Monitoring efficacy of red blood cell transfusion in sepsis by sublingual microvascular perfusion: A tongue speaks without words*

Sepsis, because of its associated mortality, is of clinical importance. In the United States, the incidence of septic shock is estimated to range from 300,000 to 500,000 annually, with an estimated crude mortality rate of 35% (1). Organ system dysfunction is commonly associated with the poor outcome of sepsis and septic shock and has been reported to be the most common cause of death in the noncoronary intensive care unit. Early detection of tissue hypoperfusion has been of recent study as a means to prevent the development of multiple organ dysfunction. Improvements in the microcirculation have been shown in survivors of septic shock but not in those dying with multiple organ failure (2).

Red blood cell transfusion is one of the most commonly used interventions in the intensive care unit (ICU) at one time or another for severe anemia, which often occurs in sepsis. In the United States, >14 million units per year of packed red blood cells (RBCs) are administered, many of which are delivered in the ICU at the time of their transfusion (3). However, even with improvements in the circulation during sepsis, the mortality rate is still high, >50% if the patient develops severe septic shock (4). This may be due to the use of stored RBCs, which do not restore the microcirculatory oxygenation as opposed to the use of fresh RBCs (5). Therefore, the question remains: What are the effects of RBC transfusion on the microcirculation?

In this issue of *Critical Care Medicine*, Dr. Sakr and colleagues (6) investigate the effects of RBC transfusion on sublingual microvascular perfusion, as well as a possible correlation of this effect with the RBC storage time in patients with severe sepsis. Utilization of sublingual capnometry has recently become a method for detection of tissue hypoperfusion, although not widely used as of yet (7). This may be, in part, due to its limitations, including technical and artifactual difficulties. This technique works by measuring the absorption of light in hemoglobin as a function of partial pressure of CO_2. It overcomes some of the inadequacies of gastric tonometry, which include ease of use and the lack of interference of acidic gastric hypersecretion (8) but still has some pitfalls, including that sublingual mucosa may not be as susceptible to ischemia as gastrointestinal mucosa (7).

Dr. Sakr and colleagues (6) use this technique to assess the sublingual microcirculation in a group of 35 patients with severe sepsis requiring RBC transfusion. These patients fulfilled four criteria, including the following: a) requiring RBC transfusion; b) having severe sepsis; c) being euvolemic; and d) being mechanically ventilated. Hemodynamic and microvideoscopic assessments were made immediately before (baseline) and 1 hr after the transfusion of RBCs, including temperature, heart rate, arterial pressure, central venous pressure, mean pulmonary artery pressure, cardiac index, hemoglobin and lactate concentrations, $Paco_2$, Pao_2, pH, Sao_2, mixed venous saturation, oxygen delivery, oxygen consumption, oxygen extraction ratio, total vascular density, percent of vessel perfusion, perfused capillary density, and percent of capillary perfusion, and were correlated with patient age, gender, source of infection, adrenergic dose, analog sedation, ICU length of stay, 28-day mortality, sequential organ failure assessment, and Acute Physiology and Chronic Health Evaluation II scores.

This study parallels only a handful of studies published in recent years in which sublingual capnometry has been the focus on study in evaluating the microcirculation in sepsis and septic shock in a similar sample size (9). In one of the earlier studies, Rackow et al. (10) examined 25 patients with circulatory failure (19 in sepsis and six in cardiac failure) in a prospective observational study, which demonstrated that P_{slCO2} (sublingual) correlated to gastric intramucosal and lactate in cardiac failure patients while P_{slCO2} correlated to venous Pco_2 in patients with septic shock. At the same time, Marik (11) similarly found that P_{slCO2} correlated well with P_{slCO2} in a prospective validation study consisting of 22 septic patients. Marik and Bankov (12) then went on to find that the baseline P_{slCO2}-diff and P_{slCO2} could be used as predictors of outcome in tissue hypoxia and were, in fact, more responsive to therapeutic interventions in one of the larger studies, consisting of 54 ICU patients. While the therapeutic interventions studied by Marik and Bankov included resuscitation with fluids and vasopressor agents, antibiotics guided by culture results, and coronary revascularization, when indicated, they did not include RBC transfusion, which is the focus of this study by Dr. Sakr and colleagues, who are the first to examine this commonly used intervention and its effect on the microcirculation.

The results reported by Dr. Sakr and colleagues provide a good starting point from which to proceed in understanding the effects of transfusion on the microcirculation. Although they were not able to find a straightforward global effect of RBC transfusion on the sublingual microvasculature, they were able to see an improvement in sublingual microvascular perfusion in those patients who already had an altered perfusion at baseline and an opposite, deleterious effect in those patients with preserved baseline function (6). This dichotomous result prompts us to further study this effect and also to question some of the limitations of this study. Although the patient size of 35 is of the same order of patients in previous studies (2, 9–11), it is still a small sample size and subject to the sampling errors inherent in small sample sizes, which may account for the considerable interindividual variability observed. Performing a similar study on a larger scale may offer more valuable information. In addition, another limitation, as mentioned by the authors themselves, is

*See also p. 1639.

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the short duration of the study, which does not give us information about organ function and outcome. The 28-day mortality rate was determined for all of the patients, but conclusions linking transfusions and microcirculation to survival or organ function cannot be made. Although sublingual capnometry may be a better predictor of outcome than the traditional markers (11), it still warrants more study.

The issue of RBC storage is also a confounding factor. Previous studies by Van Bommel et al. (5) compared fresh RBCs with stored RBCs (28 days) and saw differences in microcirculatory oxygenation. Changes associated with RBC storage are well documented and include the loss of deformability, increased interactions with vascular endothelium compromising microvascular flow of stored RBCs, impaired oxygen unloading, and adenosine triphosphate and 2,3-diphosphoglycerate depletion (13). The clinical implications of RBC storage are somewhat contradictory, and further study is needed. Although the authors of this study did not find a relationship between RBC storage time and microvascular perfusion, it may still play a role. Also, use of hemoglobin variants, such as low-affinity red blood cells, may demonstrate more beneficial effects in transfusion (14). There may also be inherent problems in arbitrarily setting the cutoff value used to separate the groups at 8%, which warrants further validation.

It is also possible that the timing chosen for posttransfusion analysis may be too early to observe any meaningful changes with this technology. Indeed, the effects of transfusion, i.e., hematocrit, may be greatest after 1 hr but may continue to rise posttransfusion (15). Analysis at these later time points may provide more meaningful data with this promising technology. Furthermore, sepsis compromises the normal posttransfusion outcomes in that oxygen uptake, and consumption does not appear to increase by raising the hemoglobin concentration (16, 17). This may also account for the lack of observed differences in patient vs. control groups by this method, which appears to be related to co-oximetry–based technology. Another concern may be that of operator variability, which may affect result consistency. The ability to learn, maintain, and train others regarding the technical considerations and applications of this technology will no doubt affect its widespread use in the clinical marketplace.

The data presented in this study show promise in determining the microvascular effects of RBC transfusion in sepsis through the use of this relatively new technique of sublingual capnometry. Hopefully, this technology will give us the information we need for better management of critically ill patients where others fall short. The chance of survival is multifactorial in the setting of sepsis, and future studies need to be performed to study the possibility of using the microcirculation as a tool for management, as well as a predictor for outcome.

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High-volume transfusion from male-only versus female donor plasma and hypoxemia in the critically ill*

In this issue of *Critical Care Medicine*, Dr. Gajic and colleagues (1) publish an interesting study in which they compare the effects of high-volume plasma transfusion (at least three units of either fresh frozen plasma or apheresis platelets) from donors who were male only versus donors who contained at least one female with patients in the medical and surgical intensive care units. The two groups were comparable among a number of variables including pretransfusion Acute Physiology and Chronic Health Evaluation III scores, age, and female gender, with increases in patients with sepsis (20 vs. 15; $p = .441$) and renal replacement therapy (14 vs. 2; $p = .003$) in the male-only transfusion group and increases in pretransfusion pulmonary edema (26 vs. 16; $p = .082$) and pretransfusion hypoxemia (Pao_2/Fio_2, 312 vs. 318; $p = .119$) in the group transfused with female donor plasma. Both groups received a similar number of transfusions; however, there was no statistical increase in the total number of patients with hypoxemia (female containing, 71 vs. male-only, 59; $p = .345$). When one examines the median interquartile ratio consisting of 64 matched patient pairs, there was a significant increase in hypoxemia in the female-containing plasma group versus the male-only group (Pao_2/Fio_2, 228 vs. 277). It is of note that transfusion-associated circulatory overload was increased to 18 following female plasma transfusion compared with 14 in the male-only transfusion group, and when these patients with transfusion-associated circulatory overload were excluded from the analysis, hypoxemia was still increased in patients infused with female donor plasma 253 (−47) vs. male-only plasma 297 (−3.3) ($p = .039$). Paradoxically, the numbers with acute lung injury were greater in the male-only transfused group: male only, 18; female containing, 14 ($p = .584$).

These data are the first evidence that transfusion of female plasma is associated with significant hypoxemia, outside of the normal range, in a cohort of patients in the intensive care unit compared with patients who received plasma from male donors. Previous work from Palfi et al. (2) did not detail abnormal Pao_2 values, i.e., out of the normal range, following the transfusion of multiparous female plasma, although they were significantly decreased vs. those patients transfused with the male-only plasma. Despite the apparent justification for the disqualification of female plasma donors owing to increases in hypoxemia after transfusion of female plasma implied by these data, there are a number of intriguing questions, which should be addressed in a large multiinstitutional, prospective, randomized trial before instituting clinical guidelines for the transfusion of ill patients. These include the following: 1) the use of a more predictive scoring system, such as injury severity scores, for injured patients (trauma) to ensure that the patients studied are truly similar; 2) the possible effects of blood system ABO incompatibility in the transfused units; and 3) the effects of different clinical practice patterns in surgical and medical intensive care units on clinical outcomes, such as the possible effects of different ventilator and resuscitation criteria on clinical outcomes, including the number of ventilator days. Interestingly, although there were a number of new episodes of acute lung injury in this study, no patients were diagnosed with transfusion-related acute lung injury, despite the documented hypoxemia and the temporal relationship to transfusion. In addition, if female plasma has an inherent substance that causes hypoxemia in its recipient, such as antibodies directed against leukocyte antigens or activated complement, both of which have been reported in transfusion-related acute lung injury caused by fresh frozen plasma, then such mediators need to be investigated (3–6). As provocative as these results appear, it is premature to make clinical decisions about what products should be transfused based on a small cohort of patients at one institution comprised of a number of intensive care units managed by different disciplines. Last, caution in interpreting these studies needs to be implemented because 25% of patients were transfused outside the clinical guidelines for plasma transfusion at this institution.

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*See also p. 1645.

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Tools for rigorous experiments in the usual clinical environment*

Dr. Fessler and colleagues (1) attempted to develop a consensus protocol for high frequency oscillatory ventilation (HFO) of adults with severe hypoxemic lung failure. This important consensus protocol includes the literature evidence and the opinions of a handful of experienced investigators with clinical trial and HFO experience. They recognize the paucity of compelling systematically acquired HFO information and admirably attempt to balance the potential benefits of HFO with its potential harms. They based their decisions on an understanding of the potential benefits and harms of lung distention, lung recruitment, and inspired oxygen concentration. They adopted a new strategy based on lower arterial pH, higher oscillation frequency, and frequent recruitment maneuvers. They appropriately avoided the seductive use of arterial oxygenation as the arbiter of success, recognizing the dissociation between oxygenation levels and important clinical outcomes, including mortality.

