Hypotension and mortality in septic shock: The "golden hour"*

Time is of the essence.—Anonymous

A guideline is just a guideline (i.e., a suggested course of action), but a performance measure is a rule (i.e., a statement that describes what should be done in most or all cases). Guidelines are made up of recommendations based on varying levels of evidence. Expert opinion is considered the lowest level of evidence (sorry to disappoint), earning a C rating, whereas randomized controlled trials provide the highest level of evidence and merit an A rating. Cohort studies and other nonrandomized trials are in between and receive a B rating (1). Consequently, a recommendation based on a C rating rarely becomes a performance measure. Guideline recommendations will be based almost exclusively on A or B evidence as they are the most credible. It follows that performance measures should be created when the recommendation has an A or B evidence rating, compliance is critical for improved patient outcome, and the disease occurs with a high frequency or has a high impact on morbidity, mortality, or cost.

Dr. Kumar and colleagues (2) have now provided us with the scientific evidence for creating a performance measure requiring antimicrobial therapy administration within an hour of onset of hypotension in patients with septic shock. They used the current adult standard definitions for septic shock (i.e., a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes) and for hypotension (i.e., a systolic arterial pressure $<$90 mm Hg, a mean arterial pressure $<$60, or a reduction in systolic blood pressure of $>$40 mm Hg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension) with slight modifications (3). In their multivariate analysis of critical factors, providing antimicrobial therapy within the hour of onset of hypotension in septic shock more often accounted for clinical improvement than did other factors such as Acute Physiology and Chronic Health Evaluation II score and other therapeutic interventions. The authors also point out that antimicrobial treatment should not be delayed until the patient is initially stabilized and the clinical evaluation is completed.

Although the study is a large retrospective cohort study (category B level of evidence), it is unlikely that a prospective randomized-controlled study will ever be done because such a study would be considered unethical. Therefore, the current study is the best that will be available.

A medical procedure once based on expert opinion now has the required evidence base to become a performance measure. Current guidelines for the initiation of antimicrobial therapy in septic shock that state therapy should be started within one hour have been based on expert opinion and a few small studies. Now, in $>$2,000 patients, Dr. Kumar and colleagues (2) have shown that a "golden hour" does exist for minimizing mortality in patients with septic shock. Their conclusions are based on studies conducted in multiple types of intensive care units as well as multiple academic and community hospitals in Canada and the United States (2).

The findings of the impact of delays in antimicrobial administration on mortality are frightening and heighten our sense of urgency in managing these patients. The authors found that when antimicrobial therapy is initiated within 1 hr of onset of hypotension from septic shock, 79.9% of patients survive hospitalization. In fact, survival was even better if therapy was initiated within the first 30 mins (82.7%) than in the second 30 mins (77.2%) of the "golden hour." After that, for each additional hour until effective therapy was initiated, survival dropped by an average of 7.7%. When it took 5–6 hrs for therapy initiation, mortality was 42.0%, and by 9–12 hrs it fell further to an appalling 25.4%.

Although the inverse relationship between time to initiation of therapy and survival during hospitalization was present in all of the groups studied by Dr. Kumar and colleagues (2), the culture-negative group fared worse than the culture-positive group and the community-acquired groups fared worse than the nosocomial-acquired patients. What are the reasons? Did patients in the culture-negative group have more comorbidities? Did the community-acquired patients take longer to come to the attention of the medical community than the nosocomial-acquired patients?

The current efforts that are underway to develop a bundle of performance measures for sepsis should be enhanced by this study. Bundles are a concept popularized by the current Campaign to Save 100,000 Lives by June 14, 2006 (4). The campaign focuses on six diseases or care processes that are targeted for improvement; the improvements have the potential to save 100,000 lives by June 14, 2006. The diseases or care processes for each hospital to target are acute myocardial infarction, a rapid response team, ventilator-associated pneumonia, central venous line infection, programs for surgical site infection prophylaxis, and prevention of adverse drug events with medication reconciliation. The bundles are a group of performance measures, all of which should be followed to prevent or minimize illness, recurrent illness, or death. The bundle for acute myocardial infarction, for example, includes early administration of aspirin, aspirin at discharge, early administration of a β-blocker, a β-blocker at discharge, an angiotensin-converting enzyme inhibitor or angioten-

*See also p. 1589.

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sin-receptor blocker at discharge for patients with systolic dysfunction, timely initiation of reperfusion with thrombolysis or percutaneous intervention, and smoking cessation. All measures in the this bundle should be completed if not contraindicated. Completion of all the measures in all the bundles by the almost 3,000 hospitals that have signed on to the campaign has the potential to reach the goal of lives saved. It is time to add a sepsis bundle to our efforts to comply with the other components of the Campaign to Save 100,000 Lives.

Previously, timely delivery of appropriate therapy in the first hour has been shown to be critical in other shock-associated states such as trauma with hypovolemic shock (5), cardiogenic shock due to acute myocardial infarction (6), and obstructive shock due to massive pulmonary embolus (7). Now septic shock must be added to the list. A performance measure should be constructed that measures compliance with antimicrobial administration within 1 hr (the "golden hour") of onset of hypotension in septic shock. If we are to save more lives, time is of the essence.

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The pulmonary artery catheter and critical care: The cart is *before* the horse*

In this issue of *Critical Care Medicine*, Dr. Friese and colleagues (1) examine the association between pulmonary artery catheter (PAC) use and mortality in a large cohort of critically injured trauma patients. These investigators reviewed data from 53,312 adult patients found in the National Trauma Data Bank, of which 1,933 patients had been managed with a PAC. This retrospective, observational, cohort study demonstrated that as age and injury severity increased, the association of death with PAC use decreased. This apparent association with improved mortality was strongest for the patient groups that were the oldest (61–90 yrs), in shock (base deficit, ≤11), and with the highest injury severity (injury severity score, 25–75). Conversely, patients without these severe injury characteristics had an increased mortality in association with the PAC. This result is similar to that found in a previous observational study (2). These study results may be a manifestation of the truth, because this type of study design possesses the advantage of having external validity via its reflection of real-world standard practice. The benefit, if true, could be explained by the earlier insertion of the PAC in patients who are severely ill with the correction of a tissue perfusion deficit that is best directed by the PAC. The treatment may have a U-shaped effect resulting in a higher mortality if the perfusion defect is under- or over-corrected and optimal outcomes resulting when it is "just right."

The disadvantage that all studies of this design suffer from include confounding by indication. The reason why clinicians decide to place the PAC is linked to the patient's outcome. These additional risk factors cannot all be known and measured and, hence, control of them is incomplete outside of properly designed randomized, controlled trials (RCTs). Why should the readership be interested in the results of the study by Dr. Friese and colleagues (1) when several previous multi-center, randomized, controlled trials involving the PAC have demonstrated "no benefit"?

We should be interested because I believe the RCTs fail to inform us adequately because of the following problems: 1) poor external validity; 2) inadequate sample size; and 3) efficacy vs. effectiveness.

The RCT is the most reliable method of determining the effectiveness of an intervention such as the PAC. The design and conduct of such trials must be such that bias is minimal to be internally valid. However, to be clinically useful, the results must also be relevant to a specified group of patients in a particular setting. The effect of an intervention such as the PAC is very dependent on factors such as the patients' characteristics, methods of application, and setting (3). Selecting RCTs that have at least an 80% power to detect a 10% difference in mortality yields four recent trials (4–7). One trial was in heart failure patients (4), two in adult intensive care unit (ICU) patients (6, 7), and one in a high-risk elective surgical population (5). None of these trials contains critically ill, traumatized patient to any significant degree. Hence, only two studies inform us of the effect of PAC in a general ICU population that may remotely reflect a population of interest for the critically injured trauma patient (6, 7).

The sample size of these two trials are such that neither study was powered to demonstrate a mortality difference of

*See also p. 1597.

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<10%, even though the difference suggested by observational trials was felt to be 5% or fewer (8).

In addition, neither trial dictated or, for that matter, measured any differences in therapy that was provided to the patients in the two groups. It is this part of randomized, controlled trial design to date that is the crux of the problem. We consistently put the *cart before the horse*! It is impossible for the presence of a monitoring device alone to alter outcome. It must be linked to a therapy that is known to improve outcome, otherwise the negative results of these trials become somewhat predictable. In addition, clinicians are probabilistic thinkers, and when faced with uncertainty in complex decisions, they will inevitably seek out more information to decrease this uncertainty (9). So, we are never comparing the information derived from the PAC with no information at all but instead with other sources of information that will be highly variable, depending on the clinician's certainty. So, the comparison is likely to be to information from things such as a more detailed physical examination, information from central venous pressure measurements, measurements of venous oxygen saturation, esophageal flow probes, and echocardiographic data. Unfortunately, we have not measured the decision making that surrounds these other sources of hemodynamic data that the clinicians in the control arm of these trials are using. Not knowing what type of interventions were provided to patients in these RCTs only raises more questions than answers. This is evidenced by mortality rates that are considerably higher than one would predict with APACHE II scores of 22 and a predicted mortality rate of <40% but an actual mortality rate of almost 70%. This result is in contrast with other reports of mortality in association with PAC use (2), which raises concerns about the types of interventions that were provided to both groups. Trials that cannot have the intervention blinded need to strongly consider strict protocolization of care. Then, and only then, can we draw reasonable conclusions about the ability of a monitoring device to direct care that ultimately improves patient outcome.

We know very little about the efficacy of our therapy with some exceptions. Take the example provided by Rivers et al. (10), in which outcomes were improved in patients receiving early goal-directed therapy that resulted in patients receiving greater amounts of resuscitative saline, transfused red blood cells, and dobutamine. If Rivers et al. had decided to use a PAC as the monitoring device, we might have an alternate opinion about its usefulness in acute resuscitation. This study suggests that the timing of our interventions may be the more important factor and that by the time the patients are in the ICU, any manipulation in fluids and vasoactive agents beyond just good supportive care is unlikely to be of benefit. I would also argue that if benefit exists in the ICU setting, the effect size of such a benefit is smaller than any we have tried to measure to date. It is in this timing phenomenon that we may find explanation for the results of Friese and colleagues (1). Traumatized patients who are older and more severely ill will have greater uncertainty surrounding their hemodynamic profile and most appropriate subsequent treatment. It may, therefore, be reasonable to assume that the PAC is placed earlier in the treatment of these patients. The phenomenon of improved outcomes may be the result of earlier intervention. Unfortunately, these data are not available in the study by Friese and colleagues.

I think we often lose site of the fact that the PAC is a diagnostic device. As with the chest radiograph, you make a diagnosis (pneumonia/shock) and institute a therapy (antibiotics/fluids and vasopressors). We understand that the chest radiograph is not a very specific tool by which to diagnose pneumonia, but no one has ever asked for it to be subjected to a RCT of its effectiveness or suggested a moratorium on its use. So why have we done this with the PAC? I would argue that it is the question of safety, not effectiveness. What our RCTs inform, together with a recent meta-analysis, is that they support the safety of the PAC, an explicit primary goal of at least two of the trials (6, 7, 11).

So where to we go from here?

The observational study by Friese and colleagues (1) has another role that is often overlooked. Observational studies play a crucial role in the optimal design and interpretation of RCTs (12). They are invaluable in stimulating the pursuit of new knowledge and improved patient outcomes. The article by Dr. Friese and colleagues does just that. I would like to congratulate Dr. Friese and colleagues on reminding us that we are by no means finished when it comes to questions about the efficacy of the PAC. I would also like to challenge them and the trauma surgery community to design a trial that takes the above into consideration. The real question is, "Does the PAC allow for more accurate titration of a known effective therapy over some alternative monitoring approach." Such a trial could be a comparison of the PAC vs. the right atrial central venous catheter with continuous oximetry using the Rivers protocol to direct therapy (10). It should include careful documentation of care decisions made as a result of the data. It needs to be early in the resuscitation phase, because this may be a time when we can influence outcome. It should also be powered to detect a 5% difference in mortality and should measure other morbid and safety events thoroughly.

One pending RCT deserves mention. This trial has adopted a design with explicit protocols directing the interventions based on the data available. The Fluids and Catheters Treatment Trial (FACTT) is a study run by the ARDSnet group of investigators. The study plans to enroll 1000 patients with acute respiratory distress syndrome in a 2×2 factorial design comparing the PAC with central venous catheter and a fluid-liberal with a fluid-conservative strategy. The study has stopped recruiting and is in active follow-up (13).

We eagerly await the results of this and future studies of the PAC.

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Blood transfusion in burns: Benefit or risk?*

Blood transfusions can improve the outcome in critically ill patients but are also associated with negative effects such as immune suppression, infection, and fluid overload (1–6). The threshold hemoglobin level when to transfuse blood is still under discussion and varies from 7 mg/dL hemoglobin to 10 mg/dL. Major burns with a total body surface area burn of >20% require blood transfusions during their acute clinical course because of the nature of the injury and the necessary treatment. The study by Dr. Palmieri and colleagues (1) in the current issue of *Critical Care Medicine* investigates the effect of blood transfusion on outcome, such as mortality after a major thermal injury in adult patients. The study was designed as a multicenter retrospective cohort analysis. The authors found that mortality of severely burned adult patients was related to patient age, total body surface area burn, presence of inhalation injury, number of units transfused outside the operation room, and total number of transfusions. They further showed that the number of infections per patient increased with each unit of blood transfused. The authors concluded that the number of transfusions is associated with mortality and infectious episodes (1).

***See also p. 1602.**

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The finding of Dr. Palmieri and colleagues (1) that high amounts of blood products worsen the outcome in burn patients is paralleled in other patient populations. Transfusion of blood products have been shown to worsen the outcome of critically ill, oncologic, and surgical patients (2–6). In a recent study that is under review in *Critical Care Medicine*, our group investigated the effect of blood transfusions on the outcome of severely burned children (7). We showed that after a similar notion as observed in burned adults, transfusion of high amounts of blood products in severely burned children is associated with an increased risk of sepsis and subsequent death.

Blood loss in burned patients is multifactorial, and significant predictive variables are age (older age > younger age), male sex, weight, height, body surface area, percentage of third-degree burn, surgery time, and total area excised (8). The single most predictive independent variable, however, is surface area excised (8). Area excised accounts for approximately 50% of the variability in operative hemorrhage. Type of excision (tangential vs. fascial), percentage of total surface area burned, donor site area, the use of saline or epinephrine, and delay from burn to excision were not significant predictors (8). The underlying causes by which blood transfusions worsen the outcome are not entirely understood. There is evidence that blood transfusion impairs the immune system, increases the risk of infections, and induces the inflammatory response (3–6, 9). The systemic inflammatory response after burn leads to hypermetabolism and thus to protein degradation and catabolism (10, 11). Consequently, the structure and function of essential organs such as the muscle, skin, heart, immune system, and liver are compromised, contributing to multiple organ failure and mortality (10–12). Uncontrolled release of proinflammatory mediators such as interleukin-6, interleukin-8, and acute-phase proteins trigger and enhance protein wasting and organ dysfunction (13, 14). Organ function breakdown can then lead to increased prevalence of infection and sepsis, ultimately leading to multiple organ failure and death (14).

The main question that results from the studies in burned patients is: what can be done to reduce the amount of blood transfused? One possible approach would be to lower the threshold for hematocrit from 30–32% to 25–28% and for hemoglobin from 10 mg/dL to 7–8 mg/dL. However, during the surgical intervention, hemoglobin and hematocrit levels have to be maintained. New surgical strategies to diminish blood loss are necessary to decrease the amount of transfused blood. We suggest that the use of tourniquets, epinephrine, or the use of fibrin sealant could be possible solutions that can be clinically applied. Newer studies further indicate that it is not the blood received during the operation but rather the blood received between operating room visits that affect survival, suggesting that emphasis should be placed on transfusion indications during the acute

postburn hospital stay. The increasing evidence derived from retrospective studies that the indication and threshold for blood product administrations has to be redefined leads us to call for a large prospective clinical trial. The prospective trial should determine whether surgical techniques can effectively decrease blood loss during the operation, determine the indications for blood transfusion, and whether the amount and timing of transfusions determine the outcome of severely burned patients.

