the database only contains data from the first 24 hrs after ICU admission defining mortality as overall ICU mortality. Thus, the reader should not compare the mortality rates in Figures 1 and 2 of Dr. Peelen and colleagues' article and take this as a proof of better therapy with less mortality in the Dutch database. This difference is important considering this is the key point of Dr. Peelen and colleagues' study. As baseline risk of 28-day mortality in the sepsis trials differed between 28.2% and 88.6%, the authors suggest interpreting treatment effects cautiously. They further argue that the effects in interventions may depend on the individual's illness severity. This certainly holds true. However, one should distinguish between relative and absolute effects of therapy. Most commonly, but with some exceptions, relative risks of trial treatment are constant, so that absolute risk differences increase with increasing baseline risk. As patients in the original trials could be enrolled for more prolonged periods, applying inclusion and exclusion criteria to the database possibly yielded subpopulations that were not representative of the original trial. In addition, some entry criteria of the RCTs were not collected within the database and some threshold values used in the database were slightly different from those in the

trials. The authors don't expect these difference to have led to the selection of substantially different patients groups; however, this remains speculative.

Using the projection method, the authors claim that in the majority of cases reported, entry criteria of the individual trials did not lead to selection of patients with different ICU and hospital mortality rates. This conclusion needs to be considered with caution due to points risen and due to the fact that three studies included in Dr. Peelen and colleagues' investigation used entry criteria that indeed did lead to a substantial selection of patients with considerably higher mortality rate. These studies either required additional systemic inflammatory response syndrome or organ failure criteria (7), omitted artificial ventilation in one of the systemic inflammatory response syndrome criteria (8), or required $\geq 50\%$ estimated mortality risk as an inclusion criterion (9). Thus, reasons for different mortality rates in control groups of RCTs are multifold, and different entry criteria may not entirely be excluded as possible cause for variation in baseline mortality rate.

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The early bird catches the worm*

There is a time for departure even when there's no certain place to go to—Tennessee Williams

Much of critical care medicine involves the assessment of risk and the prediction of outcome. This is often a subconscious activity or one that is poorly formalized and based on limited personal experience only. Nevertheless, initial risk assessment may influence both adequate timing and institution of a potentially life-saving therapeutic intervention and thereby eventually may significantly affect patients' outcomes.

In the past, a constantly increasing number of studies have shown that, irrespective of the initial insult eventually leading to intensive care unit (ICU) admission, patients' mortality is directly attributable to the number of failing organ systems (1–7). In an evolving attempt to quantify clinical improvement or deterioration, scales to objectively measure organ dysfunction as a surrogate outcome have been developed and may thus facilitate bedside diagnosis and decision making. Four such scales are currently available: the Multiple Organ Dysfunction score (MOD) (8), the Logistic Organ Dysfunction score (LOD) (9), the Sequential Organ Failure Assessment (SOFA) (10), and the Brussels score (11). The underlying principle of all scoring systems is simplicity: Complex interacting biological systems and processes are condensed to a limited number of physiologic, biochemical, and therapeutic variables. These variables may or may not be weighed to reflect the functional integrity of a specific organ system, thereby facilitating an objective characterization of the disease process. However, some of these surrogate variables may not be ideal.

In this issue of *Critical Care Medicine*, Dr. Levy and coworkers (12) reveal that in patients with severe sepsis, early improvement in respiratory, cardiovascular, or renal organ system function was predictive of subsequent 28-day survival, whereas restoration of organ dysfunction in any other organ system or improvement gained later in the course did not significantly reduce overall mortality.

For the purpose of this analysis, the placebo groups of two recent trials that enrolled patients with severe sepsis, the secretory phospholipase A₂ (sPLA₂)-inhibitor trial (13) and the PROWESS study (14), were combined with the PROWESS population, accounting for 81% of all analyzed patients. As one could expect from the slightly divergent time lines of the original study protocols, the time from the first recorded organ failure until the study drug (or placebo) had been administered was considerably longer in the sPLA₂-inhibitor group (13). With a median difference of 10.8 hrs, this exceeded the window of opportunity for an early-goal directed strategy as proposed by Rivers et al. (15). Moreover, the sPLA₂-inhibitor trial enrolled a higher proportion of patients with respiratory dysfunction, mechanical ventilation, and hematologic dysfunction, whereas cardiovascular dysfunction was similar distributed among both groups. Interestingly, 28-day mortality in the sPLA₂-inhibitor group was slightly higher despite a lower Acute Physiology and Chronic Health Evaluation II score and overall younger patients (13). However, this might be attributable to the significantly higher proportion of African-Americans in the sPLA₂-inhibitor trial, a subgroup of patients known to exhibit higher mortality rates in sepsis compared with Caucasians (16). Unfortunately, the published protocols of both studies lack an explicit description of the standard of care, which would have been desirable considering the multiple sites incorporated in patient enrollment (17). Thus, heterogeneity in the clinical manage-

ment could have led to diverse development of organ system failure with respect to the applied SOFA over time.

According to the presented data, the improvement of cardiovascular, respiratory, and renal dysfunction over the first 24–48 hrs or the lack thereof was strongly predictive of 28-day mortality. Other organ system dysfunction or failure either was not present, was not assessed (e.g., neurologic organ system), or had presumably negligible impact on patients' short-term outcome (12). In early sepsis, Russel et al. (18) reported an association between the pattern of change from day 1 to day 3 and subsequent mortality rate for neurologic, hematologic, and renal dysfunction. Moreover, neurologic, hematologic, renal, cardiovascular, and hepatic organ system dysfunction already present at the onset of sepsis syndrome was associated with a significant increase in 30-day mortality rate (18).

In general, current organ system dysfunction scores work surprisingly well considering the lack of a methodological, rigorous approach that characterizes their development. Only MOD and LOD used explicit criteria to define the initial variable set (8, 9). Selecting an appropriate surrogate variable is like trying to square the circle: The variable should be organ-specific, sensitive for rapid changes in the disease process, fast, reliable, accessible, reflective with respect to therapeutic interventions, and finally predictive of patients' outcomes. None of the instruments currently in use can claim to fulfill these goals. Moreover, validation studies in diverse patient populations investigating the responsiveness of the selected surrogate variables toward changes over short periods of time have not been performed yet. Nevertheless, performance of MOD and LOD in clinical trials did not seem to surpass SOFA, whose surrogate variables are based on expert opinion only.

For time-critical analysis, the responsiveness of a given surrogate variable is of utmost importance. Herein responsive-

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ness relates to the ability of a surrogate variable to rapidly detect and indicate clinically relevant changes in the represented organ system. A good example for high responsiveness is arterial blood pressure: A critical drop of mean arterial blood pressure below 70 mm Hg can be monitored instantaneously with an arterial catheter in place. In contrast, hematologic function is related to a platelet count and liver function to bilirubin, both neither specific nor very sensitive for the selected organ system, and the sampling frequency is usually low. The limitations of the Glasgow Coma Scale for neurologic assessment in the critically ill have already been widely acknowledged (19, 20). The surrogate variables selected for the kidneys (creatinine and urine output), the cardiovascular system (blood pressure, catecholamines, and vasopressors), and the lungs ($\text{PaO}_2/\text{FiO}_2$ ratio and mechanical ventilation) may indeed be capable of indicating rapid changes in organ system dysfunction. Nevertheless, these changes may at least in part depend on the clinical management, for example, the appropriateness of an eventual volume challenge and the ventilator settings. Notably, the function and integrity of the gut, considered the motor of shock by some authors (21), is not represented by any scoring system at all.

The direct association of progressive organ dysfunction and death emphasizes the importance of timely therapeutic interventions in patients with severe sepsis and septic shock in order to prevent further organ system deterioration (12). Appropriate and timely institution of adequate care in the ICU has still not achieved yet: A recent audit of ICUs in England and Wales revealed that the care provided for critically ill patients from admission to the first ward round was characterized by both time delay and inappropriate diagnostic and therapeutic interventions (for details, refer to www.ncepod.org.uk). Despite general awareness with regard to the importance of sepsis, only 22% of the intensivists ($n = 529$) and 5% of all other physicians ($n = 529$) managed to provide the correct definition of sepsis (22). Clearly, efforts to improve the general knowledge and thus the likelihood of timely patient identification will enhance the quality of care provided for patients with sepsis.

Patients in the ICU rarely die of (for example) isolated liver failure or new-onset hematologic dysfunction. Patients

die because of progressive multiple organ dysfunction and subsequent multiple organ failure originating from a failure to timely and sufficiently resolve cardiovascular and pulmonary failure, respectively (12). To date, early volume loading tapered along a specific protocol is the only therapeutic intervention that has been shown to reduce mortality rates for patients presenting with severe sepsis and septic shock to the emergency department (15). Again, time did matter: More volume administered later in the course (i.e., later than 6 hrs after admission to the emergency department) did not improve patients' outcome at all. In essence, Rivers et al. (15) took care of an adequate blood pressure and increased oxygen supply most likely meeting the suspected demands. Although we are aware of the disappointing (and sometimes harmful) attempts to reach supranormal oxygen delivery levels in the past (23, 24), the cardiovascular and pulmonary organ system still seems pivotal in the development of multiple organ dysfunction in sepsis (3, 25, 26). Sepsis-induced cardiomyopathy (i.e., a more or less pronounced myocardial dysfunction) may lead to hypoperfusion with inadequate oxygen delivery, to progressive end-organ dysfunction with disturbed microcirculation, and hence to insufficient oxygen consumption entering a circulus vitiosus. In basic physiology, oxygen delivery is defined as a function of cardiac index and arterial oxygen content, with the latter composed of the hemoglobin level, oxygen saturation, and arterial oxygen tension. Cardiac index itself relies on preload, afterload, and myocardial contractility. With the exception of contractility, which could have been assessed with echocardiography, the algorithm applied by Rivers et al. considered almost all variables determining oxygen delivery (15). Consequently, the limitations inherent to the surrogate variables of all scoring systems need to be considered before application to avoid gross misconceptions. This is of particular importance for the variables sought to represent the function of the liver and the neurologic and the hematologic organ system in almost all scoring systems.

Immediate and target-oriented correction of cardiovascular and pulmonary dysfunction currently seems the most encouraging approach to substantially reduce the incidence of multiple organ dysfunction syndrome and thus subsequent mortality in patients with severe sepsis

(3). Treatment algorithms proposing a rational decision-making process have already been published but need to be applied in both routine clinical practice and future clinical trials (15, 27, 28). Dr. Levy and colleagues (12) have reassured us that attention must be paid to the initial care of the patient with severe sepsis and septic shock, since "lost time may never be found again" (Benjamin Franklin).

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Errors in monitoring transcutaneous Pco₂ on the ear*

In the article by Dr. Bendjelid and associates (1), published in this issue of *Critical Care Medicine*, the authors report a study in 55 artificially ventilated intensive care patients of the accuracy of Paco₂ measurements using an ear lobe sensor (TOSCA) containing a pulse oximeter and a transcutaneous Pco₂ electrode. The device is heated to 42°C to increase capillary flow for the Pco₂ electrode. The device was used by the regular intensive care staff, as expected in routine use.

The mean bias (transcutaneous Pco₂ [TcPco₂]–Paco₂) was 1.2 ± 6.0 mm Hg SD, with 19% of the data exceeding 7.5 mm Hg error. This study is one of the first to use TOSCA clinically without intense supervision by investigators. Other reports using TOSCA have found less

variability. Eberhard et al. (2) obtained a mean bias of 1.22 ± 3.69 mm Hg in 104 comparisons in ten patients. Kagawa et al. (3) in six patients reported a mean and SD bias of 2.3 ± 2.5 mm Hg after ≥30 mins of stabilization, and subsequently in 51 samples from 32 artificially ventilated patients during surgery and anesthesia these authors found the TOSCA TcPco₂ bias to be 0.7 ± 2.5 mm Hg (unpublished). Senn et al. (4) reported a bias of 3 ± 3.5 mm Hg in 80 paired analyses in 18 patients in intensive care. Rohling and Biro (5) found the bias to be –0.6 + 2.0 mm Hg in 80 comparisons in ten patients using an earlier version of this combined heated ear probe.

With standard transcutaneous (not ear) electrodes heated to 43–44°C, in a multiple-institutional study conducted by untrained staff in 756 samples from 251 children, the mean ± SD bias was 1.3 ± 3.9 mm Hg (6).

Why, then, were the errors significantly larger in the present study? To me the data suggest an important role of user training to carefully calibrate the electrode, to mount it securely with the appropriate mounting gel ensuring exclu-

sion of air between electrode and ear, to avoid traction that might hinder circulation, to recognize problems when readings are not stable after ≥15 mins, and to avoid sampling when either Paco₂ or TcPco₂ is not stable (e.g., before full skin vasodilation has been achieved). These problems are operational or physiologic, not instrumental.

If skin blood flow is reduced or absent, positive mean bias can occur due to skin metabolic production of CO₂ or local lactic acid interacting with tissue bicarbonate. This is not unexpected in patients with inadequate circulation, especially when vasoactive drugs are in use causing skin vasoconstriction. This may account for the mean bias of 3 mm Hg in the Senn et al. (4) report. In the present report, although some patients had inadequate circulation and were undergoing vasoactive therapy, the mean bias was only 1.2 mm Hg. Low TcPco₂ readings may be caused by partial exposure to air if the contact with skin is not secure.

As temperature rises, blood Pco₂ rises 4.7% per 1°C and metabolic rate generally rises 7% per 1°C. In a patient with Paco₂ of 40 mm Hg, the uncorrected skin

*See also p. 2203.

Key Words: blood gas analysis; Pco₂ overshoot; skin blood flow; nurse training; ear probe; capnography

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surface value in heated transcutaneous Pco_2 electrodes is about 55 mm Hg at 42°C because heating raises blood Pco_2 27% and skin metabolism raises surface Pco_2 about 3–4 mm Hg compared with capillary blood. All transcutaneous Pco_2 electrodes internally correct the reported value to a mean body temperature of 37°C , as do all blood gas analyzers. This internal correction is also applied immediately when electrode temperature is deliberately changed.

Kagawa et al. (3) studied a transcutaneous Pco_2 overshoot phenomenon seen during the first half hour after mounting TOSCA at 42°C . The overshoot is believed to be caused by delayed arteriolar vasodilation after surface heating raises metabolic rate and capillary temperature. They showed that a brief period of preheating to 45°C avoids this overshoot. Figure 1 illustrates the difference when two TOSCA monitors are used simultaneously: one on each ear, one at 42°C , the other at 45°C for the first 15 mins and then at 42°C . An average overshoot of about 5 mm Hg is seen in about half of the patients studied, with little or no overshoot in others. This could account for some errors in samples taken within the first half hour after mounting the electrode.

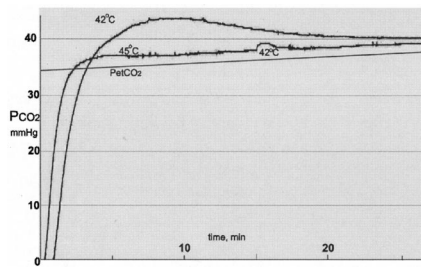


Figure 1. The Pco_2 electrode equilibration characteristics of two TOSCA monitors, mounted simultaneously on the ears of a single patient during artificial ventilation with slowly rising end-tidal Pco_2 (Petco_2). The electrode heated to 42°C shows an overshoot of about 6.5 mm Hg peaking at 10 mins after mounting, whereas the electrode heated to 45°C for the first 15 mins and then reset to 42°C correctly tracks end-tidal Pco_2 after 5 mins and shows no overshoot (Kagawa, unpublished).

The Bland-Altman method of data analysis compares test result differences between methods of uncertain precision as a function of the mean value (on the x-axis) of two test devices or methods. It is inappropriate to use the mean of the test and a gold standard instrument as the x-axis for statistical evaluation of a new unknown monitor. The “gold standard” data (e.g., arterial blood gas) should be used for the x-axis.

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Evolving paradigms in the management of severe traumatic brain injury*

Trauma is the leading cause of death and disability in the first 5 decades of life (1), and brain injury is the principal cause of death in the trauma population (2). According to the Centers for Disease Control and Prevention, of an estimated 1.4 million cases per year of traumatic brain injury (TBI) in the United States, approximately 52,000 patients die and 235,000 are hospitalized, many of whom are admitted to the intensive care unit (3). The

case fatality rate of TBI has declined in recent years (4), yet it is uncertain whether this trend relates to the implementation of any specific therapy. Indeed, the search for therapeutic interventions to improve outcomes following TBI remains largely unrewarded, despite a wealth of accumulated data on the neurobiology, pathophysiology, and epidemiology of this condition (5). Recent hypothesis-driven, multiple-center, randomized controlled trials of TBI-directed therapies have failed to demonstrate efficacy (6, 7), and current clinical guidelines for the management of TBI are based primarily on nonrandomized clinical observations, pathophysiological inferences, and expert opinion (8, 9). As management protocols emanating from these guidelines gain widespread accep-

tance, it becomes necessary to critically assess the interventions they advocate. Chief among these are the measurement and therapeutic targeting of intracranial pressure (ICP) and the derived variable, cerebral perfusion pressure (CPP, equal to the difference between ICP and mean arterial pressure).

