The Nina, the Pinta, and heart rate variability: The search for prognostic indicators after cardiac arrest*

More than 500 years ago, Christopher Columbus set sail west across the Atlantic searching for better trade routes with East Asia. Although Columbus and his team never found the route to the Orient, they opened an age of European exploration of the Americas and popularized use of the prevailing trade winds for transcontinental travel (1). In this issue of *Critical Care Medicine*, Tiainen and colleagues (2) set out to study heart rate variability as a potential indicator of prognosis after cardiac arrest. Although one parameter of heart rate variability at 48 hours had prognostic implications for patients treated with therapeutic hypothermia, this report stands out as the first to carefully study electrocardiographic data during therapeutic hypothermia in patients who had already experienced a cardiac arrest. As with Columbus, these secondary discoveries may be the results better remembered.

Therapeutic hypothermia has evolved from a novel intervention to a standard treatment for cardiac arrest survivors with encephalopathy (3–6). Although most deaths are due to hypoxic-ischemic brain injury and not recurrent cardiovascular events (7, 8), concerns regarding the safety or potential adverse events associated with hypothermia may contribute to clinician reluctance to implement this important therapy (9, 10). Two recent reviews guiding efforts to predict outcome after cardiac arrest do not include data from patients treated with hypothermia (11, 12), but do note the potential confounding effect from the 24 hours of hypothermia and the increased use of sedation and neuromuscular blockade associated with it (13). Tiainen and colleagues provide the best existing data regarding adverse electrocardiographic events during hypothermia and describe a tool that may improve prognostic efforts.

As part of the Hypothermia after Cardiac Arrest study, 70 consecutive adult patients resuscitated from out-of-hospital ventricular fibrillation at Helsinki University Hospital were randomly assigned either to therapeutic hypothermia or to normothermia (2). Twenty-four-hour electrocardiographic recordings were performed on days 1, 2, and 14, and frequency and time domain assessments of heart rate variability were performed. Premature ventricular beats were increased in the hypothermia-treated group during the first two recordings, but no difference was noted in the occurrence of ventricular tachycardia or fibrillation for patients treated with hypothermia or normothermia. Defibrillation was required by only one patient during hypothermia (compared with two patients in the normothermic group). Two of 36 patients had mean heart rates <50 during hypothermia, and one of these received a temporary pacemaker that fired for <5 minutes. In multivariate analysis, preserved heart rate variability seemed to predict a favorable outcome.

By careful documentation of electrocardiographic activity among cardiac arrest survivors treated with hypothermia and normothermia, Tiainen et al have added to previous work in neuroprognostication after cardiac arrest (14, 15). Of perhaps greater applicability, their study expands our understanding of the safety of hypothermia among patients with complex cardiac conditions. Therapeutic hypothermia was recently shown to be safe and beneficial in patients with cardiogenic shock treated with intra-aortic balloon pumps and in conjunction with percutaneous coronary intervention (16, 17). The present study confirms that ventricular arrhythmias are common, but not more prevalent in patients receiving hypothermia, and that bradycardia is common but rarely requires treatment. These findings increase our understanding and are based on data from more reliable monitoring than in existing reports.

Just as Europeans provided information facilitating further exploration of the “new world” 500 years ago, Tiainen’s group provides data that advances our understanding of therapeutic hypothermia. We can only hope that many other investigators will travel these waters to discover better and safer ways of providing this important therapy and to furnish us with tools to better predict outcomes.

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*See also p. 403.

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Hemodynamic support of shock state: Are we asking the right questions?*

Septic shock is one of the most challenging problems in the critical care. Its mortality toll in the United States ranges between 200,000 and 250,000, a number comparable with myocardial infarction. Diagnosing and treating a septic shock is like looking the stars at night: from single bright spots, you have to reconstitute the constellations to have the complete picture.

For the last 40 years, catecholamines have been used routinely in shock state, trying to restore normal or near-normal hemodynamic parameters. The rationale is to maintain a minimal level of blood pressure in septic shock patients (1). From a quasi-empirical use, more and more knowledge has emerged on the mechanisms and effect of these drugs. Our understanding of shock state improves, including myocardial depression in septic shock, the links between inflammation and coagulation, and microcirculation and cellular energetics. Our pharmacologic tool set expanded and include vasopressin and analogs, phosphodiesterase inhibitors, and calcium sensitizers. As knowledge expand, the picture gets more complex and the clinicians more confused.

The Quest for the Magic Bullet

In this issue of Critical Care Medicine, Povoa et al (2) adds to the comparison of different catecholamine in shock states. They observed a large multicentered population of septic shock patients, the various catecholamines used, and the patient's outcome. They show that dopamine, norepinephrine, and dobutamine increase mortality. Should we ban these drugs from our pharmacopoeia? Certainly not. First, the natural catecholamines are part of the acute-phase response to physiologic stress and are essential for human species. These molecules are part of our survival kit (3). Second, using a similar strategy, others (4) observed that dopamine decreases mortality in septic shock patients and that norepinephrine and dobutamine have no effect. This is contrary to the conclusion in the present study. Other cohorts have investigated this question with variable results (Table 1). One can argue that these are not randomized control trials, but most randomized control studies also failed to point out a consistent effect. Third, most of the studies do not start with patients on no adrenergic support: when a certain level of dopamine or norepinephrine is reached randomize into replace by or add “A” vs. “B.” First, the picture is blurred. Catecholamines at a usual pharmacologic range yield to concentrations 100 times above the physiologic concentrations. Second, there is a significant interindividual variability in catecholamine kinetics: a fixed dose of dopamine can yield to plasma concentrations in a 20-fold range. Third, dopamine is the natural direct precursor of norepinephrine through beta-hydroxylase. During dopamine infusion (3 μg/kg/min), plasma norepinephrine concentration increases (5).

Should We Change Our Approach to Shock States

Until recently, hemodynamic support of shock state was focused on restoring normal or near-normal physiologic parameters. In the 1980s, there was even a tendency toward supranormal physiologic goals. To easily achieve target hemodynamic parameters, having one single magical drug would make the clinician’s life easier. There is a quest toward the magic bullet applicable in all patients: Is dopamine better than norepinephrine? Is vasopressin better than norepinephrine? What is the optimal target for mean arterial blood pressure? What is the optimal cardiac output/mixed venous saturation? Consensus panel supported the use of catecholamines in septic shock with a grade E evidence (6). Clinical investigations suggest that increasing the target mean arterial pressure (MAP) from 65 to 85 mm Hg does not change oxygen-
The inlet pressure of physiologic capillaries is 20–25 mm Hg. There are no data to suggest that 50 mm Hg MAP is more deleterious in terms of microcirculatory and organ perfusion than 65 with vasopressors. Sepsis induces a state of nutrient and oxygen deficiency at the cellular level. This cellular energetic failure leads to organ dysfunction, myocardial depression, and microcirculatory dysfunction (Fig. 1). The myocardium is energetically exhausted. Increasing the catecholamines level is like whipping an exhausted horse. With worsening cellular dysfunction, the horse will not respond the whip—the shock will become refractory to cat-

NE, norepinephrine; AVP, arginine-vasopressin; Dobu, dobutamine; Dopa, dopamine; Epi, epinephrine; norEpi, norepinephrine; MAP, mean arterial pressure; MODS, Multiple Organs Dysfunction Syndrome.
The compliance to selected items of the 6-hour bundle ranges from 30% (antibiotics within 3 hours) to 80% (vasopressor). Using an all-or-none approach, Items of a bundle are inseparable: It is not a flexible contract. The strength of these bundle and outcome improvement come from 1) a standardized approach to patients in septic shock (22). Some intensivists dream about the multicentered international randomized control trial comparing norepinephrine vs. dopamine vs. vasopressin in septic shock patients: The design would be study drug “X” vs. “Y” in a concealed bag titrated to MAP of 70 mm Hg. What is the best in terms of MAP? What is the best in terms of outcome? Maybe we should change from “what is the best in term of MAP?” to “what is the best for the mitochondria?” (20).

Sepsis Bundle Is a Whole Package: Take it as a Whole

Following the fundamental study by Rivers (21), several consensus conferences proposed a structured multisystem approach to patients in septic shock (22). The compliance to the surviving sepsis campaign items of a bundle are inseparable: It is not a flexible contract. The strength of these bundle and outcome improvement come from 1) a standardized approach (23), 2) the check list effect avoiding missed items, and 3) the speed of intervention including time points were goals should be met (6 and 24 hours). Compliance to the surviving sepsis campaign bundle in the SACiUCI study was also published as a preliminary abstract (24). The compliance to selected items of the 6-hour bundle ranges from 30% (antibiotics within 3 hours) to 80% (vasopressors after adequate fluid). Using an all-or-none approach, >70% of the patients failed the 6-hour bundle. Failing the 6-hour bundle is associated with an increased mortality in the present cohort (24). There are three strategies to assess...
compliance to a set of interventions/markers (25): 1) As Povoa et al presented as item-by-item measurement, 2) as a composite variable i.e., four items of six, or 3) using an all-or-none measurement. The outcome improvement does not come from a specific intervention or a specific catecholamine. It is time to raise the bar and assess the surviving sepsis campaign recommendation as an inseparable package. We should go further than the 6-hour limit: In parallel to data from myocardial infarction regarding door-to-balloon time, we should focus on a door to sepsis bundle time. Despite an excellent worldwide campaign, endorsement by a dozen of critical care societies and organizations, practice has room for improvement. Sepsis is like myocardial infarction: its an emergency!

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In this issue of Critical Care Medicine, Heemskerk et al (1) describe a clinical trial on the effect of treatment with purified bovine intestinal alkaline phosphatase (AF) vs. placebo in a small series (n = 36) of patients with severe sepsis or septic shock from Gram-negative and Gram-positive microorganisms and having (impending or manifest) acute kidney injury and failure. Indeed, AF is capable of detoxifying endotoxin, even at physiologic concentrations, by dephosphorylation of the lipid A moiety of lipopolysaccharide (2), and exogenous administration in animals with Gram-negative sepsis and shock appeared beneficial (3, 4). The Heemskerk et al (1) trial was too small to discern a morbidity or survival benefit of AF treatment, but, nevertheless, the authors observed some effect on renal function parameters. In a small substudy (in patients not on renal replacement therapy), in which the effect of AF seemed even more pronounced, protection appeared associated with less inducible nitric oxide synthase (iNOS)-derived nitric oxide (NO) production and release of markers of the (resultant?) injury in the tubular cells and excreted in the urine. These (selected) observations should be regarded as preliminary, and protection by AF of renal function in sepsis and shock should be confirmed in larger studies with stronger end points, such as the need for renal replacement therapy, the speed of recovery of septic renal failure, and alike, which have not been studied by Heemskerk et al (1). In contrast, the authors have focused on acute kidney injury criteria including serum creatinine, even in patients already on renal replacement therapy at the start. We cannot formally exclude that AF affected tubular creatinine excretion rather than glomerular filtration. Furthermore, the mechanisms behind this potentially beneficial and relatively specific effect on the kidney remain to be demonstrated, because, among others, it is unclear how AF would also benefit patients with Gram-positive septic shock.