Dr. Fessler and colleagues recognize the limitations of using only a small number of participants, but defend their strategy well. They were not able to reach consensus on the oxygenation rules of their strategy and their protocol includes several statements and rules that still require clinician interpretation. The protocol cannot, therefore, lead to consistently specific and replicable changes in HFO support when the input data describe a specific patient state. Nevertheless, this effort represents the closest to a replicable method for HFO that this writer has seen. They recommend their protocol as a guide for clinical care until more definitive clinical study data are available. I think this is good advice, but believe the greater contribution of their protocol will be in clinical research. The level of explicitness and detail in their HFO method should enable the conduct of more rigorous clinical investigations than possible in the past.

Human decision-making limitations make replicability of clinical research and clinical care methods difficult to achieve (2, 3). Replicability of methods deserves emphasis here. Most guidelines and protocols depend largely on bedside clinician judgment. Such judgments are inconsistent and preclude a clear understanding of the method. The experimental or clinical care method using such guidelines and protocols cannot, therefore, be reproduced. If the method cannot be replicated, the clinical experiment cannot be replicated. This fundamental scientific criterion for validation of new observations (replicability) cannot, then, be satisfied for many clinical trials (4–8). This contributes to conflicting experimental results, including those among HFO studies, and to confusion among clinicians.

Replicability is a requirement of the most credible experiments, in part because of low signal-to-noise ratio for many clinical investigations (3). The signal-to-noise ratio should be maximized, if possible, and can be increased both by increasing the signal and by reducing the noise. Detailed and adequately explicit protocols can enable consistently specific and replicable changes in support for a given set of input data (a given patient state). They can increase the signal through increased consistency and adherence to the intervention protocol rules. They can also reduce the noise by reducing variation of confounding variables that operate as cointerventions (nonexperimental interventions that can influence outcome) (3).

Cointerventions can produce systematic noise (bias) in clinical studies in subtle ways. For example, fluid assessment includes an analytical scheme that addresses three fluid and electrolyte factors: a) effectiveness of the arterial circulation; b) extracellular fluid volume; and c) state of hydration, reflected by serum osmolality or serum sodium concentration (9–12). This three-category scheme seems to be infrequently considered and applied in fluid and electrolyte problem assessment and management. Investigators commonly use these categories interchangeably, and thus contribute to confusion in the medical community. This is reflected in terms such as *dehydration*, *fluid overload*, *wet*, *dry*, *fluid down*, *inadequate volume*, etc. This confusion can lead to experimental bias, because fluid therapy can be an important cointervention in clinical trials of mechanical ventilation (13). Other frequently unrecognized cointerventions include vasodilator therapy, because different classes of vasodilators may affect arterial oxygenation differently (14).

Dr. Fessler and colleagues recognize that they have addressed only some of the important HFO requirements. They could not reach consensus on oxygenation rules, and subsequently provided two strategies for responding to arterial oxygenation with HFO. They will likely be able to address this deficiency when they acquire experience with their current HFO protocol. Their roundtable discussion and the HFO protocol it produced represents an important first step in what I anticipate will be an iterative refinement process that will lead them closer and closer to a replicable HFO method. It may be valuable to ultimately include protocol rules for those cointerventions that might alter HFO clinical outcomes and thus obscure study intervention effects. These include sedation, fluid management, and hemodynamic support. This is a large but important task that will likely bring dividends in scientific rigor and experimental result credibility.

The HFO protocol of Fessler and colleagues is an exportable decision-support tool. It can link the clinical experimental environment to the clinical care environment and enable practitioners to replicate the method used in a clinical study. This is an important facet of translational research that could contribute to a leap forward in linking usual clinical care delivery with the results of medical research. This linking of research and clinical care, and the use of their protocol in clinical research itself, will be better achieved if their rules are computerized in a user-friendly bedside electronic tool. This is work for the future, if the HFO

*See also p. 1649.

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protocol proves efficacious in their intended studies.

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Fresh frozen plasma transfusion in the critically ill: Yes, no, or maybe?*

In theory, there is no difference between theory and practice. But in practice, there is.—Jan L. A. van de Snepscheut (1953–1994)

In this issue of *Critical Care Medicine*, Dr. Lauzier and colleagues (1) evaluated in a retrospective study the consistency of the Canadian guidelines for fresh frozen plasma (FFP) administration in critically ill patients. They found that only 32.4% of the FFP orders were consistent with the guideline, while 20.0% were inconsistent but appropriate for the ICU context, and 47.6% were inappropriate. Independent determinants of inappropriate FFP administration were the presence of a less severe coagulopathy, absence of bleeding, or no planned invasive procedure.

Clinical use of FFP has increased steadily over the last 2 decades. Although the study by Dr. Lauzier and colleagues is a retrospective and single-center one, their findings are consistent with those of other studies. Dr. Dara and colleagues (2) demonstrated that 38.3% of critically ill medical patients with coagulopathy but without bleeding received FFP transfusion. Audits in a non–intensive-care-unit settings in Australia and in the United Kingdom found comparable numbers of inappropriate FFP orders (3–6). In Europe, FFP use shows considerable variation both regionally and nationally (7). In the United States, FFP transfusion has become disproportionately high compared to other countries with similar levels of health care (7). Inappropriate FFP prescription is thus considerable, not only in an intensive care context but also in general practice, which is rather surprising as there is little evidence for the clinical effectiveness of FFP (6). FFP is also the most hazardous of all blood components, even though the overall level of transfusion risk is low (8). Nevertheless, transfusion-related acute lung injury has become the leading cause of transfusion-associated mortality, although it is still underrecognized and underreported. Dr. Khan and colleagues (9) demonstrated in a retrospective cohort study that the risk for developing transfusion-related acute lung injury was twice as high in patients transfused with FFP as in those who received only red blood cells.

Albert Einstein said some decades ago, "The important thing is never to stop questioning." What do we actually know about FFP? What do we know about indications, efficacy, timing and dose of transfusion, possible adverse effects, and cost-benefit? Are guidelines evidence- or rather expert-based? Are intensivists familiar with the guidelines? Regarding the substantial inappropriate use of FFP, it seems important to reflect on these questions. Therefore, the main strength of the study by Dr. Lauzier and colleagues lies in the information gained by observation of daily practice patterns of FFP orders (1). The large number of inappropriate or possibly inappropriate FFP administrations confirms the need for quality assessment. Currently, most clinical use of FFP, recommended by practice guidelines, is not supported by evidence from large randomized controlled trials (RCTs) (6). This can explain why there is lack of consensus among

*See also p. 1655.

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physicians on criteria for appropriate FFP use (10). In addition, many FFP transfusions may be appropriate for critically ill patients but inconsistent with published practice guidelines. The study by Dr. Lauzier emphasizes the necessity for RCTs to revise or adjust guidelines.

RCTs are needed when clear scientific evidence is lacking. Therefore, these are the most robust trials to determine efficacy of FFP in different clinical conditions to provide the best possible evidence base to support guidelines for appropriate FFP-transfusion practice. However, designing such RCTs may be difficult. Many questions may arise; e.g., which dose to use, which transfusion trigger to withhold, and which clinical outcome variable to measure. Current guidelines recommend a standard dose of 10–15 mL/kg (5). Dr. Chowdhury and colleagues (11) demonstrated that this dose was inadequate to correct deficiencies of specific coagulation factors. Their data also showed that coagulation tests, such as international normalized ratio or plasma prothrombin time, are poor predictors of whether critically ill patients have decreased coagulation factor levels. He concluded that global coagulation screens are poor predictors of risk of bleeding during invasive procedures. This means that some critically ill patients could be exposed to FFP transfusion risks without adequate correction of coagulation.

However, current guidelines for FFP administration emphasize therapeutic usage rather than the correction of abnormal laboratory results. Most of the evidence to guide FFP transfusion is taken from observational data (5–6, 12). Guidelines, even if validated in large series, may still not fit the problem of the individual patient and particularly not the critically ill patient. This is inherent to guidelines and also one of the reasons why some physicians do not promote the use of them (10). Anyway, guidelines should be used with intelligence, because they are intended to facilitate but not replace clinical decision-making (13).

A weakness in the study by Dr. Lauzier and colleagues lies in the fact that the authors do not describe FFP prescription before implementation of the Canadian guidelines. Therefore, we cannot evaluate the real impact of the guideline. There is no additional information about how the guideline was implemented. Can it be consulted easily? All of these factors may have influenced the number of inappropriate FFP orders. Passive dissemination of guidelines rarely leads to changes in behavior. Education, training, computer-assisted decision support, and feedback can help in sustaining use and adherence to guidelines (13). Dr. Rothschild and colleagues (14) proved in an RCT that the percentage of inappropriate transfusions decreased significantly with both education and computerized physician order entry with decision support.

Anyway, evidence-based guidelines or protocols are a valuable tool to improve quality of care and outcome, and have an important impact on reducing costs (15). Therefore, as stressed in the study by Dr. Lauzier and colleagues, large RCTs are needed for an optimal cost-effective transfusion policy.

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Implementing scientific advances into clinical practice in critical care—New challenges and new insights*

The enormous impact on public health of acute lung injury and acute respiratory distress syndrome (ALI/ARDS), comparable to that of breast cancer or HIV (1), mandates the development of preventative strategies to prevent ALI/ARDS. A key target group in this respect is patients at known increased risk for ALI/ARDS who have not yet developed this devastating disease process. The early and effective institution of risk reduction strategies may abrogate the injury process, substantially reducing the likelihood of developing ALI/ARDS in these patients.

The effectiveness—or otherwise—with which advances in clinical care generated by large-scale clinical trials are incorporated into routine clinical practice is an important issue. There have been remarkable advances over the past 15 yrs in our understanding of how to mechanically ventilate patients who have already developed ALI/ARDS. Based on a consistent body of evidence from both laboratory (2) and clinical studies (3, 4), it is now clear that outcome is improved in patients who receive a ventilatory strategy involving lower tidal volumes. However, implementing these findings at the bedside has proven problematic (5, 6). Ongoing uncertainties and indeed controversies regarding optimal ventilatory strategies, particularly in regard to the best tidal volume range (7), and the growing complexity of ventilatory strategies may contribute to these difficulties. However, what is not in doubt is that high-stretch mechanical ventilation causes further injury in patients with ALI/ARDS (8).

Similar difficulties have been encountered in regard to the implementation of restrictive transfusion practices in the management of the critically ill (9). These problems persist despite clear evidence that a more liberal transfusion strategy worsens outcome in these patients (10). Again, uncertainties persist in regard to the best transfusion strategies in certain subgroups of critically ill patients, particularly those with cardiovascular disease, although this has been addressed to some extent (11). Nevertheless, the difficulties in introducing restrictive transfusion strategies is more difficult to understand, given the relative simplicity of this strategy, in comparison to mechanical ventilatory strategies.

Why has it proven difficult to effectively introduce therapeutic strategies that have a solid evidence base into routine clinical practice for our critically ill patients? The existence of significant barriers to the changing of established clinical practices is increasingly recognized (6). These barriers greatly reduce the effectiveness of *ad hoc* approaches to changing clinical practice. In contrast, a systematic, multifaceted, team-oriented approach incorporating ongoing education and decision support tools has been demonstrated to produce effective and sustained changes in other aspects of clinical practice in critical care (6). As a specific example, the systematic implementation of evidence-based interventions by Pronovost et al. (12) produced a sustained reduction in the incidence of central venous catheter-related bloodstream infections in critically ill patients.