In summary, burned patients who require large amounts of blood products are at high risk to develop infectious complications and to die when compared with patients requiring low amounts of blood products. We suggest that the next step would be to initiate a large prospective clinical trial to determine the threshold for blood transfusions and possibly new methods to limit blood loss during surgery. This prospective randomized study should address these issues and answer these questions before recommendations can be made to change clinical practice.

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Blood product transfusion in association with coronary artery bypass grafting: Proceed with caution*

A total of 400,000 coronary artery bypass grafting (CABG) procedures are performed each year in the United States, many on productive citizens in midlife. Improving the safety of this procedure is important. In this issue of *Critical Care Medicine*, Dr. Koch and colleagues (1) report on their study in which they quantified the incremental risk associated with the transfusion of blood products on mortality and morbidity after CABG surgery. They also investigated patient- and procedure-related variables associated with the need for packed red blood cell (RBC) transfusion.

Blood transfusion and outcome after cardiac surgery have been studied extensively (2–8), and patient outcome seemed worse when blood transfusion was instituted in the perioperative period. Some of these studies were limited by small patient populations and others by combinations of cardiac procedures (e.g., CABG and valve surgery) that may have confounded the results. Some did not evaluate dose-dependent effects of RBC transfusion or patient outcome after transfusion of blood products other than RBCs. This present study addresses those issues.

Almost half of the patients (48.6%) of Dr. Koch and colleagues (1) underwent blood product transfusion. Transfusion of RBCs was associated with unit-by-unit increased risk for in-hospital mortality and morbidity, even after controlling for risk factors previously associated with adverse outcome after CABG. Higher rates of transfusion were seen in the elderly, patients with lower body mass indexes, low preoperative hematocrit, or those undergoing reoperation. Unexpectedly, platelet transfusion was associated with lower postoperative morbidity (9). Also contrary to previous findings, transfusion of fresh frozen plasma led to increased in-hospital mortality.

The greatest strength of this study is prospective. Perioperative patient data and information from the original blood component utilization forms were collected from a large homogeneous patient population. Analysis of transfusion blood products other than RBCs on outcome was also important, as there is a paucity of such information in the cardiac surgery literature. However, the design and analysis generated questions regarding

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confounding variables. Some of these concerns are outlined below.

Dr. Koch and colleagues (1) state that "patient-related disease characteristics, laboratory values and operative variables, . . . were variably associated with individual postoperative morbidities and mortality," but the specific variables were not listed. Although the authors controlled for traditional risk factors, they did not specify whether they controlled for physiologic variables (e.g., acidosis) that have been evaluated as confounding variables in other recent transfusion studies (10). They tried to account for these variables statistically by utilizing a balancing score, but concede that RBC transfusions might be a surrogate marker for sicker patients.

More detailed discrimination of the time of blood transfusion in relation to the onset of adverse outcomes would provide support for their conclusions. It is difficult to blame a blood transfusion for an adverse outcome that was diagnosed before the transfusion. Of the 20,513 units of RBCs transfused, the authors stated that 11,177 (54%) were given postoperatively in the intensive care unit. However, the majority of complications in cardiac surgery relate to events in the operating room or on the first postoperative night. Moreover, clinicians frequently transfuse cardiac surgery patients after the diagnosis of a complication. Review of those given transfusions beyond the initial 12- to 24-hr risk period for procedural complications might identify patients who fail to show a temporal relationship consistent with their conclusions that the transfused blood caused the complication. Identifying and excluding such patients from their data set would strengthen the suggestion of causality.

Specific patient and procedural questions came to mind while reviewing this article. How many of the patients in the study required a transfusion for bleeding? Might the local policy of avoiding aprotinin, the most effective measure for prophylaxis against bleeding, have led to more bleeding and the need for more blood products (11)? The investigators reported that most of the patients who underwent transfusion received only 1 or 2 units of RBCs, making bleeding a less likely indication for transfusion in those patients. What were the indications for transfusion? Fresh frozen plasma was associated with reduced odds for postoperative mortality. Was this because fresh frozen plasma led to a cessation of bleeding in these patients? This would seem unlikely according to the results of a recent meta-analysis of randomized clinical studies that showed minimal efficacy of fresh frozen plasma for this purpose (12–14). Perhaps the (nonprotocol) decision to give fresh frozen plasma signified a conscious effort by the clinician to avoid having to give cell-based transfusions (i.e., RBCs or platelets). The Cleveland Clinic Health System advertises "bloodless CABG surgery" for appropriate candidates (www.fairviewhospital.org/bloodless). This implies that they might have a fairly large cohort of low-risk patients with severe anemia after CABG. Comparing the outcome of this group vs. a matched cohort of low-risk patients who were transfused would strengthen their findings considerably.

Despite its flaws, this study is important to the critical care literature. It provides data regarding a therapy, presently under great scrutiny, on a challenging component of the ICU patient population. The correlation between blood use and poor outcome in CABG surgery is strong; therefore, decisions to utilize transfusion must be made carefully. We can save lives by being frugal in our use of blood. We can save lives by improving CABG surgery. We can save lives by improving the quality of blood products. We all have work to do.

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Achieving optimal antiarrhythmic therapy in advanced cardiac life support*

Prompt arrhythmia recognition with rapid implementation of resuscitative measures, including use of pharmacologic agents, in patients without a pulse can be a complex process. Key factors associated with survival include witnessed event, early access, cardiopulmonary resuscitation, associated rhythm, early defibrillation, and advanced cardiac life support (1, 2). Success with pharmacologic agents has generally been limited to soft outcomes such as improved survival to hospital admission, return of spontaneous circulation or survival at 24 hrs instead of increasing hospital discharge with adequate neurologic function (3). Improving the chance for survival may additionally depend on the setting, underlying health, presence of acute illnesses, symptomatic cardiac disease, or other drugs, in addition to rapid transition to advanced cardiac life support by trained healthcare professionals (1, 2, 4, 5). Equating outcomes for a given intervention solely based on a single variable will thus create notable limitations.

In this issue of *Critical Care Medicine*, Dr. Rae and colleagues (6) present the results of a retrospective analysis from three academic medical centers of the inpatient management of pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF) using either lidocaine or amiodarone or both. The primary end point was survival for 24 hrs, with a secondary end point of survival to hospital discharge irrespective of neurologic function. After adjusting for covariances, a higher mortality rate at 24 hrs or time of discharge was observed with the use of amiodarone compared with lidocaine. These results seem to question if any advantage for amiodarone over lidocaine exists in the inpatient setting.

Objective data supporting the effectiveness of lidocaine in pulseless VT or VF are limited. In one retrospective analysis, the addition of lidocaine in the setting of sustained VF resulted in a significant increase in return of spontaneous circulation ($p < .001$) and admission to the hospital (38% vs. 18% not receiving lidocaine, $p < .01$), but not hospital discharge (14% vs. 8%). The prevalence of bystander cardiopulmonary resuscitation or nurse present in the lidocaine group was significantly higher, highlighting the potential influence of a trained early responder on outcomes (7). In an open, randomized trial comparing 100 mg of lidocaine with 0.5 mg of epinephrine in outpatient VF (n = 199), no difference in return of spontaneous circulation or survival was observed (8).

In the Amiodarone Versus Lidocaine in Prehospital Ventricular Fibrillation Evaluation (ALIVE) trial, amiodarone (5 mg/kg initial dose) was associated with a greater chance to survive to hospital admission compared with 1.5 mg/kg lidocaine (23% vs. 12%, $p = .009$) but no statistical difference in hospital discharge (6.4% vs. 3.8%, $p = .32$) (9). It should be noted that 24 patients (13.3%) in the amiodarone group and 11 (6.6%) in the lidocaine group ($p = .04$) had transient return of spontaneous circulation before administration of the study drug, of which ten and four, respectively, were admitted to the hospital. Improved survival to admission was also observed with earlier administration of either amiodarone (28% vs. 18%) or lidocaine (15% vs. 6%) than the mean. Individuals receiving lidocaine earlier than the mean still had a lower rate of improved survival to admission (15%) than those receiving amiodarone later than the mean (18%), suggesting a continued advantage with amiodarone (9). Dr. Rae and colleagues (6) observed no difference in conversion rates or mortality after administration with either antiarrhythmic when given earlier than 6 mins, suggesting that no benefit exists with either agent if given early. Agent selection may not, however, be the only influencing factor to note.

Dr. Rae and colleagues (6) noted that only 25% of the patients received the recommended 300-mg dose of amiodarone and that the initial dose of amiodarone was given 14 ± 9 mins into the code, compared with 6 ± 5 mins for lidocaine ($p < .001$). The lower initial dose (150 mg) administered may have been easier to explain if there had been a guideline revision to increase the amiodarone dose, as was the case with lidocaine. Because amiodarone was a new addition to the Advanced Cardiac Life Support guidelines for pulseless VT/VF at the start of their analysis period, their observations suggest a lack of either understanding of how to use amiodarone or an undesirable delay to prepare and include a second 150-mg ampoule. The 8-min delay in administering amiodarone may also have unintentionally created a higher degree of acuity in the amiodarone comparator outside the covariates for which it was adjusted (e.g., degree of acidosis, delay in administering repeated doses of epinephrine).

It could be argued that although 69% of patients received a correct dose of lidocaine, it was lower than the 1.5 mg/kg tested in ALIVE (9). To avoid unnecessary delays in reaching the maximum 3 mg/kg lidocaine dose, the dose was condensed in 2000 from three 1-mg/kg doses to two 1.5-mg/kg doses, despite lack of supporting evidence (10). Education on using patient-specific dosing approaches may then play a vital role in optimizing current approaches for therapy. Teaching tools simplifying how much (i.e., one ampoule/syringe equals one dose for all) and when pharmacologic agents are administered (drug—shock—drug—shock) may create undesirable delays in establishing and maintaining adequate serum concentrations to achieve a desired response.

Logistic barriers with amiodarone could also have factored into the lower dose, de-

*See also p. 1617.

Key Words: advanced cardiac life support; lidocaine; amiodarone; pharmacotherapy; inpatient

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layed onset, and critical time lost in maximizing therapy. Besides the requirement to break two 150-mg glass ampoules of amiodarone for the first 300-mg dose, there was an additional recommendation to dilute with 20–30 mL, as was done in the ARREST and ALIVE trials, to minimize bradycardia and hypotension (9, 11, 12). Skrifvars et al. (12) recently reported on the use of 300 mg of undiluted amiodarone administered as central to the heart as possible with a fluid bolus to reduce the risk of hypotension and irritation of the access site in pulseless VT/VF. Amiodarone was not associated with a higher prevalence of bradycardia or hypotension, and the authors noted that most patients previously received epinephrine. However, use of amiodarone was associated with a more complicated prehospital course, including more defibrillatory shocks and higher overall amounts of epinephrine. The nonsignificant decrease in hospitalization and survival to discharge associated with the use of amiodarone left unresolved the question of whether any advantage for amiodarone exists.

In the recently published 2005 Advanced Cardiac Life Support guidelines, early drug administration after sole cardioversion is now encouraged with cardiopulmonary resuscitation continued to allow blood flow and drug distribution to the heart (3). The guidelines also encourage that pharmaceutical agents be prepared in advance to avoid delays in management, no longer requiring dilution of amiodarone. Availability of prefilled amiodarone syringes may assist in reducing delay in administration of amiodarone, especially in situations in which team members are multitasking without a member specifically assigned to preparation of medications.

The observations of Dr. Rae and colleagues (6) continue to leave open the question of whether amiodarone or lidocaine can improve outcomes in pulseless VT/VF in the inpatient setting. Critical time lost before defibrillation and insufficient drug administration may have been factors diminishing beneficial outcomes with pharmacologic adjuncts. The considerable amount of time between implementation of new guidelines and administration of the correct initial amiodarone dose observed by Dr. Rae and colleagues (6) suggests a greater need to educate code team leaders. Proving effectiveness, however, will depend not only on the agent itself, but the ability to give the correct dose promptly in that particular setting. Cardiac arrest teams need to be current on recommended treatment adjuncts, including the prompt and correct use of pharmacologic adjuncts to optimize outcomes—assuming it exists, that is.

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Is fast-track intensive care unit management still on the express track?*

In the 1990s, with a doubling in the number of coronary artery bypass graft procedures every 5 yrs (from 1981), efficient use of the limited facilities and available resources was critical for the appropriate delivery of medical care (1). Innovative thinking yielded two basic approaches to the appropriate use of these resources. The first was to bypass the intensive care unit (ICU) entirely by use of a cardiac recovery area (2). The second was the promulgation of a fast-track protocol that resulted in earlier extubation of the trachea and transfer of the patient to less costly (as compared with the ICU) clinical areas (3). The evolution of the fast-track ICU protocol resulted from the adaptation of early tracheal extubation studies in cardiac surgical patients (4, 5). The fast-track protocol becomes feasible after cardiac surgery due to improvements in perioperative anesthesia management, coupled with advancements in surgical techniques, myocardial protection, and normothermic or "tepid" cardiopulmonary bypass techniques (6). Equally important, however, is to recognize that feasibility does not equate to safety (7).

In this issue of *Critical Care Medicine*, van Mastrigt and colleagues (8) per-

*See also p. 1624.

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formed an elegant systematic review and a meta-regression analysis to assess fast-track treatment of low-risk patients undergoing coronary artery bypass surgery. The analysis identified 27 of 643 articles that met their criteria and focused on three variables: anesthetic management, temperature technique during cardiopulmonary bypass, and the presence of an institutional early extubation protocol. The dominant finding is that the introduction of an early extubation protocol is *essential* to accomplish a significant reduction in ICU and hospital length of stay in low-risk coronary artery bypass graft patients. Anesthetic choice and temperature management during cardiopulmonary bypass were, at most, only contributory factors. This study has chosen a realistic definition for differentiating high- and low-dose anesthetics and demonstrates it to be a far less important consideration than the intent to extubate and the process of early extubation care. However, this analysis does not clarify that modifying anesthetic techniques utilizing shorter-acting narcotics or muscle relaxants, inhalational agents, regional anesthesia, and the adjunct of methylprednisolone resulted in earlier extubation. One must remember that early extubation is a key step, but not the only step, in the facilitated recovery of these patients. The process of postoperative care seems to be more important and must be modified to complement early tracheal extubation for maximum cost efficiency (6).

Finally, due to the content of the studies included in the meta-regression analysis, limited data were available on long-term effects of a fast-track protocol. The only published study is a 1-yr follow-up after the index hospital discharge in a randomized assessment of resource use in a fast-track cardiac surgical protocol (vs. traditional management) by Cheng et al. (9). There were no deaths during 1-yr follow-up after initial discharge; 15 patients (25%) from both groups were readmitted to acute care hospitals in the follow-up period. However, the length of stay for acute care readmission was 0.3 ± 1.0 day in the fast-track group vs. 1.6 ± 6.3 days in the conventional group at 3 months ($p = .01$) and 0.8 ± 1.8 vs. 2.9 ± 9.6 days at 12 months ($p = .01$). Two patients (3.3%) in the fast-track group and nine patients (15%) in the conventional group were transferred to rehabilitation facilities. Percentage reduction of fast-track cardiac surgery cost was 68% at 3 months and 49.5% at 1-yr after index hospital discharge.