Endogenous AF is ubiquitous and abundant in epithelial cells and serves, among others, as an ectonucleotidase, to dephosphorylate and degrade extravascular (high energy, monoester) phosphate compounds. There are various isoenzymes for different tissues, which, for instance, play a role in bone turnover, bile excretion, and placental development and function (5). Expressed in the mucosa of the gastrointestinal tract, AF may help to limit translocation of harmful endotoxin from the lumen (5). The function of the enzyme located in the brush border of the proximal tubule is unclear and may only partly relate to resorption of phosphate. It is shed and excreted in the urine in the course of tubular injury and may be upregulated in the kidney during (experimental) sepsis (6, 7).

Extracellular phosphate compounds, released by various cells and tissues particularly on hypoxia or inflammation, may, via nucleotide signaling and purinergic receptors, affect a wide variety of processes, involving innate immunity, epithelial transport, and regulation of blood flow (8–10). This applies to both adenosine triphosphate and its dephosphorylation products adenosine diphosphate, adenosine monophosphate, and adenosine, and the kidney, but effects depend on specific receptor stimulations and conditions (11). For instance, the compounds are vasodilators in normal rats but vasoconstrictors (also in the renal bed) in endotoxin-challenged animals (12). Adenosine triphosphate and adenosine, being mediators of tubuloglomerular feedback, may also decrease renal blood flow by afferent vasoconstriction via A1-adenosine receptor stimulation (8, 11, 13, 14). The compounds may have proinflammatory actions so that (specific) adenosine (receptor) antagonists are protective, whereas, in contrast, stimulation of some (A3) adenosine receptors may have anti-inflammatory actions, even in the kidney (15, 16). We also know that inhibitors of phosphodiesterases, degrading phosphate diesters, such as cyclic adenosine monophosphate to adenosine can be protective in experimental acute kidney injury after a wide variety of challenges, including endotoxia (17). How AF might interfere with these processes is largely unknown. Indeed, the study by Heemskerk et al (1) does not give insight into the specific effect or the routing of AF in the kidney during sepsis. Nevertheless, it suggests that iNOS upregulation is associated, even perhaps in a causative manner, with proximal tubular damage and, thereby, contributes to acute kidney injury, as observed before (18). Oxidative stress, NO-derived peroxynitrite and subsequent mitochondrial and nuclear DNA damage, and protein nitrosylation may be some of the mechanisms underlying iNOS–NO-derived toxicity. This may also explain, at least in part, the often presumed maintenance of renal blood flow and the observed fall in filtration fraction and glomerular filtration in patients with impending acute renal fail-
ure during hyperdynamic sepsis (19). We cannot judge these mechanisms from the data in the study by Heemskerk et al (1), and, therefore, the clinical significance of potential renal AF-induced adenosine and iNOS-derived NO and associated benefits and harms remain to be elucidated.

Taken together, the preliminary study by Heemskerk et al (1), done in a difficult-to-study patient population, addresses important and partly novel issues on the role of AF, acute kidney injury, and iNOS in human septic shock. However, many questions remain on the new clothes of the emperor (AF) and, particularly, how they are tied together. The interesting observations need confirmation in a larger trial.

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Is target population more important than patient location when evaluating tight glycemic control?*

Clinical trials in the intensive care unit can be divided into two categories. The first category includes disease- or syndrome-specific trials that examine the effect of a drug or practice on a group of patients with that specific disease or syndrome. Examples of this type of trial would be the use of lung-protective ventilation in patients with acute lung injury (1) or the use of steroids in patients with septic shock (2). The second category of trial enrolls patients with a particular severity of disease that leads to admission to an intensive care unit. This type of treatment-specific trial would include patients with different types of disease that precipitate similar severity of illness and location within an intensive care unit. Examples of this type of trial would include the Saline versus Albumin Fluid Evaluation trial examining the use of specific forms of volume resuscitation in critically ill patients (3) or goal-directed therapy in patients with a broad range of critical illness (4). Such trials in a heterogeneous group of patients may provide improved external validity. However, variation in response to an investigation across different disease processes may obscure a potentially beneficial treatment effect. It is, therefore, important to consider whether the disease process might modify the effect of the treatment being tested when choosing which category of trial to design.

Most of the larger trials of tight glycemic control in patients with critical illness fit the second category of studies (5–8). These trials were performed on a broad range of critically ill patients, including patients with a variety of surgical and medical diagnoses, and the effects of tight glycermic control across these groups of patients were tested. Importantly, the benefits of tight glycemic control seen in

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primarily cardiovascular surgical patients (6, 9) were not replicated in two large trials in different patient populations (5, 7). In addition, tight glycemic control may also increase episodes of potentially harmful hypoglycemia. Most notably, the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis and the Glucontrol studies (7, 8) documented a potential association between hypoglycemic episodes and worsened outcomes in critically ill patients. This tension between tight glycemic control and avoidance of hypoglycemic episodes highlights the importance of selecting the proper patient population in which to test the risk–benefit ratio of tight glycemic control. The largest trial of tight glycemic control, the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation Study (NCT00220987), which continues to enroll patients, also tests the effects of glucose control in a heterogeneous group of critically ill patients.

The study by Savoli et al (10) in this issue of Critical Care Medicine fits the first category of studies, testing tight glycemic control in patients with sepsis. In their prospective, multicentered study of 90 septic patients randomized to tight glycemic control (mean glucose, 112 mg/dL) vs. conventional glycemic control (mean glucose, 159 mg/dL), blood plasminogen activating factor inhibitor-1 (PAI-1) activity, PAI-1 concentration, and tissue plasminogen activator levels were noted to decrease more rapidly over the course of 28 days in the tight glycemic control group. The treatment group also had lower Sequential Organ Failure Assessment scores over the same time period. Most of the differences between groups were found after 10–15 days of therapy, when many patients had either left the intensive care unit or died. Fibrinolysis, as measured by PAI-1 activity and concentration, was inhibited in only a subset of their septic patients and this inhibition was associated with higher baseline Sequential Organ Failure Assessment scores and mortality rates (10). Of note, with the exception of interleukin-6, no significant difference in the levels of inflammatory mediators was found between the treatment groups.

The findings of Savoli et al (10) are consistent with previous studies showing that insulin dosing may limit levels of PAI-1 in healthy adults. Further, insulin-regulated normoglycemia has been found to prevent immune dysfunction and inappropriate inflammation, endothelial function, and coagulation (11). These data, coupled with the fact that the septic state contributes to microvascular thrombosis, tissue-factor-mediated thrombin activation, impaired fibrinolysis, and increased PAI-1 levels (12), make it reasonable to propose that a potential mechanism behind the beneficial effect of tight glycemic control via intensive insulin therapy may be due to these coagulation modulatory effects. Of note, neither the findings of Savoli et al nor a recent study by Langouche et al (13) demonstrate differences in inflammatory markers between patients treated with tight glycemic control and conventional glycemic control.

Although the study by Savoli et al provides a biologically plausible rationale for improved outcomes in septic patients with tight glycemic control, it does not provide enough evidence to change practice without having the results replicated in a larger study. The lack of information on length of exposure to usual glycemic control before enrollment and the unclear mechanism that might lead to delayed inhibition of fibrinolysis in the control group limit the generalizability of the results.

As with the trial by Savoli et al, the selection of a more homogeneous patient population may permit the use of smaller sample sizes to demonstrate a treatment effect. In addition to large multicenter trials such as NICE–SUGAR, there room for additional appropriately designed smaller trials to test biologically plausible treatments in well-defined patient populations with specific syndromes or diseases.

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Myocardial depression/injury in sepsis: Two sides of the same coin?*

In the modern era, the concept of reversible myocardial depression or dysfunction was described by Wiggers (1). He postulated the existence of a myocardial depressing factor responsible for myocardial dysfunction in hemorrhagic shock. During the 1960s and 1970s, experimental studies showed evidence of transient myocardial dysfunction in several forms of critical disease, including hemorrhagic and septic shock (2, 3).

Sequential studies have shown that patients in septic shock adequately resuscitated typically displayed a high output and low-systemic resistance hemodynamic circulatory condition, with myocardial depression despite the high output (4–7). The presence of a normal or even high ejection fraction does not exclude myocardial derangements. In those patients who died, this hemodynamic pattern persisted until death.

The initial phase of understanding and the study of cardiovascular manifestations in sepsis and septic shock began with the development of radionuclide cineangiography techniques (radioisotopic ventriculography) and with the application of volumetric echocardiography in managing the critically ill patients.

Discussions on the true involvement of the heart in sepsis and septic shock, regardless of hemodynamic conditions, date back to the early 1960s (8) when some studies already used endotoxic shock models in animals. In the 1980s, using nuclear medicine techniques, Parker et al (6) demonstrated the decreased biventricular ejection fraction in these septic patients. The connection between clinical myocardial depression and the effects of myocardial depressor substances was described by Parillo et al (9), in the late 1980s, by measuring the serum levels of the substances in these patients during the septic phase. This study established a strong tie between in vivo and in vitro observations of cardiac function and the activity of myocardial depressor substances in septic shock.

In 1994, we and others (10) published the histopathologic findings of the myocardium in 71 autopsies of patients who met morphologic criteria of sepsis, comparing them with a control group and observing the presence of interstitial myocarditis in 27% of the sample, bacterial colonization in 11%, necrosis of cardiac fibers in 7%, and interstitial edema in 28%, although this last finding did not demonstrate a significant difference relative to controls. Furthermore, the identification of troponin in 1999 as a reliable marker of myocardial injury in sepsis added some new insights to this complex disease (11).

In this issue of Critical Care Medicine, Bouhemad et al (12) were auspicious in bringing some light to this matter by identifying two groups of troponin-positive septic patients whose clinical and echocardiographic features were markedly different.

Echocardiographic abnormalities showing increased left-ventricular dimensions and reduced ejection fraction were detected in those patients with severe but reversible myocardial dysfunction, whereas those who were not able to dilate, probably because of greater infiltrate of polymorphonuclear cells within the myocardial fibers rendering the myocardium less compliant, were more prone to ultimate death. It is now clear that we cannot manage every septic patient the very same way. As pointed out by the authors, the concept of preload recruitment applies exclusively to the subgroup with systolic left ventricular impairment where ventricular enlargement may represent an adaptive mechanism to maintain cardiac output, whereas those presenting with ventricular relaxation impairment despite showing no ventricular dilation at all and no drop in ejection fraction exhibit worse prognosis.

More recently, John et al (13) were able to show better outcomes in troponin-positive patients submitted to activated protein C administration.