An emerging issue is the extent to which medical interventions that are poorly conducted or unwarranted contribute to the subsequent development of ALI/ARDS. Specific concerns center on a likely association between both high-stretch mechanical ventilation and liberal blood transfusion strategies and the development of ALI/ARDS. Gajic et al. (13) previously demonstrated that the use of initial high tidal volumes was associated with the development of ALI/ARDS in both a single-center retrospective study and a subsequent analysis of an international database of mechanically ventilated patients (14). Zupancich et al. (15) demonstrated that high-stretch mechanical ventilation leads to increased cytokine levels in patients following cardiopulmonary bypass, a high-risk group for ALI/ARDS. These findings provide a potential mechanism by which adverse ventilation may lead to ALI/ARDS in high-risk patients. Liberal transfusion of blood (16, 17) and blood products (18) in the critically ill has also been associated with the development of ALI/ARDS and increased mortality (9).

In this issue of *Critical Care Medicine*, Dr. Yilmaz and coworkers (19) determine the impact of the systematic introduction of two quality improvement interventions in mechanically ventilated patients in three intensive care units at the Mayo Clinic Hospitals. In an observational cohort study, the authors evaluate the efficacy of protocol-guided limitation of large tidal volume ventilation and inappropriate transfusion in a subset of patients who did not have ALI/ARDS and who were ventilated ≥48 hrs. These protocols were devised by multidisciplinary teams, incorporated as a decision support within the institutional computerized order entry system, and supported by a comprehensive didactic program to ensure maximal compliance. The ventilatory protocol was implemented incrementally over a 3-yr period, while the transfusion protocol was implemented over a 1-yr period. Comparisons were made with a database of prospectively collected data from a similar group of patients admitted to these intensive care units before the implementation of these protocols. The authors observed an impressive decrease in the tidal volumes employed (from 10.6 to 7.7 mL/kg) and in the percentage of patients who received a blood transfusion (60% vs. 38%), in this subset of patients, following the introduction of the protocolized interventions. These findings clearly attest to the effec-

*See also p. 1660.

Key Words: mechanical ventilation; clinical protocols; acute lung injury; respiratory distress; adult blood transfusion

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tiveness of an interdisciplinary approach to the design of protocols, coupled with a multifaceted approach to their implementation, in bringing about substantial changes in clinical practice. The challenge for us all is clear: If we wish to successfully introduce evidence-based advances—particularly complex management strategies—into routine clinical practice in our critical care units, a systematic approach to protocol design and implementation is required.

Perhaps more importantly, this study provides persuasive evidence for the contention that high-stretch ventilation and unnecessary blood transfusion directly contribute to the development of ALI/ARDS in at-risk patients. Dr. Yilmaz and colleagues (19) observed a large decrease in the development of ALI and a reduction in the duration of mechanical ventilation following the implementation of both protocols. These differences persisted when adjustments were made for differences in baseline characteristics, which included a lower incidence of sepsis and pneumonia in the group after protocol implementation. Multivariate logistic regression analysis confirmed that the protocol interventions were associated with the reduction in the incidence of ALI. However, it was not possible to separately dissect the contributions of each protocol to the reduction in the incidence of ALI.

This is an observational cohort study that uses historical controls, which is entirely appropriate for this type of study. A key limitation is the extent to which one can attribute the reduction in the incidence of ALI/ARDS to the quality improvement interventions. The 3-yr interval between the pre- and postprotocol implementation data introduces a real risk that clinical advances other than the protocols might explain, at least in part, the reduction in the incidence of ALI. Such advances include tighter glycemic control, other alterations in ventilatory strategies, and the use of sedation and sepsis resuscitation protocols. While complex statistical analyses may be able to correct for differences in baseline ALI/ARDS risk, they cannot detect and eliminate the possibility that unmeasured variables contributed to the effect seen. These limitations need to be borne in mind when interpreting the findings of the study.

Nonetheless, the link between the development of ALI and inappropriately high tidal volume ventilation and blood transfusion is persuasive, given its biologically plausibility. Biological plausibility, that is, the demand that a possible association fits existing biological or medical knowledge, is a key consideration in interpreting the findings of studies such as this. In addition, these findings are consistent with, and extend, the emerging body of evidence linking inappropriate ventilation and transfusion practices with the development of ALI/ARDS. Furthermore, the potential for biases in regard to data collection was minimized by the fact that all data were collected on a prospective basis and were interpreted using blinded outcome assessors.

This important study clearly demonstrates the effectiveness of a systematic approach to the design and implementation of complex clinical protocols for the management of patients in the intensive care unit and provides strong support for the contention that high tidal volume and inappropriate transfusion practices contribute to the pathogenesis of ALI/ARDS. These findings clearly raise the specter of iatrogenically induced ALI/ARDS and mandate consideration of the core medical principle of *primum non nocere*. Extreme caution is required in regard to the use of high-stretch ventilatory and liberal blood transfusion strategies in these patients.

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Incorporating leadership training, a horizontal approach to resuscitation and performance feedback, into advanced life support*

At a cardiac arrest, the first procedure is to take your own pulse." Many will recognize this as the third law from Samuel Shem's satirical novel *The House of God* (1). Nearly 30 yrs later, this sage advice is still passed on to residents who are about to assume the leadership of resuscitation teams.

In this issue of the *Critical Care Medicine*, Dr. Hayes and his colleagues (2) from the University of Toronto have investigated the perceptions of internal medicine residents responsible for leading cardiac arrest teams. The authors should be congratulated on their ambitious attempt to survey all internal medicine trainees in Canada; unfortunately, the survey response rate was suboptimal. Despite this limitation, their study respondents represent one fourth of all Canadian internal medicine residents. As such, the authors' findings, that residents feel unprepared and unsupervised to serve as leaders of cardiac arrest teams, need to be carefully considered.

In their study, 49% of respondents felt inadequately trained to lead cardiac arrest teams. This finding is not surprising, as the responding resident leader frequently has no preexisting knowledge of the specific patient in crisis and limited experience in this role. Recent changes in duty-hour limits, which have diminished resident continuity of care, will likely further complicate this situation (3). Additive to these leadership difficulties is the confusion associated with any emergency and a room overflowing with people.

In preparation for this role, most residency programs require new trainees to complete some form of advanced life support training. Completion of Advanced Cardiac Life Support (4), Advanced Trauma Life Support (5), or Pediatric Advanced Life Support (6), however, only implies a minimal competency with resuscitative algorithms. None of these courses address the leadership skills needed to effectively direct a resuscitation team. The ineffectiveness of these courses to prepare residents for their leadership role in teaching hospitals stems, in part, from the fact that each prepares the resident for a "vertical resuscitation" format in which a single provider completes key resuscitative steps in a sequential fashion with limited assistance (7). Although this vertical resuscitation is a safe, effective approach, dependence on a single provider does not require specific leadership abilities and is not applicable in all situations.

In contrast to the vertical approach, resuscitations in teaching hospitals are typically attended by many individuals, each of whom has a specific role. In this setting, a "horizontal resuscitation" in which simultaneous efforts are undertaken by multiple providers is the norm. This type of resuscitation requires a more sophisticated level of organization and leadership (7). A horizontal approach requires a command-physician, who is not directly involved in a particular task but rather is able see the big picture. The responsibilities of this command-physician include observing the simultaneous activities of other providers, synthesizing all data obtained, and formulating a treatment plan. Effective two-way communication is essential to the success of this type of resuscitation. Adoption of an aviation-like communication feedback system, in which the leader's directions are acknowledged by repeating the command back, would likely limit confusion and may improve outcome (8). The ability to serve as a command-physician is not dependent on the seniority of the physician but rather on the understanding of the role by both the leader and the members of the team (7). The establishment of a command-physician has been found to improve team performance in both cardiac and trauma resuscitations (7, 9, 10). Future versions of advanced life support courses should consider incorporating both vertical and horizontal approaches to resuscitation as well as develop the role of the command-physician and ensure competency in team leadership.

The finding that resident physicians are not confident in their leadership abilities is not surprising and offers an opportunity for educational development. However, the finding by Dr. Hayes and colleagues (2) that 14% of residents received supervision during weekday resuscitations and only 1.4% received supervision on evening or weekends is concerning. This, coupled with the finding that only 1.3% of residents received any performance feedback, is, in a word, appalling. Where is the faculty member who is ultimately responsible for both caring for the patient and training the resident? Regrettably, it is reasonable to assume that this trend is also present in other types of residency programs.

Clearly, the resident staff needs the opportunity to develop independent, critical decision-making skills under difficult conditions. This experience, however, should not occur at the expense of patient well-being. Previous studies have demonstrated that where an attending physician is present, resident supervision and patient outcome are improved (10, 11). It is hoped that with the further establishment of rapid response teams, resident supervision during resuscitation will improve.

Provision of timely and useful feedback may be logistically difficult. However, there is mounting evidence that feedback improves experience-based judgment, decision making, and performance (12, 13). It is illustrative that it was the Fat Man (the resident) who taught the new interns the laws of the *House of God* (1), rather than the attending. Now, as then, the role of the faculty to provide educational leadership could be improved.

*See also p. 1668.

Key Words: cardiac arrest; medical education; command-physician; leadership; feedback

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The work by Dr. Hayes and colleagues (2) has identified several areas for development. Incorporation of leadership training, a horizontal approach to resuscitation, and performance feedback into advanced life support courses will likely improve resident performance and translate into better patient outcomes.

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Recombinant activated factor VII in cardiac surgery—Will we ever know for sure?*

On March 25, 1999, the U.S. Food and Drug Administration licensed recombinant human activated factor VIIa (rFVIIa) for bleeding in patients with hemophilia A or B or with inhibitors to factors VIII or IX. A growing number of case reports and small series have since described off-label uses of rFVIIa in nonhemophiliac patients with life-threatening hemorrhage, some successful (1), others complicated by thromboembolic events (2).

In 2005, a multicenter, double-blind, placebo-controlled trial from the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators showed decreased hematoma volume, decreased mortality or severe disability, and decreased 90-day mortality in the 303 patients who received rFVIIa. While there was a trend toward an increase in serious thromboembolic events in the rFVIIa-treated patients, it did not reach statistical significance (3). Importantly, in this trial, surgery was not an option (planned evacuation of hematoma was among the exclusion criteria), and standard medical care had a limited prognosis.

Also in 2005, the NovoSeven Trauma Study Group published combined results of two randomized, placebo-controlled, double-blind clinical trials. rFVIIa significantly reduced transfusion requirements and the need for massive transfusion in blunt trauma patients, with a trend toward similar benefits in penetrating trauma, without a significant increase in thromboembolic events in the 277 treated patients (4). rFVIIa has been studied prospectively in a variety of elective surgeries, including retropubic prostatectomy (5), liver resection (6), and cardiac surgery (7). These small studies have shown a reduction in transfusion requirements in treated patients, but proof of mortality benefit or long-term improvement in patient outcome has been elusive (8).

Tracking adverse outcomes in off-label application of medications is challenging; O'Connell et al. (9) recently analyzed 431 rFVIIa-associated adverse events, noting that because adverse event reporting by clinicians is voluntary, estimates based on the Food and Drug Administration's Adverse Event Reporting System significantly underrepresent actual occurrences. It is clear that well-designed, hypothesis-testing clinical trials are needed to help guide clinicians in the operating room, the intensive care unit, and elsewhere as they consider the application of this potent but expensive and potentially morbid intervention.