Importantly, the investigators give the reader a road map to design rigorous experimental clinical trials in the future. In cardiac anesthesiology, a systematic review and meta-analysis of high methodologic rigor has been published (10). However, despite the levels of evidence available for a number of aspects of practice, there remain a greater number of unresolved questions in fast-track cardiac anesthesia and surgery: choice of anesthetic agents and techniques in fast-track cardiac anesthesia (11); neurologic, cardiac, and coagulation monitoring (12–14); renal protection in cardiac surgery (15); prophylaxis for postoperative atrial fibrillation (16); safety and efficacy of regional anesthesia in cardiac surgery (17); safety and efficacy of off-pump coronary artery bypass surgery vs. conventional coronary artery bypass (18); and routine immediate operating room extubation after cardiac surgery (19).

This meta-regression analysis study was conducted on a patient population that is not seen in today's cardiac operating rooms and therefore does not adequately reflect the clinical challenges faced by physicians and nurses caring for the postoperative cardiac patient. With newer percutaneous cardiology techniques (stent placement, valve repair or replacement, septal closure devices, endovascular replacement), most cardiac operating rooms have witnessed a decline in the number of lower-risk patients undergoing surgical procedures, combined with a significant change in patient demographics. Patients with a higher number of comorbidities and poorer risk (just the group excluded in the present study) are daily challenges to all healthcare providers working with the cardiac surgical patient. Does this render the findings of van Mastrigt and colleagues (8) irrelevant? The answer is a resounding *no*! The central message of their findings is the requirement for an ICU protocol that allows one to move the patient progressively through a clinical pathway. Equally important, by use of a protocol, objective data are obtained, which again facilitates the type of innovation that brought fast-track protocols into existence in the 1990s (20). Safe and effective fast-track ICU recovery results in reductions in healthcare costs in cardiac surgery, which are needed more in 2006 than 1996.

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Rib fractures, pneumonia, and mortality*

The relationship between rib fractures, mortality, and pneumonia has remained a conundrum. In this issue of *Critical Care Medicine*, Dr. Brasel and colleagues (1) have taken a slightly different approach to this problem by performing a multivariate analysis of known risk factors and comorbidities on data collected from both trauma and non trauma centers. Their conclusions are not totally unexpected. They have confirmed that age and injury severity are the only important predictors of mortality in multiply injured patients (2).

Increasing age has long been shown to be associated with increased mortality, not just in patients with rib fractures but in other injuries as well (3, 4). Whether this is due to the inherent loss of physiologic reserve seen with the aging process or to underlying comorbidities is less clear. Although Dr. Brasel and colleagues were not able to conclusively answer this question, they did show that comorbidities in aggregate did not prove to be a significant factor in influencing mortality in the multiply injured patient. Although some comorbid conditions showed either no influence or even a protective effect, several comorbidities did have significant influence on mortality when age was controlled. It is not surprising that congestive heart failure, arrhythmias, neurologic diseases, renal failure, liver disease, and metastatic cancer were significantly associated with increased mortality. These are all disorders that make care of the trauma patient much more complicated. Many times, these patients are also much more likely to have advanced directives and want less aggressive care. Unfortunately this cannot be gleaned from this data.

Mortality from pneumonia in trauma patients is controversial. Studies have reported an increase in mortality with ventilator-associated pneumonia, but when case-controlled studies are performed, there is no difference in mortality (5–8). In Dr. Brasel and colleagues' study, pneumonia was associated with both increased age and injury severity. It was not associated with mortality in the multiply injured patient but was in patients with isolated thoracic injury.

Increased numbers of rib fractures were also associated with increased mortality, especially in those with isolated thoracic injury. This confirms the findings of others (9, 10). Interestingly, in Dr. Brasel and colleagues' data, the number of rib fractures does not correlate with pneumonia. Retrospective data collected from my institution did not show a difference in incidence of pneumonia between patients with less than or more than four rib fractures (11). However, Bulger, et al. (10) found that in elderly patients, the risk of pneumonia increased by 27% for each additional rib fracture. Studies have shown that aggressive pain control improves outcome (12, 13). In our institution, after reviewing our patients with rib fractures, we instituted a protocol especially directed at those patients >45 yrs of age with more than four rib fractures and it includes aggressive pain control and pulmonary toilet.

Overall, Dr. Brasel and colleagues' study has clarified the association between rib fractures, mortality, and pneumonia. It further exemplifies the need for aggressive care of the elderly patient with rib fractures including careful attention to patients with specific comorbidities.

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Transmitting and absorbing new information on the early identification of sepsis patients: The partial thromboplastin time biphasic waveform*

It is rare that a month passes in which *Critical Care Medicine* and other journals do not publish the results of a clinical investigation on an approach to identifying or stratifying patients with sepsis. Clinicians face a steady and often confusing stream of new data purporting to help in the early classification, treatment, or prognostication for patients with sepsis. C-reactive protein (CRP), procalcitonin, lactate, cytokines, and a diverse array other serum proteins have all been proposed as adjuncts to the bedside assessment and triage of septic patients. There are many reasons for this burgeoning publication of data, but this fundamentally represents a widespread effort to improve the criteria for categorization of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock. The fact that there are such a large number of investigations into clinical scoring systems, biochemical measures, and physiologic markers of disease reveals a significant knowledge gap in our understanding of sepsis. Specifically, current clinical definitions for SIRS and sepsis are neither sensitive nor specific. This contributes to misclassification errors and failure to separate patients with SIRS from those with sepsis. Many clinical investigations of sepsis have thus been hampered by the application of these definitions, which encompass an extremely heterogenous group of patients, diseases, and predictable outcomes (1, 2).

A major source of difficulty for clinicians who would incorporate the findings of sepsis research into practice arises from a separation of the simplified but useful clinical criteria for sepsis and the extraordinarily complex pathways through which injury and infection lead to a systemic inflammatory response. Although useful in standardizing sepsis research, a patient's temperature, respiratory rate, heart rate, white blood cell count, and clinical evidence of infection by themselves cannot be used to reliably determine prognosis, likelihood of treatment response, or pathophysiologic state. This difficulty is readily apparent in review of trials with therapeutic agents such as activated protein C, which shows clinical benefit in sepsis, but only for the subset of patients who meet Acute Physiology and Chronic Health Evaluation II scores that were not initially used as eligibility criteria (3, 4). Many clinicians believe the successful and effective application of novel therapies for SIRS and sepsis patients will require timely identification and separation of patients by underlying pathogenesis, prognostic category, and biophysiologic status. Toward this end, there have been repeated calls to conduct sepsis research using both the original consensus criteria and also a classification system that accounts for specific predisposing conditions, specific infections, biochemical markers, organ dysfunction, and prognostic categories (5–7). On an even more basic level, an adjunct test that consistently improves the distinction between patients with SIRS and no infection from those with sepsis would represent a significant advance.

Within this context of biochemical markers of infection in septic patients, Dr. Chopin and colleagues (8) present their findings on abnormal activated partial thromboplastin time waveform transmittance in this issue of *Critical Care Medicine*. This work builds on previous observations that light transmittance of serum from some patients with disseminated intravascular coagulation decreases in a time-dependent biphasic manner during measurement of the activated partial thromboplastin time, the so-called biphasic waveform (BPW) (9, 10). Although this effect cannot be measured on most commonly used laboratory coagulation analyzers, the machine and software program used in these studies is unique and permits observation and quantification of this early event in coagulation time measurement. This abnormal decrease in light transmittance results from the precipitation of a complex of lipoproteins, most likely very low density lipoprotein, and CRP, which occurs immediately after recalcification of the specimen but before coagulation. The biochemical process that accounts for this calcium-dependent precipitation of CRP–lipoprotein complexes in serum from patients with inflammation but not normal healthy controls has not been established with certainty. Evaluation of the lipoprotein content and thrombogenic properties of very low density lipoprotein isolated from patients with sepsis and disseminated intravascular coagulation reveals qualitative changes in its constituent phospholipids and increased prothrombinase activity that may contribute to sepsis-related coagulopathy (11, 12). It is not known whether these

***See also p. 1654.**

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lipoprotein alterations and the CRP–lipoprotein precipitation reflect incidental events or an integral process in the development of coagulation and inflammatory cascades. In a study involving BPW measurement in intensive care unit (ICU) patients, it seems that both CRP and very low density lipoprotein concentrations are elevated in disseminated intravascular coagulation but also that the abnormal BPW occurs earlier than findings of overt disseminated intravascular coagulation and is a better predictor of disseminated intravascular coagulation than either component alone (11).

In the present study, Dr. Chopin and colleagues (8) report their measurements of the BPW in a heterogeneous cohort of 187 consecutive adult surgical and nonsurgical patients admitted to an ICU. All included patients met criteria for SIRS or sepsis. The most striking observations were that the presence of an abnormal BPW had a sensitivity of 90% and a negative predictive value of 92% for the diagnosis of severe sepsis or septic shock on day 1 of ICU hospitalization. On day 3 of ICU hospitalization, the presence of an abnormal BPW correlated with prognosis and had a sensitivity of 77%, specificity of 91%, and negative predictive value of 98% for mortality. However, in distinguishing patients with SIRS alone from patients with any severity of sepsis, severe sepsis, or septic shock, the presence of an abnormal BPW on day 1 had a sensitivity and specificity of only 68% and 62%, respectively. Thus, the main advantage of the BPW seemed to be in identifying severe sepsis or septic shock but not necessarily in separating SIRS without significant infection from sepsis. The investigators simultaneously measured procalcitonin, CRP, and lactate with the activated partial thromboplastin time waveform. This demonstrated that the abnormal BPW had similar to slightly improved sensitivity and specificity for the diagnosis of sepsis and mortality in comparison with each of these other measures. These results are consistent with previous studies demonstrating that the presence of an abnormal BPW correlated with an increased risk for both sepsis and mortality (13, 14). The results reported in this study are also comparable with those reported by Dempfle et al. (15), obtained in a similar cohort of 331 patients, in which an abnormal BPW was associated with a higher mortality and had a 48% sensitivity and 94% specificity for sepsis using a similar threshold value.

Dr. Chopin and colleagues (8) performed their measurements and analysis in a single ICU population using a coagulation analyzer not in widespread or common use. This design and measurement procedure significantly limits the ability to generalize the findings. Other limitations include the small number of patients studied and the unexplained variability noted by the authors between patients with pneumonia, fungal, Gram-negative, and peritoneal infections. Finally, conclusions about the clinical prediction of mortality in a critical care setting without multivariate stratification and analysis may not be robust. Nevertheless, when viewed within the context of previous investigations of CRP, procalcitonin, and other biochemical markers in patients with SIRS and sepsis, these results compare favorably. Specifically, the sensitivity, specificity, and area under the receiver operating characteristic curves for the BPW are of similar magnitude to those reported in mixed ICU populations for both procalcitonin and CRP (16–19).

As with any clinical diagnostic test or marker of disease severity, the most useful tests will have high degrees of reproducibility, availability, and objectivity. Ideal markers of disease would also be rapid, inexpensive, and directly related to the underlying pathophysiologic process. Finally, an ideal marker of infection or sepsis should be proven beneficial when employed in medical decision making. Although the equipment necessary for measurement of the BPW is not widely used, the test itself seems to be reproducible, rapid, inexpensive, and linked to another common laboratory test. It remains to be determined what specific mechanism in sepsis produces an abnormal BPW and if the BPW has reliable clinical utility for determining risk, prognosis, or treatment in sepsis patients. At a minimum, BPW analysis should now be absorbed into the growing list of potentially useful markers of sepsis that warrant further study.

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Pharmacokinetic and pharmacodynamic research in the intensive care unit: An unmet need*

Very few drugs commonly used in the intensive care unit (ICU) have been specifically developed for use in the critically ill. Most dosing regimens employed in the ICU are based on extrapolation from clinical trials involving non-ICU patients or healthy volunteers, rather than systematic drug development experiments in the critical care setting. The inherent assumption underlying this extrapolation is that the pharmacokinetic (PK) variables and pharmacodynamic (PD) responses are similar between non-ICU and ICU patients. However, it is well known that the PK properties of many drugs are altered in critically ill patients due to a number of potentially interacting physiologic factors, including dynamic changes in volume status, plasma protein binding, and end organ function (1–5). Bioavailability after nonsystemic routes of administration may also be adversely affected in critically ill patients (4). These PK alterations lead to unpredictable and variable exposures to commonly used drugs when administered at currently recommended doses in the critically ill. Although even less well studied, the PD response to any given drug exposure may be highly variable in ICU patients possibly due, for example, to down-regulation of receptors, altered postreceptor responses, and underlying physiologic alterations secondary to sepsis and inflammation (5, 6).

Additional research to define PK/PD models for common drugs in the ICU is necessary to provide tools to quantitatively describe drug concentrations and subsequent responses after administration of different doses to patients with diverse concomitant drugs, underlying diseases, and severities of illness. The clinical application of these tools in the ICU offers the potential to improve therapeutic response, drug safety, and patient outcomes (7). Due to the complexity and heterogeneity of critically ill patients, models that can accommodate input from multiple nonlinear systems, such as artificial neural networks, are likely going to be required (8).

In this issue of *Critical Care Medicine*, Dr. Vincent and colleagues (9) report the first PK/PD study of recombinant human erythropoietin (rHuEPO, epoetin alfa) involving critically ill patients. Despite the uncertainty about the clinical or economic value of rHuEPO in the critically ill (10–12), the adoption of this therapy into routine clinical practice is widespread. The dose of rHuEPO most commonly employed, and administered in the current study, is a fixed dose of 40,000 IU given subcutaneously once weekly. This dose and administration schedule was extrapolated from clinical trials involving non-ICU patients and healthy volunteers (10). The current study is potentially relevant because defining a valid PK/PD model in the critically ill may permit a dose-individualization approach to maximize PD response, potentially improve clinical outcomes, and increase the cost-effectiveness of this expensive treatment.

Dr. Vincent and colleagues (9) enrolled a total of 73 mixed-ICU patients in a prospective, double-blind, randomized (2:1), placebo-controlled study. PK data after at least one dose of rHuEPO was reported for 68 patients (24 placebo, 44 rHuEPO), and PD end points were presented for 54 patients (18 placebo, 36 rHuEPO). Their sampling strategy provided detailed plasma erythropoietin concentrations after the first (n = 44) and second dose (n = 32) in the rHuEPO group and, in the placebo group, over the 2-wk period (n = 24). PD end points including hemoglobin, red blood cells, and reticulocyte indices were measured at baseline and weekly for up to 4 wks, and at day 42 when possible. The sample size and sampling strategy provided a relatively rich PK data set and a more sparse but valuable PD data set.

Unfortunately, the PK/PD analysis of the data from the current study makes only a limited contribution to our understanding of the PK/PD properties of rHuEPO in the critically ill. Dr. Vincent and colleagues (9) utilized a simple SHAM (slope, height, area, and moment) analysis utilizing noncompartmental techniques. More sophisticated PK models for rHuEPO reveal relatively complex PK behavior with dual first and zero-order absorption processes after subcutaneous administration. The prolonged terminal phase of the concentration vs. time curve after subcutaneous administration is primarily due to continued first-order absorption and not the elimination of rHuEPO (flip-flop kinetics) (13, 14). The bioavailability of rHuEPO is dose dependent, with greater bioavailability at higher doses (14). The clearance of rHuEPO has been defined using both linear and nonlinear models (13–15), and which clearance model may be most applicable to critically ill patients is unknown. At a fixed dose of 40,000 IU, the weight-adjusted dose ranged from 360 to 1000 IU/kg, which likely led to inconsistent bioavailability and the potential for dose-dependent clearance across the study sample (9). The PK variables of rHuEPO are not likely to be well characterized using the authors' noncompartmental SHAM analysis because one of the underlying assumptions, linearity, is probably inappropriate for this drug, and even if this issue is insignificant, the au-

*See also p. 1661.