Like cardiac patients, we can possibly now stratify the most severe septic patients by determining troponin levels and echocardiographic ventricular dimensions and, therefore, select the most suitable therapeutic choices and probably achieve better outcomes in these critically ill septic patients. Further studies should address these questions to clarify the most controversial issues related to this two-sided coin disease.

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How long does it take to demonstrate the value of an idea?*

In 1991, the Consensus Conference of the American College of Chest Physicians and the Society of Critical Care Medicine introduced the systemic inflammatory response syndrome, defined the presence of both infection and systemic inflammatory response syndrome as sepsis, and stated clear definitions of severe sepsis and septic shock (1). Subsequently, infection and sepsis appeared to have similar outcomes, unaffected by the presence or number of inflammatory response criteria (2). A decade after the previous Consensus Conference, the scientific community of intensivists developed the idea of a staging system for sepsis similar to that used by oncologist to stratify septic patients on the basis of their predisposition, infection, host response, and concomitant organ dysfunction (PIRO) (3).

Community-acquired pneumonia (CAP) is one of the most frequent infectious diseases. CAP refers to pneumonia in a previously healthy person who has acquired the infection from outside the hospital, and therefore, it is also responsible for high costs for the society. Furthermore, the mortality associated with CAP leading to organ dysfunction in the patients admitted to intensive care unit (ICU) is high. Taking the PROWESS study as an example of trial on severe sepsis, globally, 602 of the 1690 patients (35.6%) enrolled had CAP, and 160 of them died (26.6%) (4). Therefore, CAP is a frequent cause of severe sepsis and death.

To describe and compare CAP patients involved in clinical trials, investigators need both a clear definition of CAP and a tool to assess the severity of illness. The first one was given by the Infectious Diseases Society of America (5), which defined CAP as an acute infection of the pulmonary parenchyma in a patient not hospitalized or residing in a long-term care facility for 14 days or more before onset of symptoms. As far as the assessment of the severity of illness is concerned, mortality rate for CAP ranges from 5% in hospital ward patients to 14% in ICU patients, with a mean Simplified Acute Physiology Score II (SAPS) of 33 (6) to 43% in those with a mean SAPS II of 46 (7). Therefore, the assessment of the degree of the severity of illness in ICU patients with CAP is substantial for any patient comparison.

In this issue of Critical Care Medicine, Rello et al (8) present a scoring system specific for CAP based on the PIRO concept, aimed at stratifying critically ill patients in mortality risk groups. The authors compared the performance of the new score, named CAP PIRO, with that of two different scores: one specific, ATS-revised criteria, and the other generic, Acute Physiology and Chronic Health Evaluation II. The CAP PIRO included the presence of the following variables: comorbidities (chronic obstructive pulmonary disease, immunocompromise) and age >70 years, representing the predisposition of the PIRO concept; multilobar opacities in chest x-ray and bacteremia, representing the insult; shock and severe hypoxemia, representing the response; and acute renal failure and acute respiratory distress syndrome, as surrogate of organ dysfunction (8). The CAP PIRO, ranging 0–8, allowed stratifying the patients in the following four categories of risk: low, 0–2 points, with 28-day death rate of 3.6%; mild, 3 points, with 13% 28-day mortality; high, 4 points, with 43% 28-day mortality; and very high, 5–8 points, having a 28-day mortality of 76.3%. The discriminative ability, measured by the area under the receiver operating curve, was better for CAP PIRO than for ATS-revised criteria and Acute Physiology and Chronic Health Evaluation II. Not only mortality but also ICU length of stay and duration of mechanical ventilation were significantly different in the four levels of risk of CAP PIRO (8).

The article by Rello et al (8) has some major strengths. First, the study was performed on data prospectively collected by 33 Spanish ICUs, with a large sample of 529 adults. The wide odds ratio reported for incidence of shock, severe hypoxemia, or acute respiratory distress syndrome, as well as the wide interquartile range of lengths of mechanical ventilation and ICU stay suggest differences in case-mix and/or practices between ICUs, even in the same country, but this finding is common to multicenter studies. Second, the CAP PIRO allows stratifying the patients admitted to ICU with CAP according to the risk of death at 28 days; therefore, it can be useful for researchers involved in clinical trials on this topic (for instance, on antibiotics). Finally, it suggests a relationship between CAP PIRO and healthcare resource use.

The study by Rello et al (8) has some limitations. The authors did not collect hospital mortality data and considered patients discharged alive from ICU within 28 days as survivors. Some of those pa-

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*See also p. 456.

Key Words: pneumonia; sepsis; predisposition, infection, host response, and concomitant organ dysfunction; intensive care unit; severity of illness

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Patients may have died in the hospital after ICU discharge, according to a general documented post-ICU mortality of 10.8% (9). Even more relevant, in a group of septic patients, hospital mortality has been reported to be 48.3%, whereas 28-day and 60-day mortalities were 44.8% and 47.8%, respectively (10). The finding that hospital mortality is consistently higher than 28-day mortality in such patients suggests that a measure of long-term outcome should be associated with CAP PIRO in clinical trials.

Unfortunately, the CAP PIRO does not allow computing a probability of hospital mortality. Furthermore, it was not compared with more recent prognostic models, namely SAPS 3 Admission Score (11, 12) or Acute Physiology and Chronic Health Evaluation IV (13), which were not available at the time of data collection, or SAPS II customized for severe sepsis/septic shock (14).

Another article on the application of the PIRO concept has been published few months ago in *Intensive Care Medicine* (15). The study was performed on the SAPS 3 Admission Score database to develop a model predicting hospital mortality of patients ICU admitted with infection. There is some overlap with the study of Rello et al. (8), and not surprisingly, there are predictive variables common to the two studies, even if categorized in a different way. Despite the different target populations of the two scores based on the PIRO concept, namely, CAP and sepsis patients, the publication of those articles (8, 15) in such a short-time interval suggests that 5 years is the time lag required by the scientific community to demonstrate the value of an idea like PIRO.

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Intensive insulin therapy: The swinging pendulum of evidence*

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ince 2001, the year of publication of the first intensive insulin trial by Van den Berghe et al (1), hyperglycemia and intensive insulin therapy (IIT) are placed high on the list of critical care controversies. In this trial, Van den Berghe demonstrated a survival benefit for surgical intensive care unit (ICU) patients treated with an intensive insulin protocol to maintain normoglycemia (80–110 mg/dL; 4.6% compared with 8.0% in-hospital mortality). Although this was a single-center trial according to evidence base medicine standards is not so high, IIT was adopted by many and even incorporated in guidelines for sepsis patients, such as the Surviving Sepsis Campaign, endorsed by the Society of Critical Care Medicine, and the European Society of Intensive Care Medicine (2, 3). Since the original hallmark study, several observational trials confirmed the positive effects of normoglycemia on outcome in critically ill patients (4, 5). However, enthusiasm waned after the results came out of three other prospective randomized trials on IIT in critically ill patients. Of these, two trials are published (6, 7), one trial is finished, but only presented as an abstract (http://clinicaltrials.gov/ct/gui/show/NCT00107601). A fourth trial, the Australian–New Zealand–Canadian “Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation” trial, is still recruiting (http://www.controlled-trials.com/ISRCTN04968275). Unfortunately, the results of these trials have made things less clear. The single-center follow-up trial by Van den Berghe in medical ICU patients rendered ambivalent results (6). There was no difference in outcome between patients treated with IIT and conventional insulin therapy. However, in the subgroup of patients admitted for 3 days or more, IIT was associated with a survival benefit (in-hospital mortality in the conventional treated patients was 53.5% vs. 43% in IIT patients). This subgroup of patients could not be identified beforehand. An important difference with the previous trial of this group was that patients in the medical ICU were more severely ill. Also, there was a much higher incidence of hypoglycemia in patients treated with IIT in the medical ICU, compared with the surgical ICU trial (18.7% vs. 5.1%). The German multicenter Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis study randomized severe sepsis patients to IIT or conventional insulin therapy and Ringer’s lactate or a starch solution for fluid resuscitation (7). The study was stopped for safety reasons by the data and safety monitoring board of the study, after an interim analysis demonstrated an unexpected high rate of hypoglycemic events (17.0%) in patients randomized to IIT. The positive effects of IIT, as demonstrated in the first study by Van den Berghe et al, could not be confirmed, not even in subanalysis. In the 537 patients eligible for analysis, there was no difference in a series of outcomes including 28- and 90-day mortality between patients treated with conventional insulin therapy and IIT. The European multicenter Glucontrol study was also prematurely stopped after inclusion of 1101 patients because of a higher rate of adverse events in IIT patients. All-cause mortality was not different between patients exposed to conventional and IIT (17% vs. 15%, p = not significant). In summary, the beneficial effects of IIT were only confirmed in a subanalysis of a more sick patient cohort, by the team that invented the therapy, and could not be reproduced in two, underpowered, multicenter trials. In addition, there are concerns regarding the side effects of IIT. There was a high incidence of hypoglycemia both in the experienced hands of the Leuven team and in the less experienced hands of the centers that participated in the two multicenter studies. These results raise concerns regarding the external validity of IIT. In other words does IIT work in other, less experienced units? It also illustrates that it is not necessarily correct to translate a therapy that works in a specific patient cohort to another cohort.

In this issue of Critical Care Medicine, Bagshaw and colleagues present the results from an observational study on a very large database of 66,184 Australian ICU patients (8). Although this is an observational study, it adds a whole new dimension to the IIT controversy. In this study, normoglycemia was associated with better outcome, even after correction for other covariates for increased mortality. In other words, blood glucose levels in the normal range are good, as in the original study by Van den Berghe et al. Interestingly, the “normal” range in this study is higher than that used in the studies on IIT mentioned before (5.6–8.69 vs. 4.4–5.6 mmol/L). This range was determined as the second quartile of all average blood glucose concentrations, and it corresponds remarkably well with the conservative recommendations of the Surviving Sepsis Campaign (blood glucose <150 mg/dL or 8.25 mmol/L). An important aspect in this study is that patients were categorized on an average blood glucose concentration during a 24-hour period, and not on the morning blood glucose, as in the Leuven studies and in the VISEP study. This may be of importance, as it has been demonstrated that glucose control may vary considerably in IIT patients, during a 24-hour observation period (9). Differences in blood glucose control during a 24-hour period, may explain why IIT works in the hands of Van den Berghe’s team, and why this could not be reproduced in the VISEP and Glucontrol trials. One may assume that Van den Berghe’s team is more experienced and dedicated, and therefore is able to maintain a stricter glucose control during a 24-hour period compared with less experienced units. Higher target levels may diminish the beneficial effects of IIT, but more adequate blood glucose control during a 24-hour period may compensate for that. Therefore, average blood glucose may be a more adequate marker of the efficacy of IIT, and should be considered in future studies. In addition, higher target blood glucose concentration will probably lower the inci-

*See also p. 463.