In this issue of *Critical Care Medicine*, Dr. Tritapepe and colleagues (10) demonstrate that rescue therapy with rFVIIa is effective in reducing transfusion requirements, correcting coagulopathy, and controlling life-threatening bleeding in patients with acute aortic dissection undergoing surgery with deep hypothermic circulatory arrest. All patients received tranexamic acid, and rFVIIa was administered as rescue therapy in the operating room or intensive care unit at the end of a transfusion protocol, when significant ongoing bleeding was evident despite aggressive resuscitation and exhaustive surgical exploration. Four patients required a second dose of the drug due to ongoing bleeding.

Using a propensity score-matched analysis to compare the 23 consecutive patients who received rFVIIa with controls who did not, Dr. Tritapepe and colleagues (10) demonstrated that the drug was effective at the dose studied, 70 μg/kg. They confirmed a reduction in bleeding and transfusion requirements, but their small cohort could not show improved outcomes in terms of mortality or a composite outcome of myocardial infarction, stroke, acute liver dysfunction, or acute renal failure. A trend

*See also p. 1685.

Key Words: recombinant activated factor VII; deep hypothermic circulatory arrest; cardiac surgery; transfusion reduction; outcome; cardiopulmonary bypass; hemorrhage

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toward shorter intensive care unit length of stay did not reach statistical significance, and hospital length of stay was identical in the two groups. Adverse events did not differ between the two groups.

This is consistent with previous findings in related patient populations, including the study by Karkouti et al. (11) cited by the authors, a propensity score-matched case-control analysis of 51 consecutive cardiac surgery patients who received rescue therapy with rFVIIa for intractable blood loss.

The issues of coagulopathy and intractable hemorrhage after separation from cardiopulmonary bypass continue to challenge clinicians in the operating room and intensive care unit. Antifibrinolytic therapy with lysine derivatives (aminocaproic acid, tranexamic acid) or the serine protease inhibitor aprotinin has long been a mainstay of strategies to reduce perioperative blood loss in cardiac and other high-risk surgery (12). Because of its demonstrated efficacy, many clinicians have chosen aprotinin for their highest risk patients (including those undergoing deep hypothermic circulatory arrest) (13), but recent highly publicized analyses of data from the Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation have questioned the drug's safety both in the perioperative period and in the long term (14, 15). The Food and Drug Administration recently added significant restrictions to the on-label use of aprotinin (16), so when refractory bleeding does occur after cardiopulmonary bypass, rFVIIa may add a much-needed tool to our arsenal.

The definitive prospective, multicenter, placebo-controlled, double-blind study, adequately powered to discern differences between groups, may be a long time coming to the cardiac surgery/deep hypothermic circulatory arrest arena. The market is small, and the risks of morbidity (including acute renal failure and stroke) and mortality are high—which may deter industry sponsors. The high cost of rFVIIa (approximately $1.40/μg, nearly $7,000 for a single dose in a 70-kg patient at 70 μg/kg) (17) and the extreme circumstances under which it is administered will make it challenging for institutional review boards to approve individual hospital-sponsored studies of rFVIIa in cardiac surgery patients. As hemorrhaging postsurgical patients undergo transfusion and surgical reexploration, the rationale for randomizing such patients to rFVIIa or placebo can be supported by the data from Dr. Tritapepe and others.

Because small, single-center studies cannot individually produce meaningful safety outcome data, medical journal editors should embrace the opportunity to accelerate the development of useful meta-analyses by encouraging authors to standardize outcome reporting for off-label studies of drugs like rFVIIa. Perhaps a multicentered, hospital-supported registry of deep hypothermic circulatory arrest outcomes could provide the infrastructure for studying rFVIIa in a meaningful fashion. This collaborative approach would help local institutional review boards with their approval process and improve the chance that we will be able to use rFVIIa in an evidenced-based fashion in the future.

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Measurement of heparin-dependent platelet antibodies in the diagnosis of heparin-induced thrombocytopenia: Fact or fiction?*

In this issue of *Critical Care Medicine*, Dr. Shaheed and colleagues (1) report on the performance of a new, rapid assay for the measurement of heparin-platelet factor 4–dependent antibodies in the diagnosis of heparin-induced thrombocytopenia. The importance of this report, in my mind, is not that this assay is rapid, reliable, and reproducible but, rather, that it points out that the diagnosis of type-2 heparin-induced thrombocytopenia (HIT) still remains a clinical one for which laboratory tests support, but cannot rule out, the diagnosis. Because of the variability in clinical presentation and the importance of making an early diagnosis of HIT, various scoring systems have been developed to aid the clinician (2, 3). As these clinical scoring systems are not absolute, there is still a recognized need for rapid assays to detect heparin-platelet factor 4–dependent anti-platelet antibodies, the results of which correlate with the heparin-induced carbon-14 (^{14}C)–serotonin-release assay, generally thought to be the gold standard in the diagnosis of type-2 HIT. The unspoken assumption is that with better assays, the diagnosis of HIT will be made earlier and with greater certainty, allowing for more appropriate treatment. However, the data presented by Dr. Shaheed and colleagues (1) raise serious doubts about this assumption. Of the 11 patients assessed to be "very likely" to have HIT by the Greinacher scoring system, only four had a positive ^{14}C–serotonin-release assay, and none of the four patients assessed to have "definite" HIT by the Pouplard scoring system had positive ^{14}C–serotonin-release assays. In contrast, 9 of the 11 patients in the "very likely" (Greinacher) group and three of the four "definite" (Pouplard) patients had positive results with the enzyme-linked immunosorbent assay (ELISA).

Does this mean that the ELISA is a better predictor of type-2 HIT, or does it mean that our clinical assessment is superior to laboratory diagnosis employing the currently available assays? One's answer to that question will likely be determined by the experience of the person giving the answer. Indeed, it has been shown that more experienced clinicians were more likely to correctly identify patients with HIT on the basis of clinical scoring (4). However, as different scoring systems will frequently place the same patient into very different risk categories, who is to say who is right? If this weren't confusing enough, clinical data have clearly shown that the risk of developing HIT is distinct from that for the development of heparin-dependent antiplatelet antibodies (5, 6). Whereas cardiac patients have a prevalence of developing heparin-dependent platelet antibodies of 20% to 25%, orthopedic patients, for whom the risk of antibody development is much lower, have the higher prevalence of developing HIT and HIT with thrombosis. Indeed, this disparity between the prevalence of heparin-dependant platelet antibodies and the prevalence of HIT points out much of what we do not know about this syndrome. A recent report by Reilly et al. (7) may help us in our understanding by documenting that the presence of prothrombotic factors, platelet hyperreactivity in his study, contributes to the risk of developing HIT and HIT with thrombosis. As a result of our limited understanding of the confounding factors influencing the risk for development of thrombosis, we (clinicians) have developed an "IF . . . THEN . . ." approach to diagnosis and therapy. However, our lack of consistency in making and confirming the diagnosis may result in undertreatment, placing patients at risk for life-threatening and organ-threatening thrombosis. Conversely, if we overdiagnose HIT, we will expose patients to the unnecessary expense of alternate and prolonged anticoagulation. Neither of these consequences is desirable.

What can we do to increase the certainty of a diagnosis of type-2 HIT? Undoubtedly, a rapid ELISA with high sensitivity and specificity such as studied by Dr. Shaheed and colleagues (1) can help in the evaluation of patients suspected of having HIT. Experience to date demonstrates that currently available ELISAs indeed have high sensitivity but a relatively low specificity, thereby limiting their usefulness. The data presented by Dr. Shaheed and colleagues (1) are no different in this regard. However, when the assay optical-density cutoff was increased from the manufacturer's recommended level of 0.4 to a level of 1.0, the specificity increased from 65% to 83%, making the assay much more useful (1). A similar finding has been reported by others using different ELISAs (8, 9). This would seem to be a reasonable and useful modification to employ, although data to support this approach are not available for all commercially available assays.

So, where does that leave us when being confronted with a patient who may, or may not, have type-2 HIT? The lack of standardization of clinical scoring systems not withstanding, the diagnosis of type-2 HIT must be made on clinical grounds, with the clinician having a high level of suspicion in at-risk patients, however one defines that group. Assays to confirm the presence of heparin-platelet factor 4–dependent antiplatelet antibodies should also be obtained to assist in continued decision making once alternate anticoagulation is anticipated or initiated. When using an ELISA, an increase in discriminate optical-density from manufacturer-recommended level to 1.0 would seem to be reasonable to employ in patients with equivocal clinical grounds on which to base a diagnosis. It would also seem prudent to treat patients who present with classic laboratory and clinical findings for type-2 HIT with appropriate alternate anticoagulants, irrespective of the results of

*See also p. 1691.

Key Words: heparin-induced thrombocytopenia; heparin-dependent platelet antibodies

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ELISA or platelet injury tests. In the meantime, we need to continue to investigate the various contributing factors for thrombosis in this disorder and improve the clinical and laboratory tools at our disposal.

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Active learning*

After the 1999 publication by the Institute for Medicine (1) suggesting that >98,000 deaths per year are the result of medical errors in hospitals, there has been a public debate about patient safety and, thereafter, a shift in quality improvement activities to those that are more patient centered. Other organizations, including the Agency for Healthcare Research and Quality, the Institute for Healthcare Improvement, and the Joint Commission for Accreditation of Healthcare Organizations, have supported patient safety initiatives by identifying *best practices* and relying on *evidence-based medicine*.

Despite the identification of many practices that have been demonstrated to improve outcome, analysis of data has demonstrated a disappointing lack of clinical application (2). In many instances, physicians have not readily adopted practice changes that have been demonstrated to positively influence patient outcomes. Errors of omission are often a significant patient safety risk and more difficult to identify than errors of commission (3); it has been estimated that 30% to 40% of patients do not receive treatments that have been demonstrated to be effective (4, 5).

Why is that the case? A number of reviews and studies have attempted to identify why there is this gap between research findings and clinical practice (6, 7). Many physicians are poorly prepared to critically review published research. Even when a physician accepts that a practice change would be beneficial, there are many potential barriers (8).

Some of the barriers to change in physician practice include financial disincentives (6) and lack of equipment or personnel. Physicians may be overloaded with work or may not have the knowledge base or clinical skills to "operationalize" indicated changes.

Therefore, considerable attention has been given to initiatives focused on changing physician behaviors (9). In the past, most attempts at physician education have been centered around didactic conferences and seminars. It is clear that these passive methods are not usually effective modifiers of physician behavior. Nonetheless, continuing medical education (CME) conferences have been, and continue to be, the backbone of physician educational activities (10). Other more active interventions that have been found to be useful include the use of physician reminders (11), safety checklists (12, 13), order sets (14), the use of multidisciplinary teams (15–17), and the use of "bundles" of interventions to act as prompts (17). Other effective interventions include academic detailing (18), immediate feedback, and the use of physician champions to advocate for practice change.

In this issue of *Critical Care Medicine*, Dr. Ilan and colleagues (19) report that the use of both standard order sets and the involvement of a dedicated subspecialty consultation service were the most effective interventions leading to the acceptance and implementation of best practices in their intensive care unit. Both of these interventions are geared to making it easy for physicians to comply with the practice guideline or best practice and to involving physicians in the planning and implementation of change. Thus, it is not surprising that these interventions are effective, a finding consistent with others who have argued that more active involvement of physicians in the development of practice guidelines, as well as multidisciplinary teams, will lead to behavioral change. Indeed, multifaceted approaches (including many of these modalities) seem to receive the most support (9, 20).