The rationale for ICP- and/or CPP-guided therapy emerged from a series of key observations. First, elevated ICP is frequent following severe TBI (i.e., Glasgow Coma Scale score ≤ 8), and it is a powerful predictor of outcome (10). Second, there is a consistent association between arterial hypotension and poor outcomes after TBI (11). Third, severe TBI induces significant abnormalities in cerebral blood flow (CBF), including global hypoperfusion, regional hypoperfusion,

*See also p. 2207.

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hyperemia, and loss of autoregulation (12). Much of the secondary injury observed after TBI is ischemic in nature, and hemodynamic augmentation represents an effort to ameliorate CBF before the onset of irreversible damage. Assuming cerebrovascular resistance is invariant, this may be accomplished by decreasing ICP, increasing mean arterial pressure, or both. Retrospective and prospective nonrandomized accounts have suggested that CPP-based therapy in patients with TBI improves global and regional cerebral perfusion, decreases ischemia, and may lead to better clinical outcomes (13).

In recent years, CPP-based therapy has come under increasing scrutiny. A randomized controlled trial comparing a CPP- vs. an ICP-targeted protocol in 189 patients with severe TBI failed to demonstrate any significant difference in the Glasgow Outcome Scale assessed at 3 and 6 months (14). Of note, although CPP therapy reduced the incidence and duration of jugular venous desaturation, it was associated with a five-fold increase in the incidence of acute respiratory distress syndrome (14). There is evidence that augmenting CPP does not significantly improve perfusion to ischemic pericontusional tissue (15). Finally, it has been argued that the higher capillary hydrostatic pressure induced by elevating CPP may promote cerebral edema formation through a dysfunctional blood brain barrier. Working from this postulate, some investigators have proposed a radically different therapeutic strategy aimed at decreasing capillary hydrostatic pressure and maintaining or augmenting capillary oncotic pressure (the Lund hypothesis) (16). In summary, there is considerable uncertainty regarding the benefits, let alone the optimal targets, of CPP-based management (17).

In this issue of *Critical Care Medicine*, Dr. Cremer and colleagues (18) present a retrospective cohort of 333 patients with severe TBI who survived beyond 24 hrs and were admitted to two level I trauma centers in The Netherlands over a 5-yr period. Management was institution-specific and was driven by clinical and computed tomography findings in center A ($n = 122$) and by an ICP/ CPP-based resuscitation protocol in center B ($n = 211$). In center A, none of the patients had ICP monitoring and mean arterial pressure was maintained at >90 mm Hg, whereas in center B 67% had ICP monitoring and 48% had jugular venous oxy-

gen saturation monitoring, with goals of maintaining ICP <20 mm Hg and CPP >70 mm Hg. Demographic variables and severity of brain injury were well balanced between the two centers, although a significantly higher proportion of patients in center B were found to have arterial hypotension on admission. The results of the study can be summarized as follows: a) mortality rates and functional outcomes (extended Glasgow Outcome Scale at 12 months) were comparable in the two centers; and b) mechanical ventilation and length of intensive care unit stay were significantly prolonged in patients who received ICP/ CPP-guided management. The findings of Dr. Cremer and colleagues are at variance with other recent studies in which protocolized ICP/ CPP-driven management was associated with improved outcomes (19–21). However, it is notable that these prior reports had historical control groups and a retrospective assessment of outcomes, whereas the control group of Dr. Cremer and colleagues was concurrent and outcomes were evaluated prospectively.

Dr. Cremer and colleagues (18) postulate that the higher level of therapeutic intensity in the ICP/ CPP center may have adversely affected the outcomes of the patients in this group. Their study adds to an emerging body of data suggesting that the beneficial effects of ICP/ CPP management in reversing or preventing secondary injury may be offset by adverse systemic or central effects associated with hemodynamic augmentation, osmotherapy, muscle relaxation, sedation, and pharmacologic coma (14, 17). The study does not, however, elucidate *how* therapeutic intensity may have had an impact on outcomes. For instance, the higher incidence of acute respiratory distress syndrome observed elsewhere in patients treated according to a CPP paradigm (14) was not reproduced in this study. Perhaps because of the limitations of retrospective data ascertainment, several important data elements are missing. An analysis of causes of death (e.g., brain death vs. systemic causes such as cardiopulmonary failure, propofol infusion syndrome, etc.) might have strengthened the interpretation that aggressive therapies were detrimental. The results of serial neuroimaging studies could have provided important insights into secondary ischemic brain injury. Stratification of patients with space-occupying lesions (subdural and epidural hematoma and intraparenchymal contusions) vs. those

with diffuse cerebral edema (presence or absence of basal cisterns) might have helped identify subsets of TBI patients who are more (or less) likely to benefit from ICP/ CPP-guided care.

The work of Dr. Cremer and colleagues (18) represents an excellent example of an “effectiveness” study, in which the implementation of a therapeutic intervention is evaluated in a real-world setting, as opposed to the highly structured context of randomized controlled trials in which the primary emphasis is on therapeutic “efficacy.” Based on these findings, these authors contend that there is sufficient clinical equipoise to conduct a prospective randomized controlled trial that is adequately powered to compare ICP/ CPP-targeted management vs. supportive critical care without ICP monitoring in patients with severe TBI. Although we agree, the realization of such a trial is likely to be problematic for a number of reasons, not least of which the firmly held biases of many clinicians.

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Settling the score for disseminated intravascular coagulation*

Systemic activation of coagulation, in a close interaction with inflammatory activity, is increasingly appreciated as a pathogenetic pathway contributing to organ dysfunction in patients with systemic inflammatory diseases (1, 2). Systemic inflammation is in fact virtually always associated with activation of coagulation, ranging from changes in molecular markers in coagulation factors with equivocal clinical significance to its most full-blown variant, known as disseminated intravascular coagulation (DIC) (3). Until recently, a diagnosis of DIC was hampered by the limited availability of reliable and simple tools with sufficient diagnostic accuracy. Indeed, there is no single clinical or laboratory test that has an adequate sensitivity and specificity on itself to confirm or reject a diagnosis of DIC. However, combinations of several readily available coagulation tests may be helpful to establish this diagnosis. Fol-

lowing a previously developed Japanese scheme, the subcommittee on DIC of the International Society of Haemostasis and Thrombosis proposed a simple scoring algorithm using the platelet count, a prolongation of the prothrombin time, a decreased fibrinogen, and plasma levels of a fibrin-related marker, such as D-dimer or other fibrin degradation products (4). Importantly, the score can only be used if the patient has been diagnosed with an underlying condition known to be associated with DIC. The various components of the scoring algorithm are assigned points, and based on retrospective data a score of ≥ 5 is compatible with DIC. Prospective validation of this system in consecutive patients with a clinical suspicion of DIC confirmed a high sensitivity and specificity of this scoring system (5). Moreover, application of the score in large databases of patients with severe sepsis has revealed that the DIC score is a strong and independent predictor of mortality and that the scoring system may select patients who will have a relatively large benefit of interventions in the coagulation/inflammatory cascades, such as the administration of recombinant human activated protein C (6). Based on these observations, the DIC scoring system may be a helpful tool in clinical prac-

tice but also in the design and execution of trials aimed at improving the clinical management of patients with DIC and associated conditions. However, a disadvantage of the system may be its static nature, thereby not taking into account dynamic changes in the respective parameters over a certain period of time.

In this issue of *Critical Care Medicine*, Dr. Kinasewitz and colleagues (7) present their findings on an equally simple evolving DIC score, solely based on platelet count and prothrombin time. Interestingly, not only absolute values of these markers are included, but also changes of these variables at subsequent measurements are included in the score. A prospective exploration of this system in patients with severe sepsis showed a good correlation with organ failure and provided useful information as to the evolution of the clinical condition of the patient. The power of the scoring system of Dr. Kinasewitz and colleagues may indeed be related to the fact that changes in platelet count and prothrombin time count equally strongly as absolute values of these markers. The ideal time that should elapse between measurements, however, remains unclear. Nevertheless, the system as proposed by the authors can easily be applied at the bedside and

*See also p. 2214.

Key Words: coagulation; inflammation; disseminated intravascular coagulation

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seems an interesting addition to the original scoring system. The observations of Dr. Kinasewitz and colleagues are in line with a recent report demonstrating that a composite dynamic coagulopathy score was quite accurate in identifying patients who would progress to multiple organ failure and who would not survive (8). This composite scoring system, based on retrospective data from the PROWESS study, consisted of four factors: an absolute low level of antithrombin, changes in the first 24 hrs including a decrease in antithrombin levels by 20%, failure of the prothrombin time to shorten >2 secs, or the absence of a 20% decrease in D-dimer levels. Taking these two reports together, it seems that adding dynamic changes to scoring systems for DIC may result in valuable improvement of the predictive power of the scoring systems for DIC, although the accuracy of both systems remains to be established in prospective studies.

Another modification in the original DIC score that may be considered is the abolishment of fibrinogen levels from the algorithm. In fact, fibrinogen levels are very rarely decreased in DIC, and fibrinogen hardly ever contributes to the total score. In fact, the powerful performance of the DIC score in patients with severe sepsis was demonstrated without a single measurement of fibrinogen in this study (6). Another modification may be to replace the expression of the prothrombin time in seconds by International Normalized Ratio (INR). This modification would further standardize the system and make it more applicable to institutions where only INRs are reported by the laboratory, although one needs to realize that the INR has in fact not been developed and

standardized for monitoring a normal or slightly abnormal coagulation status and certainly not for the diagnosis of a consumption coagulopathy. Last, the optimal choice for a fibrin-related marker and the ideal cutoff values need to be established. Despite a slightly superior performance of soluble fibrin in the DIC scoring system (9), in most centers measurement of D-dimer is used, because this test is usually routinely available for the exclusion of venous thromboembolism. A recent study showed that for the use of D-dimer results in the DIC score, optimal cutoff points can be defined (10).

Simple scoring systems for DIC employing readily available laboratory tests seem to be useful for confirming or rejecting a diagnosis of this condition. Prospective validation studies show that these algorithms are quite accurate, and recent studies, including the one by Dr. Kinasewitz and colleagues in this issue of *Critical Care Medicine*, indicate that small modifications may even further improve their diagnostic accuracy. These scoring systems may be helpful at the bedside but also for use in clinical studies aimed at improving the clinical management of patients with conditions known to be associated with DIC.

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The imperfect diagnosis of acute respiratory distress syndrome*

In 2004, Esteban and colleagues (1) demonstrated that 127 of 382 patients who were autopsied after dying in an intensive care unit (ICU) in Madrid met clinical criteria for the acute respiratory distress syndrome (ARDS). ARDS was diagnosed retrospectively by two of the investigators through medical record review, using the American-European Consensus Conference (AECC) definition (2). At autopsy, only 84 of the 127 patients who met AECC criteria for ARDS had diffuse alveolar damage (DAD), the histologic pattern of alveolar and epithelial cell disruption, pulmonary edema, and hyaline membrane formation that corresponds to the early exudative phase of ARDS (3). Of the 43 patients with clinical ARDS but not DAD, 32 had autopsy evidence of pneumonia, 4 had pulmonary hemorrhage, 3 had cardiogenic pulmonary edema, 3 had pulmonary emboli, and 1 had interstitial fibrosis secondary to chemotherapy. On the other hand, of the 255 autopsied patients who did not meet AECC criteria for ARDS, 27 had DAD at autopsy. Twelve of these cases were diagnosed clinically by the investigators as pneumonia, 12 were thought to have cardiogenic pulmonary edema, and 1 had no identified pulmonary disease. Esteban and colleagues concluded from these findings that the AECC definition of ARDS was only moderately sensitive and specific with use of DAD as the reference standard.

In this issue, Ferguson and colleagues (4) analyze a subset of 138 patients from the previous study who were intubated, mechanically ventilated, and autopsied after dying in the Madrid ICU. Patients intubated for >14 days before death were excluded because their histologic findings might not reflect ARDS in its exudative phase. The records of patients included in the study were reviewed by two

of the investigators, using a somewhat different methodology than in the previous study, and ARDS was diagnosed on the basis of three definitions: the AECC definition, the lung injury score (LIS) of Murray and colleagues (5), and a new definition developed through the Delphi technique (Delphi). In addition, during their record review, the investigators determined whether the patients' physicians considered ARDS to be present when they treated them.

ARDS was diagnosed by investigators in 82 of the 138 autopsied patients on the basis of the AECC definition and in 53 and 46 on the basis of the LIS and Delphi definitions, respectively. However, only 42 of the 138 patients who met clinical criteria for ARDS had DAD at autopsy. Of the 96 who did not have DAD, 47 met the AECC criteria for ARDS during retrospective review; 22 of these patients had histologic pneumonia, 10 had pulmonary emboli, 5 had cardiogenic pulmonary edema, and 18 had no significant lung findings. At the same time, of the 42 patients who had DAD at autopsy, only 20 were suspected of having ARDS by the physicians who treated them, and of the 82 patients whose diagnosis of ARDS was made by the investigators in retrospect, only 26 were thought to have had ARDS by their treating physicians. Ferguson and colleagues determined that the clinical criteria for ARDS, with use of all three definitions in this study, were only moderately sensitive and specific; the AECC definition was the most sensitive definition, whereas the LIS and Delphi definitions were the most specific ones. They concluded that ARDS is underdiagnosed by treating physicians and that the variable specificities of existing clinical definitions may be problematic for clinical trials.

The underdiagnosis of ARDS and its possible consequences, including the failure to treat patients who have ARDS with proven therapies such as low-tidal-volume ventilation (6), were not highlighted in the investigators' previous study and are worthy of emphasis here. Yet Ferguson and colleagues have not drawn attention to an equally important

finding in their two studies: with use of DAD as a reference standard, ARDS is frequently overdiagnosed by retrospective review. If we assume that comparable prospective review is performed when patients are identified with ARDS for clinical trial enrollment, this finding suggests that a significant number of such patients would not meet the reference standard and may contaminate the results of the trials. And although Ferguson and colleagues do not provide data on this issue, it is likely that some patients who were believed by their treating physicians to have ARDS lacked autopsy evidence of DAD and therefore did not truly have ARDS by the study's reference standard.

Although Ferguson and colleagues "do not claim DAD at autopsy to be a 'gold standard' for ARDS," they nevertheless believe that "the majority of patients with severe early ARDS (such as those who died and were included in this study) should have pathologic changes consistent with DAD," which justifies their use of DAD as a reference—if not a gold standard. Recent reviews of ARDS (7, 8) also stress that DAD is the histologic equivalent of exudative ARDS. Yet because few patients with or without clinical ARDS are biopsied during life or autopsied after death, the suitability of DAD as a reference standard for ARDS remains uncertain. In this regard, some patients with ARDS may lack DAD because their lung injury is in its proliferative phase (7). Others with clinical ARDS may have histologic processes as diverse as pneumonia (as in the studies from Madrid), bronchiolitis obliterans with organizing pneumonia, pulmonary hemorrhage due to capillaritis, acute eosinophilic pneumonia, cardiogenic pulmonary edema (as found in the Madrid studies), a variety of emboli (not only the thromboemboli seen in the Madrid studies but also fat, foreign material, or tumor), bronchoalveolar cell carcinoma, pulmonary alveolar proteinosis, and acute transplant rejection, among other conditions (9).

In the final analysis, ARDS is a clinical diagnosis, DAD is a histologic diagnosis, and the two are not always congruent. As a result, comparing the diagnostic accu-

***See also p. 2228.**

Key Words: intensive care unit; acute respiratory distress syndrome; diffuse alveolar damage

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racy of the various clinical definitions of ARDS against a histologic reference standard is provocative but conceptually limited, as Ferguson and colleagues acknowledge. Other investigators (10) have evaluated published definitions of ARDS on a physiologic and outcome basis and found that they identify similar patients from at-risk groups. Yet even with this approach, the definitions are imperfect in diagnosing patients with ARDS in the absence of a true gold standard, and they will remain so until ARDS is better understood.

Given this situation, clinicians and investigators alike should use the widely accepted AECC definition in identifying patients with ARDS and determining their eligibility for clinical trials (7). Whether some of the patients actually have bronchiolitis obliterans with organizing pneumonia, acute eosinophilic pneumonia, pulmonary alveolar proteinosis, or other conditions that may respond to specific therapies in addition to supportive measures for ARDS is unclear, although in some cases lung biopsies may help guide treatment. And even

if these conditions are present, the patients generally should benefit from low-tidal-volume ventilation, which has been tested in other patients who met the AECC definition of ARDS and may or may not have had DAD.

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Lactic acidosis in sepsis: Another commentary*

Blood lactate concentration is regarded by many as the simplest marker of tissue dysoxia in the intensive care unit. The trouble with simple things, however, is that one must understand them very well. The interpretation of blood lactate concentration in critically ill patients, in particular patients with sepsis or in septic shock, is not a simple task. Lactate is an enigma. Lactate can be considered either a metabolic fuel or a metabolic waste product. Lactate is produced by hypoxic tissues but also by fully oxygenated tissues. An elevated blood lactate concentration may, or may not, be predictive of mortality. Elevations in blood lactate

concentration may be produced by increased production or by decreased clearance rates (1).