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thors' methods were improper. The investigators were unable to define the terminal slope of the concentration vs. time curve for 10 of 32 patients after the second dose of rHuEPO, leading to a limited reporting of the available PK data. The authors elected to not adjust for the contribution of endogenous erythropoietin to the PK profile of rHuEPO, despite the placebo group data suggesting that the endogenous hormone contributes approximately 20% to the area under the curve (AUC) (9). Also, the availability of the placebo data may have allowed a better characterization of the endogenous erythropoietin contribution than the assumption of zero-order input used in previous models (13, 14).

The authors did not analyze the available PD data using either direct or indirect effects models to characterize the potential relationships between individual patient rHuEPO (or endogenous erythropoietin) exposure and the response of PD end points. The red blood cell and hemoglobin end points were presumably affected by bleeding events and transfusions, so the reticulocyte indices were the only useful PD end point. The investigators standardized rHuEPO exposure data to a single average time interval (446 hrs), despite individual patients receiving anywhere from two to four doses of rHuEPO, and then reported the relationship between this adjusted AUC for rHuEPO and the AUC for reticulocyte indices using a linear graphical presentation. It was unclear if the time interval for the adjusted AUC for rHuEPO and AUC for reticulocyte indices were the same. There was no formal analysis of this relationship. Because published PD models describe a nonlinear relationship between rHuEPO exposure and PD response and the development of tolerance with continued rHuEPO exposure (13, 14), a simple linear plot is unlikely to correctly characterize the relationship between AUC for rHuEPO and PD response. A far more appropriate and informative analysis could have been achieved using nonlinear mixed-effects regression, also called population PK/PD analysis (13, 14, 16).

If on-going research is able to demonstrate that rHuEPO positively affects patient outcome, future studies will need to define the most relevant PD parameters because rHuEPO may have beneficial effects beyond erythropoiesis, including modulation of apoptosis, inflammatory responses, and vascular autoregulation in critically ill patients (17). In addition, the erythropoietic response in ICU patients may be affected by alterations in iron metabolism associated with critical illness and inflammation that may need to be measured and incorporated in a comprehensive PK/PD model (18).

The ICU is an environment of intensive monitoring of physiologic variables, and we believe that the ICU should also be an environment for intensive monitoring and individualization of drug therapy through the application of PK/PD principles with the goal of maximizing the clinical response and safety of drug therapy. The first step in realizing this goal is research defining valid PK/PD models for selected drugs in complex ICU patients. Generating adequate PK/PD data sets in critically ill patients is expensive and logistically difficult, so it is imperative that appropriate analysis and modeling of the data are performed to maximize our understanding of the factors affecting PK variables and PD responses. If adequate PK/PD models are defined, the effect of adaptive feedback control to optimize the attainment of defined PD targets on patient outcomes will need to be evaluated. The current practice of using "borrowed" or "one-size-fits-all" drug regimens for complex, critically ill patients is unlikely to achieve optimal outcomes.

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Permissive hypercapnia: Does a high $Paco_2$ level require high sedative doses?*

Despite recent advances in sedation protocols and therapeutic strategies to prevent oversedation and decrease sedative use (1, 2), sedative and analgesic requirement vary considerably according to age, weight, and other clinical conditions. It may also vary according to several therapeutic interventions. In this issue of *Critical Care Medicine*, Dr. Vinayak and colleagues (3) assessed sedative requirements in patients within the first 72 hrs of receiving mechanical ventilation with or without the use of permissive hypercapnia. They rigorously evaluated existing data on 124 patients who had randomly received either propofol or midazolam as part of a previous study comparing daily interruption of sedatives to standard sedation. In the present study, the effect of important variables, including age, weight, presence of renal or hepatic failure, and level of sedation, on propofol and midazolam doses was analyzed. Permissive hypercapnia was used in ten of the 60 patients who received propofol and 13 of the 64 patients who received midazolam. Eighteen of these 23 patients had acute respiratory distress syndrome (ARDS). The influence of permissive hypercapnia on doses of propofol and midazolam was also assessed.

Among the propofol-treated patients, higher propofol dose was independently associated with younger age and permissive hypercapnia, although the relatively small sample size may have masked the role of other important variables. Whereas the impact of age on sedatives requirements is a common finding (4), the association between permissive hypercapnia induced by a low tidal volume strategy and sedative doses has been recently questioned. In two *post hoc* analyses of patients enrolled in two participating centers in the ARDS network trial (5, 6), sedative dose was similar in ARDS patients whether high or low tidal volume was used. Why do the results of the present study differ? First, the number of patients treated with propofol in the two single-center analyses was low (<20 in each study, compared with 60 in the present study), which may have occulted a potential association between low tidal volume and propofol dose. Second, $Paco_2$ level in permissive hypercapnia patients was 54 mm Hg in the study by Dr. Vinayak and colleagues (3), whereas among patients in the low tidal volume group in the ARDS network, $Paco_2$ levels were about 10 mm Hg lower. This finding suggests that among patients with ARDS, those with a high $Paco_2$ level might thus require more propofol. Several factors might contribute to the higher propofol dose in these patients. Patients with severe ARDS and permissive hypercapnia are often considered to require strict adaptation to the ventilator to provide adequate oxygenation and avoid high intrathoracic pressure. Although slight overtaking of the ventilator respiratory rate setting by the patient and use of inspiratory or expiratory muscles are acceptable in many mechanically ventilated patients, these factors would be considered undesirable by most physicians treating patients with ARDS. Furthermore, to maintain this strict level of adaptation to the ventilator, higher sedative doses may be required in patients with permissive hypercapnia due to hypercapnia-induced increase in respiratory drive.

In patients receiving midazolam, permissive hypercapnia did not influence midazolam dosage. It is possible that, unlike propofol dose, midazolam dose does not need to be increased in patients with low tidal volume, regardless of whether $Paco_2$ level is maintained in the normal range (5, 6), or, as in the present study, is significantly higher than the normal value. However, the results of the multivariate analysis of factors influencing midazolam dosage may have been weakened somewhat by the inclusion of morphinics dose in the statistical model. This was the only variable significantly associated with midazolam dose. Since it is current practice that prescription of midazolam is closely "coupled" with administration of opioid analgesics, as pointed out by the authors, the particularly strong association between use of midazolam and morphine might have masked other relevant associations.

The important finding suggesting that permissive hypercapnia requires higher doses of propofol raises several important questions for the clinician. High doses of propofol expose patients to arterial hypotension and hypertriglyceridemia (7), and increased sedatives dosage leads to abnormally prolonged duration of mechanical ventilation (8). Addressing these adverse events would help physicians to decide whether high propofol doses represent a real clinical problem at the bedside and whether other sedative drugs should be preferred in the permissive hypercapnia setting. Although in the study by Dr. Vinayak and colleagues the propofol dose was significantly higher in patients with permissive hypercapnia than in those without, it was well below the dose described in both children and adults (>5 mg/kg/hr for >5 days) for propofol-induced syndrome (9), suggesting that patients in the present study were not at particularly high risk of propofol-induced syndrome. It would also be useful for the clinician to know the extent to which the level of hypercapnia could be reduced in some patients, thereby allowing for lower propofol dosages. Finally, the findings by Dr. Vinayak and colleagues raise the underlying question of the sedation strategy

*See also p. 1668.

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in patients with ARDS. What level of patient-ventilator dyssynchrony is acceptable, particularly when gas exchange and pulmonary pressure goals are reached? Should higher doses of opioid analgesics be used to control the high respiratory drive frequently present in ARDS patients? When dyssynchrony persists in a nonreactive sedated patient, should sedatives and opioids be further increased or should neuromuscular blockers be used early—an important question given that unnecessary high doses of sedatives and neuromuscular blockers both carry the risk of delayed weaning and prolonged mechanical ventilation? The study by Dr. Vinayak and colleagues is a step forward in identifying clinical issues that affect achieving optimal sedation strategy in patients treated with permissive hypercapnia, and it opens the way for further investigation.

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Do intensive care unit patients have intensive care unit physicians? Unfortunately not*

The last 10 yrs have seen an explosion in critical care research. Newer therapies for sepsis, improved ventilator management and organ support, and aggressive approaches to resuscitation have the potential to improve outcomes, decrease morbidity, and save lives (1). But who will apply this evidence at the bedside in the intensive care unit (ICU)? Based on the results of the survey by Dr. Parshuram and colleagues (2) in this issue of *Critical Care Medicine*, it seems likely that this care will often not be provided by a physician. Dr. Parshuram and colleagues (2) describe the results of a survey of Canadian ICU directors. They note that nearly half of ICUs lacked dedicated in-house physician coverage after standard duty hours. In many cases, the most senior physician in the ICU when one was present was a resident. This resident often had responsibilities outside the ICU and worked shifts that were long. More important, nearly nine of ten ICUs operated outside the recommendations of the Society of Critical Care Medicine (SCCM) staffing guidelines. Interestingly, institutions with larger ICUs were more likely to have physician coverage during nonstandard hours. Pediatric ICUs, in contrast to adult ICUs, had more extensive physician staffing.

These estimates seem bleak, but the situation may be better than in the past. A conservative estimate from the early 1990s suggested that only 5% of ICUs in the United States had full-time attending physician ICU coverage 24 hrs a day (3). In a recent analysis of the COMPACCS study, we found a similar proportion in the late 1990s (4). In contrast, Dr. Parshuram and colleagues estimate the presence of full-time intensivists in 15–20% of ICUs. Of course, there is no particular reason to believe that ICU physician staffing should be in parallel in Canada and the United States, and even if 15–20% is an accurate estimate for both countries, it will still be a long time at current growth until all ICUs are staffed by intensivists. The bad news does not end there: With the aging of the baby boomers, we are now entering a period of almost exponential growth in the number of individuals likely to need ICU services. Without draconian change in the workforce, by 2020, we will fall far short in our ability even to provide the current level of care, let alone increase the access for the critically ill to intensivists (5).

So, what are our options as individual intensivists and as an organized professional society? There are probably a number of things that could be done in parallel. We can certainly gather more detailed information on the current workforce allocation across institutions. With initiatives such as Leapfrog, there could have been important changes in the last 10 yrs since COMPACCS. As a matter of policy we cannot determine how to emerge from the present intensivist deficit without knowing its extent and geographic distribution. Second, we need to conceive of the shape and size of the "optimal" workforce allocation. Hence we must study how various staffing patterns and schemes affect

*See also p. 1674.

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outcomes. Quite possibly, the appropriate staffing model for enhancing outcomes may vary based on the patient case mix and severity of illness. Intensivist staffing is a well-studied organizational variable in health care, but the study designs have often been less than ideal, and we have little information on the mechanism by which intensivists might improve outcome (6). In short, since we do not have a surfeit of clinicians for ICUs, we must decide where they are needed most and how to replace them if not available. The lack of high-quality research into these questions hampers any attempt to make specific policy recommendations.

But the lack of robust data should probably not be used as justification for inactivity. There are a number of empirical observations, or principles, that one might make, or endorse, without further research. To wit, patients who are critically ill should likely be cared for by clinicians who are able to respond in a timely manner and who have the requisite skill to respond appropriately. Access to such clinicians, and the accompanying health care resources, should likely be based on clinical grounds, and not on other patient characteristics such as race, gender, locale, or socioeconomic status. If we embrace these notions, and place them above other priorities, then a number of consequences ensue.

First, because there are not enough intensivists to go around, patients need to be moved to the intensivists based on clinical need. One approach to solve this dilemma is regionalization (7). Nascent efforts are already underway in this area. SCCM has proposed levels of ICUs based on capabilities, and the next steps would be to match patients to levels and launch accreditation programs. Precedents for this model exist in trauma and neonatal intensive care. However, the barriers are considerable, including reimbursement issues and regulatory hurdles. These issues, though, can be addressed through more extensive research into this topic and through a dialogue between physicians, institutional representatives, and policy makers.

Second, also because of our shortage, we need to train nonintensivists in the "first aid" of intensive care. Again, there are nascent efforts in this regard, with a variety of efforts, such as Fundamentals of Critical Care Support, to provide rudimentary intensivist skills. Trauma is again a precedent—the Advanced Trauma Life Support courses do not convert nontrauma surgeons into trauma surgeons, but they help promote standard, safe early triage and management of the trauma victim before that person reaches the right site for definitive care.

Finally, novel staffing paradigms must be created. Expanding reliance on nonphysician health care professionals could be key to plugging the gap in ICU coverage. Advanced care nurse practitioners and physicians' assistants can and should assume an expanded role in ICU care. With appropriate training, these individuals can supervise the care of ICU patients. The ICU remains a key area for the training of young physicians, but with a shorter trainee work week, it does not seem likely that residents should be expected to share as much of the ICU coverage as in previous years. Telemedicine represents another resource to help address the staffing supply. As noted previously, tools for replacing intensivists and for augmenting the currently available supply of intensivists are needed now. Several reports have shown how telemedicine in the ICU can enhance patient outcomes through closer monitoring of patients and direction of nurses (8, 9). Irrespective of one's personal beliefs about telemedicine, it is accessible and available now. It has limitations, imperfections, and acquisition costs, but we hope it can continue to evolve as a technology.

There are other efforts that we might consider. For example, at present in the United States it is difficult to recertify in medical critical care if one is also boarded in another medical subspeciality without first taking the recertification examination for the "primary" subspeciality. In such an environment, how can one conclude anything but that critical care is "secondary"? Moreover, we as intensivists, whether primarily as surgeons, as anesthesiologists, or as internists, should push for a uniform certification process in critical care. Becoming more homogeneous as a group will reinforce the maturation of critical care medicine. To support this endeavor, perhaps even the SCCM should abandon an organizational scheme that forces us to dichotomize ourselves and, in turn, should adopt a structure based on our interests (e.g., sepsis, mechanical ventilation, etc.) rather than our training.

In the words of the poet Robert Frost, we have miles to go before we sleep. Physician staffing is a pressing issue for the ICU. If we do not own and address this problem, others, less dedicated to our patients, will dictate policy. For both our profession's sake and for our patients, we need to move forward aggressively and institute change within our professional organizations, our ICUs, and our society.

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Family satisfaction from clinician statements or patient-provider concordance?*

In this issue of Critical Care Medicine, Dr. Stapleton and colleagues report (1) on clinician statements and family satisfaction with family conferences in the intensive care unit. This article reports audiotaped and analyzed family meetings, looking specifically at which statements and behaviors were associated with family satisfaction. The three main findings of this study are the association with the following statements and family satisfaction: a) assurances that the patient will not be abandoned before death; b) assurances that the patient will be comfortable and will not suffer; and c) support for family's decision about end-of-life care, including support for the family's decision to withdraw or not withdraw life support. These authors should be commended on this area of research, as research on communication at the end of life in the intensive care unit is a necessary area of study (2). In addition, the majority of patients who die in an intensive care unit do so after decisions have been made to limit technological support (3).

The significant concern of the patient being abandoned before death should be incorporated into our family discussions. In my experience, the fear of abandonment is a common concern in end-of-life care and palliative care. This is one reason why it is essential to discuss withdrawal of technological support, rather than withdrawal of care or withdrawal of support. Families must perceive that their loved one will continue to get high-level care. In palliative care, we sometimes refer to aggressive comfort care, so families understand how comfort is a chief priority. It is not about giving up or abandoning the patient but rather refocusing goals on aggressive comfort care (4). This approach incorporates the first two findings of the study, about not abandoning the patient and ensuring comfort. This approach also avoids the dichotomy between palliative care and aggressive care, by discussing aggressive palliative care to relieve symptoms of suffering. Palliative care needs to be incorporated into the intensive care setting (5, 6). In addition, if a family chooses to sustain technological support in a futile situation, the physicians should still respond to and treat symptoms of pain and suffering (7). This is supported by the family satisfaction associated with the statement that the patient will be kept comfortable, irrespective of what decision is made by the family.