What are the implications of these findings? It would seem that the time has come to reevaluate our traditional approach to continuing medical education. Conference and seminar attendance, no matter how

*See also p. 1696.

Key Words: continuing medical education; practice guidelines; order sets; physician education; intensive care unit; quality improvement.

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well planned and informational, should no longer be deemed to be sufficient approaches to continuing medical education in the absence of a more active component of the CME activity.

The American Board of Internal Medicine has integrated performance improvement into its recertification process. Seventy-five percent of diplomates who have completed the process find the self-evaluation modules relevant to their clinical practice, and 98% reported that the educational objectives were met (21). While the American Board of Internal Medicine is to be congratulated, all organizers of medical education activities should attempt to integrate active learning in an attempt to make educational programs effective. This will take a commitment from providers of CME, such as professional societies and others accredited to provide CME credit.

If we have a sincere commitment to patient safety and improved outcomes, it is time to make fundamental changes in our approach to continuing medical education. Effective translation of research into clinical practice is not easy and will require renewed commitment from all CME providers.

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A new prognostic scoring system for severe acute pancreatitis*

I have but one lamp by which my feet are guided, and that is the lamp of experience. I know no way of judging of the future but by the past.—Patrick Henry, Speech at the Virginia Convention, March 1775

Acute pancreatitis is a multietiology inflammatory condition that varies in severity from a self-limiting inflammation of the pancreas gland to a rapidly deteriorating, life-threatening condition involving multiple organs. Up to 20% of patients with acute pancreatitis will develop severe pancreatitis with a mortality rate upwards of 25% (1). Accurate predictors of the severity of acute pancreatitis are important because they influence clinical decision making regarding therapeutic interventions, such as endoscopic papillotomy (2), antibiotics (3), and intensive care unit (ICU) care (4), which have been shown to improve survival if they can be initiated early in the patient's course. The various prognostic scoring systems for severe acute pancreatitis are based on expert consensus, such as the Atlanta classification (5), or small specialist center populations, such as the Ranson (6), Glasgow (7), and modified Glasgow (8) criteria. These scoring systems contain a small proportion of patients with severe acute pancreatitis and are decades old.

In the current issue of *Critical Care Medicine*, Dr. Harrison and colleagues (9) propose a new prognostic index for patients with severe acute pancreatitis, the Pancreatitis Outcome Prediction (POP) Score. In an elegant retrospective cohort study of 2,462 patients with severe acute pancreatitis admitted to 159 U.K. intensive care units from 1995 to 2003, the authors identified six variables collected within the first 24 hrs of ICU admission that had the strongest relationship to hospital outcome: arterial pH, age, serum urea, mean arterial pressure, Pao_2/Fio_2 ratio, and total serum calcium (in order of decreasing impact). These six variables produced a model with a prognostic discrimination superior to other models and were used to develop an objectively weighted multivariate prognostic score ranging from 0 to 40 points. The major strength of this study is the large database obtained from a number of general ICUs in the United Kingdom. However, the retrospective nature of the study did not permit the validation of the diagnosis of pancreatitis (amylase levels or computed tomography scans) or the evaluation of all available prognostic variables (such as serum lactate dehydrogenase, as is included in the modified Glasgow criteria). Important details, such as the etiology of the pancreatitis, and comorbidities, such as diabetes mellitus and mild to moderate congestive heart failure, were also missing. A possibly surprising finding in this study was the rather high ICU and hospital mortality rates of 31.6% and 41.9%, respectively, reinforcing the notion that patients with severe acute pancreatitis often deteriorate despite intensive care.

Despite the proliferation of scoring systems for grading severe acute pancreatitis, none of the currently available systems is ideal. Two important principles should guide the development of scoring systems in severe acute pancreatitis. First, the scoring system should measure an important outcome, in this case ICU and hospital mortality. But what about other outcomes, such as long-term mortality and functional status? An ideal scoring system would take into account these other variables as well. Second, the scoring system must be easy to use and readily available due to the time-consuming and costly nature of collecting data on critically ill patients. Currently, the use of serum markers, such as interleukin-6, interleukin-8, neutrophil elastase, trypsinogen activation peptide, procalcitonin, serum amyloid protein, and phospholipase A_2, is not routine in the ICU patient with severe acute pancreatitis, but these markers may play a role in the future. Contrast-enhanced computed tomography of the pancreas and/or magnetic resonance imaging/magnetic resonance cholangiopancreatography are extremely useful imaging tools in pancreatitis; however, they are costly, may not be widely available, and necessitate a prolonged patient examination time with the possibility that the radiographic findings may be normal in the first 48 hrs of illness, before pancreatic necrosis has had time to develop (10, 11). Dr. Harrison and colleagues (9) have clearly taken us toward the future of clinical decision making in severe acute pancreatitis. Prospective validation of the POP score in the international medical community should be anticipated.

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*See also p. 1703.

Key Words: severe acute pancreatitis; scoring system; intensive care unit; prognosis

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CO_2: Friend or foe?*

Increases in arterial blood P_{CO_2}—particularly when associated with decreases in pH—are regarded as a life-threatening emergency that requires rapid intervention and close monitoring. However, in this issue of *Critical Care Medicine*, Dr. Lavani and colleagues (1) report salutary effects associated with high levels of P_{CO_2} in isolated ventricular embryonic chick cardiomyocytes subjected to simulated reperfusion after 60 mins of simulated ischemia. The percentage of cardiomyocytes surviving during simulated reperfusion was dramatically different depending on whether reperfusion occurred under normocarbic (P_{CO_2} 36 torr, pH 7.40), hypercarbic (P_{CO_2} 71 torr, pH 6.80), or hypocarbic (P_{CO_2} 7 torr, pH 7.90) conditions, with the highest survival linked to hypercarbia and the lowest to hypocarbia.

The authors further examined the underlying mechanisms. They found that a burst of reactive oxygen species (ROS), which started at reperfusion and peaked after ≈5 mins, was markedly reduced by hypercarbia but intensified by hypocarbia. When stigmatellin, an inhibitor of electron transport chain complex III, was given during hypocarbic reperfusion, a similar salutary effect occurred, reducing both the burst of ROS and cell death. These data suggest that hypercarbia at the time of reperfusion protects cells by attenuating oxidative injury. The authors further found that the effects of hypercarbia on the burst of ROS and cell death were abrogated by N^G-nitro-L-arginine methyl ester, an inhibitor of nitric oxide (NO) production, suggesting that NO production is required for the effects of hypercarbia. Intriguingly, manipulations of CO_2 failed to alter NO production before the burst of ROS. Increases in NO production were observed only after the burst of ROS and were associated with both hypocarbia (approximately from minute 10 to 20) and hypercarbia (approximately from minute 30 and onward). The late effect of hypercarbia on NO production was abrogated by N^G-nitro-L-arginine methyl ester. However, late effects may be difficult to interpret as dying cells would cease to produce the metabolite being analyzed.

Regardless of the specific downstream mechanisms, hypercarbia was convincingly shown to suppress the burst of ROS at the time of reperfusion and to promote cell survival. However, was this effect directly linked to hypercarbia? Three levels of CO_2 were investigated but without controlling for the effects of pH. Each level of CO_2 was accompanied by directional changes in pH such that acidosis accompanied hypercarbia and alkalosis accompanied hypocarbia. Several studies—using *in vitro* models such as isolated cardiomyocytes (2), perfused papillary muscles (2), and isolated perfused hearts (3, 4) and *in vivo* models such as coronary occlusion and reperfusion (5, 6)—have shown that acidosis at the time of reperfusion is protective. In some of the studies (4, 5), metabolic and respiratory acidosis were compared yielding virtually identical results. Accordingly, hypercarbia in the present study could have been the means (and a practical one) to deliver a low pH at the time of reperfusion. Recent work also suggests that acidosis could prevent opening of the mitochondrial permeability transition pore at the time of reperfusion (7, 8), an event that may determine ultimate cell fate. Further work is required to elucidate the precise mechanisms of cardioprotection by CO_2, identifying the specific signaling mechanisms, their time sensitivity, the intervening functional effectors, and whether they occur independently of pH.

Whether CO_2 is friend or foe depends on the clinical setting. Under normal conditions of adequate blood supply and oxygenation, excess CO_2 is not welcomed by the body. Excess CO_2 can depress myocardial function (9) and trigger a prominent neuroendocrine stress response characterized by a vigorous sympathetic discharge leading to increases in blood pressure, cardiac output, and heart rate. However, as demonstrated by Dr. Lavani and colleagues (1) and other investigators, CO_2 can also protect cells and organs during episodes of ischemia and at the time of reperfusion. This concept could have practical implications under certain clinical settings. The authors pointed to cardiopulmonary resuscitation as one possible setting in which tissue protection could be elicited by promoting arterial hypercarbia (i.e., through alveolar hypoventilation). However, this particular setting may not be amenable to manipulation of CO_2 at the tissue level. Ischemia, as correctly modeled in the present studies, is accompanied by prominent hypercarbic acidosis at the tissue level. However, the scant flow generated by current resuscitation methods typically fails to reverse ischemia and the consequent tissue hypercarbic acidosis.

Previous studies have shown that in the myocardium, hypercarbic acidosis a) persists during closed-chest resuscitation; b) is not affected to a substantial degree by changes in blood pH and P_{CO_2}; and c) reverses only after return of spontaneous circulation (10, 11). Accordingly, the rapid CO_2 removal modeled at the start of reperfusion in isolated cardiomyocytes (and found to be detrimental) is not likely to occur during cardiopulmonary resuscitation. The data on cardiomyocytes would in fact suggest that hypercarbia that occurs "naturally" when resuscitation is attempted is cardioprotective. Yet, it would be important to determine whether a second window of opportunity exists at the return of spontaneous circulation, when higher systemic and regional blood flows would enable arterial P_{CO_2} to influence tissue P_{CO_2}.

*See also p. 1709.

Key Words: carbon dioxide; cardiomyocytes; cardiopulmonary resuscitation; myocardial ischemia; nitric oxide; reactive oxygen species; reperfusion injury

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When considering a potential second window of opportunity, it is pertinent to remember the pivotal role that reoxygenation plays. Reoxygenation is essential both to the return of function through reestablishment of oxidative phosphorylation and to cell injury through generation of ROS. Thus, oxidative injury could be spared initially by hypercarbia followed by return of function without the need of protracted hypercarbia. However, if cells remain in a vulnerable state, abrupt reduction in CO_2 could remove needed protection. This is an important question that could be answered by Dr. Lavani and colleagues (1). It would require that initial hypercarbic reperfusion simulating cardiopulmonary resuscitation be followed—at some point—by an abrupt change in CO_2 simulating return of spontaneous circulation with the option of varying the CO_2 level.

If cardiopulmonary resuscitation turns out not to be the best setting for translating the current findings, many other settings could be well poised for translation in which full reperfusion occurs at the discretion of the physician. Examples of these settings include the opening of an occluded artery (i.e., management of acute myocardial infarction and stroke), the removal of an arterial clamp during vascular operations, and the removal of a tourniquet after vascular injury.

This is an important area of scientific enquiry in which an impressive amount of scientific productivity has accumulated over the past 3–4 decades but yet failed to yield specific clinical interventions. Dr. Lavani and colleagues (1) have brought forth an important concept that could lead to new approaches for ameliorating reperfusion injury. More work in this area is awaited.