Key Words: intensive insulin therapy; blood glucose; outcome; critically ill; hypoglycemia; hyperglycemia

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Cardiocerebral resuscitation: Few answers, more questions*

A major concern since the advent of the modern age of cardiac resuscitation is that we might be resuscitating patients but leaving a large group of patients with prolonged neurologic disability. Cobbe et al (1) found that about 40% of initial survivors of out-of-hospital cardiac arrest could be discharged home without major neurologic disability. Adrie et al (2) found that while early death from refractory shock occurred in 42 patients from a group of 130 patients achieving restoration of spontaneous circulation (ROSC) for >1 hour, 60 of the remaining 88 patients died of complications related to neurologic failure later in the hospital course. Concern that survivors from cardiac arrest could become a long-term burden on the society was ameliorated by studies like these showing that there was a high rate of mortality in severely neurologically impaired patients in the period immediately after resuscitation. Cole and Corday (3) found that only two patients (7% of the total) requiring more than 4 minutes of advance cardiac life support could be resuscitated and discharged alive, both with permanent brain damage. In a study of resuscitated in-hospital intensive care unit and nonintensive care unit victims of cardiac arrest, Bell and Hodgson (4) found that although 30% and 45% of patients, respectively, were comatose after resuscitation, most of these patients died. Only 3% and 4.5% of patients from these groups were discharged alive with brain damage.

No-reflow, the concept of achieving ROSC, but subsequently suffering a fall in cerebral blood flow, which, in turn, contributed to poor cerebral outcome, and ultimately, the demise of the patient was postulated by Negovsky (5) and shown to exist in animal and clinical models. Safar (6), challenging the prevailing emphasis on cardiac resuscitation, noted that too many victims achieve ROSC as demonstrated in the studies earlier, only to die of cerebral failure, emphasizing the need for a new type of cardiopulmonary resuscitation (CPR), cardiocerebral CPR, or CPCR.

Mullner et al (7) demonstrated that prearrest variables and postarrest neurologic function influenced outcome. Adverse outcome increased with increasing age and in patients with increasing numbers of prearrest diseases, especially congestive heart failure and diabetes mellitus. Again, long-term survival with profound neurologic impairment was not found to be a problem with 106 of the 121 patients (29% of the survivors) with unfavorable neurologic recovery dead within 6 months of the initial cardiac arrest. Age and an ejection fraction <35% were also shown to be associated with unfavorable outcomes by Bunch et al (8) in a study of ischemic vs. nonischemic heart disease-associated cardiac arrests. The influence of left ventricular function was confirmed in a study of in-hospital cardiac arrest. Gonzalez et al (9) found a 19% survival to discharge in patients with a normal systolic pressure >100 mm Hg on presentation.

*See also p. 471.

Key Words: cardiac arrest; heart failure; cerebral oxygenation; ventricular fibrillation; cardiocerebral resuscitation

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mal prearrest ejection fraction vs. 8% in those with moderate to severe left ventricular dysfunction.

In this issue of *Critical Care Medicine*, Skhirtladze et al (10) help explain the influence of heart failure on neurologic outcome from cardiac arrest in their fascinating model of reversible human cardiac arrest by studying patients having a cardiodefibrillator tested during implantation. Although physiologic studies have been conducted on victims of cardiac arrest, most have been on patients with long downtimes before instrumentation. In this study, ventricular fibrillation is induced to test the cardiodefibrillator, offering the opportunity to measure cerebral oxygenation before and after ROSC. In this elegant study, the authors showed that despite similar blood pressure, heart rate, and pulse oximetry values, patients with severe heart failure were more likely to have clinically important cerebral desaturation detected by near infrared spectroscopy. This was evident at baseline and after brief periods of cardiac arrest. This might explain why patients with heart failure suffering cardiac arrest do so poorly. Cohan et al (11) found seemingly paradoxical results in a xenon study of cerebral blood flow in humans after cardiac arrest. In this study, comatose patients who regained consciousness had relatively normal cerebral blood flow before regaining consciousness, whereas those who died without awakening developed hyperemic cerebral blood flow after ROSC. Inoue et al (12) also found early hyperemia to be associated with a poor prognosis after cardiac arrest. Conversely, Mullner et al (13) found higher cerebral oxygen extraction to be associated with better cerebral recovery. Different models and different techniques do not allow us to directly compare the studies, but the results emphasize that we need to understand more about postresuscitation cerebral blood flow and its relationship to underlying brain ischemia before we can know the correct approach to CPRC in the many different situations that present to us. It does not mean that a hyperemic flush is not helpful after attainment of ROSC, but emphasizes that we really do not know the “formula” for postresuscitation care. Prearrest variables, such as heart failure, vascular disease, diabetes, and intra-arrest variables, such as duration of no-flow and low-flow may all need to be accounted for to determine the appropriate approach to post-ROSC care for the individual patient. Optimal cerebral resuscitation will probably turn out to be similar to defibrillation—one approach will not fit all patients. Just as we may need to do chest compression before defibrillation in patients with prolonged no-flow times, we may need to tailor our approach differently for patients with premorbid conditions, long no-flow, or low-flow times.

Perhaps to achieve better outcomes, we should monitor efficacy of artificial circulation with widely available, easily applied tools, such as end-tidal CO₂ (14) while maximizing cardiac output with techniques, such as continuous chest compression-CPR. Kellum et al (15) showed that with continuous chest compression-CPR, survival increased from 19% to 48%, compared with a control group derived from the 3 years preceding the test period. In addition, neurologically intact survival increased from 77% in the first period vs. 84% in the experimental period.

Unfortunately, after >50 years of CPR and advanced cardiac life support, the majority of patients still either cannot achieve ROSC or die of postresuscitation disease. Basic physiologic studies in animals and humans, such as the study by Skhirtladze et al in this issue of *Critical Care Medicine* help answer small parts of the question. In turn, these clues need to be taken back to bench models and cell-based studies to develop better techniques for the key variables involved in resuscitation from cardiac arrest: generation of cardiac output during the arrest phase, generation of an organized rhythm, and finally functional cardiac and cerebral recovery.

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Vasopressin and its copilot copeptin in sepsis and septic shock*

Vasopressin levels increase early in septic shock because hypotension is the most potent stimulus of increased synthesis and release of vasopressin. Indeed, if an animal is challenged with conflicting signals to vasopressin release (such as hypotension and hypoxemia), the animal will increase vasopressin because hypotension is a more potent stimulus than hypoxemia is an inhibitor of vasopressin release. After the initial increase of vasopressin levels in septic shock, vasopressin levels then decline rapidly to levels that are inappropriately low (compared with hypotensive patients who have cardiogenic shock) (1–3). Thus, few endocrine systems are so rapidly activated (to increase serum levels) and then are so rapidly exhausted (such that serum levels decrease) as the vasopressin axis in sepsis.

Serum levels of vasopressin—a nonapeptide—represent the interactions of the synthesis, release, and metabolism of vasopressin. Synthesis of preprovasopressin occurs in various nuclei of the hypothalamus. Subsequently, there is conversion to provasopressin followed by conversion of provasopressin by subtilisin-like proprotein convertase (SPC3) to vasopressin (4). Vasopressin is metabolized by insulin-regulated aminopeptidase also known as vasopressinase (5).

Vasopressin and copeptin levels are altered in sepsis and septic shock. In this issue of Critical Care Medicine, Jochberger et al (6) report an observational cohort study designed to compare serum levels of vasopressin and copeptin of patients who had infection (n = 10), severe sepsis (n = 22), and septic shock (n = 28). Measurements of serum levels of vasopressin and copeptin were made for the first 7 days of admission. Patients with severe sepsis and septic shock had higher vasopressin (and copeptin) levels than patients who had infection. However, there was no difference in serum vasopressin levels between patients who had severe sepsis vs. septic shock. This is novel information that requires thoughtful interpretation. Should the levels of vasopressin have been higher in septic shock (than severe sepsis) because of the additional stimulus of hypotension in patients who had septic shock? Alternatively, does this study teach us that serum levels of vasopressin (and copeptin) of patients who have severe sepsis and septic shock are similar and so those patients should be treated similarly?

Copeptin is a 39-amino acid glycopeptide that is the C terminal part of provasopressin, very similar to the C peptide of insulin (7). Jochberger et al (6) found that plasma vasopressin levels correlated significantly with copeptin levels. Is the correlation of serum levels of copeptin and vasopressin tight enough so that copeptin could be measured as a surrogate for vasopressin? Alternatively, does this study teach us that serum levels of vasopressin must be measured in patients who have severe sepsis and septic shock (because renal dysfunction was common and disturbed the tight correlation of serum vasopressin and copeptin levels)?

This study extends studies of serum levels of vasopressin and copeptin. Lin et al (8) studied patients in the emergency department and found lower vasopressin levels in patients who went on to septic shock (3.6 pg/mL) compared with patients who had sepsis (10.6 pg/mL) and severe sepsis (21.8 pg/mL) (Table 1). Struck et al (9) described the rationale and methods for measurement of copeptin. Dunser et al (10) published a case report showing increased levels of copeptin and vasopressin early (first 36 hours) in septic shock, which decreased during recovery. Jochberger et al (11) found, as in other studies, critically ill patients had higher copeptin levels than controls. Patients who had cardiac surgery had higher copeptin levels than patients who had sepsis or controls. Vasopressin and copeptin levels were highly correlated. Interestingly, the ratio of copeptin to vasopressin was higher in sepsis than after cardiac surgery suggesting altered estimation of vasopressin by copeptin in patients who have sepsis. In another study, Jochberger et al (12) confirmed that critically ill patients had higher vasopressin levels (11.9 pg/mL) than controls (0.9 pg/mL). Patients who had hemodynamic dysfunction had higher vasopressin levels than patients without hemodynamic dysfunction (14.1 vs. 8.7 pg/mL). As in previous studies, patients who had cardiac surgery had higher vasopressin (1) and copeptin (11, 12) levels than septic patients.

Morgentaler et al (13) reported a sandwich assay with two antibodies for copeptin and found higher levels in critically ill patients than healthy controls (79.5 vs. 4.2 pmol/L, respectively) with good correlation between vasopressin and copeptin levels. Morgentaler et al (7) showed that hemorrhagic shock in baboons quickly lead to markedly increased serum copeptin levels (from 7.5 to 269 pM), and resuscitation was associated with declining copeptin (to 27 pM) indicating that copeptin levels are modulated profoundly and rapidly in hemorrhagic shock. Morgentaler et al (7) also evaluated critically ill patients and found increased copeptin levels in sepsis: healthy controls 4 pM; critically ill without sepsis 27 pM; sepsis 50 pM; severe sepsis 74 pM; and septic shock 171 pM. Muller et al (14) assessed copeptin levels in 545 patients who had lower respiratory tract infection vs. 50 healthy controls. Copeptin levels were higher in patients than healthy controls and increased as severity of pneumonia increased. Both Morgenthaler et al (7, 13) and Muller et al found higher levels of copeptin in nonsurvivors compared with survivors (Morgenthaler et al [7], 171 vs. 87 pM; Muller et al [14], 70 vs. 24 pM).