Anaerobic organisms derive their energy from glycolysis by oxidizing and splitting a six-carbon glucose molecule into two three-carbon pyruvate molecules. The energy released during glycolysis is conserved in forming adenosine triphosphate (ATP) and reducing nicotinamide adenine dinucleotide (NAD⁺) to NADH. Lacking a continuous supply of NAD⁺, glycolysis comes to a sudden and disastrous halt. To the delight of wine aficionados, yeast regenerates NAD⁺ by reducing pyruvate to ethanol. Higher organisms reduce pyruvate to lactate via the enzyme lactate dehydrogenase. This reaction averts pyruvate accumulation in the cytosol and supplies glycolysis with the required NAD⁺.

Aerobic organisms dispose of pyruvate in the mitochondria by transferring electrons to oxygen while generating vast quantities of cellular energy. Lactate pro-

duction increases in hypoxia (type A hyperlactatemia) as the rate of glycolysis accelerates, providing normally aerobic cells with a readily available source of nonmitochondrial ATP (Crabtree effect) (2). Lactate production also may occur in fully oxygenated tissues (type B hyperlactatemia) in response to various inducers, such as metformin and epinephrine (3, 4).

The production of lactate does not cause the acidosis associated with heavy exercise or with hypoxia (5). Cellular acidosis in these conditions is produced by the hydrolysis of nonmitochondrial ATP. Each time a molecule of ATP undergoes hydrolysis, a proton is released. When oxygen is readily available, protons, along with the other products of ATP breakdown, adenosine diphosphate and inorganic phosphate, are recycled by mitochondria and cellular pH remains constant. During hypoxia or exercise, mitochondrial turnover rate drops below the rate of ATP hydrolysis. As more pro-

*See also p. 2235.

Key Words: lactic acidosis; lactate; hyperlactatemia; sepsis; hypoxia; metabolism

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tons are produced by the hydrolysis of nonmitochondrial ATP, intracellular pH falls (6). Lactate helps retard cellular acidosis by binding to protons and forming lactic acid (7).

Returning to the example of ethanol-forming yeast, one may ask why higher organisms did not evolve this strategy as a mean to dispose of pyruvate. After all, it may be argued somewhat cynically, ethanol production could make life a bit more pleasant for many of our hypoxic patients. The answer appears to be that, far from being just a metabolic waste product, lactate is also a very busy transport molecule. There is evidence that lactate shuttling from cytosol to mitochondria, bypassing pyruvate oxidation, promotes glycolytic flux and helps preserve mitochondrial redox (8). Lactate also carries protons from actively metabolic tissues to quiescent or fully aerobic tissues as it diffuses in the blood stream as lactic acid. Acidemia facilitates the uptake of lactic acid from blood whereas the opposite occurs with alkalemia (9). Freshwater turtles survive prolonged conditions of anoxia at low temperature and represent an extreme example of lactate as a proton transporter. Lactic acid efflux from anoxic cells is promoted in these animals by forming calcium lactate in blood and incorporating this compound into the turtle's shell and skeleton (10).

A single measurement of lactate concentration in tissue or body fluids is difficult to interpret since it represents the balance between lactate production and removal. The production of lactate occurs commonly in skeletal muscles during heavy exercise. In fact, fully aerobic, working skeletal muscle produces and uses lactate simultaneously as lactate formed in glycolytic fibers is oxidized by adjacent oxidative fibers (11). Other important sources of lactate production are the ischemic gut (12) and acutely injured lungs (13, 14). Several organs participate in lactate removal from blood. The liver efficiently removes lactate from blood, converting it to glycogen (Cori cycle) (15), and septic patients with chronic liver disease are prone to the development of hyperlactatemia (16). The heart is another efficient user of lactate, deriving up to 20% of its aerobic energy from lactate oxidation (17). Other organs capable of removing lactate from blood are the kidneys, the brain, and skeletal muscle (18, 19).

The generally accepted view of lactate as a hypoxia-related noxious metabolite dates to the 19th century when Pasteur noted the association between hypoxia and lactate accumulation in tissue. Data supporting the "harmful" role of lactate are provided by clinical studies showing mortality rates of 83% and 90% for blood lactate concentrations >5 mmol/L on intensive care unit admission (20) or >8 mmol/L after cardiopulmonary resuscitation (21), respectively.

Much of our understanding of lactate accumulation in tissue derives not from studies of tissue hypoxia but from exercise physiology (22). A.V. Hill (23) defined the "oxygen debt" as the "total amount of oxygen used after cessation of exercise in recovery therefrom." Margaria et al. (24) further established the foundations of the lactic oxygen debt by noting lactate's disappearance from blood after exercise with a half life approximately 15 mins long.

Shoemaker and colleagues (25) expanded the concept of *exercise*-related lactic oxygen debt into a *hypoxia*-related lactic oxygen debt and further proposed that hyperlactatemia was evidence of "covert" tissue hypoxia in sepsis. Coupled with the paradigm of pathologic supply dependence (26), the presence of hyperlactatemia served as the rationale for increasing the rate of oxygen delivery to very high values in septic patients. Although an attractive hypothesis, the presence of a persistent, hypoxia-related lactic oxygen debt is difficult to prove since septic patients usually lack evidence of tissue hypoxia, other than hyperlactatemia. Large clinical trials aimed at increasing the rate of systemic oxygen delivery to "supranormal" values were utter failures since patient mortality either increased (27) or did not change (28) when compared with control groups. In our opinion, the failure of these clinical trials to improve survival is related to the notion that septic hyperlactatemia is not tantamount to tissue hypoxia.

There is accumulating evidence that lactate in septic patients is the product of nonhypoxic increases in glycolytic flux, not "covert" tissue hypoxia. Moreover, considerable argument exists as to whether the hyperlactatemia of sepsis results from increased cellular production or from decreased clearance rate. Levraut and colleagues (29) measured lactate clearance in stable septic patients with normal (1.2 ± 0.2 mmol/L) or mildly elevated (2.6 ± 0.6 mmol/L) blood lactate concentrations and noted lower lactate

clearance in the hyperlactatemic patients. A follow-up study in severely ill septic patients with normal or mildly elevated blood lactate concentration (<3 mmol/L) showed that low lactate clearance was predictive of poor outcome (30).

Findings opposite to those of Levraut et al. were reported by Chioloro and colleagues (31) in postoperative cardiogenic shock hyperlactatemia. The latter concluded that hyperlactatemia in their study subjects could be explained by increases in lactate production, with alterations in lactate utilization playing a minor role. Since many of the patients in their study had marked increases in glucose production, Chioloro et al. also concluded that increased rates of glycolysis contributed significantly to the development of hyperlactatemia. It is significant to note that patients in the study by Chioloro et al. had high levels of arterial lactate (7.8 ± 3.4 mmol/L) when compared with those of Levraut et al. (2.6 ± 0.6 mmol/L).

In the present issue of *Critical Care Medicine*, Dr. Revelly and colleagues (32) evaluated lactate production and clearance in patients with septic shock, patients with circulatory failure, and normal volunteers. They infused ^{13}C -labeled sodium lactate and ^2H -labeled glucose in these individuals and calculated the rate of gluconeogenesis from lactate by measuring plasma ^{13}C -glucose and that of lactate oxidation from measurements of expired $^{13}\text{CO}_2$. Lactate clearance was computed using a pharmacokinetic model. The authors found that the increased lactate production in patients with septic or cardiogenic shock was present despite lactate clearance being similar to healthy subjects. Baseline arterial lactate concentrations were 3.2 ± 2.6 mmol/L in septic shock patients, 2.8 ± 0.4 mmol/L in cardiogenic shock patients, and 0.9 ± 0.2 mmol/L in healthy subjects.

Dr. Revelly and colleagues (32) should be congratulated for the care shown in performing these very difficult clinical studies. Given the complexity of the experiments, and as acknowledged in their article, the statistical power of the study is limited by the small number of subjects in each group. A methodological concern is the application of a steady-state pharmacokinetic model that assumes steady state to a condition in which the subjects failed to achieve a lactate concentration plateau. Using the last measured point as an estimate of the plateau value makes the results of the model highly dependent

on the assumption of having reached a steady-state condition. Perhaps it would have been more satisfying, although perhaps not more valid, to extrapolate a fitted mathematical function of the data to a plateau value.

The divergent findings of Dr. Revelly and colleagues (32) and those of Levraut et al. (29) perhaps can be explained by methodological differences in measuring lactate clearance. Dr. Revelly and colleagues used a continuous infusion method, as opposed by the bolus injection method used by Levraut et al. There were also small differences in patient population, with the subjects in Revelly et al. study having higher lactate concentration values.

Except in those individuals with clear evidence of systemic or regional cessation of blood flow, elevations in blood lactate concentration in critical ill patients probably bear little relation to tissue hypoxia. Most likely, the metabolism of lactate and glucose in sepsis is tied to the cellular inflammatory response (33). Some tissues will produce lactate in concert with their degree of inflammation whereas other tissues will consume it. We applaud the efforts of Dr. Revelly and colleagues (32), as well as those of Chiolero et al. (31) and Levraut et al. (29), in attempting to define the complexity of lactate kinetics in critically ill patients.

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The unpretentious role of 2,3-diphosphoglycerate in critical illness*

The structure of hemoglobin was determined by Perutz and Kendrew (1) with x-ray crystallography almost a century after its discovery by the German chemist Felix Hoppe-Seyler in 1871. The function of hemoglobin as an oxygen carrier was established in the early 20th century by Bohr, Hasselbalch, and Krogh (2), who first described the sigmoid shape of the oxyhemoglobin dissociation curve (ODC).

The hemoglobin protein is a tetramer composed of two α and two β polypeptide chains. Each chain contains a heme group capable of binding reversibly to oxygen. The sigmoid shape of the ODC is characteristic of an allosteric enzyme system, in which the substrate also serves to modulate catalytic activity (3). Fully deoxygenated hemoglobin has low oxygen affinity. Initial binding to an oxygen molecule produces mechanical and chemical stresses that relax the α - β chains of hemoglobin and expose inner oxygen-binding sites. This conformational change increases the affinity of hemoglobin for the next oxygen molecule. As all binding sites are filled, oxygen affinity again decreases. The ability to alter oxygen affinity as a function of oxygen saturation makes hemoglobin an ideal oxygen carrier. Partially deoxygenated venous blood enters pulmonary capillaries, avidly searching for oxygen. Fully oxygenated arterial blood enters tissue capillaries ready to yield its precious cargo.

Alterations in hemoglobin affinity are best characterized by changes in P50, the oxygen tension at which hemoglobin is 50% saturated. Increases in P50 (right shift of the ODC) correspond to lower hemoglobin oxygen affinity. Decreases in P50 (left shift of the ODC) correspond to higher oxygen affinity. Increases in blood temperature, hydrogen ion concentra-

tion, and P_{CO_2} independently lower oxygen affinity through a conformational change in the hemoglobin molecule, albeit to a lesser extent than that produced by heme-to-oxygen binding. Decreased-oxygen-affinity hemoglobin promotes oxygen release in organs with a high metabolic rate, whereas increased-oxygen-affinity hemoglobin facilitates blood oxygen uptake when alveolar P_{O_2} is low.

Cell-free hemoglobin produces substantial vasoconstriction in some endothelial beds (4) since hemoglobin is a potent nitric oxide scavenger (5) with an affinity for nitric oxide 8,000 times that for oxygen (6). Erythrocytes isolate hemoglobin from the endothelial milieu. Furthermore, they do not consume oxygen to generate adenosine triphosphate but instead use glycolysis as their exclusive source of energy. The fermentation of glucose into pyruvate and lactate results in the generation of adenosine triphosphate and in the accumulation of 2,3-diphosphoglycerate (2,3-DPG) (7). Deoxyhemoglobin binds to 2,3-DPG, decreasing hemoglobin oxygen affinity (8, 9). 2,3-DPG also acts on the ODC by altering the Gibbs-Donnan equilibrium in the cell, with consequent lowering of intracellular pH (10).

Unlike the rapid swings in P50 produced by changes in pH or temperature, 2,3-DPG accumulates slowly as a function of the erythrocyte glycolytic rate. Measurable changes in P50 produced by 2,3-DPG require 4–24 hrs to occur (11). Acidosis and reductions in inorganic phosphate decrease blood 2,3-DPG concentration, whereas hypoxia and altitude tend to increase it (12).

Few studies have measured blood 2,3-DPG concentration in critically ill patients or the effect that alterations in 2,3-DPG have on P50 *in vivo*. Of particular interest is the effect that depletion of 2,3-DPG in stored blood (13) has on tissue oxygen delivery (14, 15). Blood transfusions depress overall 2,3-DPG concentration in heart surgery patients (16) but apparently do not affect hemodynamic or oxygen-transport parameters.

Morgan et al. (17) noted decreases in 2,3-DPG concentrations in a mixed group

of critically ill patients but no changes in P50 or in tissue oxygenation. Agusti et al. (18) found higher pH and 2,3-DPG concentrations in a group of mechanically ventilated patients with acute respiratory failure than in a nonventilated cohort. The *in vivo* P50, however, was lower in the ventilated patients. This finding supports the notion that the position of the ODC in critically ill patients is determined primarily by alterations in blood pH, not by changes in 2,3-DPG levels.

The study by Ibrahim and colleagues (19) in this issue of *Critical Care Medicine* explores the relationship between ICU mortality rate and erythrocyte 2,3-DPG concentration. Little is known about this subject, and the authors should be congratulated for their efforts. They measured 2,3-DPG concentrations in a large, heterogeneous cohort of critically ill patients within 24 hrs of ICU admission and compared them with concentrations for a healthy reference group matched by age and sex. They excluded patients who had received a blood transfusion within the previous 24 hrs, ensuring that 2,3-DPG measurements were of either native or *in vivo* rejuvenated erythrocytes.

Ibrahim et al. (19) found no association between ICU mortality and blood 2,3-DPG concentration. Moreover, 2,3-DPG concentration was lower in the ICU patients than in the reference group. This difference could be attributed exclusively to a lower 2,3-DPG concentration in female patients, a remarkable and unexpected finding. A multivariate analysis of the data found no association between gender and 2,3-DPG concentration, so perhaps small but cumulative variances between male and female patient groups were responsible for a lower 2,3-DPG in female patients. This finding certainly merits attention in future investigations.

The study by Ibrahim et al. (19) showed a normal mean *in vivo* P50 (28.5 Torr, or 3.8 kPa) and a reciprocal relationship between blood hydrogen ion and 2,3-DPG concentrations. This relationship appears to be strongest in female patients (Fig. 3 of their article). Ibrahim et al. hypothesize that decreases in 2,3-

*See also p. 2247.

Key Words: 2,3-diphosphoglycerate; critical illness; hemoglobin; P50; oxygen delivery; blood transfusion

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DPG may affect adversely the unloading of oxygen from blood in tissue capillaries by shifting the ODC curve to the left, or at least by hindering a hydrogen ion-induced rightward shift.

Although it is commonly accepted that decreases in hemoglobin affinity promote the release of oxygen in the tissue capillaries, it is not certain that leftward shift of the ODC impairs tissue oxygen delivery. In fact, Barcroft et al. (20) suggested that acclimatization to a hypoxic environment requires a left shift of the ODC to fully saturate hemoglobin at lower alveolar P_{O_2} values. Subsequent measurements at high altitude, however, showed that acclimatized subjects develop chronic hyperventilation and respiratory alkalosis (21), a response that is accompanied by increases in 2,3-DPG, resulting in constant P50 or even a slight increase in oxygen affinity (22).

As Fairweather et al. (23) proposed >30 yrs ago, perhaps the function of 2,3-DPG is to unobtrusively defend a normal P50 from persistent acid-base disturbances. Increases in hemoglobin oxygen affinity resulting from acidemia are moderated by decreases in 2,3-DPG, whereas the opposite occurs with alkalemia. Avoiding large alterations in P50 might help position the ODC optimally to swing left when loading oxygen and swing right when releasing it. This phasic adjustment in P50 would create the most favorable conditions for oxygen transfer from the lungs to the tissues.

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When shall the lung be opened up: During or after cardiac surgery?*

Pulmonary function is impaired after cardiac and abdominal surgery; hypoxemic periods are frequent, and pneumonia occurs in 3% to 10% of patients, a figure that may exceed 20% following emergency surgery (1–4). There may be half a million patients per year who develop pulmonary complications in the European Union or the United States. A prolongation of the hospital stay by 4 days, followed by a sick leave of 4–7 days, may result in a cost of \$5,000 per patient, a total cost of \$2.5 billion per year in the United States or European Union! To this monetary cost can be added the strain on family and workplace.

One cause of intraoperative and postoperative lung complications is reduced functional residual capacity (FRC) during anesthesia (5). Airways are narrowed, causing airway closure and gas adsorption, leading to atelectasis formation. Atelectasis can be seen in almost all anesthetized subjects, independent of age (6).

Atelectasis causes shunt and is a potential cause of inflammation and pneumonia. The opening of atelectasis in the anesthetized subject requires a “vital capacity” maneuver, that is, inflation of the lung to an airway pressure of 40 cm H₂O. However, atelectasis reappears within minutes if ventilation is done with high oxygen concentration, unless a positive end-expiratory pressure (PEEP) is applied (6).

Cardiac surgery causes large atelectasis and shunt. If no precautions are taken in the immediate postoperative period, the lung will recruit slowly, and more than half the lung may be collapsed both 1 and 2 days later, with shunt around 20% to 30% of cardiac output (7–9).