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Returning to the pre-antibiotic era in the critically ill: The XDR problem*

There are few physicians alive today who practiced medicine in the pre-antibiotic era. However, many physicians in intensive care units around the world are entering an era in which they attempt to manage serious infections with Gram-negative bacteria resistant to most, if not all, antibiotics. The typical organisms responsible for such widespread resistance are *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and occasionally *Stenotrophomonas maltophilia* and *Burkholderia cepacia*. Disturbingly, however, commonly isolated organisms such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* are being found that harbor multiple resistance mechanisms, including some that lead to resistance to all antibiotics including the carbapenems (1, 2).

Multidrug resistance is variably defined but may be regarded as resistance to two or more of the following five antibiotic classes: antipseudomonal cephalosporins, antipseudomonal carbapenems, β-lactam/β-lactamase inhibitor combinations, antipseudomonal fluoroquinolones, and aminoglycosides (2). *Panresistance* has been defined as diminished susceptibility to all of these antibiotic classes (with the exception of aminoglycosides, which are not recommended as monotherapy for serious infections of nonurinary origin) (2). Unfortunately, isolates now exist that are resistant to all five of these antibiotic classes, plus all antibiotics used in salvage therapy such as colistin, polymyxin B, and tigecycline. Such a resistance profile has never previously been defined, but we refer to these strains as XDR, *extreme drug resistance*.

More than a decade ago there was no commercially available antibiotic therapy

*See also p. 1717.

Key Words: Gram-negative bacteria; multidrug resistance; infection

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to treat serious vancomycin-resistant enterococcal infections. Fortunately, the pharmaceutical industry came to the rescue, sensing a real possibility that vancomycin resistance would become widespread. The armamentarium available to treat vancomycin-resistant Gram-positive organisms now includes a number of new drugs. In contrast, the pharmaceutical industry has barely responded to the threat of XDR Gram-negative bacilli. Organisms such as *P. aeruginosa* are an intrinsically more difficult target for drug discovery teams than are Gram-positive organisms. Furthermore, novel agents may have unforeseen toxicities or pharmacokinetic hurdles that may make commercialization of these compounds more difficult. Therefore, it is not certain that the costs of discovering new antibiotics active against the most resistant hospital pathogens will be recouped in sales.

What are we to do while waiting for new agents to become available with activity against panresistant or XDR strains? It may well be a wait of >10 yrs, so we need alternative strategies urgently! Prevention is of paramount importance. There is ample evidence that resistant Gram-negative bacilli, like resistant Gram positive organisms such as resistant enterococci, can be passed from person to person on our hands (3). Antibiotic use strategies, such as limiting duration of antibiotic courses, are also important. Finally, we must optimize dosing regimens of commonly used antibiotics (4) by using strategies that target the pharmacodynamic variables most likely to result in bacteriologic eradication (and probably also most likely to prevent emergence of resistant clones). Extended or continuous infusions of β-lactam antibiotics and the use of large aminoglycoside and quinolone doses are examples of such strategies (5).

Panresistant strains of *A. baumannii* typically retain susceptibility to tigecycline, amikacin, and polymyxins (polymyxin B or colistin). Although tigecycline may appear to be an attractive option, it has some limitations. First, it does not achieve sufficient blood concentrations to enable its reliable use in the treatment of bloodstream infections (6). Second, it has been speculated that resistance of *A. baumannii* to tigecycline may occur during treatment (6), mediated by up-regulation of efflux pumps (7, 8). Tigecycline is not an option for the treatment of serious *P. aeruginosa* infections because of intrinsic resistance of the organism to the antibiotic. Therefore, amikacin and polymyxins may be the only alternatives for use in panresistant pseudomonal strains.

Unfortunately, amikacin is not active against every panresistant strain—an emerging amikacin resistance mechanism, whereby bacterial 16S ribosomal RNA is methylated thus providing protection from aminoglycosides, has recently been described in *P. aeruginosa* (9). These strains may also produce β-lactamases capable of destroying carbapenems, thereby wiping out all options except polymyxins, such as colistin. How then should we optimize the use of colistin in critically ill patients, if it is the only antibiotic left standing? Colistin was developed several decades ago, and no studies were ever performed to characterize its pharmacokinetic profile in critically ill patients or individuals undergoing renal replacement therapy (10). A multicenter clinical pharmacokinetic study of colistin in critically ill patients is being performed, but until that study is completed, the optimal dosing regimen for critically ill patients is unknown. In this issue of *Critical Care Medicine*, Dr. Cirioni and colleagues (11) describe an animal model in which they assess the efficacy of a colistin/rifampin combination for serious *P. aeruginosa* infection. The synergy between colistin and rifampin has certainly been demonstrated *in vitro* against multiresistant *A. baumannii* (12). In the study by Dr. Cirioni and colleagues using the rat model of *P. aeruginosa* infection, colistin in combination with rifampin showed greater antimicrobial activity than colistin alone. While this is by no means a definitive outcome study, it is an important one, adding to the body of experimental evidence for the beneficial effect of combining colistin with rifampicin (12, 13).

Are we ready to use this approach in critically ill individuals? At least two groups have studied colistin plus rifampin in small numbers of patients with ventilator-associated pneumonia caused by carbapenem-resistant *A. baumannii* or *P. aeruginosa* (14, 15). Microbiological eradication occurred in the majority of patients, but no control group treated with colistin alone was assessed to determine whether any clinical benefit was provided by combination therapy. We suspect that clinicians will be tempted to use colistin/rifampin combination therapy in panresistant strains. Other combinations have been tried *in vitro* including a triple combination of polymyxin, imipenem, and rifampin (13). The challenge is to perform a large multicenter randomized trial of combination therapy vs. colistin alone. Without such a study, we may be guided purely by anecdote and animal studies for the immediate future. While this may be the best available evidence, this is not a desirable situation in this era of evidence-based intensive care unit care.

The XDR problem is here. We are returning to the pre-antibiotic era where some infections are untreatable. Strict infection control practices must now be routinely enforced, and antibiotics that are still helpful should be prudently and optimally used.

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Pulse contour analysis: Fairy tale or new reality?*

The idea to compute stroke volume from arterial pressure waveform is not new. It was proposed for the first time in 1904 (1) and further improved and refined by many investigators and companies over the last century. Most pulse contour methods are based on modified Wesseling principles and require precalibration by an independent technique of cardiac output measurement (2–7). Deriving stroke volume from arterial pressure is very challenging. Difficulties vary according to the algorithm used but usually include the need to accurately determine the systolic portion of the arterial pressure curve and to estimate arterial compliance and its spontaneous or therapeutic changes over time (8).

In this issue of *Critical Care Medicine*, Drs. Cooper and Muir (9) challenge the value of the PulseCO method to track changes in cardiac output during experimental hemorrhage and volume loading. This original pulse contour method is based on the analysis of the first harmonic of the arterial pressure waveform and, to quote Linton and Linton (10), on "a series of approximations regarding the relationship between radial artery pressure and aortic pressure, aortic pressure and aortic flow, aortic flow and cardiac output." This method has the theoretical advantage of not depending on the detection of the systolic portion of the curve and may be less sensitive to the effects of damping than Wesseling-based methods. Although the first description (10) was quite encouraging, further clinical studies have yielded conflicting results: Hamilton et al. (11) reported a good agreement between PulseCO and thermodilution cardiac output values in the postoperative period of cardiac surgery, while more recently Yamashita et al. (12) suggested that both variables are not interchangeable in patients undergoing off-pump coronary artery bypass grafting.

The potential advantage of continuous pulse contour methods over gold standard intermittent methods (like thermodilution and echocardiography) is clearly the possibility to detect without any delay acute changes in cardiac output. Only few studies have really investigated the value of pulse contour methods to track changes in cardiac output in unstable conditions (2–5). As clinicians, we need to know if the method we are using is able to detect a sudden decrease in cardiac output or a fluid loading or drug-induced increase in cardiac output. No more, but no less! In this respect, the contribution of Drs. Cooper and Muir (9) is significant, because they have focused on the ability of the PulseCO method to track changes in cardiac output induced by large variations in volemic status, without interfering with any calibration. Unfortunately, the results are clearly disappointing, with percentage errors reaching 97% during hemorrhage and 98% during volume loading. Of course, caution must be exercised before extrapolating these experimental findings to human beings. However, these findings do not encourage use of such a method before further clinical validations. Drs. Cooper and Muir (9) conclude that we should perform recalibrations after any major alterations in hemodynamic status. This is simply not a realistic solution, because how would we know that the hemodynamic status is changing? Several studies (13, 14) have shown that clinical monitoring is not reliable in predicting the volume status or the cardiac output of

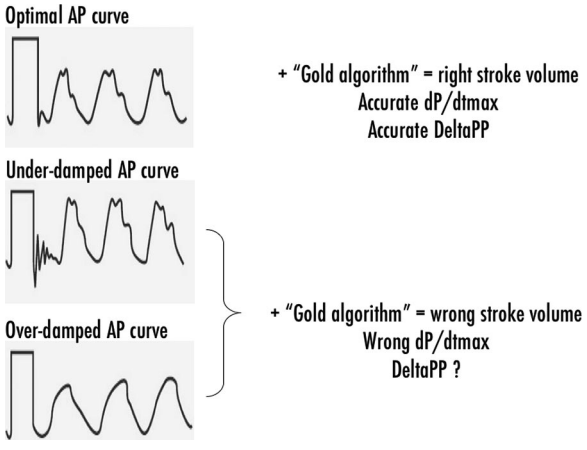

Figure 1. Arterial pressure (*AP*) waveform analysis can be very informative as long as the curve analyzed is not underdamped or overdamped.

*See also p. 1724.

Key Words: cardiac output; experimental hemorrhage; arterial pressure waveform

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critically ill patients, and this is actually the reason why we need objective measurements from hemodynamic monitors!

Recently, another pulse contour method was launched on the market. This method is primarily based on the analysis of radial pulse pressure SD and patient characteristics (age, gender, weight, height). This method has the theoretical advantage of being calibration-free. At least four peer-reviewed English-language studies (15–18) have been published so far regarding this method, and they have reported percentage errors always above the clinically acceptable 30% cutoff value proposed by Critchley and Critchley (19). Whether the algorithm, the lack of calibration, both, or any other reason explains these results remains to be determined. Moreover, nothing is known about the ability of this method to accurately track changes in cardiac output.

Finally, one may also consider that computing under- or overdamped arterial pressure curves, as is too often the case in real life, limits the possibility to accurately measure stroke volume, whatever the quality of the pulse contour algorithm (Fig. 1). Further improvement of pulse contour methods may also come from a better quality of arterial pressure recordings. It should also improve the quality of measurements of maximal pressure derivative (dP/dt_{max}) and pulse pressure variation (deltaPP), both variables derived as well from the arterial pressure curve and useful to track changes in left ventricular contractility (20) or to guide fluid therapy (21).

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Myocardial reperfusion injury and the challenging quest for its prevention*

Acute myocardial infarction is one of the most prevalent health problems in the world and thus a major cause of morbidity and mortality. As a result, approaches to salvage ischemic myocardium have long been at the core of cardiovascular research. Over the last three decades, revascularization with thrombolytic therapy or percutaneous coronary intervention has emerged as the single established regimen to limit infarct size. While timely reperfusion of acute ischemic myocardium is the essential step in optimal treatment, reperfusion itself has been proposed to cause irreversible myocardial damage, termed *reperfusion injury* (RI), beyond the damage inflicted by the causative period of ischemia. This implies that optimization of reperfusion therapy could further improve acute myocardial infarction management by salvaging myocardium currently lost due to RI.