The strengths of this study include the audiotaping of the family meetings. This diminishes recollection bias, as the results are not based on the memory of the clinician or the family members. In addition, the use of grounded theory to analyze the transcripts to identify specific themes and statements associated with family satisfaction is a strength. Good communication is essential when making decisions about end-of-life care, which is why this is a crucial study (8). End-of-life literature has very few examples of how to improve family communication, other than previous reports from these authors (9). Previously, they have reported that giving family members an opportunity to share their viewpoints will provide greater family satisfaction (10).

The weaknesses of this study include the low participation rate and high concordance of patient provider race. The participation rate was 51 of 111 families, of which 17 were excluded by physicians and nurses, two were excluded for risk management reasons, 24 were excluded because family members refused to speak with study personnel, and 17 were excluded because family members declined participation after discussing it with study personnel. That 19 of 111 were excluded by hospital personnel is concerning for selection bias, as any potential disgruntled family members were not even approached and invited to participate in the study. The family members who agreed to participate may be those who already had a high satisfaction level with the care their family member was receiving, thus introducing another potential level of selection bias. An additional level of selection bias is the impact of study participation on the physician's behavior. Physicians who agreed to participate in the study, with full knowledge they were being audiotaped, may have gone out of their way to reassure the family about any concerns they have. This is a "best behavior" selection bias, as physicians may have altered their practice in hopes of higher family satisfaction.

The high patient-provider concordance may affect the high level of family satisfaction. In this study, 86% of physicians were white and 81% family members were white, which is a high level of concordance. In addition, no race/ethnicity data were presented on those who refused participation, which may be meaningful. The homogeneity of the patients is a significant factor, as racial/ethnic minorities are less likely to have advanced directives and thus are more likely to have their family members making decisions without prior knowledge or discussion of wishes (10). Other studies examining health care disparities have reported the important role of cultural differences in end-of-life care and pain management (11, 12). Had there been more of a racial/ethnic mix, then we may have been able to interpret the clinician statements and behaviors independent of the role of race/ethnicity. Racial/ethnic minorities are also less likely to use palliative care and hospice services (13). This study needs to be interpreted in light of the high patient-provider concordance, as it may not be generalizable to those who are racial/ethnic minorities.

This significant study gives clinicians specific behaviors and phrases to use when discussing end-of-life care in the intensive care unit. All physicians will benefit from incorporating the key phrases of nonabandonment, treating pain and suffering, and support for the families' decision. The importance of minimizing suffering is independent of decisions about foregoing life-sustaining medical technology; thus, it is

*See also p. 1679.

Key Words: end-of-life decision making; communication; health care disparities

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paramount that palliative care be incorporated into intensive care, regardless of decisions to forego life-sustaining technology.

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End-of-life variations around the world: Can we improve our caring?*

Care of the dying patient is an inevitable reality in intensive care. Debates on end-of-life decisions and practices are increasing and are gaining importance around the world, but these are influenced by legal, cultural, social, and religious factors. Different societies have developed different approaches and laws to help guide end-of-life decisions.

End-of-life decisions are very common and have been reported mostly from intensive care units and hospitals (1–9). There have been variations between countries in end-of-life practices (cardiopulmonary resuscitation, withholding or withdrawing life-sustaining treatments, active shortening of the dying process, and active euthanasia) and discussions with patients, families, and other caregivers (4–9). Differences have been demonstrated to be related to legal, cultural, religious, and social factors (4–9). Although patient preferences may shape end-of-life practices in some countries, the North American autonomous approach to the patient-physician relationship (10) differs from the European paternalistic path (4, 8, 9).

The study by Dr. van Delden and colleagues (11) of do-not-resuscitate (DNR) decisions for nonsudden deaths in six European countries provides another important contribution to the area. It provides countrywide data for individuals aged one or older, including new information for people not hospitalized or in institutions. DNR decisions were diverse and highest in hospitals (19–86%) but also common outside of the hospital (13–62%). It is important for intensivists to recognize that end-of-life decisions do not only occur in intensive care units. The study also provides data on changes during the years studied. There was great variation in autonomous decision making by competent patients: 10–85% patients agreeing with DNR, 14–67% families agreeing, and 1–27% neither patient or family agreeing. For incompetent patients, 5–37% of DNR decisions were made without relative involvement. Institutional DNR decisions (institutional rule not to resuscitate any patient) were made without any patient involvement in 5–22% of nonsudden deaths. The fact that DNR decisions are made by many healthcare professionals implicitly and not explicitly is troublesome. The study would have been even more helpful if it provided data on differences in other limitations including mechanical ventilation, nutrition and fluids, and active shortening of the dying process and active euthanasia.

There has been an increase in the incidence of end-of-life limitations, patient involvement, and communication during the last several years (2, 11). These changes may be related to new laws, guidelines, greater religious flexibility, physician education, and increased public awareness to these issues, including the importance of advance directives. Similar changes in practice may occur in different countries at different rates or not at all, depending on these and other factors.

Changes certainly occur with new statutes and court decisions. Interestingly, a new Law for the Dying Patient was just passed by the Israeli Parliament (12). The law was developed after a multidisciplinary committee, including representatives of most sectors within the society, achieved a broad consensus. The law balances the value of life and patient autonomy, based on the value system of Israel as a Jewish and democratic state, determining the boundaries between prolonging life and avoiding suffering. The law provides explicit mechanisms for issues that were previously unaddressed in Israel and remain unclear in many countries. These include mechanisms for autonomous individual decision making with legally binding advance medical directives and/or the appointment of a surrogate decision maker, a national bank of advance medical directives, a citizen's right to receive palliative care, lucid directives of a physician's responsibilities toward the dying patient, clear guidance for

*See also p. 1686.

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doctors to know what is permitted or not, and resolution of disputes including the innovative establishment of a National Ethics Committee composed of experts in all relevant fields. As religion and culture play important roles in end-of-life practices in Israel (13), as they do in several other countries (4–6, 8), the law prohibits stopping continuous life-sustaining therapies (such as a ventilator), because this is viewed as an act that shortens life. It does allow stopping intermittent life-sustaining treatments (antibiotics or dialysis). As the continuation of an unwanted ventilatory therapy may prolong suffering, the law enables doctors to change the ventilator from a continuous therapy to an intermittent one, by using a timer that allows the ventilator to stop periodically (14). Although the new law may not be appropriate for other countries with different cultures, such a process with consensus development and the explicit mechanisms to help dying patients may give useful insights to other countries.

The large variations in end-of-life practices around the world (4–9) or even in the same city (15) point to the lack of consensual guidelines for end-of-life care. Consensus recommendations for intensive care unit end-of-life decisions have been developed for individual countries (10, 16–18). Although there are many differences between attitudes and practices among physicians around the world, there are more similarities. National and international critical care societies are now involved in a new initiative in ≥35 countries to provide such a worldwide consensus entitled "Consensus Guidelines for Worldwide End of Life Practice for Patients in Intensive Care Units: WELPICUS." We hope that the development of worldwide standards and guidelines will lead to better and more consistent care with a greater regard for patient desires and beliefs.

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Managing pain and agitation in the critically ill—Are we there yet?*

Historically, pain and agitation have been inadequately managed in critically ill patients (1, 2). During the past decade, there has been improving awareness of the liabilities imposed by poor management (3, 4). In fact, the number of articles related to agitation and pain in the ICU found by searching Medline has nearly doubled during the past decade, compared with the previous decade. Increased risks and costs associated with inadequate treatment have been identified, including unplanned extubations and line removals, longer intensive care unit (ICU) stays and duration of mechanical ventilation, and the even the likelihood of developing posttraumatic stress disorder (5–7). Pain and anxiety can contribute to agitation (8). There are multiple effective therapies available to manage pain, anxiety, and agitation. Despite an increasing awareness of the negative impact of these conditions, we have made only small advances in the past decade. The term *therapies* is intended in its broadest context—medications; injections; topical agents; modalities such as heat, cold, massage, or transcutaneous electrical nerve stimulation; cognitive therapies; and music. All have been shown to provide potential benefit in pain and/or anxiety conditions. The availability of a wide range of treatment options in conjunction with the recognized importance of adequate management provides a

***See also p. 1691.**

Key Words: pain; agitation; sedation; analgesia; intensive care unit; practice guidelines

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mandate to better understand, evaluate, and manage agitation, pain, anxiety, and delirium in the critically ill patient.

Efforts have been made to establish practice guidelines (9). Yet, few studies have attempted to evaluate the impact of a systematic approach to evaluation and treatment of pain and anxiety or any associated changes in outcomes (10–12). In the current issue of *Critical Care Medicine*, Dr. Chanques and colleagues. (13) endeavor to do just that. The authors used a two-phase prospective, controlled design to assess current practice in a university hospital ICU (control group). They implemented an educational program and, subsequently, a protocol for the evaluation of pain and agitation. Dr. Chanques and colleagues were able to show a significant decrease in the number of severe events, as measured by the numerical rating scale for pain and the Richmond Agitation Sedation Scale for agitation. The intervention group had significantly more daily ratings for both pain and anxiety than the controls. More patients in the intervention group received medications, but the duration of hypnotic and analgesic infusions was significantly lower. This suggests that regular assessments resulted in more adjustments to medication doses, both increases and decreases. The protocol led to a better match between pain or anxiety levels and subsequent treatment. Perhaps, more importantly, the authors were able to document clinically relevant outcome effects. There were substantial decreases in nosocomial infection rates as well as hours of ventilation. Although the authors did not perform an economic analysis, it takes little imagination of realize that this is a potentially momentous finding.

One could question the assessment tools used by Dr. Chanques and colleagues. Studies comparing various scales including Richmond Agitation Sedation Scale, the Sedation-Agitation Scale, the Behavioral Pain Scale, and others have shown no clear advantage to a particular instrument (14). Even bispectral electroencephalographic analysis (BIS), an expensive technology, offers no significant edge (15). The most recent version of this, BIS-XP, has shown better correlations with the Richmond Agitation Sedation Scale and the Confusion Assessment Method than has BIS 3.4 regarding level of arousal, but BIS has been unable to identify the presence or absence of delirium (16).

I submit that the specific evaluation tool is less important than the education of nurses and physicians. Dr. Chanques and colleagues have shown us that by training nurses to recognize significant events, educating physicians about evaluation and management of pain and agitation, and defining a systematic method for assessment and subsequent response, the incidence of severe pain and severe agitation could be significantly decreased. As we continue to search for ways to provide better care for our patients with ever fewer resources, it becomes clear that we cannot afford to continue to manage our patients' discomfort and distress in a random manner. The incorporation of systematic education, evaluation, and management protocols for pain and agitation should be a standard in all ICUs. How often can we institute such a simple and inexpensive intervention that can decrease the rate of nosocomial infections by 50%? Do the math. The implications are staggering. Using a simple assessment process and education, Dr. Chanques and colleagues have shown that attention to pain and agitation coupled with appropriate intervention can make a difference. This article is a notable step toward the goal of universal, effective pain and anxiety management for our sickest patients.

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Medical emergency teams: Are improved outcomes really like day and night?*

Previous studies have shown that >80% of in-hospital cardiac arrests were preceded by vital sign abnormalities (1). In an effort to reduce these high mortality arrest events, medical emergency teams (METs) have been implemented in many United States hospitals. Criteria for MET calls have been developed, focusing mainly on vital sign abnormalities and neurologic change. Any hospital employee can make calls to the team when there is concern that a patient may require intensive care or is at risk for impending cardiac arrest. Usually composed of a critical care physician, nurse, and respiratory therapist, these teams serve as a "precode" consult service, responding to the clinical changes often preceding cardiopulmonary decompensation and implementing interventions to reduce both morbidity and mortality due to cardiac arrest.

The data demonstrating the impact of METs in reduction of intensive care unit (ICU) transfers and in-hospital cardiac arrests are variable. Buist et al. (2) demonstrated a 50% reduction in the incidence of unexpected cardiac arrests when a MET was used. In addition to showing a reduction of in-hospital cardiac events, Bellomo and colleagues (3) demonstrated decreased ICU admissions, postoperative death, and postoperative length of stay when a MET system was implemented. However, the 2005 data from the MERIT study, the largest randomized controlled trial evaluating the role of METs in reducing in-hospital cardiac arrests, were less convincing (4). The only statistically significant difference between METs and control hospitals was the number of calls before unplanned ICU admission. In addition, the MERIT study demonstrated that only 30% of calls were for patients who fulfilled MET criteria or were eventually admitted to the ICU.

In this issue of *Critical Care Medicine*, Dr. Galhotra and colleagues (5) examine the role of time of day and day of week, as well as patient monitoring, on MET events and cardiac arrests. This study raises an interesting question: Is there a diurnal variation to MET calls as well as cardiac arrests and, if so, is this related to hospital staffing, patient monitoring, or a combination of the two?

In this study, MET activation events occurred more frequently during the day (between 7 am and 7 pm) in both monitored and unmonitored units, with the highest number of calls occurring on monitored units (i.e., step-down units and telemetry areas). The authors suggest this may be due to the arrival of "fresh" medical personnel in the morning and the detection of at-risk patients who may not have been recognized overnight. Overall, there was no diurnal variation for cardiac arrests, with a mean event rate of 2.93 per 100,000 beds per hour (regardless of the time of day, day of week, or the level of monitoring). Further analysis assessed the role of monitoring on MET events and cardiac arrests. There was not significant variation in the diurnal nature of the calls based on patient monitoring, and the majority of MET events occurred on monitored units, regardless of the time of day. The greatest variation in MET calls occurred on unmonitored units, with the authors suggesting the existence of a "sick hospital syndrome," one in which both staffing and monitoring capabilities have an impact on the quality of patient care. Within the ICU, there was no variation of either MET events or cardiac arrests based on the time of day or day of week, further suggesting that a higher level of monitoring and staffing play a role in identification of at-risk patients.

The question posed by the authors has significant implications for hospital resource allocation. However, there is no discussion in this study of the outcomes of the MET events. Whether MET events are more frequent, but no more clinically significant, during daylight hours is vital in interpreting the significance of this data. If the results of the study indicate that more patients deteriorate during the day, leading to ICU transfer and cardiac arrest, then the results of this study indicate a need for increased daytime resources to care for these patients. On the other hand, if daytime calls to the team include patients who do not meet criteria, then the findings imply the need for further staff education. With the efficacy of METs not yet fully established by available data, further research on this topic should evaluate both the staffing implications of MET teams as well as the role of METs in preventing patient decompensation.

Medical emergency teams are increasing in popularity in an effort to reduce unexpected in-hospital cardiac arrests. The conclusion of the current study is that staff recognition of physiologic signs of impending cardiopulmonary collapse appears to be the most crucial component of a successful MET program. With improved staff education to correctly identify patients at risk, unexpected in-hospital cardiac arrests can be reduced. Future research on interventions to improve identification of at-risk patients would facilitate determining the effectiveness of the MET system in improving patient outcomes. Until the effectiveness of METs is supported by adequate data, further research should be focused on both the staffing implications of MET teams and the role of METs in improving patient outcomes.

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*See also p. 1700.

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Beta-2–agonist treatment as a potential therapy for acute inhalational lung injury*

Acute lung injury and adult respiratory distress syndrome (ALI/ARDS) are major causes of morbidity and mortality in critically ill patients who have been exposed to a variety of direct and indirect pulmonary insults (1). Clinically, patients with ALI/ARDS present with bilateral lung infiltrates and arterial hypoxemia in the absence of clinical evidence for left atrial hypertension (2). The only proven treatment that reduces mortality in ALI/ARDS is a lung-protective ventilation strategy with a low tidal volume (6 mL · kg^{-1} · predicted body $weight^{-1}$) and a plateau pressure of $<$30 cm H_2O (3). However, some pharmacologic treatments have demonstrated efficacy in preclinical studies in animal models of lung injury, including β2 adrenergic agonists (4, 5).