The effects on arterial oxygenation of making recruitment maneuvers after cardiac surgery have been tested in different

clinical trials, mostly with clear improvement of PaO₂ (10–12). In a study by Dyhr et al. (13) a recruitment maneuver of four 10-sec inflations to an airway pressure of 45 cm H₂O plus PEEP of 12 cm H₂O increased FRC and more than doubled PaO₂ during a limited study period of 75 min. In this issue of *Critical Care Medicine*, Miranda and co-workers have tested effects of a slightly different “open lung concept” on FRC and hypoxemia after cardiac surgery, and they followed the patients over a much longer period of 5 days (14). They tested whether a recruitment maneuver to a peak inspiratory airway pressure of 40 cm H₂O during 15 sec could raise the PaO₂/FIO₂ ratio to a value >375 mm Hg. They repeated the maneuver with increasing peak inspiratory airway pressure, up to a maximum of 60 cm H₂O if necessary, to reach the intended PaO₂/FIO₂ ratio.

In one group this procedure was initiated in the postoperative ward around 1 hr after cessation of surgery (“late open lung” concept). In another group, the open lung concept was instituted during the early phase of anesthesia before surgery (“early open lung” concept), followed by minor ventilation (tidal volume of 1 mL/kg and a PEEP of 10 cm H₂O (with few exceptions). A control group underwent continuous positive airway pressure of 3–5 cm H₂O during surgery, followed by manual bagging up to an airway pressure of 35 cm H₂O with 100% oxygen at the end of surgery, mechanical ventilation with a tidal volume of 6–8 mL/kg, and a PEEP of 5 cm H₂O.

On the first postoperative day, FRC was reduced to one-half in the controls. Surprisingly, the late open lung group showed no better results. However, in the early open lung group, FRC was much better preserved, with 50% higher values than in the control group on the first postoperative day. Moreover, fewer recruitment maneuvers had to be performed in this group than in the late open lung group to maintain a PaO₂/FIO₂ >375 mm Hg, and the recruitment was performed with lower airway pressure.

The control group had more hypoxic episodes than either of the two open lung

groups, and there was no difference between the two latter groups. There was no difference between the three groups regarding pneumothorax, pneumonia, or cardiac performance. Thus, the higher airway pressure in the two open lung concept groups did not cause more barotrauma/volutrauma or more impairment of cardiac function than in the control group.

What can we learn from these results? The authors found that the open lung concept reduced the risk of developing hypoxemia, similar to findings in previous studies of lung recruitment after cardiac surgery (10–13). However, early application of the open lung concept was needed to increase FRC well above that of controls, and the authors attribute this to less cyclic collapse that may reduce stress and activation of inflammatory markers. This is a tempting explanation but not proven, and cyclic collapse can hardly be expected in the nonventilated lung. Moreover, atelectasis seems not to be reopened during ordinary tidal ventilation during anesthesia (5). Thus, prevention of cyclic collapse by the open lung concept may be limited to the postoperative period.

The early open lung group was ventilated according to the open lung concept for the whole postoperative ventilator period, whereas the late open lung group underwent conventional mechanical ventilation for 30–60 min before the open lung concept was applied. That this short period should have caused the nonrecruitable drop in FRC is almost surprising, but there is no immediate alternative explanation. However, as a prevention of hypoxemic episodes, the late open lung concept was rather efficient.

This is similar to the successful use of continuous positive airway pressure in hypoxemic patients after abdominal surgery (15). A compromise would be to apply the open lung concept as soon as full ventilation is resumed after surgery instead of waiting until the patient is in the postoperative ward or intensive care unit. This might eliminate the need for high PEEP/continuous positive airway pressure during surgery (part of the open

*See also p. 2253.

Key Words: anesthesia; atelectasis; cardiac surgery; pneumonia

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lung concept), with its potential of limiting the visual field for the surgeon.

In conclusion, an increased interest in improving postoperative lung function has emerged during the past few years, partly because of new insights into atelectasis formation in the perioperative period. The study by Miranda et al. is proof of that, although their finding that early, intraoperative lung recruitment was superior to late recruitment must be met with some caution. The reproduction of their results by another group is eagerly waited for.

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Reassessing recombinant human activated protein C for sepsis: Time for a new randomized controlled trial*

In this issue of *Critical Care Medicine*, Dr. Vincent and colleagues (1) present an uncontrolled evaluation of recombinant human activated protein C (rhAPC) (Extended Evaluation of rhAPC trial, ENHANCE) in sepsis. This trial suggests that the risk of hemorrhage with rhAPC may be greater than originally estimated in the phase III rhAPC Worldwide Evaluation in Severe Sepsis Trial (PROWESS) (2). In addition to ENHANCE and PROWESS, however, two as yet unpublished randomized controlled trials have been completed in adults and children that prospectively tested the efficacy of rhAPC in sepsis (3,

4). Neither of these controlled trials reproduced the beneficial effect of rhAPC reported in PROWESS, raising the question whether there is a population of septic patients who can be identified *a priori* who will benefit from this agent. We believe this question can only be answered with an additional prospective placebo-controlled trial.

Analysis of the mortality data from the PROWESS trial by the Food and Drug Administration (FDA) was based on prospectively defined subsets of patients (5, 6). This analysis found that the mortality difference between rhAPC and placebo was limited to those patients with a higher risk of death, as defined by an Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥ 25 (i.e., the third and fourth quartile APACHE II scores). In the FDA analysis, the APACHE II appeared most effective in classifying patients by risk of death and by likelihood of benefit from rhAPC. After approval, based on this analysis and risk-benefit

assessment, the package insert indicated that rhAPC was for use in patients with severe sepsis and a high risk of death as determined by, for example, APACHE II score (6, 7). In approving rhAPC, the FDA also anticipated receiving the results of additional testing planned by the manufacturer in lower risk adult patients (APACHE < 25) and in children (5). These two randomized placebo-controlled trials were conducted in patients with low APACHE II scores (Administration of Drotrecogin Alfa (Activated) During Early Severe Sepsis [ADDRESS] trial) and pediatric patients. Both trials were stopped by their respective data monitoring committees for futility (Table 1). In the ADDRESS trial, the control mortality rate was low (17%) and similar to the low-risk groups (APACHE II 3–24, 19%) in the PROWESS trial (Table 1, Fig. 1). When the results from the ADDRESS trial are analyzed in combination with the APACHE II subgroups from PROWESS, the lack of benefit from rhAPC for adult pa-

*See also p. 2266.

Key Words: recombinant human activated protein C; ENHANCE; PROWESS

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Table 1. Mortality rate (28 day) in the ADDRESS and Pediatric Trials Testing rhAPC

| Trial | Mortality Rate (No. of Patients Studied) | |
|---------------|--|-------------|
| | Placebo, % | rhAPC, % |
| ADDRESS (3) | 17.0 (1307) | 18.5 (1333) |
| Pediatric (4) | 18.0 (198) | 17.0 (201) |

ADDRESS, Administration of Drotrecogin Alfa (Activated) During Early Severe Sepsis Trial.

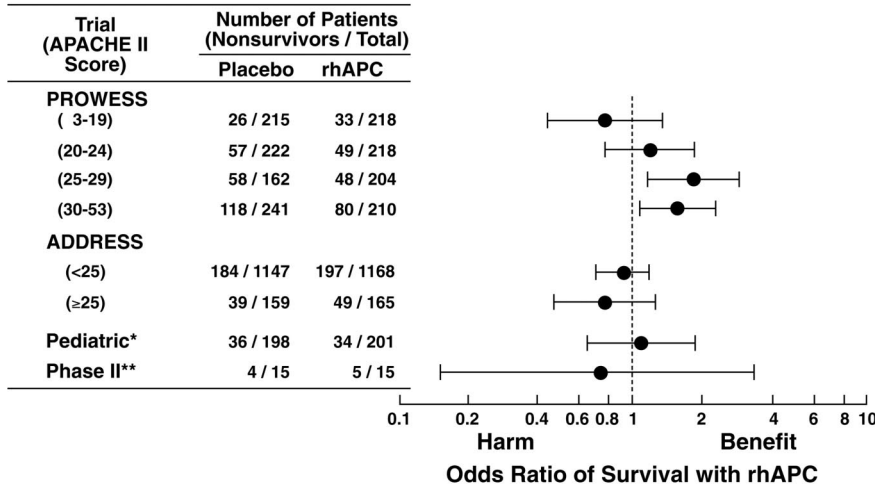


Figure 1. The odds ratio of survival (95% confidence interval) for the effects of recombinant human activated protein C (rhAPC) vs. placebo in the PROWESS, ADDRESS, Pediatric, and phase II trials based on 28-day survival data. Trials were further categorized based on Acute Physiology and Chronic Health Evaluation (APACHE) II scores when available. *Data available from interim analysis at the time of the trial's termination; **data from the subgroups of patients receiving 96-hr infusions of rhAPC (24 mg/kg/hr), the regimen studied in later trials, or 96 hrs of placebo. Overall in the phase II trial, which tested seven different rhAPC regimens, 14 of 41 placebo and 26 of 90 rhAPC patients died.

tients with a lower risk of death is convincing (Fig. 1). This lack of benefit in lower risk patients, however, does not prospectively confirm the *post hoc* analysis indicating that rhAPC would be beneficial in higher risk patients (i.e., APACHE II ≥ 25). In fact, data from the ADDRESS trial raise concern about its efficacy in this group (3).

Although ADDRESS was designed to test rhAPC in patients with severe sepsis and a lower risk of death, of the 2,613 patients with 28-day mortality rates recorded, 321 had APACHE II scores at enrollment ≥ 25 . Although this latter group with higher APACHE II scores was possibly too small to show statistically significant benefit, mortality rates with rhAPC were actually higher than in patients given placebo (Fig. 1). Thus, the beneficial effect noted with rhAPC in the PROWESS trial was not reproduced in ADDRESS. Furthermore, in the phase II trial of rhAPC, patients receiving the same regimen of rhAPC subsequently approved by the FDA (24 $\mu\text{g}/\text{kg}/\text{hr}$ for 96 hrs) also showed no benefit (33% mortality) compared either with overall controls (34% mortality with 48- or 96-hr placebo infusions) or with controls receiving 96-hr placebo infusions alone (27% mortality) (Fig. 1) (8). These findings raise serious questions about the purported benefit of rhAPC in sepsis. Its efficacy has not been confirmed in a prospective study for any population, including patients with a high-risk of death as originally defined by the FDA.

Of equal concern, the risk of severe hemorrhage with rhAPC has been higher in subsequent trials and clinical practice than originally determined in PROWESS. Although the ENHANCE trial was uncontrolled, the incidence of intracerebral hemorrhage in patients was greater than in PROWESS, even though the two trials employed similar inclusion and exclusion criteria (Fig. 2) (1, 2). In the placebo-controlled pediatric trial, the incidence of intracerebral hemorrhage with rhAPC was greater compared with placebo alone (Fig. 2) (4). This risk in combination with lack of efficacy caused early termination of the trial (4). In ADDRESS, the overall incidence of serious bleeding with rhAPC was increased significantly over placebo, but this was not different from PROWESS. However, 28-day mortality rate in surgical patients with single organ dysfunction and presumably at higher risk of hemorrhage than other patients was increased with rhAPC (21% of 323) vs. placebo (14% of

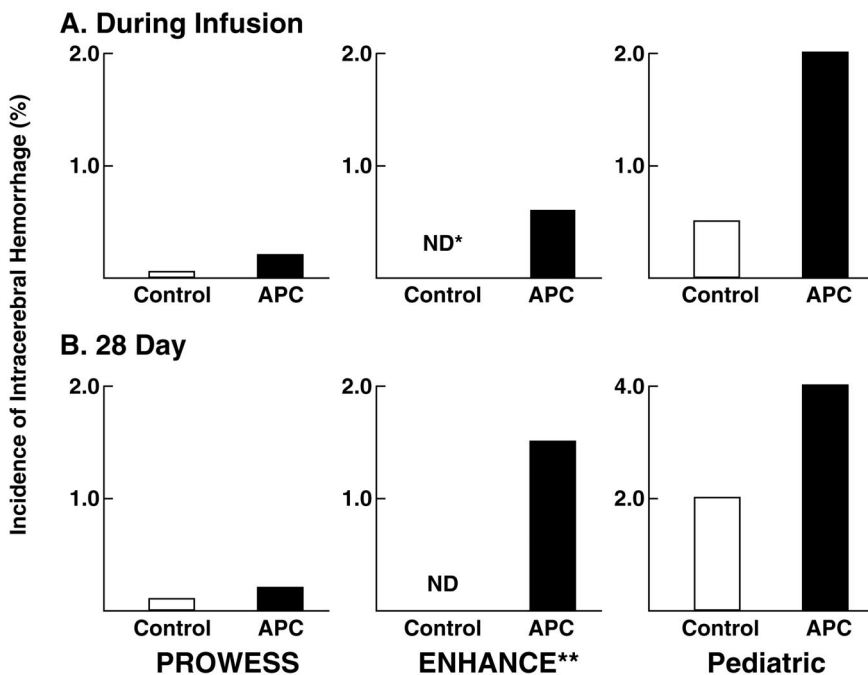


Figure 2. The incidence of intracerebral hemorrhage during drug infusion or at 28 days in the PROWESS (phase III), ENHANCE (uncontrolled), or Pediatric (placebo controlled) trials in patients receiving recombinant human activated protein C (APC) or placebo (control). *Similar inclusion and exclusion criteria as PROWESS; **Not done.

313) (9). Based on this finding in ADDRESS and a similar trend in PROWESS, additional warnings regarding the use of rhAPC have been published (9). Last, in two medical utilization evaluations of rhAPC in a total of 599 patients, the overall rate of adverse drug reactions, primarily related to bleeding, and the need to discontinue drug infusion due to adverse drug reactions were both higher during clinical use than in PROWESS (18.0 vs. 12.5% and 10.4 vs. 6.4%, respectively) (10, 11).

Questions about consistency of benefit and risk of hemorrhage arising from the PROWESS trial and other data led ten of 20 members of the FDA Advisory Committee for Anti-Infectives to vote for additional phase III testing before FDA approval of rhAPC (12, 13). The data from randomized trials subsequent to PROWESS have raised additional concerns. Comparing all patients ($n \approx 2,399$) who received rhAPC using the currently approved regimen to their concurrent controls ($n \approx 2,359$), only two subgroups from the PROWESS trial have shown clear benefit (the two highest APACHE II quartiles) (Fig. 1). These two PROWESS subgroups included only 414 patients receiving rhAPC (i.e., 17% of all patients receiving rhAPC in controlled trials). At least one prospective randomized controlled trial should be conducted to confirm that rhAPC is effective in those patients with sepsis for whom it is currently recommended. This is especially important in light of rhAPCs increased hemorrhagic risk and lack of benefit in low-risk patients and its inconsistent effects in

two randomized controlled clinical trials that have included higher risk patients (i.e., PROWESS and ADDRESS).

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Drotrecogin alfa (activated) treatment in severe sepsis: A “journal club” review of the global ENHANCE trial*

This editorial is structured and formatted as a journal club review and report. I used a typical review template for a therapeutic trial, commonly employed by students of evidence-based medicine everywhere. I

reviewed “Drotrecogin Alfa (Activated) Treatment in Severe Sepsis From the Global Open-Label Trial ENHANCE: Further Evidence for Survival and Safety and Implications for Early Treatment” by Dr. Vincent and colleagues (1), found in this issue of *Critical Care Medicine*.

a. Primary Study Question: In patients with severe sepsis, does drotrecogin alfa (activated) treatment lower 28-day all-cause mortality?

b. Secondary Study Question: What was the rate of serious adverse bleeding

events during the 96-hr infusion period and for the 28-day study duration?

How Was the Study Conducted?

1. Study Type: Therapy or prevention.
2. Study Design: Multi-institutional, single arm, nonrandomized, open-label study. This trial was conducted as an FDA phase III-b trial intended to expand the clinical safety and efficacy knowledge base for an already approved drug. The

*See also p. 2266.

Key Words: drotrecogin alfa (activated); ENHANCE trial; bleeding

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study design did not include a control or placebo arm. Treatment data from this trial were statistically compared with the previously published placebo and treatment arms of the PROWESS study (a separate trial). This comparison was a fundamental component of the clinical safety and efficacy analysis of the Global ENHANCE trial.

3. Study Funding Source: Eli Lilly and Company funded this study.

4. Conflict of Interest and Financial Disclosure: Drs. Vincent, Bernard, Beale, Doig, Putensen, Dhainaut, Artigas and Fumagalli have participated as investigators in Eli Lilly and Co. sponsored clinical trials. Drs. Vincent, Bernard, Beale, Doig, Putensen, and Dhainaut have served as consultants for Eli Lilly and Co. Drs. Vincent, Bernard, Beale and Dhainaut have been invited speakers at conferences supported by Eli Lilly and Co. Drs. Macias, Wright, Wong, Sundin, and Janes and RN/MSc Turlo are employees and stockholders of Eli Lilly and Co.

5. Enrolled Patients: Enrolled patients included adults admitted to an intensive care unit at a participating institution who a) had known or suspected infection; b) met at least three of the four defining criteria for systemic inflammatory response syndrome; and c) had evidence of one or more sepsis-induced organ dysfunctions at the time of study enrollment.