Indeed, the field has generated tremendous research interest, with a PubMed search of *myocardial reperfusion injury* currently identifying 7,244 publications. Dr. Roesner and colleagues (1), in the current issue of *Critical Care Medicine*, add to this growing body of knowledge with an elegant study involving a fibrin-derived peptide previously shown to reduce infarct size in rodent models of ischemia-reperfusion (2). The present study extends the promising rodent data three-fold: It provides a) evidence that the fibrin-derived peptide reduces myocardial infarct size in a large animal model (pigs); b) biodistribution and pharmacokinetic data; and c) safety data from a phase I trial studying 30 male healthy volunteers.

The authors are to be lauded for comparing their substance to ischemic preconditioning (IPC) in the positive control group, as IPC has remained, since its landmark discovery by Murry et al. (3) in 1986, the most potent infarct size-limiting intervention apart from reducing ischemia duration. Unfortunately, direct therapeutic application of IPC is naturally limited to models of myocardial infarction. Nevertheless, IPC has stimulated research into its signal transduction to identify triggers, mediators, and effectors of IPC and thus generate targets for pharmaceutical intervention. Numerous therapeutic approaches derived in this way have shown a reduction in infarct size and improved left ventricular function in animal models (for a recent review, see Ref. 4).

However, clinical trials of the respective modalities have yielded mostly disappointing results (for excellent reviews, see Refs. 5 and 6). This discordance between the often successful experimental studies and the predominantly negative clinical trials is not entirely unexpected. Patients in clinical trials are frequently characterized by comorbidities leading to ischemic heart disease, such as atherosclerosis, hypertension, diabetes, and hypercholesterolemia. In addition, they are usually middle-aged or elderly and taking concomitant medication, and many have experienced preinfarct angina pectoris, which, in this context, could be interpreted as naturally occurring IPC. All these aspects are prone to blunt the efficacy of cardioprotective therapies applied at the time of reperfusion to prevent RI.

Another significant challenge in the clinical evaluation of RI treatment lies in the assessment of effects on infarct size. While infarct size is verified as percentage of area at risk in experimental studies, it has to be related to total left ventricular mass in the clinical setting. Furthermore, severity and duration of ischemia as well as mode of occlusion and reperfusion are easily controlled in experimental studies while very difficult to determine in clinical trials. Importantly, the repetitive ischemia-reperfusion typically associated with revascularization (incomplete and fluctuating reperfusion in the case of thrombolysis and balloon dilation followed by stent implantation in the case of percutaneous coronary intervention) may constitute a form of postconditioning. Postconditioning parallels IPC in several aspects (7) with the obvious advantage of being clinically feasible. So far, two small clinical trials, involving 17 and 30 patients, have applied postconditioning strategies and have led to improved ST-segment resolution and decreased creatinine kinase release, respectively (8, 9). However, large-scale clinical trials are clearly needed to substantiate these findings.

A further sobering point lies in the fact that RI remains incompletely understood and thus the most promising therapeutic targets may remain to be discovered. For example, studies of RI modulation by nitric oxide (NO), NO donors, or drugs that enhance NO release (statins, calcium antagonists, angiotensin-converting enzyme inhibitors, dexamethasone) suffer potential confounding factors that might affect experimental results on the role of NO in myocardial ischemia-reperfusion, such as a) the lack of characterization of the involved NO synthase isoforms in myocardial ischemia-reperfusion injury in different animal species; b) the lack of direct measurements of myocardial NO concentration and/or NO synthase activity to ensure sufficient NO synthase inhibition; c) the lack of consideration of nonenzymatic NO production as a potential source of NO; and d) the absence of plasma or blood components in *in vitro* studies influencing NO delivery and metabolism (for review, see Ref. 10).

So, given the tremendous challenges outlined here, is all hope lost for IPC mimetic agents to be clinically successful? Certainly not! In fact, the substance studied by Dr. Roesner and colleagues (1) has two very promising properties in this context. First, decreased interleukin-6 levels were observed in the treated animals that might point toward an anti-inflammatory effect of the fibrin-derived peptide, although it remains unclear whether this contributes to the observed treatment benefit. Second, the very short half-life of 15 mins documented for the substance might be considered ad-

*See also p. 1730.

Key Words: acute myocardial infarction; ischemic myocardium; myocardial damage; reperfusion injury

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vantageous in the context of a biphasic inflammatory response following reperfusion with the second, delayed response required for optimal wound healing (11). A phase II, multinational, double-blind, randomized, placebo-controlled clinical trial of the substance is currently under way (F.I.R.E. study, ClinicalTrials.gov/NCT00326976) with an expected enrollment of 220 patients and completion scheduled for March 2008. In the interest of our patients we should all hope that this clinical study lives up to its experimental promise.

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Norepinephrine in septic shock—Does the early bird catch the worm?*

Septic shock is a distributive shock characterized by marked arteriolar and venous vasodilation associated with an impairment of blood flow to vital organs. Taking into account the pathophysiology, two distinct therapeutic aspects may be of special interest for the treatment of arterial hypotension and hypovolemia resulting from septic shock. First, there is *relative* hypovolemia as a consequence of systemic vasodilation that is mainly mediated by a) increased synthesis of nitric oxide; b) relative vasopressin insufficiency; c) increased opening probability of adenosine triphosphate-sensitive potassium channels; and d) adrenal insufficiency. Second, endothelial injury resulting from leukocyte adhesion, reactive oxygen species and proinflammatory mediators is associated with vascular leakage and thus *absolute* hypovolemia (1). Therefore, fluid resuscitation aiming to counterbalance both relative and absolute hypovolemia is a cornerstone in the treatment of patients with septic shock. In this context, it is noteworthy that Rivers et al. (2) demonstrated that early hemodynamic optimization (guided by myocardial filling pressures) aiming to achieve a balanced oxygen delivery/consumption relationship improves outcome of septic shock patients.

Due to an impaired endothelial barrier function, however, crystalloids and potentially colloids may leak into the extravascular space, thereby increasing extracellular edema and compromising tissue oxygenation. Therefore, massive fluid resuscitation may require aggressive mechanical ventilation, which in turn may further aggravate pulmonary dysfunction (3). In this regard, it is important that fluid overload has been shown to be an independent risk factor for poor outcome in critically ill patients (4).

Early institution of vasopressor treatment counteracting vasodilation and thus relative hypovolemia may, therefore, be a rational approach to reduce fluid requirements and improve pulmonary fluid clearance (5) in septic shock patients. Since volume resuscitation is time-consuming in the presence of severe hypovolemia, early onset of vasoconstrictor therapy often is a lifesaving "bridge" to maintain a sufficient perfusion pressure. Conversely, norepinephrine infusion before or simultaneously with fluid resuscitation may mask intravascular volume deficit and contribute to a so-called "vasoconstrictor-masked hypovolemia" (6). This, in turn, may impair tissue perfusion and oxygenation, thereby possibly fostering the pathogenesis of multiple organ failure.

In the current issue of *Critical Care Medicine*, Dr. Sennoun and coworkers (7) compare the effects of early vs. delayed use of norepinephrine infusion in resuscitated endotoxemic rats. In this carefully conducted study, the authors randomly allocated 35 endotoxemic Wistar rats to five groups (n = 7 each) treated with either no therapy, only fluids, only norepinephrine, or fluids combined with early or late norepinephrine infusion. Whereas norepinephrine infusion was started 90 mins after fluid challenge in the late norepinephrine group, it was given concurrently with fluid resuscitation in the early norepinephrine group. The aim of the study was to assess hemodynamics, tissue perfusion, and tissue oxygenation by comparing the traditional concept (fluid resuscitation followed by vasopressor treatment) with an alternative approach (early vasopressor therapy).

As anticipated, aortic blood flow was only maintained in the groups receiving aggressive fluid substitution. Mesenteric perfusion and liver Po_2, however, were only preserved in animals receiving nor-

*See also p. 1736.

Key Words: catecholamines; fluid therapy; norepinephrine; sepsis; septic shock; vasopressin

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epinephrine infusion. Importantly, mesenteric-to-aortic blood flow ratio was even higher in the group allocated to the early norepinephrine group. The improvement in splanchnic blood flow in the latter group was associated with lower plasma lactate concentrations compared with the other four groups, reflecting an improved oxygen supply/demand relationship. In addition, early norepinephrine treatment spared approximately 30% of the fluid amount required in the late or noncatecholamine groups. Probably due to the small sample size and the short interventional period, however, the authors were unable to demonstrate beneficial pulmonary effects as indicated by differences in P_{O_2}/F_{IO_2} ratio. Future studies are therefore needed to elucidate the impact of early vs. delayed vasopressor therapy on pulmonary function in septic shock in more detail.

Nonetheless, it may well be that early infusion of vasopressin agonists has even more beneficial effects than norepinephrine. In this regard, Hall et al. (8) reported an increased occurrence of acute respiratory distress syndrome in septic shock patients treated with exogenous catecholamines (dopamine, norepinephrine) compared with those treated with vasopressin analogs as first-line vasopressor agents (34% vs. 18%). Using an acute model of resuscitated endotoxemic rats, the research group of Dr. Levy (9) likewise demonstrated that vascular leakage in the pulmonary circulation was more severe in animals treated with norepinephrine compared with arginine vasopressin. Due to the absence of comparative prospective clinical trials, however, the question whether vasopressin agonists are superior to norepinephrine in improving pulmonary function remains unanswered.

Notably, the mean norepinephrine dosages required to stabilize arterial blood pressure in the current study were very high and ranged between 3.8 and 4.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (7). In this context, it may be relevant that rats require higher doses of vasopressors to increase vascular tone in septic shock (10). On the other hand, it should be taken into account that high norepinephrine doses (>0.5 or 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$) represent an independent risk factor for increased mortality in patients with vasodilatory shock resulting from sepsis and systemic inflammatory response syndrome (11, 12). This fact again stresses the usefulness of additional nonadrenergic vasopressors to spare catecholamine requirements in septic shock patients (11, 13).

The study by Dr. Sennoun and coworkers (7) demonstrates that early norepinephrine infusion may improve organ perfusion and reduce the need for volume resuscitation in endotoxemic rats. In view of these imperative findings, it appears rational to treat absolute hypovolemia resulting from plasma extravasation with aggressive fluid challenge. Systemic vasodilation, however, may be primarily counteracted by early initiation of vasopressor support. The current literature on this topic, although limited in extent, supports the view that the early bird catches the worm. Whether the bird's name will be norepinephrine or another nonadrenergic vasopressor remains to be investigated.

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Lung protection in acute respiratory distress syndrome: The neglected vascular side*

In the therapy of acute respiratory distress syndrome, enormous attention has been leveled at the problem of reducing airspace stress and strain. Yet, the lung is primarily a gas *exchanger* whose vasculature binds intimately to its gas-filled counterpart at every level of their shared branching network. Despite this close relationship, recent recommendations give relatively little consideration as to how perfusion can be modified so as to reduce morbidity. A noteworthy article by Dr. Schreiber and colleagues (1) in this issue of *Critical Care Medicine* addresses the potential for vascular pressures and flows to modify the severity of an induced state of lung inflammation. Using acid instillation to induce unilateral lung injury 24 hrs before initiating a 4-hr period of ventilation, these investigators found that increasing dobutamine-augmented blood flows (and perfusion pressures) accentuated injury in the *opposite* lung. This observation is interesting on two counts: first, the lung excluded from acid instillation also incurred inflammatory injury; second, and more importantly, tissue that was spared direct acid exposure was made vulnerable by a seemingly unrelated intervention seldom considered as an injury cofactor in the clinical setting.