One cause of acute lung injury is inhalation injury from smoke and associated toxic particles. In general, care for these patients has been limited to supportive measures with lung-protective ventilation, judicious fluid management, and appropriate use of antibiotics. However, a new experimental study in this issue of *Critical Care Medicine* by Dr. Palmieri and colleagues (6) suggests that β2-agonist therapy may reduce the quantity of lung edema after smoke inhalation.

In this study, Dr. Palmieri and colleagues (6) evaluated the effects of a nebulized β2-agonist (albuterol) administered to sheep with severe inhalation injury from smoke. Anesthetized, instrumented sheep were given a 40% total body surface area burn and then exposed to smoke inhalation via a modified bee smoker filled with 40 g of burning cotton toweling attached to the tracheostomy tubes. The sheep were then treated with either saline nebulization or with continuous nebulized albuterol at 20 mg/hr or at 40 mg/hr albuterol. Another group of control sheep did not receive smoke inhalation or burns but received all the same catheters and instrumentation as the other three groups of sheep.

After the burns and inhalation injury, the sheep remained ventilated with supplemental oxygen for 48 hrs. Nebulization was initiated 1 hr after the smoke and burn injuries, and fluid resuscitation was done following the Parkland formula. Pulmonary hemodynamics, arterial blood gases, airway pressures, and lung lymph flow were measured. Animals were killed 48 hrs after the injury, and lung weights and lung histology were done.

All of the sheep exposed to smoke had a marked increase in peak and plateau airway pressures consistent with both an increase in airway resistance and the development of pulmonary edema. The peak and plateau airway pressures were significantly decreased by approximately 30% with both doses of albuterol. Oxygenation as measured by the Pao_2/Fio_2 ratio and the pulmonary shunt fraction were significantly improved by albuterol at all the doses. The administration of albuterol did significantly increase heart rate in the sheep that received the 40-mg/hr dose compared with the saline group, but the other hemodynamic pressures and the cardiac outputs were not different between these two groups.

Perhaps most interestingly, the increase in lung lymph flow, a measure of transvascular fluid flux in the lung (7), was significantly attenuated in the sheep that received albuterol. Also, in the sheep that received 40 mg/hr albuterol, the lung permeability index, a measure of lung endothelial permeability to protein derived from the lymph flow and protein concentration in the lymph, was significantly decreased. The lung wet-to-dry weight, a measure of pulmonary edema, was significantly decreased in the sheep that received either dose of albuterol. The untreated sheep has an extravascular lung H_2O of 7.0 g H_2O/g dry weight compared with 5.8 g H_2O/g dry weight in the 40-mg-albuterol dose and 6.6 g H_2O/g dry weight in the sheep treated with the 20-mg dose ($p < .05$ by analysis of variance).

Thus, treatment of acute smoke inhalation injury in sheep with a β2-agonist, albuterol, resulted in improved lung physiology as assessed by airway pressures and oxygenation and also a reduction in pulmonary edema, apparently in part by reducing lung vascular permeability to protein. The authors did not explore the mechanisms by which albuterol reduced lung vascular injury. There are several studies that have reported significant anti-inflammatory effects of β2-agonists, including a decrease in the release of mast cell mediators, a decrease in T-cell activation, and reduced neutrophil-mediated injury (8). Furthermore, β-agonists increase the resolution of alveolar edema by upregulating the transport of sodium and fluid by several mechanisms, including an increased sodium- and potassium-activated adenosine triphosphatase activity and an enhanced uptake of sodium by apical channels on lung epithelium (9).

The importance of this experimental investigation by Dr. Palmieri and colleagues (6) is that albuterol is already available and utilized in critically ill pa-

***See also p. 1719.**

Key Words: burns; inhalation injury; airway obstruction; beta agonists; acute lung injury; gas exchange; alveolar epithelium

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tients and could be tested in patients with ALI/ARDS. One recent small phase II trial of 40 patients reported that intravenous salbutamol (albuterol) can reduce lung H_2O in patients with ALI/ARDS, although there were some patients who developed supraventricular arrhythmias with the intravenous administration of albuterol (10). There is also evidence that use of an inhaled β2-agonist can reduce the severity of high-altitude pulmonary edema in subjects who are prone to develop it (11). The results of this study also match studies of another inhalation injury model from chlorine gas in which β2-agonists reduced lung injury (12).

Because of the encouraging results from experimental studies such as the one by Dr. Palmieri and colleagues (6) in this issue of *Critical Care Medicine* and the favorable results in a small clinical trial (10), the National Heart, Lung, and Blood Institute ARDS Network is planning to conduct a large, multicenter, prospective clinical trial to test the potential efficacy of aerosolized albuterol in ventilated patients with ALI/ARDS. Albuterol could be an effective treatment to reduce pulmonary edema in patients with ALI/ARDS, both by reducing formation of edema and enhancing the resolution of alveolar edema. However, an adequately powered, double-blind, randomized clinical trial is needed to assess this possibility before it can be recommended for clinical use.

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Do coagulation abnormalities contribute to sepsis associated organ failure?*

Activation of coagulation cascades has been postulated to play a major role in contributing to morbidity and mortality associated with severe local infection and systemic sepsis. In these settings, endothelial damage leading to microvascular dysfunction was hypothesized to produce altered tissue perfusion and local inflammatory responses that together resulted in clinically significant organ dysfunction, such as acute lung injury. Several agents with potent anticoagulant properties, including recombinant human activated protein C, tissue factor pathway inhibitor, and antithrombin, have been examined in large clinical trials, with only recombinant human activated protein C showing benefit, and then only in patients with high risk of death. The largely negative results associated with interruption of coagulation cascades in patient studies has brought into question the importance of such pathophysiologic mechanisms in producing organ dysfunction in critically ill patients.

The article by Dr. Rijneveld and colleagues (1) in this issue of *Critical Care Medicine* provides further insights into the possible association or lack thereof between infection-induced coagulation alterations and inflammation. In this study, elevated levels of activated factor VII (FVIIa), tissue factor, and thrombin-antithrombin complexes (TATc) were found in bronchoalveolar lavage fluid from the infected segments of the lungs in patients with pneumonia. Mice with pneumococcal pneumonia also showed increased tissue factor expression as well as TATc in bronchoalveolar lavage fluid. However, whereas inhibition of the tissue factor pathway in *Streptococcus pneumonia*-infected mice corrected coagulation abnormalities in the lung, there was no effect on mortality from pneumococcal pneumonia or pulmonary inflammatory responses, as determined by neutrophil accumulation in the lungs or levels of macrophage inflammatory protein-2 or keratinocyte-derived chemokine, two

***See also p. 1725.**

Key Words: coagulation cascade; infection; sepsis

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murine CXC chemokines that are related to interleukin-8, an important mediator of pulmonary inflammation in human acute lung injury. Interestingly, recent studies with recombinant human activated protein C (rhAPC) showed similar results, with rhAPC being able to affect coagulation alterations found in the lungs of human volunteers exposed to pulmonary lipopolysaccharide, but without modulating cytokine release (2, 3). However, in those studies, rhAPC did decrease neutrophil accumulation into the airspaces, apparently by inhibiting the movement of neutrophils to proinflammatory mediators, such as interleukin-8.

Previous studies using animal models of sepsis had shown that interruption of tissue factor related events resulted in improved survival and less organ system dysfunction. For example, in baboons infused with bacteria, administration of tissue factor pathway inhibitor (TFPI), a recombinant protein that binds to activated factors VII and X to block tissue factor associated signaling, improved survival, decreased circulating proinflammatory cytokine levels, and diminished the severity of organ injury compared with placebo-treated animals (4, 5). Similar beneficial effects were found in baboons treated with anti-tissue factor antibodies in the setting of bacteremia (6). However, TFPI showed no effect on circulating cytokine levels when given to humans exposed to intravenous lipopolysaccharide, even though it completely prevented the endotoxemia-induced coagulopathy (7). At least one possible explanation for these apparently disparate findings is that the animal models in which TFPI or anti-tissue factor antibodies showed efficacy are characterized by the rapid development of profound disseminated intravascular coagulation. Evidence of disseminated intravascular coagulation is found in almost all patients with sepsis and organ dysfunction, as shown by increased circulating levels of D-dimers and TATc, as well as diminished concentrations of protein C and antithrombin (8). However, the degree of activation of coagulation cascades in septic patients is generally less than that present when animals are treated with large infusions of bacteria or high doses of lipopolysaccharide. The efficacy of such anti-tissue factor therapies in the preclinical setting, but not in large clinical trials, may therefore reflect the selection of animal models that do not duplicate the pathophysiologic alterations found in patients with severe sepsis.

The results of Dr. Rijneveld and colleagues take on additional significance in the context of a large ongoing clinical trial that examines the use of TFPI in patients with severe pneumonia. Whereas the phase III TFPI study was negative in the overall group of enrolled septic patients (9), a retrospective analysis suggested benefit in patients with a pulmonary site of infection. In the past, such subset analyses from sepsis trials have not translated into positive results when the group that appeared to respond to the therapy was examined in a prospective manner. The fact that inhibition of tissue factor did not improve survival in a relevant animal model of pneumonia raises additional concern about the potential therapeutic benefit of TFPI in this clinical setting.

Tissue factor plays a primary role in the initiation of the extrinsic coagulation cascade, a series of events often associated with endothelial injury, as is postulated to occur in sepsis. Although the article by Dr. Rijneveld and colleagues adds to the increasing evidence that therapies able to block tissue factor may be ineffective in sepsis, there is still reason to believe that other approaches that modulate coagulation, such as rhAPC, may reduce inflammatory processes and organ injury in this setting. An ongoing question with rhAPC, however, is how much of its benefit is really due to effects on coagulation vs. other actions that are entirely distinct from such properties. Recent evidence indicates that rhAPC decreases neutrophil and monocyte chemotaxis through interaction with the same receptor as had previously been described on endothelial cells (endothelial protein C receptor) (2, 10). This ability of rhAPC to decrease movement of neutrophils toward a proinflammatory gradient, such as that established in the airways by release of bacterial products during pneumonia, has been shown to occur at relevant therapeutic doses in humans exposed to pulmonary lipopolysaccharide (2). Other mechanisms induced by rhAPC that are distinct from its anticoagulant effects, such as induction of signaling through protease activated receptor-1 on endothelial cells, have been hypothesized to contribute to its benefit in sepsis (11).

Although most therapeutic trials have approached sepsis as having common pathophysiologic events leading to organ failure and contributing to mortality, there has been growing appreciation of the heterogeneity of signaling pathways activated by severe infection. Peripheral blood mononuclear cells from humans demonstrate stable patterns of response to lipopolysaccharide that result in a wide spectrum of cytokine release and gene expression profiles (12). Similarly, varying activation of the transcriptional factor nuclear factor-κB has been found in patients with sepsis-induced acute lung injury and is associated with outcome in this setting (13). The diversity of cellular responses in patients clinically characterized as being "septic" is likely to reflect multiple genetic factors as well as the differing microorganisms and sites of infection in such patients. Given the likelihood that differing cellular pathways are activated in patients with severe infection, it is difficult to propose individual therapies that may be of benefit for all septic patients. Rather, an important future direction in the treatment of sepsis will be to identify specific pathways that are activated in each patient and then to choose therapies tailored to those cellular alterations. Such an approach is presently being used in oncology, where chemotherapeutic regimens are based on tumor gene array profiles. In teasing apart the multiplicity of cellular alterations that are likely to lead to organ dysfunction in sepsis, there may well be a role for tissue factor inhibition in specific settings. However, much additional future work will be necessary to identify these situations.

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To breathe or not to breathe: Is spontaneous ventilation the answer for acute lung injury?*

Hypoxemic respiratory failure and the almost invariable need for mechanical ventilation characterize the early presentation of acute lung injury (ALI) and the acute respiratory distress syndrome. Although oxygenation, as a marker of lung function, has not been shown to be strongly predictive of mortality in early ALI (1, 2), outcomes have been linked to abnormal respiratory compliance and deadspace (3). Furthermore, since the greatest danger posed to patients with ALI is the development of multiple organ failure (4), establishing supportive ventilation modes that optimize hemodynamic function and oxygen delivery remains a worthy objective for research in this field. The physiologic shunt that is responsible for refractory hypoxemia in ALI is believed to be, at least in part, due to a predominance of alveolar collapse within the gravitationally dependent regions of the lung (5) without a compensatory decrement in perfusion to these regions. Partial support modes of ventilation can effectively help unload respiratory workload, while allowing for variable degrees of spontaneous breathing (6), and have been shown in previous studies to improve aeration and ventilation/perfusion ($\dot{V}_A/\dot{Q}$) matching within dependent lung regions (7). This latter effect is believed to be due to more pronounced transpulmonary pressures generated within dependent lung regions by an actively moving diaphragm. Importantly, from a translational perspective, studies have also shown that noninvasive partial support ventilation can be used safely to treat acute respiratory distress syndrome in the clinical setting (8). Thus, it is important to determine which partial support modes best improve alveolar recruitment and minimize shunt associated with the typical supine positioning of these patients.

In this month's issue of *Critical Care Medicine*, Dr. Henzler and colleagues (9) present an elegant study comparing the effects of pressure controlled mechanical ventilation (PCV) with those of various modalities of partial support ventilation on breathing pattern, gas exchange, $\dot{V}_A/\dot{Q}$ matching, and hemodynamic function in pigs following saline-lavage lung injury. This was a randomized crossover study, in which PCV, pressure-controlled assist ventilation (P-ACV), bilevel positive airway pressure (BIPAP), and pressure support ventilation (PSV) were each applied in a random order, with equal inspiratory and positive end-expiratory pressures. The authors conclude that all partial support modes were superior to PCV in maintaining oxygenation and hemodynamic function with reduced overall sedation needs. Among the partial support modes, only BIPAP resulted in a significant reduction in shunt. PSV actually resulted in greater deadspace ventilation, due to more rapid and shallow breathing. On the other hand, P-ACV preserved oxygenation and hemodynamic function with deadspace comparable to that of PCV and BIPAP. The finding of lower deadspace during P-ACV compared with PSV was attributed to the time-cycled inspiratory phase of P-ACV, which led to a more preserved inspiratory time and tidal volume.

Although the authors' findings support anecdotal experience, there is limited available literature on sedation requirements during partial support modes of ventilation. Without defining the guidelines for sedation dosing, it is unclear from the Methods section why PCV led to higher sedation requirements than the partial support modes. Curiously, although all partial support modes were associated with less sedation and improved hemodynamics, this does not appear to have been due to an improvement in cardiac function during spontaneous breathing, as demonstrated in previous studies (10). Although there was a trend toward increased cardiac output during partial support modes, this trend was more the product of an increased heart rate than an actual increase in stroke volume. This suggests that the "preservation of hemodynamic function" during partial support ventilation was primarily due to the suppressive effects of sedation on heart rate during PCV. The authors point out that the partial support modes resulted in lower mean pulmonary artery pressure and pulmonary vascular resistance when compared with that measured during PCV, and they imply that

***See also p. 1738.**

Key Words: ventilation-perfusion ratio; adult respiratory distress syndrome; positive-pressure respiration; artificial respiration

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this was due to a reduction in mean intrathoracic pressures during spontaneous breathing. This in theory should result in improved cardiac filling and hemodynamics. For unclear reasons, however, these findings did not translate into a significantly improved stroke volume in this study. Importantly, pulmonary hypertension is a known predictor of mortality in ALI (11). Although it remains unclear whether this represents a direct causal effect or is simply a marker of advanced disease, it has been shown that pulmonary hypertension can lead to increased loading and dysfunction of the right ventricle in these patients (11, 12). Hence, the reduction in pulmonary vascular resistance and mean pulmonary artery pressure during partial support ventilation may be this study's greatest endorsement for the use of these modes in patients with ALI.