6. Excluded Patients: Patients were excluded a) if their age was <18 yrs; b) if a patient was pregnant or breast feeding; c) if other conditions were present that increased the risk of bleeding; d) if a patient had a known hypercoagulable condition; e) if patient demise was likely; f) if a patient had HIV; g) if a patient was an organ transplant recipient; h) for chronic renal failure requiring dialysis; i) for end-stage liver disease; or j) for concurrent or recent administration of heparinoids, warfarin, thrombolytic therapy, glycoprotein IIb/IIIa antagonists, or antithrombin III dosing.

Are the Results of the Study Valid?

What was the validity and accuracy of the results? Do the results reported in the article represent the true direction and magnitude of the treatment effect?

Was the Assignment of Patients to Treatments Randomized? No. All enrolled patients who met study entry criteria were administered drotrecogin alfa.

Were All Enrolled Patients Properly Accounted for by the Trial Design and Data Analysis? Yes. Data tracking and analysis included all enrolled patients. Follow-up and data collection were performed for all patients according to an institutional review board approved study design.

Were Patients Analyzed in the Groups to Which They Were Randomized? Yes and No. No randomization techniques were employed in this trial. All patients who received treatment during this trial (Global ENHANCE) were compared with a nontreatment group from a different/separate trial (PROWESS) (2). These two trials included overlapping institutions and intensive care units; however, there were several or more institutions and intensive care units that were involved in only one or the other of these two trials (3). These two trials were conducted with nonoverlapping timelines. A single study center was identified and used for all data management and analysis.

Were Patients, Care Providers, and Study Personnel "Blind" to Patients Who Received The Study Drug? No. This study was conducted as a single arm, open-label study.

Were the Groups Similar at the Initiation of the Trial? Yes. Treatment patients from the Global ENHANCE trial and nontreatment patients from the PROWESS trial were acceptably matched for age, gender, variables related to infection, severity of illness, and organ system dysfunction.

In Other Aspects of Their Care, Did Patients From Both Treatment and Nontreatment Groups Receive the Same Diagnostic and Therapeutic Interventions? Unknown. To the extent inferred by the authors of both trials (Global ENHANCE and PROWESS), other aspects of sepsis and intensive care were consistent between trials. Neither study protocol employed a standardized approach to the use of fluids, antibiotic selection, vasopressor therapy, or mechanical ventilation. Variability of diagnosis and treatment was not reported for either study.

What Were the Study Results?

What is the size and precision of the treatment effect?

What Is the Measurable Treatment Effect? A total of 2,378 patients from the Global ENHANCE trial received drotrecogin alfa and were statistically compared

with 840 placebo patients and 850 treatment patients from the previously reported PROWESS trial. The primary outcome variable for the Global ENHANCE trial was 28-day all-cause mortality. The secondary outcome variable was rate of serious adverse bleeding events. Both of these were expressed as dichotomous (yes/no) variables—that is, did the patient die or did the patient have a serious adverse bleeding event? These are expressed as a percent of the total and subset study populations.

For the ENHANCE patients, I calculated basic comparative mortality statistics as follows:

risk of death without therapy (X) = Not measured; use PROWESS trial data?

risk of death with therapy (Y) = $599/2375 = 0.252$

extrapolated absolute risk reduction (ARR = X - Y) = $0.308 - 0.252 = 0.056$

extrapolated relative risk (Y/X) = $0.252/0.308 = 0.818$

extrapolated relative risk reduction (RRR = $[1 - Y/X] \times 100$) = $[1 - 0.818] \times 100 = 18.2\%$

extrapolated number needed to treat (NNT = $1/ARR$) = $1/0.056 \approx 18$ patients

For the PROWESS patients, I calculated basic comparative mortality statistics as follows:

risk of death without therapy (X) = $259/840 = 0.308$

risk of death with therapy (Y) = $210/850 = 0.247$

absolute risk reduction (ARR = X - Y) = $0.308 - 0.247 = 0.061$

relative risk (Y/X) = $0.247/0.308 = 0.802$

relative risk reduction (RRR = $[1 - Y/X] \times 100$) = $[1 - 0.802] \times 100 = 19.8\%$

number needed to treat (NNT = $1/ARR$) = $1/0.061 \approx 16$ patients

For the ENHANCE patients, I calculated serious adverse bleeding events statistics as follows:

risk of bleeding without therapy (X) = Not measured; use PROWESS trial data?

risk of bleeding with therapy (Y) = $208/2378 = 0.087$

Table 1. Clinical significance

| Clinical Significance Measure | Value, % (n) | Lower 95% CI Boundary | Upper 95% CI Boundary |
|--|-----------------|--------------------------|--------------------------|
| Global ENHANCE cumulative 28-day mortality | 25.2 (599) | 23.5 | 27.1 |
| Mortality ARR ^a | 5.6 | — | — |
| Mortality RRR ^a | 18.2 | — | — |
| Mortality NNT ^a | 18 patients | — | — |
| Global ENHANCE cumulative 28-day bleeding incidence ^b | 6.5 (155) | 5.6 | 7.6 |
| Global ENHANCE bleeding incidence ICH—total | 1.5 (35) | 1.0 | 2.0 |
| Global ENHANCE bleeding incidence ICH—fatal | 0.5 (12) | 0.3 | 0.9 |
| Bleeding ARI ^a | 6.4 | — | — |
| Bleeding RRI ^a | 73.6 | — | — |
| Bleeding complication NNT ¹ | 16 patients | — | — |

CI, confidence interval; ARR, RRR, NNT; ICH, intracranial hemorrhage; ARI, RRI.

^aThese numbers are my calculations and were not reported in the study; ^bthere were six patients with two bleeding incidents tallied once by the authors.

extrapolated absolute risk increase (ARI = Y - X) = 0.087 - 0.023 = 0.064

extrapolated relative risk (X/Y) = 0.023/0.087 = 0.264

extrapolated relative risk increase (RRI = [1 - X/Y] × 100) = [1 - 0.264] × 100 = 73.6%

extrapolated number needed to treat in order to see a patient with a significant adverse bleeding event = (NNT = 1/ARI) = 1/0.064 ≈ 16 patients

For the PROWESS patients, I calculated serious adverse bleeding events statistics as follows:

risk of bleeding without therapy (X) = 19/840 = 0.023

risk of bleeding with therapy (Y) = 34/850 = 0.040

absolute risk increase (ARI = Y - X) = 0.040 - 0.023 = 0.017

relative risk (X/Y) = 0.023/0.040 = 0.575

relative risk increase (RRI = [1 - X/Y] × 100) = [1 - 0.575] × 100 = 42.5%

number needed to treat in order to see a patient with significant adverse bleeding event = (NNT = 1/ARI) = 1/0.017 ≈ 59 patients

How Precise Was the Estimate of Treatment Effect? Those confidence intervals that are reported are acceptably narrow, are reassuring, and are consistent with the large sample sizes included in the PROWESS and Global ENHANCE trials (Table 1). However, the predominant “results section” focus on this article targets the reliability of comparison between these two trials. You can neither

impute nor determine the impact of treatment without importing data from the PROWESS trial. For example, basic comparisons of treatment effect on mortality and relative risk reductions, like the simple calculation of treatment vs. placebo *p* values, cannot be accomplished because the available data are insufficient.

Will the Results Help Me in Caring for My Patients?

Are the study results applicable to my patients? Are my patients similar to those described in the trial? Is the described study outcome that is improved relevant to my patients? If the results are applicable, then what is the net impact of treatment?

Can These Results Be Applied to My Patient Care? Drotrecogin alfa is already approved for use in patients with severe sepsis. This article expands the reported population of intensive care unit patients who have received drotrecogin alfa and who have had their mortality and rate of serious adverse bleeding events measured and published. In this regard, these results can be viewed as “favorable.” These data also seek to support the contention that drotrecogin alfa treatment administered earlier in the clinical course of severe sepsis may improve outcome (Table 1). However, because this was conducted as a therapeutic trial, but was not accomplished according to a randomized protocol, there are explicit limitations. By itself, this trial cannot define the therapeutic impact of the drug. This weakness is acknowledged within the discussion section of the article and is underscored by efforts to mix and match data from separate but similar clin-

ical trials. As the authors noted, a randomized trial design would have been otherwise preferred. However, they believed that conducting another drotrecogin alfa randomized trial with a placebo arm (patient assignment by chance), in light of their results from the PROWESS trial, would have been a serious ethical breach. This perspective is not unique to this trial; Deeks and colleagues (6) eloquently described the ongoing debate in therapeutic trial design. Similarly, Rubenfeld (9) acknowledged the fluid interface between treatment preference and data interpretation.

Were All Clinically Important Outcomes Considered? First, following the PROWESS trial, one of the central concerns articulated related to increased risk of serious bleeding. Reporting the overall rate of serious adverse bleeding events in the PROWESS trial did not comprehensively address these questions. Most recently, the pediatric drotrecogin alfa trial also raised concerns about increased risk of bleeding. I believe that these issues might have been better clarified by tabulating and reporting the appropriate laboratory studies longitudinally (at baseline, during infusion, and postinfusion). More specifically, was the administration of drotrecogin alfa associated with the development of thrombocytopenia, a decrement in hemoglobin or hematocrit, or a perturbation in baseline coagulation variables (beyond that attributable to activated protein C administration)? For the Global ENHANCE trial, it would have been reassuring to many to have included these data and their analyses in this article.

Second, improving outcome for patients with severe sepsis encompasses numerous aspects of care. Examples include prompt initiation of appropriate antibiotic therapy, prompt volume resuscitation, maintaining “tight” plasma glucose control, appropriate ventilator management in septic patients with ARDS, and proper avoidance of secondary complications like deep vein thrombosis, gastrointestinal stress ulceration, ventilator-acquired pneumonia, and so forth. Given the large number and type of institutions involved in the Global ENHANCE trial, it is reasonable to consider the potential impact of care variability among these other aspects of severe sepsis patient management. By design, the Global ENHANCE trial did not protocolize these aspects of care, nor did the investigators specifically report their potential effect. Whether these possible variances affected observed results is unknown but remains open to question.

Are the Likely Treatment Benefits Worth the Potential Harm and Costs? For the Global ENHANCE trial, the extrapolated NNT to save one life is 18 patients, compared with the placebo arm of the PROWESS trial. The extrapolated NNT to see one serious adverse bleeding event is 16 patients. A detailed analysis of these events, their associated morbidity, or their costs was not offered by the investigators. However, the estimated NNT to see one fatal intracranial hemorrhage, as derived from the reported data, is approximately 1 per 250 patients treated. No other complications were tallied by the authors, and they specifically commented that bleeding was the only adverse event related to treatment with drotrecogin alfa.

A Final Comment

Severe sepsis is a complex and frustrating condition that is associated with an unacceptably high mortality rate. The modulation of deleterious cellular and subcellular responses in sepsis has been a therapeutic goal of the astute critical care clinician for a very, very long time. Along

this path, we have navigated around many negative therapeutic trials.

For this article, the most important unanswered question is, How big does the treatment effect of a nonrandomized study design (like ENHANCE) have to be before it compellingly alters the therapeutic opinions of clinicians (4, 5, 8)? Many of our finest and most industrious intellects in critical care scientifically support drotrecogin alfa as a life-saving therapy. I study and learn from these individuals as a respectful student (7). Conversely, numerous equally respected critical care scientists have energetically called into question the PROWESS and some other drotrecogin alfa trials. They too should be accorded a constructive voice in advancing the science of sepsis therapy. It is my concern that the design and the results from the Global ENHANCE trial will do little to merge these disparate perspectives.

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Exogenous surfactant in acute lung injury: No longer a question?*

A number of conditions, such as pneumonia, sepsis, and trauma, may result in respiratory failure and contribute to multiple organ failure or even death. One specific interest has been focused on the role of the surfactant system in these settings (1). Pulmonary surfactant is a complex of highly active phospholipids and proteins, synthesized in alveolar type II pneumocytes, stored in the lamellar bodies, and secreted into the alveolar space, where it undergoes various changes (2). The central function of surfactant is to reduce surface tension at the air-liquid interface of the lung according to Laplace's law: $\Delta p = 2 \gamma/r$, where p

represents the pressure gradient across the alveolus (tendency for the alveolus to collapse), γ the surface tension value, and r the radius of the alveolus. A high surface tension that does not change during exhalation (when r typically decreases) results in increased transalveolar pressure, thereby contributing to alveolar collapse and/or pulmonary edema formation secondary to hydrostatic pressure changes across the alveolar-capillary barrier (3). It is commonly accepted that abnormalities of surfactant play a major role in the pathophysiology of acute respiratory distress syndrome (ARDS) not only in the acutely inflamed mature lung but also in the immature lung (4). The pathophysiologic changes in this syndrome (e.g., injured alveolar type II cells, disturbed surfactant production), in turn, may foster the pathogenesis of surfactant dysfunction, thereby leading into a vicious cycle.

The rationale to administer exogenous surfactant in patients with acute lung in-

jury (ALI) or ARDS is, therefore, to restore the normal composition of the surfactant system and to overcome ongoing inactivation of endogenous surfactant (5). Although administration of surfactant may theoretically reestablish an equilibrium of the surfactant system and subsequently improve pulmonary function, such approach is not inevitably effective. In contrast to successful studies in neonates, infants, and children (6, 7), surfactant replenishment has proven inconsistent as a therapeutic modality in adults with respiratory failure (3).

The reason for the clinical equipoise with exogenous surfactant therapy is still not fully understood and may be explained by differences in the nature of the injury at the time of treatment; the specific composition of the surfactant used; the timing, dose, and delivery method chosen; and the mode of ventilation used during and following surfactant administration (3). Because numerous factors appear to have a significant impact on the

*See also p. 2286.

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outcome of patients with respiratory failure, surfactant replacement therapy remains a clinical challenge.

In the current issue of *Critical Care Medicine*, Dr. Strohmaier and colleagues (8) present the results of an interesting and timely study elucidating the effects of Curosurf, a natural, protein-containing surfactant derived from porcine lung tissue, on pulmonary function in an established pig model of ALI. The authors report that unilateral lung contusion, resulting from a bolt shot, contributed to rapid and significant decreases in $\text{PaO}_2/\text{FIO}_2$ ratio and pulmonary compliance that were accompanied by an increase in peak inspiratory airway pressure. In the animals randomized to receive a bilateral, sequential, and segmental surfactant lavage (25 mg/kg in 5 mL/kg normal saline), the changes in $\text{PaO}_2/\text{FIO}_2$ ratio and compliance were reversed and the increase in peak inspiratory airway pressure was attenuated. Compared with injured controls, surfactant administration also reduced mean pulmonary artery pressure and pulmonary vascular resistance, thereby reducing the workload of the right ventricle.

In view of the published studies on this topic, although limited in extent, it is tempting to postulate that the discrepancy between negative results of large clinical trials (9–11) may be basically due to the mode of surfactant administration and the dosing schedule. This assumption is supported by experimental studies showing that therapeutic lavage with diluted surfactant was superior over conventional aerosol and bolus therapy with regard to distribution and need for surfactant (12, 13). In this context, it has also been reported that in patients with ARDS, only 4.5% of aerosolized radiolabeled surfactant reached the lungs (14), thereby providing an explanation why some clinical studies, using the nebulization technique, may have failed.

The approach of bronchoscopic surfactant lavage that is described in this issue of *Critical Care Medicine* (8) enables the administration of larger volumes of the compound, as was recently recommended by Anzueto (2). In this context, it is noteworthy that surfactant lavage not only allows for a better distribution of surfactant but also facilitates the removal of alveolar edema protein, cellular breakdown products, and blood components, as well as proteolytic and lipolytic enzymes (8, 12). Because the greater part of the fluid is removed by

suction or passive drainage, the volume load after lavage is no higher than after bolus administration (8). However, although the present authors reported that the lavage procedure was well tolerated by all animals, future clinical studies are needed before a final conclusion about the efficacy and feasibility of this new experimental concept can be drawn.

Another interesting finding by the current authors (8) is the observation that the pathophysiologic changes in response to the trauma were not restricted to the ipsilateral (injured) lung but were also present in the contralateral (uninjured) one. As such, the unilateral thorax injury contributed to a bilateral increase in alveolar neutrophils. Notably, surfactant treatment limited neutrophil accumulation and therewith potentially harmful side effects linked to the production of toxic metabolites and reactive oxygen species. The hypothesis that surfactant exerted anti-inflammatory properties is supported by the fact that leukocyte neutral proteinase inhibitor was significantly increased in bronchoalveolar lavage fluid in the injured lung compared with the lungs of the sham and control groups. These results are in full agreement with other studies, in which exogenous surfactant inhibited proinflammatory cytokines and augmented the innate host defense (10, 15). With the recognition that surfactant also improves mucociliary clearance (16), future clinical studies are warranted to evaluate the role of surfactant lavage in subacute pulmonary diseases, such as asthmatic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, interstitial lung disease, and alveolar proteinosis (17).

The bottom line is that the study by Dr. Strohmaier and his colleagues (8) has an important recommendation: that surfactant treatment should be initiated in the early phase of lung trauma and should include not only the injured areas of the lung but also the unaffected ones. In fact, the findings of the present study (8) suggest that early surfactant treatment of the intact lung may be protective by limiting the spread of proinflammatory mediators from injured to uninjured tissue. The absence of direct comparisons between unilateral vs. bilateral treatment effects, however, renders this interesting speculation inconclusive.