Experimental evidence abounds that modifying certain cofactors profoundly influences the manifestations of ventilator-induced lung injury. Prominent among these are position, temperature, $Paco_2$, and vascular pressure (2–5). Body temperature provides one good example. For exactly the same airway stresses (end-inspiratory and end-expiratory alveolar pressures), chilling previously healthy lungs to the lower limit of the physiologic range all but eliminates the damage that is normally encountered (2). One "hit"— the high mechanical stress of tidal respiration—is not sufficient to inflict injury when the metabolic milieu is altered. As another example, either increasing the precapillary pressure or reducing the postcapillary pressure is damaging when high tidal volumes and low positive end-expiratory pressure values are applied (4). One plausible explanation is that the shearing forces generated across the vascular endothelium assume importance once the blood–gas barrier is stressed sufficiently. In both instances, it seems as if two or more factors—one mechanical, one not—synergize to induce tissue injury. The complexity of such interactions may help account for the difficulty in identifying a sharp injury threshold for tidal plateau pressure (6).

In the work of Dr. Schreiber and colleagues (1), tidal airspace pressures, although not directly measured, were unlikely to exceed 25–30 cm H_2O during the 4-hr course of ventilation (1). What accounts for the perfusion-accentuated damage in the healthy lung not exposed to acid? Blood flow through the non–acid-instilled lung was estimated by embolized microspheres to be two and one-half times greater than that through the damaged side. That blood would tend to divert away from the site of acute injury and flow toward healthier zones is expected. But substantially higher blood flows pour through the healthy lungs of elite athletes without obvious damage, even when their exertional tidal volumes apply transalveolar pressures in the range of 20 cm H_2O for hours on end.

One possibility is that lengthy exposure to circulating products of inflammation primed the healthy tissue for subsequent damage by ventilating pressures that are usually innocuous. Even moderate stresses may not be well tolerated when sustained (7, 8). Although the animals in the study by Dr. Schreiber and colleagues (1) were mechanically ventilated for only 4 hrs, previous perfusion of the opposite "healthy" lung with blood carrying inflammatory mediators might have predisposed it to later injury by high vascular flows combined with otherwise marginally stressful ventilation during the intubation period. The "multi-hit" hypothesis for triggering injury seems an attractive explanation.

Another possibility worth considering to explain damage occurring within the non–acid-instilled lung is that the protected side was not entirely healthy from the start. Those of us who have attempted to induce unilateral lung injury by acid instillation or lavage have respect for the purely technical challenges of lung isolation during injury induction. Acid is quickly neutralized to a nondamaging pH value after contact with body tissues. However, even if we assume that the lungs were, in fact, perfectly separated during that phase of the preparation, there is no guarantee that alveolar liquids formed in the damaged and flooded alveoli remained confined to their sites of origin. Intra-airway propagation of noxious products resulting from the injury (surfactant-neutralizing edema and proinflammatory mediators) might be expected to occur in a spontaneously breathing animal in the postinstillation recovery period—a consequence of breathing deeply without positive end-expiratory pressure and periodically coughing these fluids toward the mouth. In this way, considerable (although lesser) *primary* injury might have resulted as well in the lung assumed protected during acid instillation. Such a "propagation injury" mechanism does not depend either on injurious mechanical strain of the airspaces or the presence of noxious circulating mediators, although I have little reason to doubt that these were simultaneously present, as well.

On initial consideration, the behavior of this "unilateral" injury model seems to have limited relevance to generalized acute lung injury encountered in the clinical setting. Nonetheless, these conditions share important characteristics. More than in most experiments, this model was given time to mature; by comparison with our clinical experience of acute respiratory dis-

*See also p. 1741.

Key Words: vascular; acute respiratory distress syndrome; ventilator-induced lung injury; mechanical ventilation; catecholamines

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tress syndrome onset, the experimental time frame of was not unrealistic. Furthermore, the lungs in acute respiratory distress syndrome have a physiologically dichotomous nature, being composed simultaneously of lung units that work in near-normal fashion and those that do not. Functionally, the lungs are *small*, rather than uniformly injured—the "baby lung" concept (9). In this sense, on the microscopic level, acute respiratory distress syndrome lungs can be considered to be a patchwork of functional and damaged units. Of these, well-functioning alveoli are almost certain to receive disproportionate blood flow, as in the unilateral acid-injury preparation.

It is certainly reasonable to ask what lessons an artificial animal model such as this one might hold for everyday practice. Perhaps none of which we can be sure. However, the suggestion is strong that increases of cardiac output have the potential to accentuate damage within the injured lung. These data are certainly consistent with the notion that events on the vascular side of the gas exchanger cannot be ignored—either before or after overt barrier breakdown has occurred. Unless the insult is overwhelming, the evolution of acute lung injury is likely to be a multifactorial process influenced by a host of synergistic cofactors, of which circulatory dynamics are crucial. Multihit dependence of the injury mechanism suggests multiple avenues of prophylaxis and therapeutic attack.

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Preventing "bored-lung disease" when treating patients with ventilatory failure*

Despite more than a half century of experience, the optimal approach to providing ventilatory support to patients with respiratory failure remains unknown, and some paradigms may compound the biological and physiologic effects of the disease process. In the 1970s Webb and Tierney (1) highlighted the potentially injurious effects of mechanical ventilation in their description of ventilation-induced lung edema. Elucidation of mechanisms and identification of proinflammatory ventilatory support strategies began shortly thereafter (2, 3). Seminal work in the setting of asthma demonstrated that minimizing mechanical stress, even at the expense of hypercapnia, can improve outcomes for intubated asthmatic patients (4) Controlling mechanical strain or "stretch limitation" has become a cornerstone of contemporary approaches to mechanical ventilation in the setting of acute lung injury/acute respiratory distress syndrome (ALI/ARDS) (5, 6).

Assessment of ventilatory support strategies must be informed both by cognizance of the adverse consequences of volutrauma/barotrauma and by awareness that oxygenation and carbon dioxide excretion during mechanical ventilation can be critically compromised by factors that reduce functioning gas exchange units. In ALI/ARDS, this may reflect atelectasis in dependent lung regions or alveolar flooding (7, 8). In obstructive airway disease, this may reflect airway closure and significant delays in airway opening during lung inflation (9). The complexity of these interactive elements has been highlighted using sophisticated mathematical and experimental analyses (10).

Biologically variable ventilation (BVV) has potential benefits in the setting of ALI/ARDS that are most likely related to its capacity to open collapsed lung units (11–13). In this mode of mechanical ventilation, applied patterns of tidal volume and ventilatory frequency mimic those that may occur naturally in that there are larger breaths (at low respiratory rate) interspersed among smaller breaths (in conjunction with a higher respiratory rate). The pattern of applied frequency and tidal volume is predefined, based on recordings from normal subjects. The precise mechanisms underlying the benefit of BVV are uncertain, and there are a number of plausible (and not mutually exclusive) explanations. Potential contributors to the salutary effects of BVV range from those rooted in the statistical distributions describing the closed airways, through dynamics, to muscular responses to monotonous ventilation. It is possible that the main advantage of BVV lies in the delivery of a sufficient propor-

*See also p. 1749.

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tion of breaths with larger than average tidal volumes that are of sufficient size to recruit additional respiratory units. If this were true, a similar benefit on oxygenation might be obtained with variable volume ventilation without the requirement of providing biological variability in the driving ventilatory patterns. Whatever the mechanisms, a growing body of evidence suggests that monotonous ventilation is not as beneficial to lung function as a variable ventilatory pattern.

In this issue of *Critical Care Medicine*, Dr. Mutch and colleagues (14) extend their previous work, largely focused on ALI/ARDS, to airway obstruction in a porcine model of bronchospasm. The investigators used methacholine to induce bronchoconstriction in pharmacologically paralyzed swine. The animals then were ventilated with either conventional controlled ventilation or BVV at the same minute ventilation and mean tidal volume. The total respiratory cycle times of sequential breaths applied in BVV duplicated the pattern observed in a 1,733-breath tracing from a normal human. Tidal volume varied reciprocally with frequency: Larger tidal volumes were associated with lower breathing rates and vice versa. Animals subjected to BVV displayed higher arterial oxygen tension, lower $Paco_2$, lower peak inspiratory pressures, and lower respiratory system resistance than those exposed to conventional ventilation. Of particular note, respiratory system resistance, peak inspiratory pressure, and $Paco_2$ increased over the course of the experiment during conventional controlled ventilation, whereas they remained stable in the BVV group. The authors suggest that BVV may be more effective than conventional controlled ventilation in the setting of bronchoconstriction, and their data support this contention.

These important results suggest that a monotonous pattern of ventilatory assistance might be suboptimal in the setting of bronchoconstriction. Perhaps the advantages associated with BVV are related less to conferring a unique benefit than to avoiding adverse physiologic consequences of applying an artificially monotonous respiratory pattern. This research begs us to consider shifting our attention to evaluating the adverse effects of a monotonous ventilatory pattern. Such a change in focus might have important implications for the ventilation of asthma patients in the clinical setting.

The scope of reference in this work is limited by application of BVV to paralyzed swine, thereby eliminating any interaction between the animal's native respiratory pattern and that applied by the ventilator. Respiratory entrainment during volume-cycled ventilation is a phenomenon in which the patient adopts a stable pattern of interaction with the ventilator. This is an extremely complex process in which specific zones of frequency and tidal volume result in substantially different interaction between the patient and the ventilator (15). The process of adaptation might extend over several breaths, corresponding to earlier work in pressure support ventilation (16). Imposing an arbitrary and varying pattern of respiratory cycle lengths and tidal volumes on an awake and nonparalyzed patient could lead to patient-ventilator conflict. Significant patient-ventilator conflict might have adverse consequences beyond those of increased work of breathing, patient discomfort, and potential barotraumas, such as promoting a systemic inflammatory response (17). Given current concerns regarding paralysis—particularly in the setting of steroid administration—and the growing inclination to minimize sedation in mechanically ventilated patients, the authors' findings have both proximate and more general implications.

Human studies of BVV in the setting of airway obstruction as well as other clinical contexts would be of great interest. Such investigations might provide clinically useful information regarding the effectiveness of this mode of ventilation and the degree to which moderately sedated, nonparalyzed patients tolerate imposition of a variable but arbitrary respiratory pattern. This would represent direct translation of the authors' work to the clinical setting.

The potential benefits of a biologically relevant, variable breathing pattern *per se* also suggest that modes of ventilation that permit patient control of breathing architecture also merit further evaluation in the setting of acute bronchoconstriction and beyond. Both well-adjusted pressure support ventilation and proportional assist ventilation offer the patient control over respiratory rate and the size and timing of individual breaths (18, 19). Here, breath-to-breath variability is driven by a lightly sedated or nonsedated patient's native respiratory pattern, with the potential additional benefits of ventilatory muscle activity. The inclusion of such alternative modes of ventilation, each also providing variable tidal volumes, will be crucial in the design of future studies comparing BVV with other modes of ventilation.

As is often the case with such investigations, this study suggests as many questions as it answers. However, it does demonstrate that physiologically relevant variability of the breathing pattern can offer benefit, at least in an animal model of bronchoconstriction. BVV, as described by Dr. Mutch and coworkers (14), is one approach to providing such variability. Variety is the spice . . .

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