With respect to the central focus on the study, the authors relate the improvement in oxygenation during partial support ventilation modes to changes in shunt and alveolar deadspace by using the multiple inert gas elimination technique. Interestingly, all partial support modes resulted in less shunt than during PCV, but this only reached statistical significance during BIPAP. However, it is unclear why BiPAP only led to a modest redistribution of perfusion from regions of absolute shunt to regions of low $\dot{V}_A/\dot{Q}$, whereas preceding studies have demonstrated a more dramatic increase in perfusion to regions of normal $\dot{V}_A/\dot{Q}$ during support with BiPAP (10). This discrepancy could be due to the current investigators' use of a saline lavage injury model. This may have resulted in less alveolar instability in gravitationally dependent lung (13) when compared with the oleic acid injury model that was used to demonstrate the benefits of spontaneous breathing in previous work (7, 10). It is also interesting to note that although BIPAP led to a decrease in shunt, presumably by recruiting regions of dependent atelectasis, breath sounds in the dependent regions were not significantly improved during this mode. Of course this incongruity could simply represent a reduced sensitivity of physical exam findings relative to that of Pa_{O_2} measurement and the inert gas elimination technique.

Curiously, the primary conclusion of the study is that "P-ACV preserves oxygenation and hemodynamic function with less respiratory effort compared with BIPAP and reduces the need for sedation compared with PCV." This seems a somewhat biased endorsement of P-ACV over BIPAP when the latter was associated with the greatest improvement in Pa_{O_2}, oxygen delivery, and cardiac output and the greatest reduction in shunt. Admittedly some of the improvement in oxygenation during BIPAP was likely due to the increased intrinsic positive end-expiratory pressure during this mode relative to all others. Furthermore, the pressure tracings and visual analog scale employed in this study demonstrated improved patient-ventilator synchrony and reduced work of breathing during P-ACV relative to BIPAP. However, it is unclear whether a reduction in work of breathing, although a worthy objective, is as important a goal as improved oxygen delivery and hemodynamic function.

Regardless of the endorsement of one partial support mode over another, I believe this study makes yet another important argument to reappraise the traditional use of deep sedation and controlled mechanical ventilation in the support of patients with ALI. In fact, if spontaneous breathing during partial support modes reduces shunt by increasing ventilation to the dependent regions of the lung (7), then one must reflect on whether spontaneous ventilation could also help protect the lung from added lung injury. Through the promotion of more homogeneous aeration, spontaneous ventilation may in fact help achieve what recruitment strategies are intended to accomplish: improvement in oxygenation with attenuation of added injury from regional overdistention and prolonged alveolar closure. Through the promotion of improved oxygen delivery and regional aeration, spontaneous breathing during partial support ventilation could represent a means to prevent both multiple organ dysfunction and ventilator-induced lung injury. Considering the demonstrated clinical benefits of daily sedation interruption (14), the reduction in sedation requirements during partial support ventilation in the present study makes an even greater case to further study the use of these modes in patients with ALI.

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Sepsis and stretch: Synergistic effects on alveolar epithelial cell death?*

Acute lung injury (ALI) and adult respiratory distress syndrome (ARDS) are major causes of acute respiratory failure in critically ill patients. There is recent evidence that there are approximately 200,000 cases per year in the United States alone, with a mortality rate of approximately 40% (1). Mechanical ventilation is a critical component in the supportive treatment of ALI/ARDS. However, it has been recognized in both experimental and clinical studies that higher tidal volumes and elevated airway pressures exacerbate the underlying lung injury. The most convincing evidence for this conclusion derives from a multiple-center, randomized trial in which ALI/ARDS patients who received lower tidal volume ventilation (6 mL/kg predicted body weight) and a plateau pressure limit <30 cm H_2O had significantly improved survival compared with patients who received a higher tidal volume (12 mL/kg predicted body weight) (2). The mechanisms that account for the deleterious effects of the higher tidal volumes and higher airway pressures that were commonly used in the past have been the subject of several experimental and clinical studies.

Excessive lung stretch can activate intracellular pathways that lead to the production of proinflammatory cytokines that may worsen the severity of lung injury and predispose to nonpulmonary organ dysfunction when there is systemic release. Tremblay et al. (3) provided evidence that mechanical ventilation could worsen lung injury by up-regulating the inflammatory response in an *ex vivo* rat lung preparation using endotoxin. In the rats that received endotoxin and excessive lung stretch, there was a higher production of proinflammatory cytokines (tumor necrosis factor-α, macrophage inflammatory protein-2, and interleukin [IL]-6) in the bronchoalveolar lavage fluid. Subsequent work confirmed that injurious ventilation of lungs isolated from septic rats led to higher levels of bronchoalveolar lavage proinflammatory cytokines (4). Based on these studies, the potential cellular sources of the stretch-induced inflammatory response included alveolar macrophages, vascular endothelial cells, and alveolar epithelial cells. One group reported that stretch of monocytes transcriptionally up-regulated the production of IL-8, a major neutrophil chemotactic factor (5), whereas other investigators have found that rat alveolar epithelial cells release IL-8 in response to mechanical stretch (6, 7). Therefore, alveolar epithelial cells have the capacity to translate mechanical stress into inflammatory signals that may play a role in the pathogenesis of ALI/ARDS. The experimental data have recently been confirmed in a clinical study by Parsons et al. (8) in which lower levels of IL-8 and IL-6 were measured in the plasma of patients ventilated with the lower tidal volume strategy. Similarly, another clinical study reported lower inflammatory responses in the bronchoalveolar lavage and plasma of patients with ARDS treated with reduced tidal volumes (9). Thus, enhanced release of proinflammatory cytokines occurs in the presence of excessive lung stretch, especially in the injured lung, and can be attenuated by protective lung ventilation.

Other work has focused on how different aspects of the mechanical stress may alter alveolar epithelial cell viability. Tschumperlin et al. (10, 11) found that alveolar epithelial type II cell viability was reduced by higher magnitudes of stretch or deformation. In this issue of *Critical Care Medicine*, Dr. Levine and colleagues (12) tested the hypothesis that rat alveolar epithelial type II cells isolated from septic rats would be more susceptible to injury than type II cells from nonseptic rats. The rats were randomized to either cecal ligation and puncture or a sham laparotomy, and after 24–48 hrs alveolar epithelial cells were isolated and cultured for 48 hrs and then exposed to increasing levels of mechanical stretch. High levels of cyclic stretch alone led to increased cell death in the sham group. However, the cells isolated from septic rats were more vulnerable to the cyclic stretch and there were higher rates of cell death in this group vs. the sham rats at both moderate and high magnitudes of deformation. In addition, nuclear factor-κB was activated by both high-magnitude stretch and sepsis independently as well as when both conditions were applied to the same cells. This finding suggests that sepsis and cyclic stretch may have additive effects on proinflammatory signaling, although the data in this study do not specifically support this conclusion. Furthermore, there was not a clear correlation demonstrated between nuclear factor-κB activation and cell death.

The results are interesting because they provide evidence that alveolar epithelial cells are especially vulnerable to mechanical stress if they have been recently exposed to an *in vivo* environment of bacterial induced inflammation. The most impressive result of the study was the evidence that cell death more than doubled in alveolar epithelial cells exposed to sepsis and mechanical stretch vs. cells that were only stretched. The authors were not able to identify specific mechanisms of cell death beyond the broad categories of apoptosis and necrosis. However, whatever the mechanisms for the enhanced death of alveolar epithelial cells, the loss of a functional alveolar epithelium plays a pivotal role in the pathogenesis and severity of ALI based on studies by Bachofen and Weibel (13) as well as more recent studies by our own group (14). Specifically, injured alveolar epithelium is associated with impaired alveolar fluid clearance (15) and facilitates translocation of bacteria and cytokines to the systemic circulation, poten-

***See also p. 1746.**

Key Words: ventilator-induced lung injury; sepsis; acute lung injury; acute respiratory distress syndrome; pulmonary edema

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tially leading to multiple system organ failure (16).

Although this study advances the field, the relative contributions of other resident lung cell types, such as endothelial cells and alveolar macrophages, to the pathogenesis of mechanical injury to the lung warrant further study. In addition, as the authors themselves point out, it is unclear whether the *in vitro* system used in this study to induce mechanical injury in cultured cells reliably replicates *in vivo* pathophysiology. This model of mechanical cell injury produces a homogeneous degree of stretch to the cells, whereas in the *in vivo* setting mechanical lung injury is not homogeneous since different regions of the lung are exposed to different distending pressures. Nevertheless, this study by Dr. Levine and colleagues (12) provides new evidence that the alveolar epithelium is especially susceptible to cell death in the presence of a combined insult from both systemic infection and mechanical stretch.

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L-Arginine and vasopressor agents: When antagonists have unexpected synergistic effects*

Recent studies suggest that microcirculatory alterations play a major role in the development of sepsis-induced multiple organ failure (1, 2). We have recently demonstrated in patients with septic shock that the sublingual microcirculation is markedly altered and that these alterations include absent and intermittent blood flow in various capillaries, while blood flow in larger vessels is still preserved (1). Furthermore, the addition of a topical vasodilatory agent, acetylcholine, was able to totally reverse these alterations (1). These data suggest that vasodilatory agents may have a place in the treatment of sepsis. However, current practice still includes the administration of vasopressor agents to restore perfusion pressure in patients with septic shock. The choice of the ideal vasopressor agent is highly debated. Adrenergic agents are used as first-line agents in most cases, but several studies have suggested that vasopressin may be added to adrenergic vasopressor (3), even though there is a fear that this strong vasopressor agent may further impair tissue perfusion.

An unanswered question concerns the effect of different vasopressor agents on the already altered microcirculation in patients with septic shock. This question is quite difficult to answer in septic patients, as it would require allowing these patients to remain hypotensive during the time required for the investigation of the microcirculation. A second important question is whether vasodilatory agents may improve the microcirculation in septic shock, and if beneficial effects are observed, whether these would counterbalance the effects of vasopressor agents or whether these may be impaired by the con-

***See also p. 1752.**

Key Words: microcirculation; nitric oxide; vasopressor agents; arginine; vasopressin

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comitant use of vasoconstrictive agents. The data presented in this issue of Critical Care Medicine by Dr. Nakajima and colleagues (4) in an experimental model of septic shock put some new light on these aspects.

In mice submitted to endotoxic shock, Dr. Nakajima and colleagues (4) investigated the effects of norepinephrine, vasopressin, and L-arginine on the perfusion of gut villi (assessed by intravital videomicroscopy). Blood pressure decreased after endotoxin administration in all groups and was restored in norepinephrine- and vasopressin-treated animals (this was expected as both agents were titrated to restore baseline blood pressure levels), whereas it further decreased in animals receiving L-arginine. Thereafter L-arginine was also added to norepinephrine or vasopressin but did not alter blood pressure in these animals. Villus perfusion decreased after endotoxin; norepinephrine and vasopressin similarly prevented the further decrease that occurred in control animals. L-arginine alone decreased blood pressure but also prevented the decrease in mucosal perfusion. The addition of L-arginine to norepinephrine or vasopressin further improved mucosal perfusion that almost normalized.

What are the lessons of this study? First, endotoxin alters the mucosal microcirculation. This is in accordance with previous experimental (5) and human (1, 2, 6) observations. Second, vasopressor agents do not impair microvascular blood flow in sepsis. Experimental studies suggest that norepinephrine does not impair microvascular blood flow in sepsis (7). The effects of vasopressin are more controversial. Some studies suggested that vasopressin, even at low doses, can impair the mesenteric microcirculation (8), but these findings were challenged (9). We reported that vasopressin administration did not alter the sublingual microcirculation in a patient with a severe distributive shock (10), but no definitive conclusion can be drawn at this stage. Third, norepinephrine and vasopressin have similar impact on gut microvascular perfusion. This may be somewhat unexpected as several experimental studies showed that vasopressin improved cellular oxygenation in endotoxic shock (11) or outcome (12) compared with norepinephrine. Fourth, L-arginine improved mucosal microcirculation. Several authors have shown that nitric oxide plays a critical role in the maintenance of microcirculatory blood flow (1, 6, 13). We initially reported that topical acetylcholine application fully restored the sublingual microcirculation of patients with severe sepsis (1). Spronk et al. (6) subsequently showed in a small cohort of patients with septic shock that nitroglycerin infusion improved the sublingual microcirculation in patients with septic shock. The study by Dr. Nakajima and colleagues (4) nicely confirms these findings. Fifth, the microcirculatory effects of the various agents are independent of their systemic effects. Indeed, Dr. Nakajima and colleagues (4) reported that arginine improved microvascular blood flow while decreasing blood pressure when given alone or without affecting blood pressure when given in combination with the other vasopressor agents. The effects of norepinephrine are probably not related to its vasopressor effect, as pure α-adrenergic stimulation does not increase gut or liver microvascular blood flow despite correction of hypotension (14). In accordance with these findings, we recently demonstrated in patients with septic shock that changes in sublingual microvascular perfusion are independent of changes in cardiac index and changes in blood pressure during dobutamine administration (15). Finally, the effects of potent vasoconstrictive and potent vasodilatory agents do not antagonize each other but rather lead to an additive beneficial on mucosal perfusion. Hypotension is the most important limitation to the use of vasodilatory agents in septic shock, and one may fear that the introduction of vasopressor agents would annihilate the potential benefit of vasodilation. This is clearly not the case; these data suggest that the addition of a vasodilatory agent to norepinephrine or vasopressin may be of interest.

This study has several limitations. As frequently in small animal models, it was difficult to ensure that fluid resuscitation was optimized, and the effects of these agents may differ according to the volemic state. Also, cardiac output and mesenteric blood flow were not measured and changes in these variables may perhaps have occurred. Finally, and more important, the authors were unable to provide any indication that the changes in microvascular blood flow were associated with any improvement in tissue metabolism. Indeed, the proof is still lacking that these interventions aimed at improving the microcirculation were beneficial. The findings by Levy et al. (11) that vasopressin and nitric oxide inhibition can improve tissue adenosine triphosphate levels suggest that it may be the case, but other mechanisms may be involved. In particular, the administration of nitric oxide may be deleterious to organ function, especially during prolonged administration, as nitric oxide has also been involved in some of the cellular effects of sepsis. Thus it is unfortunately much too soon to treat our patients with septic shock with a combination of arginine and norepinephrine or vasopressin, but the data of Dr. Nakajima and colleagues (4) should prompt new research in this direction.

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Resuscitation with hypertonic saline in burn shock and sepsis*

We read with great interest the article by Dr. Chen and colleagues (1) in this issue of *Critical Care Medicine*. The authors have shown that hypertonic saline (HTS) decreased thermal injury induced bacterial translocation in a mouse model of burn injury with septic challenge. HTS increased bacterial clearance, phagocytic activity, and Toll-like receptor (TLR)2, TLR4, CXCR2 chemokine receptors, pp38, and p44/42 expression of peritoneal cells. HTS treatment after thermal injury decreased reactive oxygen species (ROS) production and increased TLR2, TLR4, and pp38 expression of neutrophils. *In vitro*, treatment of neutrophils with HTS increased phagocytic activity and TLR2 and TLR4 expression. Commensal depletion with oral antibiotics decreased TLR2 and TLR4 expression of neutrophils, and lipopolysaccharide increased TLR4 expression of neutrophils and decreased thermal injury-induced bacterial translocation. The authors concluded that HTS enhances host defenses to bacterial challenge through the augmentation of TLRs.

Proper fluid management is critical to the survival of the victim of a major thermal injury and when septic complications occur. Modern fluid resuscitation formulas originate from experimental studies in the pathophysiology of burn shock (2). Burn shock is both hypovolemic shock and cellular shock, and it is characterized by specific hemodynamic changes including decreased cardiac output, extracellular fluid, plasma volume, and oliguria. As in the treatment of other shock forms, the primary goal is to restore and preserve tissue perfusion to avoid ischemia. However, in burn shock, resuscitation is complicated by obligatory burn edema, and the voluminous transvascular fluid shifts that result from a major burn are unique to thermal trauma (3).