Inasmuch as experimental studies suggest that the efficacy of exogenous surfactant may be further improved by asymmetric high-frequency jet ventila-

tion (18, 19), future studies, elucidating this issue in more detail, are warranted.

The study by Dr. Strohmaier and colleagues (8) supports the concept that bronchoalveolar lavage with diluted surfactant is a safe and valuable approach to improve pulmonary function in the common setting of lung contusion. In agreement with the results of a recent clinical trial, in which intratracheal instillation of natural lung surfactant (calfactant) acutely improved oxygenation and significantly reduced mortality rate compared with the placebo group (6), exogenous surfactant emerges as an interesting addition to the intensive care armamentarium. Since there is little doubt that surfactant has the potential to improve pulmonary function in the setting of ALI and ARDS, the question that remains to be answered is, therefore, not whether to administer surfactant but rather when, which one, and how (much).

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β-blockade during sepsis: Inspired or insane?*

In an interesting article published in this issue of *Critical Care Medicine*, Dr. Suzuki and colleagues (1) challenge us to think outside of the box in treatment of experimental sepsis. They demonstrate that the selective blockade of β-1 receptors is actually good for rats subjected to Dr. Chaudry's model of cecal ligation and puncture (CCLP) (2, 3). I probably would not have bet that this would be the case. They demonstrated that esmolol infusion after CCLP (clinically relevant timing in a clinically relevant model) decreased tumor necrosis factor-α levels and improved cardiac output and cardiac efficiency. Brilliant—and it makes sense when examined in the context of what we have learned about the benefits of β-receptor blockade in burn shock (4, 5) and cardiogenic shock (6–9). If shock, and specifically shock caused by CCLP, is the “rude unhinging of the machinery of life” characterized by disrupted cellular oxygen consumption capabilities, perhaps driving more oxygen to the tissues is not the answer—the cells want it, but they

cannot take it, so maybe we need to quit killing the heart in our noble attempts to coerce the cell to consume what it needs but is unable to use. Perhaps we should look at the other side. Perhaps we should help the tissues need less oxygen. Septic shock from CCLP drives myocardial oxygen requirements through the roof. In an environment where the cardiomyocyte handles oxygen less efficiently and needs more of it, it makes sense to cut the heart a break. However, at some level, there must be a critical inflection point where the attempt to decrease cardiac work leads to a decrease in cardiac output below the level needed to meet the decreased oxygen uptake of the tissues. As we are caring, compassionate physicians and clinically oriented scientists, pushing oxygen delivery to the point of flow-independent oxygen consumption makes our hearts feel good (10), but how does the patient's heart feel? Furthermore, it is possible that decreased tumor necrosis factor-α (as shown by the authors to be a bonus feature of β-receptor blockade) is actually good for other tissues as well. Decreasing tumor necrosis factor-α may decrease the oxygen required to maintain cellular homeostasis (11). However, some obvious questions remain. Patients are complicated; will this be yet another encouraging treatment of experimental sepsis that disappoints us clinically? What are the mechanisms of the anti-inflammatory effects of esmolol in CCLP, myocardial infarction, hypoxia, trauma-hemorrhage, and burn trauma? This

study was conducted in male animals: Will a similar benefit be observed in females, who possess a different myocardial inflammation profile (12–14)? In this regard, the most important things that this editorial can accomplish are two-fold: a) It can draw the reader's attention to this potentially clinically important article by Dr. Suzuki and colleagues (1); and b) it can point out Herndon and colleagues' earth-shattering related work in burn shock (5). I point out their work here because a) I think it changed the way we think about shock resuscitation forever; b) it was conducted in patients; c) there are obvious parallels with the current article; and d) in an honest oversight it was not discussed by Dr. Suzuki and colleagues (12). Rather than go on about myocardial inflammation, I will direct the reader's attention to the article by Dr. Suzuki and colleagues (12). β-blockade in sepsis: inspired or insane? The idea is definitely inspired! But will it work in patients? I think that it is too early to try, outside of an Institutional Review Board approved study setting.

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*See also p. 2294.

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Cardiac high-risk patients: From “permissive” to “deliberate” anemia*

Although safer than ever, allogeneic blood transfusion is still associated with risks for the recipient: transfusion of ABO incompatible blood (“clerical error”), bacterial and viral infection, immunosuppression, wound infection, transfusion-related acute lung injury (1–3). Furthermore, the costs for allogeneic blood products are expected to rise in the future due to an increasing imbalance between blood donors and potential transfusion recipients—particularly elderly patients undergoing major surgery (1).

To further reduce the risks and to control costs, allogeneic transfusion should whenever possible be completely avoided or at least minimized during surgical procedures. To realize this, multimodal concepts (4) have been developed aiming at “bloodless surgery” by a) intraoperative transfusion of autologous blood collected preoperatively (autologous blood donation, acute normovolemic hemodilution)

or intraoperatively (blood salvage); b) reduction of the amount of blood lost (skillful surgical technique, permissive hypotension, administration of antifibrinolytic drugs); and c) “permissive anemia,” that is, the tolerance of low perioperative hemoglobin (Hb) concentrations.

The concept of perioperative permissive anemia comprehends that an intraoperative blood loss is not immediately compensated with red blood cell transfusion, but that the shed blood is first replaced by red cell-free solutions, that is, crystalloid (3:1) and colloid (1:1) infusion solutions. This procedure is intended to maintain a normal circulating intravascular volume (normovolemia); at the same time the dilution of all circulating blood components is tolerated (hemodilution).

It has been known for long that the human body does not depend on a “normal” Hb concentration. In healthy anesthetized subjects, dilutional anemia over a large Hb range is fully compensated for by the increase of cardiac output and tissue oxygen extraction. Total body oxygen supply dependency and manifest tissue hypoxia occur only at extremely low Hb concentrations (<5 g/dL).

During normovolemic hemodilution, the heart becomes at the same time the “motor” for the compensation of dilu-

tional anemia (increase of cardiac output) and the organ at highest risk for anemic tissue hypoxia. Since myocardial oxygen extraction is almost complete under physiologic conditions, myocardial oxygen supply depends exclusively on the enhancement of coronary blood flow (i.e., on maximal coronary vasodilation). This mechanism is either impossible or at least restrained in the presence of coronary artery disease. In case of under-shooting a critical myocardial oxygen supply, myocardial oxygen demand is no longer satisfied and cardiac output starts to fall. In the presence of coronary artery disease and thus restricted coronary reserve, the cardiac compensatory mechanisms of dilutional anemia should become exhausted at higher Hb concentrations, and anemia tolerance should therefore be significantly restricted.

Today, moderate perioperative anemia (i.e., Hb 8–10 g/dL) is considered safe in cardiac high-risk patients. Presuming that normovolemia is maintained, the cardiac compensatory mechanisms are still preserved—even under medication with β -receptor blocking agents (5, 6). Although results of a retrospective observational analysis of 78,974 elderly patients admitted with acute myocardial infarction in the United States suggested a

*See also p. 2302.

Key Words: hemodilution; anemia; coronary artery disease; myocardial infarct; transfusion

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significantly reduced 30-day mortality rate when transfusion was initiated at a hematocrit of 33% and lower Hb (i.e., <11 g/dL) (7), a recent report in 24,112 patients suffering from acute coronary syndrome showed no impact of transfusion on survival when nadir hematocrit values were in the range of 20–25% (i.e., Hb 7–8 g/dL) but clearly revealed worsened outcome when hematocrit values were >30% (i.e., Hb 10 g/dL) (8). In a retrospective cohort analysis of cardiac risk patients undergoing noncardiac surgery and refusing allogeneic transfusion for religious reasons (affiliation with Jehovah's Witnesses), a significantly higher 30-day mortality was found if the postoperative Hb concentration fell below 8 g/dL (9). In intensive care patients with cardiac comorbidity, 30-day mortality was identical with either restrictive (target Hb 7–9 g/dL) or liberal (target Hb 10–12 g/dL) transfusion strategy (10). This held also true for a subgroup of 257 patients with severe ischemic heart disease (myocardial infarction, unstable angina) (11).

Intraoperative permissive anemia offers several incentives for the patient: a) The lower the Hb-concentration, the less the red cell loss per milliliter of blood loss; and b) the more delayed the onset of transfusion (at best after achievement of surgical control of bleeding), the higher the percentage of red cells transfused remaining inside the vascular system. By that, perioperative permissive anemia should contribute essentially to the perioperative avoidance of allogeneic transfusion.

In the current issue of *Critical Care Medicine*, Dr. Licker and coworkers (12) present another important finding in favor of permissive anemia in cardiac high-risk patients. In their rat model, both myocardial infarct size and mortality observed after a 30-min left coronary artery occlusion and subsequent 48 hrs of reperfusion were significantly reduced when the animals

were previously hemodiluted to a Hb concentration of 8–9 g/dL. Although the underlying mechanisms remain speculative (increased microvascular blood flow homogeneity, cytoprotective effect of erythropoietin) and although it is difficult to compare the coronary vasculature of healthy rats to the globally affected coronary system of coronary artery disease patients, the potential clinical impact of these findings is nevertheless evident: Pharmacologic thrombolysis as well as endovascular (percutaneous transluminal angioplasty) and surgical (coronary artery bypass grafting) coronary revascularization might be better tolerated in hemodiluted subjects than in subjects with normal Hb concentrations.

Moderate permissive anemia (Hb 8–10 g/dL) not only may be considered safe in cardiac high-risk patients but might even represent an effective measure to improve the outcome of this patient group by the reduction or avoidance of transfusion-associated risks and the protection from ischemia/reperfusion injuries after revascularization. This might finally lead to a change of paradigm away from the sole tolerance of anemia (permissive anemia) in cardiac high-risk patients toward active induction of normovolemic anemia (deliberate anemia) in well-defined clinical situations. The latter step, of course, needs further reinforcement by experimental and clinical investigations.

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Peroxisome proliferator-activated receptor- γ ligands protect against lung injury: Potential therapeutic targets?*

Acute lung injury that clinically manifests as acute respiratory distress syndrome (ARDS) is a major component of multiple organ dysfunction syndrome of various etiologies, such as sepsis, severe burns, acute pancreatitis, hemorrhagic shock, and trauma (1, 2). ARDS is the primary cause of death in these conditions (1, 2).

ARDS of different etiologies is characterized by a local inflammatory response. The inflammatory mediators also spill over into the general circulation. The severity of an attack of ARDS appears to be determined by the magnitude of the resultant systemic inflammatory response. In general terms, the systemic inflammatory response syndrome (SIRS) is an entirely normal response to injury. Sepsis is defined as SIRS in which there is an identifiable focus on infection. Several infective and noninfective causes of SIRS are recognized. Systemic leukocyte activation (cytokine mediated) is a direct consequence of a SIRS and, if excessive, can lead to organ dysfunction syndrome and multiple organ failure. As a consequence of an overactive SIRS response, leukocytes become activated within the general circulation and some then lodge within the pulmonary microcirculation. As the condition develops, leukocytes migrate into the pulmonary interstitium, and increased endothelial permeability leads to tissue edema. The leukocytes in the lungs both respond and contribute to the inflammatory process in ARDS (1, 2).

Recent research has shown that inflammatory mediators play a key role in

the pathogenesis of ARDS. The major inflammatory mediators implicated in ARDS include tumor necrosis factor- α , interleukin-1 β , interleukin-6, interleukin-8, cytokine-induced neutrophil chemoattractant/GRO- α , monocyte chemoattractant protein-1, macrophage inflammatory protein-1 α , regulated upon activating normal T cell expressed and secreted, platelet activating factor, interleukin-10, granulocyte-macrophage colony-stimulating factor, C5a, intercellular adhesion molecule-1, Substance P, reactive oxygen species, and reactive nitrogen species (1, 2), although it is likely that over the next few years, other as yet unidentified mediators will be added. It is therefore reasonable to speculate that elucidation of the key mediators in acute lung injury coupled with the discovery of specific pharmacologic agents would make it possible to develop clinically effective anti-inflammatory therapy.

In this issue of *Critical Care Medicine*, Dr. Liu and colleagues (3) have investigated the effect of treatment of rosiglitazone, an agonist of the peroxisome proliferator-activated receptor (PPAR)- γ , on acute lung injury induced by endotoxin in rats. The authors found a significant protection against lung injury by pretreatment of rats with rosiglitazone. Furthermore, to clearly establish that the protective effects of rosiglitazone are related to the activation of the PPAR- γ receptor, the authors have demonstrated the reversal of the protective effects of rosiglitazone by GW9662, a specific antagonist of PPAR- γ (3).

Gaseous mediators, such as nitric oxide (NO) and hydrogen sulfide, have been shown to play an important role in lung injury of different etiologies, including that induced by endotoxin (4–8). Excessive NO release from the inducible NO synthase has been suggested to play a crucial role in the development of endotoxin-induced acute lung injury (6–8). In their experiments, Dr. Liu and colleagues (3) found that the lipopolysaccharide-induced pulmonary production of NO, inducible NO synthase, messenger RNA,

and protein were significantly attenuated by rosiglitazone pretreatment. Rosiglitazone also inhibited the formation of nitrotyrosine, a marker for peroxynitrite reactivity, in the lung tissue (3). This study, therefore, provides evidence that the PPAR- γ agonist rosiglitazone significantly reduces endotoxin-induced ALI in rats.

There has been a lot of interest in recently in PPAR- γ and its ligands in inflammation. For example, rosiglitazone has previously been shown to reduce carrageenan-induced hind paw edema (9), nonseptic shock induced by zymosan (10), and bleomycin-induced lung injury (11). However, in studies including the present one (3), PPAR- γ ligands have been protective only when given prophylactically. It would be interesting to see if these ligands have the same protective action against lung injury when given therapeutically, that is, when the disease has already been induced.

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*See also p. 2309.

Key Words: peroxisome proliferator-activated receptor- γ ; endotoxin; acute lung injury; acute respiratory distress syndrome; multiple organ dysfunction syndrome

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The dynamic interface between hemodynamic variables and autonomic tone*

The hemodynamic management of cardiovascular insufficiency is not a static treatment, but a highly interactive one, wherein specific resuscitative treatments induce changes in cardiac output, perfusion pressure, and autonomic tone. The resultant blood pressure may not reflect fundamental physiologic reserve as much as the associated stress response of the drug interactions. For example, both acute myocardial infarction and acute postoperative surgical bleeding in the awake patient may present with hypertension, tachycardia, and increased agitation, rather than hypotension and decreasing mental status. Furthermore, venous return, the primary determinant of cardiac output, is a function of mean systemic pressure, right atrial pressure, and the resistance to venous return through the large venous conduits. Mean systemic pressure, for its part, is a theoretical value at best. It reflects the lump sum of all the regional blood volumes and these vascular spaces' unstressed volume and stressed volume compliance.

In the evolution of autonomic control, hypovolemia was the overriding threat to survival. Whether due to hemorrhage or dehydration, hypovolemia was and continues to be the primary cause of death all

animals, including humans. We respond to all forms of circulatory shock, whether hemorrhagic, cardiogenic, or septic, as if we have hypovolemia. Under normal autonomic control, hypovolemia is readily sensed by right atrial volume receptors and arterial baroreceptors. The combined reduced right atrial and aortic wall stress stimulate increased sympathetic tone. This induces an orchestrated global cardiovascular response consisting of increased α -adrenergic receptor stimulation, increased inotropy and heart rate, plus salt and water retention. The associated vasoconstriction is distributed unevenly throughout the vascular tree. Those areas with the highest concentrations of α -adrenergic receptors, like the skin and muscle, constrict more than the gut and kidney, whereas the heart constricts minimally and the brain not at all. The increased adrenergic stimulation-induced increased vasomotor tone causes both an increase in arterial vasomotor tone in those vascular trees and an increase in venomotor tone. The increase in venomotor tone is the essential component of the sympathetic response that is primarily responsible for sustaining venous return in hypovolemic states and the increase in arterial vasomotor tone that sustains systemic blood pressure as cardiac output decreases. Exogenous vasopressors also stimulate the same adrenergic receptors and induce similar cardiovascular responses as their endogenous cousins. That is why treatment with vasopressors alone in the initial management of the hypotensive patient in shock is not recommended. Even if the cause of hypotension were hypovolemia, one would see a transient increase in both arterial pressure and cardiac output as venous unstressed volume decreases, ar-

terial tone increases, and venous compliance decreases.

However, almost half of the patients presenting with acute cardiovascular insufficiency have limited or absent cardiac responsiveness, such that a fluid challenge will not increase cardiac output (1). Patients with acute submassive pulmonary thromboembolism, myocardial infarction, progressive end-stage congestive heart failure, and chronic cor pulmonale may all fall into this category. Performing a volume challenge in these patients not only will have no impact on cardiac output but will also delay starting definitive therapy and may worsen cardiac function and gas exchange. Relevant to this clinical issue, the recent literature has documented that arterial systolic pressure, arterial pulse pressure (2), and left ventricular stroke volume variations (3, 4) induced by positive-pressure ventilation are sensitive and specific markers of preload-responsiveness. These are referred to as systolic pressure variation (SPV) (6), pulse pressure variation (PPV) (2, 5), and stroke volume variation (SVV) (3, 7), respectively. PPV and SVV are calculated as the ratio of the difference between the maximal and minimal pulse pressure (or stroke volume) over three consecutive breaths and the mean of the maximal and minimal pulse pressure (or stroke volume), usually expressed as a percentage. Thus, a PPV of 15% would equal a difference between maximum and minimum pulse pressures of 6 mm Hg if the mean pulse pressure were 40 mm Hg. These sorts of values cannot easily be estimated from a quick inspection of the pressure profile over time but require accurate measures and calculations. Importantly, several studies have demonstrated that the greater the PPV or SVV, the more likely the subject is to increase his or her

*See also p. 2339.