Russell et al (3) found that vasopressin levels were extremely low in severe septic shock (median 3.2 pmol/L) and increased during low-dose (0.03 U/min) vasopressin infusion to about 74 pM (6 hours) and 98 pM (24 hours).

Lodha et al (15) found that serum vasopressin levels in pediatric septic shock are similar to the results of Jochberger et al (6). Vasopressin levels were increased in septic shock (116 pg/mL) and severe sepsis (106 pg/mL), and vasopressin levels did not change over 96 hours of evaluation. As in Morgenthaler et al (7) and Muller et al (14),
nonsurvivors had higher vasopressin levels than survivors (118 vs. 76 pg/mL).

Can copeptin levels be used as a surrogate for vasopressin levels? I suggest that copeptin levels cannot be used as a surrogate for vasopressin levels without further evaluation because of several aspects presented by Jochberger et al and other studies. Important considerations are that the sample size was relatively small, these are single-center studies, and the correlation between vasopressin and copeptin levels overall was adequate, but was not adequate if there was continuous veno-venous hemofiltration or renal function was not adequate if there was continuous and copeptin levels overall was adequate, but relatively small, these are single-center studies, and the correlation between vasopressin and copeptin levels was 0.06). Thus, I suggest that copeptin and vasopressin levels did not correlate well enough for individual patient evaluation.

To make matters worse in patients who have septic shock, there is downregulation of vasopressin receptors in addition to the deficiency of vasopressin levels in sepsis (16) and that further exacerbates the vasopressin deficiency of sepsis.

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Routine nursing procedures—Take care of the patient and the splanchnic circulation!*  

Care of the critically ill not only comprises invasive monitoring, complex pharmacologic intervention, and eventually organ replacement, but also requires careful nursing of the patient. Routine nursing procedures consist of mechanical ventilation–associated procedures, e.g., endotracheal suctioning; hygiene measures, e.g., oral care and washing; diagnostics, e.g., chest radiograph and physical examinations; removal/insertion of catheters; and physical treatment, e.g., physiotherapy and patient turning. It has been well established for decades that many of these routine nursing procedures may affect patient homeostasis (1–4), in particular, when associated with endotracheal suctioning in mechanically ventilated patients (5–7). In fact, nearly five decades ago, the group of Landmesser already reported a marked fall in arterial oxygen saturation during and after endotracheal suctioning, which could only be partly prevented by preoxygenation with an FIO2 of 1.0 (8). Increased oxygen consumption and CO₂ production resulting from enhanced sympathetic tone (9–11) clearly assumes major importance in this context as a result of increased respiratory muscle activity because of agitation or coughing episodes. In fact, sedation and analgesia with short-acting narcotics markedly attenuated the hemodynamic response to routine nursing procedures (11, 12). Despite this obvious and potentially important role of nursing procedures for patient stability, clinical data dealing with this phenomenon are scarce, and up to now no study is available on the effects of such procedures on hepatosplanchnic perfusion, a region which has been identified as a high-risk area in the pathogenesis of multiple organ failure, in particular, in the presence of a mismatch between metabolic demands and oxygen supply (13).

In the current issue of Critical Care Medicine, Jakob et al (14) present a study exploring the role of routine nursing procedures for decreases of hepatic venous oxygen saturation, a well-accepted marker of splanchnic perfusion and metabolism, and the relationship of these desaturation episodes and outcome. In 36 patients with acute respiratory or circulatory failure, the majority suffering from septic shock (59%), mixed and hepatic venous oxygen saturations were continuously recorded during various nursing procedures that were part of the routine care of the patients during their intensive care unit stay. The main finding was that patients are repeatedly exposed to episodes of hepatic venous desaturation—and thereby possibly to reduced splanchnic perfusion—during routine nursing procedures, and that these episodes were mostly mirrored, in part, only by changes in peripheral arterial or mixed venous oxygen saturation. In addition, the total number of desaturation episodes, regardless of their association with procedures, were directly related to the maximal Sequential Organ Failure Assessment score, but not with length of stay or mortality. What do we learn from this study? Jakob et al confirm the well-established fact that regional, i.e., hepatic, venous oxygen saturation cannot necessarily be derived from the arterial or mixed venous one, in particular in the presence of regional oxygen supply demand dependency (13). Furthermore, most desaturation episodes were due to ventilator-related procedures, and endotracheal suctioning caused the most pronounced fall in hepatic venous oxygen saturation and increase in the hepatic-mixed venous oxygen saturation gradient. As mentioned earlier, endotracheal suctioning is well known to impair pulmonary gas exchange, and given the high proportion of patients with septic shock, it is not surprising that endotracheal suctioning caused the largest decrease in hepatic venous oxygen saturation: these patients often present with a high hepatosplanchnic oxygen extraction, and even a small change in oxygen demand and supply may cause large decreases in regional venous saturation (13). Unfortunately, Jakob et al did not mention whether they used measures to counteract any endotracheal suctioning–induced impairment of pulmonary gas exchange, i.e., application of hyperoxia (6, 8) or alveolar recruitment maneuvers (15), or whether they performed open or closed suction (16, 17). The latter was demonstrated to attenuate the suction-induced fall in arterial oxygen saturation, albeit its benefit for morbidity remains a matter of debate (18).

A very interesting finding of the study by Jakob et al is that more than one quarter (27%) of all observed hepatic venous desaturation episodes occurred independently of any nursing procedure. Although only marginally discussed by the authors, this finding may nevertheless highlight the importance of spontaneous physiologic fluctuations such as heart rate and blood pressure variability (19). As a consequence, regional oxygen saturations are also likely to show spontaneous variations, and this phenomenon may have contributed to the authors’ findings. It should be noted, however, that the degree of heart rate variability, the currently best studied parameter of spontaneous physiologic variation, was inversely related to outcome in several subpopulations of intensive care unit patients (20–22). By contrast, albeit Jakob et al did not analyze the relation between spontaneous drops of hepatic venous oxygen saturation and the Sequential Organ Failure Assessment score, the authors report that the total—and not only of procedure-associated—number of regional venous desaturation episodes was directly related to the severity of the disease. As a logic consequence, they suggest that hepatic venous desaturation

*See also p. 483.

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episodes, hence, mirror the patients’ compromised capacity if not inability to increase blood flow in response to a rise in regional oxygen demand.

In conclusion, Jakob et al elegantly demonstrate that routine nursing procedures may deleteriously affect the hepato-splanchnic circulation and, consequently, visceral organ function. Furthermore, most of it will remain undetected by systemic monitoring parameters, because splanchnic perfusion can only be detected by invasive procedures such as hepatic vein catheterization. Because more than one quarter of all recorded hepatic venous desaturations were not procedure related, the clinical relevance of these findings remains open. Nevertheless, in analogy to the sepsis bundles, nursing procedure guidelines are probably needed to reduce the impact of these measures on patient outcome, and Jakob et al have the merit to highlight this often underestimated issue of critical care medicine.

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Video instruction for dispatch-assisted cardiopulmonary resuscitation: Two steps forward and one step back!*

Survival from cardiac arrest is dependent on the alignment of the steps outlined in the revised chain of survival: early recognition and call for help, early cardiopulmonary resuscitation (CPR), early defibrillation, and early postresuscitation care (1). Increasing the proportion of the community, willing to provide bystander CPR, would certainly facilitate “early CPR.”

Much attention has been recently paid to bystander CPR: its importance and ways of reducing the barriers to its performance (2). This has been accompanied by the reiteration by the American Heart Association that hands-only (compression-only) CPR is an acceptable alternative when bystanders are untrained, unable, or unwilling to provide ventilation as well as compressions (3).

Compression-only CPR appears particularly pertinent when applied to dispatch-assisted CPR. The ability to provide instructions over the phone to a bystander is a widely established and effective practice (2, 4), especially if the instructions are simplified (such as removing the additional instructions for ventilation [5, 6]). If the advancing technology associated with telecommunication could be translated into a more sophisticated tool for instruction, then dispatch-assisted bystander CPR could be taken to a new level. Reports of some potential benefits and limitations of such technology are starting to appear (7–9).

In a randomized study, the authors evaluated the potential benefits of using interactive video instruction to improve the quality of dispatch-assisted, compression-only CPR performed on a manikin by “bystanders” who had only limited (if any) training in CPR. They used an optimally placed video cell phone in hand-free mode and provided either voice-only instruction or “interactive voice and video demonstration and feedback.” The addition of video communication (and, in particular, the real-time feedback) improved the rate of chest compressions (from a median of 63 to 95.5 compressions per minute) and the depth of compressions (from a median of 25 to 36 mm). The published literature suggests that an increase in at least short-term survival would be expected from such improvements in compression rate (11) and depth (12, 13). The downside of the interactive video group was a near 30-second delay in the time till first compression, but given the fact that a median of 0% of the compressions in the control group was of an “appropriate” depth (38–51 mm [1.5–2 inches]), and that increased to a median of 20% in the interactive video group, this delay becomes much less important.

This study provides many messages. Clearly, the ideal positioning of the video cell phone is crucial, and improvements could be made to the instructions and the time required to deliver them. As the technology, coverage, and expertise with these devices are enhanced, we can expect further improvements in their effectiveness.

In summary, the study published by Yang et al (10) has many limitations and is obviously only a starting point for the incorporation of some of the more advanced functions of the modern-day communication devices. It appears that more sophisticated interactions (such as the use of video instruction) can improve some aspects of the quality of dispatch-assisted chest compressions (depth and rate), but at this stage, it comes at a cost (delayed commencement of compressions). It may be considered two steps forward and one step back, but at least we appear to be making progress.

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Continuous renal replacement therapy circuit contamination: New tale of an old problem?*

Dialysis and continuous renal replacement therapies (CRRT) technology improved tremendously since the first hemodialysis for chronic renal failure in 1960 and the first CRRT in 1977 (1, 2). As technical challenges of dialysis treatment were overcome and patients began to survive, problems of preparing dialysate from tap water became apparent. Chemical and bacterial contamination of the water used to prepare the dialysate led to the developments of strict standards for water used for hemodialysis by various organizations, with slight differences (3). Although CRRT is the main form of renal support provided in intensive care units worldwide (4), widely recognized standards have not been applied to CRRT as yet.

Microbial contamination of intravenous (IV) fluids has been known for long. Episodes of sepsis due to association with IV therapy were reported in the 1970s, which were linked to manufactured infusion products; however, extrinsic sources of contamination during use were also identified in a significant proportion of IV therapy infusion systems (5) and are considered to be a more common source of contamination (5–7). Guidelines for the prevention of intravascular catheter-related infections address how to reduce the microbial contamination of IV infusions and potential hazards to the patients (6).