Although the exact pathophysiology of the postburn vascular changes and fluid shifts is unclear, major components of burn shock are the increase in total body vascular permeability and the changes in microcirculation. Fluid resuscitation is aimed to support the patient throughout the initial 24- to 48-hr period of hypovolemia and has existed since the early 1950s (2). Even after thousands of patients have been saved by fluid resuscitation, resuscitation formulas are still controversially discussed, depending on advantages and disadvantages for the individual patient. Crystalloid solutions, such as lactated Ringer's solution (sodium concentration 130 MEq/L) are the most popular resuscitation fluids currently used. Crystalloid formulas include the Parkland formula (recommends 4 mL/kg/% burn in the first 24 hrs, with one half of the amount administered in the first 8 hrs) and the modified Brooke formula (recommends 2 mL/kg/% burn). Colloid formulas (Evans, Brooke, Slater), the Dextran formula (Demling), and hypertonic saline formulas (Monafo, Warden) are also in use (2–4). Hypertonic salt solutions have been known for many years for effectiveness in the treatment of burn shock by fluid-sparing effects and a reduction of volume load in the early phase of injury (5, 6). Rapid infusion leads to serum hyperosmolarity and hypernatremia, reducing the shift of fluids from intravascular to interstitial areas and the third compartment and therefore preventing edema formation and the need for laparotomy and escharotomy (7–9). The use of HTS, however, is controversially discussed; not only positive effects as mentioned above have been shown but also negative ones. One comparative trial even found an increase in mortality with HTS treatment in major burns (10).

In addition to hypovolemia, the risk of infection for burn patients is extraordinarily high. Shirani and coworkers (11) showed that inhalation injury alone increased mortality rate of burn patients by a maximum of 20% and pneumonia by a maximum of 40%, with a maximum increase of approximately 60% when both are present. These data indicate that inhalation injury and septic complications such as pneumonia have significant, independent, additive effects on burn mortality and that these effects vary with age and burn size. The presence of inhalation injury and sepsis increases the fluid requirements for resuscitation from burn shock after thermal injury (12). Since Dr. Chen and colleagues (1) have demonstrated that HTS not only has beneficial effects on burn shock but also reduces bacterial translocation and enhances host defenses by several mechanisms in the treatment of burn shock and sepsis, it is of high interest to further investigate HTS in animal models and later in humans. Future studies with HTS alone and in combination with established resuscitation formulas are needed, to find a risk/benefit ratio for such a treatment. HTS may have the potential to improve resuscitation strategies and outcome in burn care.

***See also p. 1758.**

Key Words: bacterial translocation; burn; hypertonic saline; resuscitation; sepsis; shock

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Brain tissue oxygen monitoring: A measure of supply and demand*

A fundamental goal of neurocritical care is to ensure adequate delivery of oxygen to the brain at all times. Depriving the brain of oxygen rapidly results in cellular dysfunction and cell death. This conceptual model of brain ischemia has been applied to all types of brain injury, including traumatic brain injury (TBI) and subarachnoid hemorrhage. To prevent brain ischemia, critical care is designed to maintain cerebral perfusion pressure (CPP) and control intracranial pressure (ICP). Consensus values for CPP (>60–70 mm Hg), ICP (<20 mm Hg), and arterial oxygen pressure (>100 mm Hg) have been routinely employed in clinical practice. These thresholds assume that cerebrovascular pressure autoregulation, the mechanism that normally keeps blood flow and oxygen delivery in the brain constant despite changes in blood pressure, is impaired. However, recent studies suggest that some of these goal-directed treatment strategies can result in excess morbidity and mortality (1, 2). For example, in Robertson et al.'s (1) randomized controlled study comparing two treatment regimens, ICP-targeted treatment vs. goal-directed cerebral blood flow (CBF)/CPP-targeted treatment, the CBF/CPP-targeted group experienced worse pulmonary edema and adult respiratory distress syndrome (ARDS) (2) and did not benefit from this treatment. Thus, given the potential risks, it is incumbent on clinicians to accurately and reliably identify deficiencies in brain oxygenation and correct these, rather than employ arbitrary goal-directed protocols.

In the last decade, several direct measures of brain oxygenation have become clinically available. Many studies have documented an absolute reduction in cerebral blood flow in normal- and abnormal-appearing areas of the brain after brain injury (3–8) using a variety of imaging and monitoring techniques including computed tomography and magnetic resonance perfusion imaging, jugular venous oximetry, brain tissue oxygen probe, and positron emission tomography (PET). However, the reduction in cerebral blood flow does not always correlate with brain ischemia, especially after traumatic brain injury. Only PET can reliably measure ischemia using the oxygen extraction fraction (OEF). The ischemic threshold on PET OEF is a value >0.75 (9–11) or a reduction in cerebral metabolic rate of oxygen <1.4 mL/100 mL/min (12, 13). Several PET studies in neurocritical care have been done using these thresholds with conflicting results about the incidence and distribution of brain ischemia. Diringer et al. (6) found global and regional increases in OEF without reduction in cerebral metabolic rate of oxygen. Coles and colleagues (4) used oxidative PET studies in TBI patients and found that at baseline CO_2 of 30–34 mm Hg, the mean ischemic brain volume was 67 mL or roughly 6% of the total brain volume on average, and in six of 15 patients the ischemic volume averaged 50 mL, especially with induced hyperventilation. In contrast, PET imaging during hours 24–72 after TBI demonstrate a lower mean ischemic brain volume, 1.5 mL or 1.5% of total brain volume (14), and areas of low CBF were metabolically less active.

Given that PET scans are generally not available to monitor neurocritical care patients, other monitors have been developed. Principal among these are jugular

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Key Words: brain injury; ischemia; positron emission tomography; brain oxygenation; critical care; coma

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venous oximeters, brain tissue oxygen probes ($Ptio_2$). Jugular venous oximetry readings of <50% indicate brain ischemia (8). $Ptio_2$ has been used as a measure of the balance between oxygen supply and utilization, with decrements in the $Ptio_2$ value indicating a lack of oxygen supply. Unfortunately, the sensitivity and specificity of $Ptio_2$ to detect brain ischemia under clinical conditions are fair at best (15, 16) while correlating with alterations in cerebral blood flow quite readily. Despite this shortcoming, $Ptio_2$ is being used to detect brain ischemia in comatose patients with TBI and subarachnoid hemorrhage. In these settings, $Ptio_2$ <20 mm Hg is considered to be an indicator of brain ischemia. With the onset of brain death, the $Ptio_2$ drops to zero (17). Hence, $Ptio_2$ is an available on-line monitor that measures the balance between oxygen supply and demand and can be used to determine moment-to-moment changes in this balance.

It is in this context that we consider the current article by Dr. Jaeger and colleagues (18) in this issue of *Critical Care Medicine*, Dr. Jaeger and colleagues report on the use of $Ptio_2$ to measure cerebrovascular pressure autoregulation after severe TBI, with which they have a long experience. The authors used the $Ptio_2$ probe placed into normal-appearing brain on the hemisphere demonstrating the most injury and measured spontaneous fluctuations in CPP, ICP, and $Ptio_2$ during various periods of time, including 1, 6, and 12 hrs. The authors then performed a moving linear correlation analysis between the CPP and $Ptio_2$ values during these arbitrary periods and calculated derived correlational measures from these data. The two derived measures were ORx (the actual linear correlation between CPP and $Ptio_2$) and b_{PtiO_2} (the slope of the linear correlation between CPP and $Ptio_2$). As explained, ORx may vary between -1 and $+1$, with a value of 0 corresponding to intact autoregulation and no correlation between CPP and $Ptio_2$. The authors also correlated mean arterial pressure and ICP using the standard PRx correlation first described by Czosnyka et al. (19). Finally, the authors compared ORx and the classic PRx measure of autoregulation.

Using this complicated analysis, Dr. Jaeger and colleagues conclude that ORx correlated well with PRx and that in general patients with impaired autoregulation are prone to decreases in $Ptio_2$. In patients with very low or very high $Ptio_2$ values, the ORx and PRx demonstrate impaired pressure autoregulation. Hence, the $Ptio_2$ value behaved in a fashion similar to a cerebral blood flow monitor, rather than a measure of oxygen utilization. It is interesting, that under conditions of hyperemia, that $Ptio_2$ values increase, suggesting that the delivery of more blood flow does not result in a decrease in $Ptio_2$ or an increase in oxygen consumption. One caveat in this study, which was conducted during long periods of monitoring, is that changes in oxidative metabolism may have occurred between and within subjects during the period of testing, which may have affected the baseline $Ptio_2$ values as well as longer duration ORx values (ORx-6 and ORx-12). Another caveat is that pressure autoregulation can vary between normal and pericontusional regions of brain within the same subject or can vary as a function of time after injury. Nonetheless, it is clear from this study and others that $Ptio_2$ is not a simple measure of oxygen utilization and needs to be interpreted as a rough measure of the balance between oxygen supply and demand. Moreover, $Ptio_2$ can be affected by various forces including the state of pressure autoregulation.

The complicated analysis of several dynamic physiologic values (CPP, ICP, and $Ptio_2$) performed by Dr. Jaeger and colleagues illustrates the potential value as well as the complexity of advanced brain monitoring in neurocritical care. At this time, the derived measures of ORx and PRx are not practically available for the everyday intensivist or for the subspeciality neurointensivist. To use ORx, PRx, or other sophisticated derivations, both software and user-interface tools will need to be developed to be clinically useful. Currently, simple observations about the change in $Ptio_2$ after a deliberate alteration in CPP may be a practical application of the knowledge conveyed in Dr. Jaeger and colleagues' article. If an increase in CPP results in an increase in $Ptio_2$, then autoregulation may be disturbed, and a higher CPP may be optimal. Hence, the work by Dr. Jaeger and colleagues is intriguing, but the message is not easily implemented at present and calls for the development of better information technology to handle these complex data. Nonetheless, this article is influential in that it further refines the uses and limitations of the brain tissue oxygen monitoring and points to a potential use of this technology to better guide our treatment goals for comatose brain-injured patients.

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Critical illness: A view from the kidney*

In this edition of *Critical Care Medicine*, Dr. Gopal and colleagues (1) present a meta-analysis of studies comparing microalbuminuria with outcome and physiologic scores in critically ill patients. Their conclusion is that microalbuminuria may be a predictor of illness severity and mortality in the critically ill.

Microalbuminuria is pathologically significant albuminuria in the 20–250 mg/L range detectable only by sensitive immunoassay. In diabetes microalbuminuria predicts clinical proteinuria, and in affected patients, early intervention slows the progress of renal disease (2). Later studies showed that microalbuminuria is also associated with vascular risk and vascular disease in diabetic and nondiabetic patients (3).

So why should microalbuminuria be predictive of outcome in the critically ill? There is increasing evidence that microalbuminuria reflects systemic vascular endothelial dysfunction (4). The capillary endothelium plays a very early role in the response to injury or infection and is at the center of the acute inflammatory process. When this is a systemic process, the kidneys are ideally placed to detect these changes, since they receive 25% of the cardiac output and as the permeability of the glomeruli increases there is increased passage of albumin and other plasma proteins into the filtrate. Since renal tubular resorption of filtered albumin is near maximal, much of this albumin reaches the urine, the levels being further increased by the renal concentrating mechanism.

Transitory microalbuminuria occurs within an hour of trauma, burn injury, or elective surgery and is proportional to the magnitude of the insult. The finding that levels were higher in those patients who later developed complications led to the suggestion that microalbuminuria is a manifestation of increased systemic vascular permeability and may predict complications (5, 6). This concept was supported by animal and clinical studies in which increased glomerular permeability and microalbuminuria were detected in a wide variety of acute inflammatory conditions including peritonitis, acute myocardial infarction, acute pancreatitis, meningitis, and ischemia reperfusion injury (7–11). Patients suffering intermittent claudication showed transient microalbuminuria and leukocyte activation after exercise, both of which disappeared after corrective surgery (11). In addition, patients who were rendered leukopenic before cardiac bypass surgery showed a reduced microalbuminuric response to operation (12) suggesting a cell-mediated mechanism for systemic vascular endothelial activation and transient microalbuminuria.

Any clinical role for assessing microalbuminuria in the critically ill is still speculative. However, in patients undergoing cardiac bypass surgery in whom there were no significant complications, microalbuminuria 2 hrs postbypass was significantly associated with pulmonary function 12 hrs later, the duration of mechanical ventilation, and serum creatinine for the next 48 hrs (13). This demonstrates that even in uncomplicated surgery, subtle vascular endothelial changes during operation, manifest as perioperative microalbuminuria, predict later organ function, and it implies that microalbuminuria may have a role in early identification of surgical patients at risk of systemic inflammatory response syndrome (SIRS) and multiple organ failure.

The capillary endothelium reacts rapidly to the panoply of proinflammatory mediators, which are balanced by their anti-inflammatory counterparts, and a feature of SIRS is failure of this homeostatic control (14). The microvascular response and hence microalbuminuria may represent the "bottom line" of the pro- and anti-inflammatory balance sheet. To continue the accounting analogy, assessment of microalbuminuria may be a better predictor of outcome than measuring specific pro- and anti-inflammatory mediators on the "credit and debit" sides of the inflammation balance sheet. This is because inflammatory mediators have overlapping roles, so that assessment of a single mediator, even if its response was sufficiently rapid to be a potential early warning of SIRS, may have limited predictive value. The therapeutic corollary to this is that blocking an individual pathway will also be unsuccessful in a patient with SIRS. Microalbuminuria not only may provide an early warning of SIRS but also may provide a means of assessing the efficacy of those interventions designed to bring acute "runaway" inflammation back under homeostatic control.

We must be realistic about the limitations of microalbuminuria. It will not identify the cause of an inflammatory response, merely its impact on the micro-

***See also p. 1805.**

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vasculature hour by hour. It is essential that the direction of change in microalbuminuria following intensive care unit (ICU) admission is monitored. High admission levels combined with a failure to decrease toward baseline after a few hours are a sign of increased risk of ICU death (15). It is likely that microalbuminuria "action limits" at key time points after ICU admission will have to be tailored to individual patient groups. A further limitation is the contribution to microalbuminuria of preexisting primary renal disease, again emphasizing the need for monitoring the direction of change following ICU admission rather than relying on absolute values under these circumstances. The rapid turnaround required for serial monitoring can be a problem; however, it is now possible for reliable albumin creatinine ratio results to be obtained at the bedside by ICU nursing staff.

Of the ten studies analyzed by Dr. Gopal and colleagues, seven compared microalbuminuria with illness severity scores and found an association. So where do we go from here? There seems little point in further comparisons of microalbuminuria with illness severity scores, since the latter are not used to manage individual patients. More relevant questions are, Does knowledge of microalbuminuria assist in the clinical assessment of risk of ICU death? and Can this knowledge be used to improve patient outcome?

To realize the potential of microalbuminuria, a rational next step would be comparison of microalbuminuria during the first few hours after ICU admission with outcome in clinically defined patient groups. From these results, microalbuminuria cutoff values at defined time points following ICU admission need to be established for predicting outcome in each patient group. Finally, prospective randomized studies should be conducted where interventions are targeted to at-risk patients based on clinical assessment and the degree of microalbuminuria. If this approach provides evidence of reduced ICU morbidity and mortality and better use of expensive ICU resources by, for example, "ruling in" and "ruling out" high-risk patients, only then can microalbuminuria monitoring in the ICU be justified. Dr. Gopal and colleagues are correct in their comment that presently there is no evidence base for microalbumin measurement in the ICU—but there is some promise for the future.

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