Key Words: circulatory shock; invasive hemodynamic monitoring; functional hemodynamic monitoring; pulse pressure variation; vasopressors

The author has consulted for MAB Arrow International, has received honoraria from Edwards Lifesciences, and is involved with a patent for the use of arterial pressure and flow variation to diagnose and treat cardiovascular insufficiency.

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cardiac output in response to a volume challenge and the greater that increase will be (2). SPV, otherwise known as pulse paradoxus, has the advantage of being easily measured using a sphygmomanometer but does not take into account the changes in diastolic arterial pressure that always occur during breathing. Thus, in head-to-head comparisons, SPV, although good, always performs less well than either PPV or SVV in predicting preload-responsiveness (2).

Although the primary determinant of PPV over three consecutive breaths is SVV, because aortic impedance and arterial tone cannot change that rapidly (8–10), over time changes in arterial tone will alter the relationship between PPV and SVV. With fluid resuscitation, for example, sympathetic tone decreases and the stress of hypovolemia is reduced. Thus, for the same stroke volume, both mean arterial pressure and pulse pressure will be less. Similarly, arterial tone will increase during progressive hemorrhage as sympathetic responses are turned on. Thus, for the same stroke volume, arterial pulse pressure will be greater. Slama et al. (7) noted that during progressive hemorrhage, SVV became more sensitive than PPV as a marker of preload-responsiveness. Presumably, as vasomotor tone increases, the varying stroke volumes have a greater impact on arterial pulse pressure, exaggerating their dynamic swings during ventilation. If one uses a threshold value of PPV to identify preload-responsiveness, then one may see this threshold actually increasing in proportion to the increase in vasomotor.

The impact of exogenous vasopressors on this dynamic interplay of preload, venous return, and arterial tone must also

play an important role. Relevant to this point, Nouira and colleagues (11) report in this issue of *Critical Care Medicine* the impact of norepinephrine on the SPV and PPV in the setting of acute blood volume loss in an acute anesthetized canine preparation. They validated the earlier studies showing that PPV is superior to SPV in following volume loss during hemorrhage. More important, however, they demonstrated that for the same level of graded hypovolemia norepinephrine infusion, both SPV and PPV decrease, consistent with a decrease in unstressed volume despite an increase in arterial tone. This simple observation elegantly underscores the dynamic interactions described here. The authors correctly caution clinicians in the use of either SPV or PPV to define volume loss when exogenous vasopressors therapy is being used. It would have been interesting to see if measures of SVV were similarly affected. Based on the data of Slama et al. (7) and the theoretical constructs described here, one would predict that SVV would hold its discriminatory power better. However, one must ask, Did norepinephrine actually reduce the ability of PPV to identify hypovolemia, or did the norepinephrine alter the cardiovascular balance, such that for the same level of hypovolemia, norepinephrine increased cardiac output, so that physiologically speaking there was functionally less hypovolemia to be measured?

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Collateral damage: Sepsis-induced gut injury*

Infection, major surgery, and other physical or thermal injury can evoke an extensive inflammatory response, affecting any organ system and resulting in shock and multiple organ failure. The systemic inflammatory response syndrome occurs with severe infection of any site and may result from an exaggerated immune response. Coagulopathy, microvascular thrombosis, neutrophil-endothelial adherence, and impaired tissue perfusion cause tissue injury in variable patterns (1, 2). Heart, lung, kidney, and liver are the organ systems of greatest concern, and their dysfunctions are measurable. These have been the focus of both clinical and laboratory investigations to clarify the pathophysiologic mechanisms of septic shock and tissue injury. Gut is affected probably as often as other organ systems, but its derangement is neither as conspicuous nor as readily quantifiable and is not well characterized.

Gut is often suspected as the source of systemic infection because of increased mucosal permeability in systemic illness and its large microbial population. Its dysfunction has been attributed to locally delivered microbial products including lipopolysaccharide (LPS). Increased permeability, when caused by extraintestinal factors, facilitates access for bacteria or their products (3). Bacterial translocation most likely requires compromise of the gut mucosal barrier since the mesenteric lymph nodes do not normally permit commensal bacteria access to the circulation (4). Gut-derived sepsis has been experimentally replicated in cecal ligation and puncture animal models. As in human peritonitis and sepsis, cecal ligation and puncture results in hemodynamic instability and pulmonary injury, the first among the extraintestinal systems affected. The underlying mechanisms include secretion of proinflamma-

tory mediators and neutrophil chemotaxis with sequestration in the lung (5). Systemic inflammatory response syndrome in noninfectious conditions develops in the absence of bacterial products and involves compromised hemodynamics and a cascade of the mediators of inflammation.

Integrity and homeostasis of the intestinal mucosa require continuous proliferation and differentiation of the epithelial cells, which proliferate in crypts, migrate up the villi, and either die or are shed at the villus tip. The proliferation rate of gastrointestinal cells is high, second only to hematopoietic cells (6, 7). Unlike the latter, the tissue architecture of the gut permits quantification and analysis of cellular dynamics. Hypo- and hyperproliferative states are known; cell proliferation is decreased in starvation and increased in celiac disease. Enteral nutrition is necessary for maintenance of bowel homeostasis; there is profound mucosal atrophy in animals during parenteral nutrition (7). Increased apoptosis and proliferation of enterocytes are seen in sepsis (8–11). Despite this compensatory change, there may still be a loss of villus height (11).

In this issue of *Critical Care Medicine*, Dr. Husain and colleagues (12), using a murine model of LPS-induced acute lung injury, examine enterocyte proliferation and loss. In contrast to conventional wisdom, they report increased apoptosis and decreased intestinal epithelial proliferation. Previous studies have shown increased intestinal epithelial proliferation in the rat cecal ligation and puncture model and decreased intestinal epithelial proliferation in a murine pneumonia model (9–11). Assessment of experimental results is further complicated by different animal species (rats vs. mice), sites of LPS delivery (systemic vs. lung vs. peritoneum), and even the use of different enteric epithelial cell lines *in vitro*. There is a need to reconcile the discordant results of different studies.

This study extends the authors' previous observations of pneumonia-induced lung injury to LPS-induced lung injury and resultant changes in the gut (9). It successfully documents lung injury following LPS administration and subsequent gut muco-

sal alterations but does not posit a likely mechanism for the observed changes in the gut epithelium. The use of Toll-like receptor (TLR) 4 deficient mice and administration of anti-tumor necrosis factor (TNF)- α were well-conceived, but the results are inconclusive. The authors state that impurities in the LPS preparation used may have resulted in signaling in TLR4-deficient mice through other TLRs. It is difficult to assess whether anti-TNF- α neutralized the circulating TNF- α , since it was not measured.

LPS activates a variety of cell types through CD14. Enterocytes lack CD14; LPS presumably activates them through TLR4. It induces enterocytes to release several cytokines and chemokines including TNF- α , interleukin (IL)-6, and IL-8. All three factors are potent proinflammatory mediators in the intestinal mucosa; they help recruit immune competent cells, greatly enhancing the primary inflammatory reaction. LPS modulates intestinal epithelial cell turnover: It inhibits proliferation in human enterocytes (HIEC cells) but promotes it in rat epithelial (IEC-6) cells. However, TNF- α induces apoptosis in both cell lines. Although enterocytes produce IL-6 and IL-8 in large quantities, it is TNF- α that modulates enterocyte turnover. The different growth patterns observed between human HIEC and the rat IEC-6 crypt cells may reflect differing degrees of maturation of the two cell lines. IEC-6 cells constitutively express TLR2 and TLR4. LPS down-regulates TLR4 in HIEC cells (13). Because of chronic exposure to bacterial products *in vivo*, TLR2 and TLR4 might be down-regulated on enterocytes, avoiding a pathologic stimulation of the inflammatory reaction (14, 15). Additional factors, such as IL-13 and CXCL10 (interferon- γ -induced protein [IP-10]), also regulate enterocyte proliferation (16).

Several endogenously produced substances, including enteric hormones, promote enterocyte proliferation. These include glucagon-like peptide-2, gastrin, epidermal growth factor, transforming growth factor- α , and prostaglandins (7). Evidence suggests that gut mucosal damage, at least in the ischemia-reperfusion model, is mediated by gut macrophages

*See also p. 2350.

Key Words: enterocytes; gut; lipopolysaccharide; sepsis; systemic inflammatory response; Toll-like receptors; tumor necrosis factor

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and their released products and not by neutrophils; anti-neutrophil provides limited protection but macrophage depletion reduces gut mucosal damage (17). Trefoil factors are up-regulated rapidly following mucosal injury and contribute to its repair (18).

The pathogenesis of multiple organ injury in infection remains enigmatic with several mechanisms known to mediate the patchwork of pathologic processes. An overexuberant systemic inflammatory response to bacteria or their products is perhaps central to the remote tissue injury in systemic inflammatory response syndrome. Tissue damage may also result from hypoperfusion with hypoxia due to a deficient oxygen supply or compromised diffusion or in ischemia-reperfusion from oxidative stress. The dynamic relationship of infection, local tissue, and systemic inflammatory responses varies with the target tissue examined. It is hoped that further elucidation of the pathogenesis will result in a unifying concept to facilitate diagnosis and management of multiple organ failure.

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An old debate joined again: Should we give steroids to all head-injured patients?*

In this issue of *Critical Care Medicine*, the article by Dr. Cohan and colleagues (1) is an important contribution to an old but critical issue—namely, even if steroids do not improve neurologic recovery from severe traumatic brain injury (TBI) *per se*, should they initially be given to all

trauma victims because of the risk of secondary adrenal axis insufficiency? The study in this issue demonstrates a 53% rate of adrenal insufficiency in TBI; the condition was strongly associated with injury severity and vascular instability (1). A similar recent study by another group demonstrated a 15% rate of adrenal insufficiency, although they used different patient selection criteria and acute low-dose corticotrophin stimulation testing (2). Does a short-term trial of steroid administration in TBI patients make sense despite the known risks of gastrointestinal hemorrhage, systemic infection, and impaired wound healing? The issue is complex and the evidence contra-

dictory. My personal perspective is based on a long and intimate involvement with the subject.

The brain is a secretory organ, perhaps the single most important component of the endocrine system. The limbic system of the brain, including the hypothalamus, is not only the highest seat of the human sexual response but also directly yoked to peripheral hormonal secretion. More than 35 yrs ago, Dick Egdahl and I demonstrated that electrical stimulation of the canine amygdala resulted in peripheral elevation of corticosteroid levels (3). The direct effects of TBI on the brain may cause a similar increase, as seen in the acute phase of the present study (1). The

*See also p. 2358.

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brain is not only involved in the stress response but in moment-by-moment control of the pituitary-adrenal axis. In the late 1960s, the now-routine use of dexamethasone in the postoperative support of craniotomy patients permitted them to rapidly awaken from iatrogenic trauma and revolutionized modern neurosurgery; it was but a short step from this observation to the general recommendation that steroids be given to all patients admitted to the hospital with TBI. Unfortunately, a number of uncontrolled clinical trials gave conflicting results in regard to the efficacy of this policy; meta-analysis of such studies did not indicate a benefit of >2%. In a prospective, randomized trial at the Maryland Institute of Emergency Medical Services (Shock Trauma), we were unable to show that steroid administration improved either the survival rate or the functional status of treated patients (4). The recent international, multiple-center, randomized CRASH trial of short-term methylprednisolone infusion not only demonstrated no improvement in long-term outcome but a relative increase in the risk of mortality during the first 2 wks; the cause for this could not be identified (5).

And yet, clinical neuroscientists know that hypopituitarism is common in subarachnoid hemorrhage and in TBI (6) and that steroids reduce posttraumatic neuronal degeneration in experimental animals (7, 8). In addition, the use of methylprednisolone within 8 hrs of traumatic spinal cord injury has been shown to increase neurologic outcomes in randomized clinical trials (9, 10). Of not incidental interest is the fact that a more potent corticosteroid (dexamethasone) is almost uniformly used to treat cerebral edema in brain tumor patients but not in patients with TBI (11)—just another unexplored variable in a notoriously heterogeneous patient population, the analysis of which is made more difficult by the imponderable nature of the intracranial insult in most TBI cases, the presence

of associated systemic injuries, the level of intracranial pressure, the use of adjuvant therapies, and the variability in surgical and treatment protocols known to occur between centers in controlled clinical trials of diseases with surgical implications.

So the data provided by Dr. Cohan and colleagues (1) do nothing but reinforce my old suspicion that the use of corticosteroids not only may reduce brain swelling/neuronal injury in a few select cases but that their use may also be important to counter the negative effects of TBI on the stress response to systemic trauma. Even in the emergency room and in the ICU, I am not sure that treatment in the first few hours can await the results of endocrine testing; I *do* know that the impetus for emergency administration of therapeutic agents at the roadside cannot await the development of certain types of information. In any case, the diagnosis of adrenal insufficiency may not become apparent for days, and this alone may frustrate the selective use of steroids in the clinical trial being planned by Dr. Cohan and colleagues (1). Long ago, I blithely instructed the neurosurgical residents at the University of Maryland to ignore the negative evidence of our own randomized trial (4) and urged them to support me with steroid medication should I ever present to our emergency room. Furthermore, I believed then and believe now that most systemic complications from the use of steroids can be avoided by rapidly withdrawing them once a patient's failure to improve neurologically clearly identifies him or her as a nonresponder. This usually becomes apparent in the first 48 hrs, and by then, the laboratory diagnosis of adrenal insufficiency can be safely established or excluded.

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Aneurysmal subarachnoid hemorrhage and positive end-expiratory pressure*

The use of positive end-expiratory pressure (PEEP) in neurosurgical patients is frequently essential to prevent additional neurologic, as well as systemic, damage. Despite the longstanding accepted use of PEEP in this patient population, it has been difficult to find clean data that have enabled clinicians to make reliable predictions regarding the intracranial risks and benefits of the therapeutic application of PEEP in a given patient. After close to 30 yrs of studying PEEP in neurosurgical patients, there remains inadequate evidence to either support or refute its use (1–9). In this issue of *Critical Care Medicine*, Dr. Muench and colleagues (10) have tried to get meaningful information regarding the effects of PEEP on the brain by carefully monitoring a group of neurosurgical patients being treated for aneurysmal subarachnoid hemorrhage.

Designing an experiment to determine the effects of PEEP on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation in humans under normal, physiologic conditions is not realistic because of the need to use invasive intracranial monitors. In an attempt to deal with this unavoidable experimental design problem, the authors have used an animal control. This assumes, of course, that the pharmacologically paralyzed pig with a normal brain and normal lungs will have intracranial responses to PEEP equivalent to those of the human.

The objective of this investigation is “to examine the influence of various PEEP levels on intracranial pressure, brain tissue oxygen tension, regional cerebral blood flow, and systemic hemodynamic variables.” There is no hypothesis;

it is an observational investigation. It appears that the intent is to understand the effects of PEEP on the brain under physiologic circumstances; however, the only subjects in whom monitoring of these variables is feasible are pathologic neurosurgical patients, hence the design to introduce a normal component to the study using an animal model. Between the sick human and the normal animal, further understanding is likely. Certainly, this is true, but given the absence of a hypothesis, I’m not sure how an experimental arm using an animal “control” helps the strength of their findings.

Nonetheless, despite an attempt to find a creative solution to the unsolvable experimental problem of invasive intracranial monitoring in normal humans, the ultimate conclusion of this experiment doesn’t help me understand the effects of PEEP on the normal brain. However, the authors have presented new information on one of the most uniform neurosurgical patient populations evaluated in the literature relative to PEEP: aneurysmal subarachnoid hemorrhage (SAH). Not that this patient population in and of itself is a uniform group; on the contrary, there is great diversity among SAH patients. But, the authors did not mix this neurosurgical population with trauma, stroke, hydrocephalus, and/or intracerebral hemorrhage, as has been done in many other studies whose only common denominator has been an intracranial monitor (1, 2, 3, 11, 12). I was unable to find another article describing the impact of PEEP on all of the physiologic variables measured in this study among an exclusive, uniform patient population with aneurysmal SAH. We know from previous, large studies of ruptured aneurysm patients that there can be as many physiologic differences among well-matched populations as there are similarities; however, Dr. Muench and colleagues (10) have restricted their focus on this population to an admittedly small but relatively uniform group, that is, mostly higher grade, pharmacologically

paralyzed, and ventilated patients with anterior circulation aneurysms and Fisher grade 3 hemorrhages.

This particular patient population has a unique pathophysiologic risk of developing cerebral vasospasm and, predictably, 60% of their patients were diagnosed with spasm by standard techniques. Although we still know relatively little about the ultimate and proximate cause of cerebral vasospasm, we know even less about effecting a cure for this dreaded process. We have, however, developed useful tools for preventing and managing spasm, some of which include hypertension, hypervolemia, hemodilution, nimodopine, and interventional techniques. By far, the most effective of these modalities is the maintenance of blood pressure.