Furthermore, significant advances during the same time periods led to guidelines for surgical site infection prophylaxis and operating room conditions (8). The source of pathogens in many surgical site infections is the endogenous flora of the patient’s skin, mucous membranes, or hollow visceras; however, exogenous sources include surgical personnel, the operating room environment (including air), instruments, and other materials brought to the sterile field during an operation. Room air may contain microbial-laden dust, lint, skin squames, or respiratory droplets that can also contribute to contamination of IV infusion equipment during use (8).

In this issue of Critical Care Medicine, Kanagasundaram et al (9) look at the microbiological integrity of a continuous venovenous hemofiltration (a form of CRRT) circuit using a commercially available replacement solution. They found that of the 24 replacement fluid cultures, 9 breached European Pharmacopoeia standards for ultrapure water. One of 24 endotoxin measurements breached European Pharmacopoeia standards. Internal tubing cultures were negative, but electron microscopy revealed 13 of the 24 collected tubing samples to be contaminated with biofilm. Only 7 of the 24 studied circuits proved to be free from microbial contamination. They found no clear relationship between circuit lifespan and rates of contamination, but this should be interpreted with caution because of their small sample size.

Kanagasundaram et al used highly sensitive microbiological techniques to examine replacement fluid, quantitatively assess endotoxin, and examine tubing specimens via electron microscopy for biofilms. They took precautions to minimize contamination during sampling; however, they did not separately analyze unused tubing or commercially available solutions directly from the bags before use or other bags of unused fluid with the same lot numbers. They also did not evaluate room air as a potential source of microbial contamination (9).

CRRT systems involve a roller blood pump device with additional pumps to provide the circulation of dialysate and replacement fluids, a dialysis filter, dialysate and replacement fluids, and the necessary infusion tubing systems, all of which are usually incorporated in a disposable cartridge or assembled separately depending on the device used (2). The continuous venovenous hemofiltration system that Kanagasundaram et al used was an integrated, single-use circuitry with a commercially available replacement fluid (as usual in the current practice). This CRRT system is essentially a combination of a dialysis filter and a needleless infusion system. Thus, their findings should be interpreted in the same context. Indeed, their results are not surprising and are reminiscent of data on “in use contamination of IV fluids” (5).

There are four potential routes of access for the organisms to colonize an intravascular device and subsequently cause blood stream infections: invasion of the skin insertion site, contamination of the catheter hub, hematogenous spread from a distant site of infection, or rarely infusion of contaminated fluid through the device. The first two sources are the most important. Surface colonization of the tubing, probably originating from the skin, predominates in short-term catheters (in place less than 10 days), such as peripheral IV catheters, nontunneled central venous catheters, and arterial catheters. In-
traluminal colonization due to hub contamination increases over time and becomes predominant after 30 days of long-term devices (tunneled central venous catheters, peripherally inserted central catheters, and subcutaneous ports) (6, 7, 10). Stopcocks (used for injection of medications, administration of IV infusions, and collection of blood samples) represent a potential portal of entry for microorganisms into vascular access catheters and IV fluids (6).

Catheter material/structure and virulence of microorganisms are important factors along with biofilm formation (6, 7, 10–12). Biofilm is a living community of microorganisms, embedded in their extracellular polymeric matrix and other components deposited from bodily fluids adherent to the catheter surface. Biofilm development within a few hours of device placement (both inside and outside the lumen in the case of a catheter). Biofilms major medical significance. Biofilms are less susceptible to the effects of antimicrobial agents and host defenses, making the treatment of infections very difficult (7, 10–12).

Where do we go from here? Can we blame the dialysate/replacement fluids for the contamination? This can only be answered by specifically culturing and assaying these fluids before, and during, inline use. More important, we should implement all preventive measures as recommended by current guidelines to prevent catheter-related infections and surgical site infections first. Educating all personnel involved is critical. Achieving operating conditions in intensive care unit is not feasible, but maximum protection during CRRT set up and disconnection of the circuit can be used by nursing staff. We may need to use new antiseptic barrier caps with 2% chlorhexidine gluconate in alcohol rather than routine alcohol swabs for disinfection of needless catheter connectors and access ports (13). We should begin culturing CRRT fluids when the patients develop fever or evidence of sepsis. Because biofilms can form rapidly on the intraluminal surfaces of IV tubing, we should probably adopt shorter changing periods (i.e., 24 hours) for the CRRT circuit filter and tubing, especially because their cost decreased over time, and maintaining patency is also an issue. For the same token, we should perhaps begin routine use of catheter lock solutions with antibiotics and chelating agents that are promising in eliminating biofilms in the catheter lumens (7, 10, 14). Clearly, more work needs to be done in this area, but this is a step forward.

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Arginine pharmacokinetics: Not a new paradigm but the old pharmacology*

In the last 15 yrs, an increasing number of articles have dealt with the hypothesis that critically ill patients in the catabolic state will develop nutrient deficiencies and immune dysfunction. They usually show low plasmatic levels of glutamine and arginine despite adequate nutritional support and are considered conditionally essential in this setting (1, 2). Both have been empirically added, alone or in combination with other substrates, to standard diets trying to demonstrate their beneficial effects on laboratory, immunologic, and clinical parameters in comparison with standard diets. These formulas have been included in the wide concept of immunonutrition with variable success in terms of clinical outcomes but with entertained controversies (3–5). Furthermore, this concept has been questioned, and now the new paradigm of pharmaconutrition has been introduced (6). In fact, what we must do is rethink the research we are doing and, if we will use arginine or glutamine like a drug, we are urged to apply the principles of the pharmacology to get accurate and reproducible results.

In this issue of Critical Care Medicine, Loi et al (7) present a good example of pharmacologic study. They administered two different isocaloric and isonitrogenous diets, one standard and the other enriched with arginine, to observe the changes in plasmatic levels of glutamine in the first 90 minutes of diet administration, once the patients were fed enterally and with a washout period of 3 hours. The authors found a significant increase of plasmatic levels of arginine and glutamine in patients treated with the arginine–containing diet. Furthermore, the areas under the curve between arginine and proline and arginine and ornithine showed a good correlation. Interestingly, both groups of patients had similar nitrogen balance or proteolysis. This study confirms in humans that there is a common fate between arginine and glutamine through ornithine in the liver, as the authors suggested in a previous experimental study (8). Nevertheless, this study has some limitations. First, the study diet contains high amounts of omega-3 fatty acids, vitamins C and E, and selenium. We do not know if changes in interleukin production mediated for these fatty acids or a higher level of antioxidants can modify glutamine consumption by immune cells or for glutathione production. Besides, the washout period seems to be very short and a longer fasting period like 8 or 12 hours will be a better approach (9). Second, the study population has in fact two subgroups: one group of patients with cancer underwent an elective surgical procedure and another group of patients with septic shock and pancreatitis underwent an emergent surgical procedure. Although the interaction between the two groups of patients is not significant, it makes the overall population heterogeneous enough to extrapolate these results to different populations without a separate analysis of the data.

Nevertheless, Loi et al present a solid pharmacokinetic study that demonstrates that arginine delivered enterally increases the levels of plasmatic glutamine. Arginine and glutamine regulate the immune response through different effects (10, 11). Furthermore, glutamine and arginine share complex metabolic pathways well explained in a recent review of this journal (12). Arginine is metabolized by arginase and produces urea, and ornithine and the last one gives citrulline or glutamine and proline, as demonstrated by Loi et al. Arginine is also transformed to citrulline and nitric oxide by inducible nitric oxide synthase. The temporal switch of arginine as a substrate for the inducible nitric oxide synthase to ornithine–proline axis is regulated by inflammatory cytokines and by the arginine metabolites themselves (13). On the other hand, glutamine is a primary fuel for enterocytes and for gluconeogenesis in the liver, is a precursor of pyridoxine and purine, is incorporated to glutathione, and serves as a precursor for the de novo production of arginine through the citruline–arginine intestinal–renal pathway (14). Close to the complexity of these metabolic pathways, we should consider gene expression of different isoenzymes, different patterns of tissue expression, and the route of administration.

Glutamine seems to be beneficial in critically ill patients, whereas arginine supplementation is still under debate. Administering high doses of these amino acids needs further research looking at the dose, the way of administration, and the physiologic and clinical effects like other drugs. Maybe this is an unrealistic approach, but it is clear that both amino acids exert regulatory functions different from being only nutrients. And finally, if arginine can produce an excessive and sometimes deleterious amount of nitric oxide, and therefore is an adverse event, why not use glutamine alone?

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Meaning of pulse pressure variation during cardiac surgery: Everything is open*

Fluid management is of major importance in critically ill patients and in surgery patients. Static preload indicators, like cardiac filling pressures, are of poor value to assess fluid responsiveness (1–3). Functional hemodynamic parameters, like arterial pulse pressure variation (PPV) and pulse contour stroke volume variation (SVV), have gained wide popularity as predictors of fluid responsiveness in mechanically ventilated patients (4). It must be remembered that the mechanical insufflation decreases preload and increases afterload of the right ventricle. The right ventricular preload reduction is secondary to the decrease of the venous return pressure gradient related to the inspiratory increase in intrathoracic pressure. The increase in right ventricular afterload is related to the inspiratory increase in transpulmonary pressure (alveolar pressure minus intrathoracic pressure). The reduction in preload and the increase in afterload of the right ventricle both lead to a decrease in right ventricular stroke volume, which, in turn, leads to a decrease in left ventricular filling after a phase lag of 2–3 heart beats related to the long blood pulmonary transit time. The resulting left ventricular preload reduction may induce a decrease in the left ventricular stroke volume, which is minimal during the expiratory period.

Interestingly, the cyclic changes in right ventricular preload induced by mechanical ventilation, result in greater cyclic changes in right ventricular stroke volume when the right ventricle operates on the steep rather than on the flat portion of the Frank–Starling curve. The cyclic changes in right ventricular stroke volume and, hence, in left ventricular preload result in greater cyclic changes in left ventricular stroke volume when the left ventricle operates on the steep portion of the Frank–Starling curve. Thus, the magnitude of the respiratory changes in left ventricular stroke volume should be an indicator of biventricular preload responsiveness and, hence, of fluid responsiveness. In this regard, PPV (5–7) and SVV (7–9) have been demonstrated as good predictors of fluid responsiveness in various clinical settings. Two obvious conditions are required to adequately interpret such dynamic parameters: controlled positive pressure ventilation with no spontaneous breathing activity (10, 11) and absence of cardiac arrhythmias (10). Because changes in intrathoracic pressure and transpulmonary pressure are the major determinants of the cyclic cardiovascular consequences of positive pressure ventilation, a sufficiently high tidal volume (≥7 mL/kg) is obviously also required for well interpreting functional dynamic parameters (12). These three conditions are generally met in anesthetized patients undergoing surgery. Nevertheless, under open chest conditions, respiratory changes in intrathoracic pressure are less pronounced so that respiratory changes in stroke volume or in pulse pressure are expected to be low even in fluid responsive patients. In this issue of Critical Care Medicine, de Waal et al (13) have tested this hypothesis by evaluating the ability of PPV and SVV to predict fluid responsiveness under both open and closed chest conditions in patients undergoing coronary artery bypass graft surgery. First, they confirmed that in closed chest conditions (tidal volume: 8 mL/kg), PPV and SVV were better predictors of fluid responsiveness than static measures of preload, such as central venous pressure or global end-diastolic volume. Second, they showed that neither PPV and SVV nor static preload indicators were able to predict accurately fluid responsiveness under open chest conditions, although the number of nonresponders was very low (3 of 18 patients). In half of the fluid responders, PPV was <10%, a value in agreement with the authors’ hypothesis (13). It is likely that the attenuation of cyclic changes in intrathoracic pressure in open chest conditions accounted for these findings. It must be stressed, however, that in the other half of the fluid responders, PPV was higher than 11% (up to 22%). Surprisingly, the authors did not highlight these striking results. One could postulate that under open chest conditions, a high PPV (or SVV) is secondary to the cyclic changes in transpulmonary pressure, which are potentially large in the absence of significant changes in intrathoracic pressure. A marked inspiratory increase in transpulmonary pressure could decrease right ventricular stroke

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*See also p. 510.

Key Words: open chest surgery; cardiac surgery; pulse pressure variation; stroke volume variation; fluid responsiveness; cardiac preload

The author has consulted for Pulsion Medical Systems.

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volume at inspiration through an increase in the resistance of intra-alveolar microvessels. Thus, even if the pulmonary vasculature was in West's zone 3 conditions at expiration in these patients, the marked increase in transpulmonary pressure had probably produced zone 2 conditions at inspiration in some of them (14). It could then be postulated that fluid infusion by increasing the pulmonary venous pressure attenuated the transfer from zone 3 to zone 2 at inspiration and, hence, the inspiratory decrease in right ventricular stroke volume. Although this hypothesis is speculative, it is supported by the fact that PPV (and SVV) decreased while stroke volume increased after fluid infusion in this subgroup of patients. Similar findings were previously reported in open chest surgery patients ventilated with a tidal volume of 10 mL/kg (15). Although they enrolled a limited number of patients, de Waal et al (13) have thus brought evidence that the presence of high PPV (or SVV) is indicative of fluid responsiveness under both closed and open chest conditions. However, under open chest conditions, other tools are still required to diagnose the origin of hemodynamic instability because the presence of low PPV and SVV cannot preclude a positive hemodynamic response to fluid.

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Antioxidant therapy: Reducing malaria severity??

E ach year, infection with Plasmodium falciparum causes 300–600 million illnesses worldwide (1). A significant number of patients will progress to severe malaria with organ dysfunction, which is more common in the immunologically naïve: young children and travelers or other adults with only sporadic exposure to infected mosquitoes. Mortality from severe malaria ranges from 5% to 40%, and death often occurs shortly after hospital admission. Despite improved survival with artesunate treatment (2), mortality remains high in the first 24 hours of hospitalization, and therefore, adjunctive therapies are still urgently needed.

Neither hypovolemia, cardiogenic shock, nor vasodilatory shock is necessary for organ dysfunction in severe malaria (3). The impairment of tissue perfusion occurs within microvessels, where paralyzed red blood cells (RBCs) adhere to endothelial cells and circulating immune cells via specific interactions between the parasite-encoded adherence ligand P. falciparum erythrocyte membrane protein 1 on the RBC surface and the host-encoded adhesion receptors cluster of differentiation 36 and intercellular adhesion molecule-1 (4). Adherence is associated with inflammatory cytokine secretion, adhesion molecule expression, tissue factor display, and platelet aggregation (5)—findings that are evident on postmortem examination of patients with severe malaria (6). Microcirculatory dysfunction may be worsened as nitric oxide is scavenged by cell-free hemoglobin released during hemolysis and by reactive oxygen species (7).

*See also p. 516.

Key Words: oxidative stress; cytoadherence; Plasmodium falciparum; endothelium; artesunate; N-acetylcysteine; lactate; glucose-6-phosphate dehydrogenase deficiency
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In severe malaria, reactive oxygen species are generated by parasite hemoglobin metabolism in RBCs, nicotinamide adenine dinucleotide phosphate oxidase in phagocytes, and nitric oxide synthase when the substrate arginine or cofactor tetrahydrobiopterin is lacking. Plasma hemoglobin released from lysed RBCs may also catalyze the generation of reactive oxygen species. Patients with severe malaria have increased reactive oxygen species products in urine (8), decreased alpha-tocopherol in RBC membranes (9), and decreased deformability of RBCs under shear stress. Decreased deformability of RBCs is associated with mortality (10); this was the impetus for the study by Charunwatthana et al (8), who hypothesized that decreased deformability impedes the transit of RBCs through capillaries, impairing oxygen delivery. Because N-acetylcysteine (NAC) restores normal deformability of RBCs in vitro by repleting glutathione reserves (11), treatment with NAC was expected to improve RBC deformability and oxygen delivery in vitro.

However, oxidant stress in RBCs could offer some compensatory benefits to a patient with severe malaria. First, oxidative stress is a fundamental mechanism for killing phagocytosed pathogens, including Plasmodium falciparum. Treatment with a potent antioxidant might conceivably protect parasites from the oxidative burst of phagocytes and could antagonize the oxidation-mediated alaminal effects of artesunate. In vitro, the parasitidal effect of artesunate is reduced when given simultaneously with NAC, but is unaffected when NAC is given 2 hours after artesunate (12). In the present study, Charunwatthana et al administered NAC 2 hours after the first dose of artesunate and measured parasitemia every 6 hours to see whether NAC would impair parasite killing by artesunate.

Second, oxidative stress in RBCs may play a role in weakening adherence interactions between the parasitized RBCs and the microvascular endothelium. This is best illustrated by the classic protective effect of sickle cell trait against severe malaria. Infected RBCs from patients with sickle cell trait show aberrant display of the parasite-encoded adhesion ligand P. falciparum erythrocyte membrane protein 1 and reduced strength of adhesion to microvascular endothelial cells and blood monocytes in vitro (13). This phenotype may be reproduced in RBCs with glucose-6-phosphate dehydrogenase deficiency or other states of oxidative stress.

Third, although oxidative stress in infected RBCs might be beneficial, oxidative stress in endothelial cells causes adhesion molecule expression, apoptosis, and capillary leak. Endothelial cell injury by adherent parasitized RBCs is ameliorated by superoxide dismutase, ascorbic acid, or tocopherol in vitro, highlighting the potential therapeutic benefit of antioxidants as endothelial cell protectors (14).

So what will be the effect of a systemic antioxidant in severe malaria? In the study by Charunwatthana et al (8), adults with severe malaria were treated with artesunate and randomized to receive NAC (dosed as for acetalaminophen overdose) or placebo. NAC had no effect on the primary or secondary end points of the study: lactate clearance time, coma recovery time, parasite clearance time, fever clearance time, or mortality. End products of oxidative stress (F2-isoprostanes) were found to be elevated in the urine of patients with severe malaria compared with uncomplicated malaria, but were unchanged by NAC treatment. Although red cell deformability was lower in fatal cases than in survivors of severe malaria, it was not changed by NAC treatment.

Why was NAC ineffective? In a pilot study (15), 30 patients were randomized to NAC or placebo, and at 24 hours a greater proportion of patients in the NAC-treated arm had normal lactate levels compared with the placebo arm (10 of 15 vs. 3 of 15, \( p = 0.01 \)); however, the placebo group had higher baseline parasitemia and bilirubin and lower Glasgow coma scores than the treatment group. Baseline differences in disease severity could have overestimated the benefit, if any, of NAC treatment. As a consequence, the current study may have been underpowered to detect the true effect of NAC treatment on severe malaria. Almamorial treatment was also different in the current study: NAC was given 2 hours after artesunate, a pro-oxidant drug, compared with NAC being given simultaneously with quinine in the pilot study. Furthermore, genetic polymorphisms that influence RBC oxidative stress (such as glucose-6-phosphate dehydrogenase deficiency) were not accounted for, but could have modified the response to antioxidant therapy.

In hindsight, it is unclear what effect NAC should have had on severe malaria. Oxidative stress is considered beneficial for parasite killing and for weakening the adherence between infected RBCs and endothelial cells or monocytes. On the other hand, oxidative stress causes endothelial injury and impairs RBC deformability. The results of the current study are neutral. Does this close the book on antioxidants for severe malaria? No, but future strategies might specifically target antioxidants to the endothelium while enhancing oxidative stress in infected RBCs.

On second thought, combining a systemic antioxidant NAC with an RBC-specific pro-oxidant artesunate may have accomplished just that.

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Is responsiveness to family wishes an expression of professional transcendence?*

The authors are to be praised for proactively exploring the concept of involving family wishes in the decision to admit to the intensive care unit. Participation in a shared decision-making model is endorsed by the Society of Critical Care Medicine (1). In this issue of Critical Care Medicine, Escher et al (2) determine from the results of surveys administered to physicians in Switzerland that older physicians and those with self-determined knowledge of ethics were more likely to admit a hypothetical young woman with uremic syndrome in the intensive care unit. Physicians were also more likely to admit if the family stated that they wanted everything done vs. "spare useless suffering."

As a point of discussion, for those engaged in providing critical care to the ill and injured, the manner in which the phrase “spare useless suffering” was used in this study prompts a guttural reaction to exclaim that critical care does not uniformly produce “useless suffering”! If a few days of intensive treatment and tests produce a dramatic effect on symptomatology vs. weeks of protracted untreated illness on the ward, which is suffering? One would wonder how lay people would react. Do they know that when they use the phrase “do everything” that the physician interprets that as “admit to the intensive care unit” and when they use the phrase “do not let her suffer” that they may actually be pointing the physician in the direction of withholding care or treatment? It would be interesting to reconstruct the scenarios to evaluate whether the terms are congruent with the wishes of the general public, as posited in the basic assumptions in the research design of Escher et al.

With that said, the proposition that older physicians and those with greater knowledge in ethics responded in a manner more congruent with family wishes is intriguing. Do the results point more toward the concept of professional-transcendence? Transcendence is defined as, the ability to expand self-boundaries intrapersonally (through increased awareness of one’s beliefs and values), interpersonally (by reaching out to others), and temporally (integrating the past and future into the present), and may be measured by valid and reliable tools (3). Transcendence is associated with experiences that increase awareness of human vulnerability and mortality (4). Do those physicians with more life experience, who have witnessed the suffering of others over longer periods of time, and are in tune to the vulnerabilities of our existence on earth extend beyond themselves and listen more attentively and empathetically to others? As suggested by Weaver et al (5), ethical sensitivity may have an effect on decision making and is related to professional transcendence. Do physicians who are less paternalistic in their views about decision making have greater professional transcendence? If the study by Escher et al (2) were extended to explore a situation where the nurse had suggested that we “spare useless suffering,” would these same older physicians with greater confidence in their skills related to ethics have listened and not admitted to the intensive care unit? The question left to ponder is whether age and experience provide us with a greater self-perceived understanding of ethics and a higher level of professional transcendence.