The results of the study are clear: Increasing levels of PEEP caused a decrease in mean arterial blood pressure (MABP), and this in turn was associated with a decrease in regional cerebral blood flow. Restoring MABP caused regional cerebral blood flow to normalize, despite persistently elevated PEEP. The decreases in MABP measured in this investigation were reduced to a statistically significant degree, but none of the mean values reported were lower than a MABP of 81, a value well within the normal range of autoregulation. Even when the extremes are calculated from the reported standard deviations, the lowest MABP reported is 55 mm Hg—clearly low, but not enough to affect cerebral blood flow significantly under normal circumstances. Despite this, these authors documented a consistent and direct relationship between lowering MABP and decreasing regional cerebral blood flow. This relationship was true even for the smaller group of patients not diagnosed with spasm. Why? Because higher grade aneurysmal subarachnoid hemorrhage patients have impaired cerebrovascular autoregulation (10, 13).

This important finding is no surprise to anyone who takes care of these high-

*See also p. 2367.

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grade aneurysmal SAH patients; anything that lowers MABP is a potential problem. In this case, it is increasing levels of PEEP that lower blood pressure.

The authors ask an important question: What does PEEP do to the brain? The answer is that increasing PEEP can lower MABP. This we know (7, 11). We also know that lowering MABP in a high-grade aneurysm patient is potentially dangerous. This study shows us why.

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Genetic polymorphisms in acute respiratory distress syndrome: New approach to an old problem*

Despite apparent progress in the management of patients with acute respiratory distress syndrome (ARDS), the overall mortality remains high (1, 2). The heterogeneity of inciting factors in ARDS has long frustrated efforts to characterize and classify patients into relevant subgroups. In the landmark ARDSnet trial, which demonstrated the beneficial effects of limiting tidal volumes during mechanical ventilation in ARDS, the patient population included primary diagnoses of pneumonia, sepsis, aspiration, trauma, and multiple transfusions (1). Furthermore, the cellular and humoral immune responses in humans are subject to polymorphic genetic control and may explain the diverse clinical features of a complex disorder such as ARDS. The application of

newer molecular biology techniques should allow characterization of the molecular phenotype of key lung cells and structures and enhance our understanding of complex cellular pathways involved in the pathogenesis of the syndrome. Candidate genes related to surfactant production, inflammatory response, endocrine pathways (angiotensin-converting enzyme), and pathogen receptors (such as toll-like receptors and CD14) have been linked to susceptibility, severity, and outcome of multifactorial disorders like ARDS, acute lung injury, and sepsis (3-8). Table 1 illustrates some recent studies evaluating the association of gene-based single-nucleotide polymorphism with the severity and outcome of ARDS. Future inquiries directed at the interplay between the genotype, the clinical environment, and the resulting ARDS phenotype are essential. In this issue of *Critical Care Medicine*, Frerking and colleagues (9) take an important step in this direction by examining the role of a single-nucleotide polymorphism in a pulmonary epithelial cell (Clara cell) in adults with ARDS.

Clara cells are nonciliated secretory epithelial cells lining the pulmonary airways, located predominantly in the bronchial epithelium. CC16 (also known as CC10, Clara cell related protein, Clara cell secretory protein, or uteroglobin), the main secretory product of Clara cells, down-regulates synthesis and activity of interferon gamma and tumor necrosis factor- α and inhibits interleukin-1 β and phospholipase A₂ (10). Pneumoproteins such as CC16 have been detected in bronchoalveolar lavage fluid and can leak into the vascular system due to increased permeability of the alveolar capillary barrier in acute lung injury/ARDS and ventilator-induced lung injury. The ability to detect pneumoproteins in bronchoalveolar lavage fluid or blood makes them potential biomarkers of lung injury and inflammation (11). The expression of Clara cell protein is regulated by the *CC16* gene located on chromosome 11q12-13, where it is in close proximity to other genes involved in the regulation of the inflammatory process. The anti-inflammatory effects of CC16 make it an attractive protein to study in the ARDS model, in

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Key Words: acute respiratory distress syndrome; Clara cell protein 16; polymorphism

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Table 1. Genomics and acute respiratory distress syndrome (ARDS): Recent investigations

| Authors | Gene | Polymorphism | Phenotype | Genotype | Cohort | Association |
|---------------------|--|--|---|--|---|-------------------|
| Medford et al. (3) | VEGF gene | T allele +936 CT polymorphism | Lower levels of VEGF Associated with development of ARDS | CT and TT genotype frequencies | ARDS (n = 117), control (n = 137), at risk (n = 103) | Positive |
| Chan et al. (5) | ACE gene | D allele ACE I/D polymorphism | Development of ARDS/ICU admission after SARS | D allele genotype frequency | SARS (n = 140), controls (n = 326) | Negative |
| Marshall et al. (4) | Human ACE gene (DCP1) chromosome 17q23 | I or D of a 287-base pair intronic sequence D allele | Higher ACE levels associated with development of ARDS | D allele genotype frequency | ARDS (n = 96), ventilated non-ARDS respiratory failure (n = 88), coronary artery bypass patients (n = 174), controls (n = 1906) | Positive |
| Ye et al. (6) | PBEF gene | PBEF promoter variants, SNPs (T-1001G and C-1543T) | Higher PBEF protein levels associated with sepsis induced ALI | PBEF gene expression | BAL: ALI (n = 3), controls (n = 3); serum: ALI (n = 8), controls (n = 8) | Positive |
| Gong et al. (7) | SP-B gene on short arm of chromosome 2 | SP-B intronic polymorphism | Proposed association with decreased SP-B levels; association between gene polymorphism and development of ARDS | SP-B polymorphism genotyping | ARDS (n = 72), risk of ARDS (n = 117) | Positive in women |
| Quasney et al. (8) | ICAM type 1 gene | ICAM-1 G231R | Increased levels of ICAM and increased inflammation; association between allele frequency and CAP complicated by ARDS | ICAM-1 G231R site detected using allele-specific PCR | CAP (n = 289) | Negative |

which inhibition of neutrophil activation and phospholipase A₂ by CC16 are relevant. Jorens et al. (12) found a significant increase in bronchoalveolar lavage fluid CC16 levels from patients with acute lung injury. Geerts et al. (13) have shown that increased CC16 levels in bronchoalveolar lavage fluid correlated with decreased neutrophil-mediated lung damage (decreased elastase and increased Pao₂/Fio₂ ratio) in patients with ARDS. If the functional polymorphisms were indeed correlated with the phenotypic expression of this protein, the characterization of the genotype would allow us to classify individual patients based on their disease susceptibility and severity and possibly allow prediction of outcome from ARDS.

Frerking and colleagues (9) studied the role of the single-nucleotide polymorphism CC16 -26G>A (previously known as A38G), within the gene encoding Clara cell-specific protein, in adults with ARDS. Adults with ARDS were recruited from intensive care units, and genotype frequencies for the CC16 protein expression gene in this group (n = 117) were compared with those from healthy newborns (n = 373). Subjects, diagnosed to have ARDS according to the American European Consensus Conference guidelines, were recruited over a period of 7 yrs. The cohort included patients with a wide range of inciting causes and an over-

all mortality of 23%. Fluorescent resonance energy transfer probes were applied to polymerase chain reaction products obtained with the restriction fragment length polymorphism method. The donor probe complementary to the mutant sequence on the Clara cell 16kd protein expression gene was used, and samples were genotyped by the LightCycler system (which allows faster heating and cooling cycles as compared with a conventional thermal cycler). A melting-curve analysis was performed, which allows identification of polymerase chain reaction products by using melting profiles, a specific feature of DNA. The shape of the curve is related to the sequence, size, and base pair (GC) content of the product. Complementary probes labeled with fluorescent resonance energy transfer dyes hybridize with the mutant sequence, and the melting-curve analysis allows detection of polymerase chain reaction products by the characteristic shape of the curve and the distinct melting points. The authors found no significant differences in genotype frequencies (26GG, 26GA, and 26AA) between patients and controls or between subgroups of patients with varying causes of ARDS. The homozygous genotype (26AA) did not correlate with mortality. This is an important observation, and the study adds to existing data on the role of Clara cells

in acute lung injury. Although clear answers are not yet forthcoming, there is a sound and biologically plausible relationship between the anti-inflammatory CC16 protein expression and severity of lung inflammation. The study is well conducted, with recruitment of a typical representative ARDS population from two intensive care units. The use of newborn screening samples as controls eliminates the possibility of environmental factors such as smoking from interfering with results. The authors have utilized a novel molecular biology technique to answer their question in this study.

As is the case with all scientific inquiries, this study was not a perfect one. Candidate gene identification in a complex lung disorder such as ARDS is challenging due to the heterogeneity of inciting stimuli and the lack of available linkage studies. Posttranslational modifications, environmental factors, and the limitations of conducting robust association studies in the intensive care unit are some of the complexities surrounding genotypic investigations of multifactorial disorders like ARDS. Frerking and colleagues (9) found no correlation between the genotype and the clinical features of ARDS. However, they did not measure the levels of CC16 protein in either bronchoalveolar lavage or serum, information that would have added to the strength of

their observations. In addition, the authors did not account for the potential role of therapeutic interventions such as corticosteroid administration on gene expression. The addition of glucocorticoids to rabbit fetal lung explants has been shown to induce uteroglobin (CC16) gene in a dose-dependent manner without affecting total protein synthesis (14). Patients who may have received steroids should be excluded to account for this variable and its potential confounding effect on the observations. The correlation between genotype and CC16 protein levels in ARDS remains unclear and is likely to be complex. This is illustrated by Hackett et al. (15), who showed that induction of lung injury in rats failed to increase the Clara cell secretory protein messenger RNA expression in lungs, despite significant histopathologic changes. The negative results of the study by Frerking and colleagues (9) could be a result of therapeutic and environmental influences, other posttranslational alterations, timing of sample collection in relation to the lung injury, or a true absence of correlation between genotype and clinical features of ARDS. Furthermore, due to the small sample size, the study is not powered to permit meaningful subgroup comparisons in this study.

On balance, the work by Frerking and colleagues (9) is a small but important step. ARDS is a heterogeneous disease with varying causes and outcomes. There exist significant gaps in our understanding of the complex cellular and molecular pathways involved in the response to lung injury and development of ARDS. The role of the alveolar and airway epithelium in modulation of inflammation in lung

injury has recently been recognized. CC16 protein expression may be associated with susceptibility, severity, and outcomes in ARDS. Frerking and colleagues (9) could not demonstrate this association in their analysis. A more robust patient population focusing on specific subgroups or acute lung injury pathogenesis may bear fruit in the future. Finally, the role of CC16 genotype frequencies in ARDS will need to be further elucidated by studies simultaneously evaluating correlation between genotype, environmental factors, protein levels, and clinical features of the syndrome.

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Controlling antibiotic-resistant bacteria: What's an intensivist to do?*

Antibiotic-resistant bacteria have been a concern since the introduction of antimicrobials into clinical practice. Current problem pathogens include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and multiple-drug-resistant Gram-negative bacilli, especially *Acinetobacter* and *Pseudomonas aeruginosa*. In the 1980s, development of new antimicrobial agents often trumped concerns about resistance. But that period of complacency is long gone, and prevention and control of resistant bacteria have become a major focus of hospital infection control programs. Guidance has been provided by the Centers for Disease Control and Prevention and its Healthcare Infection Control Practices Advisory Committee; by professional societies, such as the Society for Healthcare Epidemiology of America; and by numerous scientific publications. These recommendations traditionally focus on improving asepsis and hand hygiene, isolating (or cohorting) infected and colonized patients, instituting antibiotic controls, eliminating any significant environmental reservoirs, and preventing (or eliminating) patient carriage of antibiotic-resistant strains (1).

In this issue of *Critical Care Medicine*, Salgado and colleagues present their recommendations for prevention and control of antibiotic-resistant infections in intensive care patients (2). What are the important take-home messages for intensivists, based on this review, other guidelines, and the extensive literature that addresses epidemiology and control measures?

First, frequent lapses in healthcare worker attention to hand hygiene are probably a major cause of transmission of MRSA and VRE in intensive care units

(ICUs) and are especially troubling, given the ease of use and rapid action of sinkless alcohol-based hand rubs (3, 4). Use of these products in hospitals must become a ritual, virtually religious behavior. Because the large groups of trainees who follow senior intensivists on their daily rounds exhibit classic "imprinting behavior," it is essential that ICU leaders make hand hygiene a priority. Alcohol hand rub dispensers should be on every doorpost of every patient room, and staff must use these products when they enter and leave each room, as if patients' lives depended on this behavior. This is particularly important for physicians because of their sequential contact with many patients (5) and in ICUs with high "colonization pressure" (6). Intensivists must ensure that all ICU staff members are observed and given direct immediate feedback until hand hygiene becomes everyone's ritual (4).

Second, antimicrobial pressures are an important driver of resistance, particularly for Gram-negative bacilli. The potential for worse outcomes for critically ill patients whose initial empirical therapy is not adequate against infecting pathogens has led to a mantra that broader is better. Unit-specific antibiograms may be of use in directing empirical therapy, but emerging pathogens, such as community-acquired MRSA and multiple-drug-resistant *Acinetobacter*, may become major problems between periodic production of reports. Therefore, day-to-day attention to resistance is important. Unfortunately, conventional wisdom and common practice are to "never quit a winning team," so antibiotic treatment often is not narrowed when bacterial susceptibility results become available. Intensivists should monitor use of antimicrobials and provide feedback to ensure that therapy is focused and even discontinued (7) as soon as possible. Rotating or cycling antibiotics, to confuse bacterial pathogens and preempt resistance, remains a tempting but unproven strategy.

Third, the role of environmental contamination in the spread of nosocomial pathogens—for years a "nonconcern"—

has resurfaced. Specifically, epidemiologic studies have linked the spread of VRE, *Clostridium difficile*, *Acinetobacter*, MRSA, and *Pseudomonas* to contaminated fomites (8). The surprisingly frequent shuttling of VRE between contaminated environmental sites and patients, via staff members' hands, helps to explain how quickly VRE has become a prominent nosocomial pathogen (9). Although there has been concern about the ability of environmental disinfectants to remove nosocomial pathogens, especially VRE, careful studies have shown that cleaning failures are largely failures to clean rather than failures of environmental detergent-disinfectants (10). To minimize contributions of environmental contaminants to the spread of antibiotic-resistant bacteria, intensivists should insist that the performance of ICU cleaning staff is reviewed routinely.

Fourth, the epidemiologic importance of the "antibiotic-resistance iceberg"—the large number of patients with occult colonization by resistant bacteria—has been known for 4 decades and has led to long-standing recommendations to identify reservoirs of colonized and infected patients and to isolate these individuals (1, 11). Most studies that have assessed the value of detecting resistance icebergs by surveillance cultures are quasi-experimental and have included multiple other interventions, such as heightened attention to hand hygiene, environmental cleaning, and antibiotic control. It is understandable that when faced with an epidemic resistance problem, hospital epidemiologists attack aggressively (1). Nevertheless, as a result, we cannot evaluate the relative contribution of individual control measures, and there are conflicting data.

In a short-term study in which we applied a single intervention—daily surveillance cultures for MRSA and susceptible staphylococci, *without* providing results to staff—we demonstrated absence of any cross-transmission among ICU patients, despite ongoing introduction of these pathogens (12), which suggests that a major benefit of surveillance cultures may be a Hawthorne effect. We have

*See also p. 2373.

Key Words: antibiotic resistance; control measures; hand hygiene; hospital acquired infections; isolation; nosocomial infections; surveillance

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also seen a dramatic decline in nosocomial VRE in one of our inner-city hospitals, which is cited by Salgado and colleagues as lacking their recommended "proactive surveillance approach" (2). This decrease was coincident with an aggressive 5-yr educational effort to improve hand hygiene, universal gloving, and antibiotic use and with a move from an old institution with Florence Nightingale-style wards (that had few sinks and one bathroom for every 30 patient-beds) to a modern healthcare facility (13).

While use of surveillance cultures should continue to be a tool for epidemiologists and intensivists who wish to eliminate specific resistant pathogens, there are insufficient data to support making this measure a national standard of care (12), especially given the potential downsides (2). A cluster-randomized trial by the National Institutes of Health currently is evaluating benefits of rapid-turnaround surveillance to isolate the resistance iceberg in ICUs. The results may place this approach into better perspective. We also need to assess the role of more innovative interventions, such as degerming patient skin (14) and having healthcare workers use "killer gloves" (15) to reduce transmission of resistant bacteria.

Finally, many well-conducted studies suggest that a major focus for control of antimicrobial resistance in ICUs should be prevention of device-related infections. Marked decreases in and even elimination of central vascular catheter-related infections in ICUs appear possible (16). It is important to note that if there is no line sepsis, then there is much less chance of bloodstream infection due to MRSA, VRE, or other pathogens. Intensivists should ensure that their units adopt, follow, and monitor adherence to well-supported performance measures for prevention of device-related infections (17, 18). Most of these interventions de-

pend on assiduous application of low-technology measures, which at present provide the best return on investment for ICU infection control.

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