A future study could be one centered on measuring self-transcendence in physicians and the relationship between decision-making models used in the decision to admit and/or collaborate with team members. One question could be, “Is there a relationship between degree of self-transcendence in physicians and use of the shared decision making vs. paternalistic model of decision making.” Another could be, “Does the degree of self-transcendence in physicians relate to collaboration in the workplace?”

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Diuresis in renal failure: Treat the patient, not the urine output*

When critically ill patients develop acute kidney injury (AKI), other than treating the underlying cause, there are very limited therapeutic options that have been proven to improve renal recovery. When we observe a drop in urine output associated with AKI, a natural reaction is to administer agents that will increase the urine output, such as loop diuretics (e.g., furosemide or bumetanide) and dopamine. But even if these therapies increase urine output, will they provide any meaningful benefit to the patient in terms of morbidity and mortality? During multidisciplinary rounds in the intensive care unit, I frequently observe that when nurses contact an attending physician because of a low urine output and rising serum creatinine, an almost reflex reaction is to “give furosemide.” This is rather analogous to ordering aspirin for a headache without analyzing the cause of the problem. In the case of diuretics, if the cause of the decrease in urine output is hypovolemia, clearly, diuretics are not an appropriate choice.

The literature regarding dopamine in AKI is clear: although it may increase urine output, there is no benefit in any measure of morbidity or mortality, and it should not be used (1–3). The data regarding the use of loop diuretics in AKI were recently summarized by Bagshaw et al (4). In brief, although loop diuretics may have some theoretical benefits in AKI, such as flushing debris from the kidney tubules and maintaining fluid, electrolyte, and acid–base homeostasis, clinical trials have not shown any benefit in terms of renal recovery or any measure of morbidity or mortality. One observational trial actually showed an increase in mortality with loop diuretics (5). As summarized by Bagshaw et al (4), there are many limitations with published clinical trials, such as lack of generalizability to modern intensive care unit patients, not including intensive care unit patients, confounding cointerventions such as dopamine and mannitol, delayed or late intervention, and bolus diuretic administration without specific therapeutic end points. Despite lack of data showing benefit, a recent survey suggests that the majority of physicians use diuretics in patients with AKI but do not believe that diuretics can reduce mortality or improve renal recovery (6). This survey also found that the majority of physicians would be willing to participate in randomized clinical trials of loop diuretics in AKI. Clearly, more randomized controlled clinical trials are needed.

In this issue of Critical Care Medicine, Van Der Voort et al (7) report the results of a randomized, double-blind, placebo-controlled trial in the specific setting of intensive care unit patients with AKI after hemofiltration. The purpose was to determine whether giving furosemide after hemofiltration to increase urine output would provide any benefit on recovery of renal function in terms of creatinine clearance and duration of continuous renal replacement therapy. Not surprisingly, there was no significant effect on creatinine clearance or renal recovery despite the fact that furosemide significantly increased sodium excretion and urine output as compared with placebo. In fact, there was a slight trend favoring placebo in terms of renal recovery (92% in the furosemide group vs. 100% in the placebo group). The limitations of the trial are clearly stated by the authors: it was a small trial (71 patients), the furosemide patients had a higher baseline Sepsis-Related Organ Failure Score and were slightly older than patients in the placebo group, and the fact that measured creatinine clearance was used to assess renal function, which may not accurately reflect glomerular filtration rate in critically ill patients.

When considering the main mechanism of action of loop diuretics, the results are not surprising. Loop diuretics inhibit sodium and water resorption from the loop of Henle and do not improve glomerular filtration. In fact, some data suggest that furosemide may actually decrease glomerular filtration rate (8). Conversely, animal models suggest other mechanisms that may be beneficial, such as attenuation of ischemia-related gene expression (9), but the clinical significance of this effect in humans is unknown.

Despite the limitations of the trial, the conclusions seem clear. Routine use of furosemide after hemofiltration does not improve renal recovery. Despite the need for more randomized controlled trials, the current literature regarding loop diuretics in AKI does not support routine use. As summarized by Venkataraman and Kellum (10), diuretics and dopamine are ineffective in preventing AKI or improving outcomes once AKI occurs. For now, we need to attempt to prevent renal failure with strategies such as adequate hydration, maintaining an adequate mean arterial pressure, and minimizing nephrotoxin exposure (10).

If a patient with AKI has a clinical indication for fluid removal such as pulmonary edema, loop diuretics may be a reasonable therapeutic approach, but the bottom line is to treat the patient not the urine output.

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Prevention of pulmonary dysfunction after cardiac surgery by a vital capacity maneuver: Is it so simple?*

Respiratory dysfunction is a frequently encountered complication in postoperative intensive care unit (ICU) patients. After cardiac surgery, pulmonary dysfunction is a well-known encumbering postoperative issue. Hence, this can result in a significantly increased mortality up to 25% and an attributable morbidity with an importantly prolonged stay in the ICU.

In this issue of Critical Care Medicine, Shim et al (1) tackled pulmonary impairment after an off-pump cardiac surgery. Respiratory failure after cardiac surgery with cardiopulmonary bypass results in factors leading to major pulmonary complications: atelectasis is present to a much larger extent than induced by solely anesthesia or sternotomy (2), stasis of secretions, due to insufficient coughing capacity, inflammation and infection. In conjunction with advanced age, preexisting lung disease, impaired cardiac performance, and secondary prolonged duration of mechanical ventilation (3, 4), these risk factors intensify respiratory failure. Furthermore, coronary bypass surgery with and without extracorporeal circulation results in a dramatic impairment of respiratory system mechanics (5), not in the least hampered by an intraoperative positive fluid balance (5, 6). All these complications result in hypoxemia and gas exchange impairment, commonly observed after cardiac surgery. Hachenberg et al (7) demonstrated a nearly doubled intrapulmonary shunting during and after cardiac surgery, with subsequent augmented extravascular lung water and further collapse (8). Although multifactorial in nature, pulmonary dysfunction seems to be mostly related to intrapulmonary right-to-left shunt.

Several investigators applied different techniques to eliminate or diminish the impaired gas exchange after cardiac surgery. Recruitment maneuvers, such as continuous positive airway pressure, bilevel positive airway pressure, or vital capacity maneuver (VCM), at the end of the cardiopulmonary bypass have been used, to alleviate atelectasis and shunting.

Continuous positive airway pressure with varying levels of airway pressure has lead to conflicting results: either decreased or improved lung function was shown, although moderate continuous positive airway pressure appeared to result in the optimization of postbypass pulmonary dysfunction (9). Bilevel positive airway pressure was observed to be beneficial in general anesthesia to prevent ventilation-perfusion mismatch and to improve oxygenation (10).

With VCM, the lungs are inflated to a peak airway pressure of 40 cm H_2O for 15 seconds. With respect to on-pump cardiac surgery, several investigators clearly demonstrated a beneficial effect of VCM on postoperative extubation times. However, the influence on pulmonary gas exchange in the ICU remains controversial. Magnusson et al (11) assessed the effects of VCM to prevent atelectasis after cardiopulmonary bypass in a study on pigs. Control pigs developed extensive atelectasis, whereas VCM-treated pigs showed a significantly smaller proportion of atelectasis, the least in those animals ventilated with lower oxygen concentrations. Repetition within 6 hours seemed to provide no additional advantages based on both laboratory and computed tomographic data (12).

In a human study, Murphy et al (13) could not demonstrate any improvement of gas exchange in the ICU after an on-pump cardiac surgery between control and VCM-supported patients, whereas the latter were extubated significantly earlier, after 6.5 ± 2.1 hours vs. 9.4 ± 4.2 hours. In a subset of cardiac surgical patients with cardiopulmonary bypass, Tschernko et al (14) also showed a reduction of intrapulmonary shunting using VCM after termination of cardiopulmonary bypass, although shunting increased considerably after extubation. Finally, Minkovich et al (15) performed VCM twice: both before cessation of cardiopulmonary bypass (35 cm H_2O—15 seconds) and after admission in the ICU (50 cm H_2O—5 seconds). In contrast to the data on animals presented by Magnusson et al (11), VCM resulted in an improved and prolonged arterial oxygenation for 24 hours in patients. No data, however, were provided concerning the timing of extubation.

With respect to off-pump cardiac surgery, less information is available. In the previously referred study, Tschernko et al (14) could not show any effect of VCM on the duration of mechanical ventilation between patients operated on bypass (control), those supported with VCM, and off-pump cardiac surgery patients. In addition, they showed an increased shunting after extubation, although much less than in those patients with cardiopulmonary bypass and with direct impact on length of stay in the ICU and in the hospital, compared with control and on-pump cardiac surgical patients.

The findings of Shim et al (1) now clearly demonstrate that VCM leads to earlier extubation in off-pump cardiac surgery patients albeit without demonstrable effects on respiratory mechanics, length of stay in the ICU nor in the hospital. Although strict extubation criteria

*See also p. 539.

Key Words: pulmonary dysfunction; cardiac surgery; shunting; vital capacity maneuver; respiratory failure

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were followed, extubation remains a rather arbitrary factor. Many interfering issues, as listed earlier, interfere, not in the least an appropriate sensorium. In this study, patients who were not ready for extubation were sedated with midazolam. At least duration and level of sedation can be a major point of discussion.

Also, the value of VCM in this particular study could be questioned as there was no need at all to increase FIO2 throughout the study, even in non-VCM-supported patients, in whom shunting and atelectasis could have been expected throughout a 4-hour-lasting procedure. Another point of discussion is the timing of VCM: Shim et al performed the VCM immediately after sternotomy. As anesthesia may help the development of atelectasis, could there be a supplementary beneficial effect of a VCM before closure of the sternum? Finally, in none of the patients was respiratory infection a cause for prolonged mechanical ventilation, although the importance of this issue cannot be denied (16, 17). From larger studies, it could be expected that ±20% of cardiac surgical patients are prone to tracheobronchial or pulmonary infection, associated with prolonged stay in the hospital, multiple organ dysfunction, and increased hospital mortality (16, 18).

With respect to prevention of atelectasis and decreased intrapulmonary shunting after cardiac surgery, the last word has not been said. Altering the gas mixture from FIO2 1.0 to 30% oxygen in nitrogen during induction of anesthesia could avoid early atelectasis and shunting (19). In view of the multifactorial nature of this problem, further investigations are needed to ascertain a simple approach of pulmonary dysfunction after cardiac surgery.

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And the winner is: Regional citrate anticoagulation*

Acute kidney injury requiring renal replacement therapy (RRT) is an independent mortality risk factor in intensive care patients. Most likely, the unwanted consequences of both acute kidney injury and RRT contribute to this increased mortality. Continuous RRT is often the procedure of choice in these patients. One requirement for continuous RRT having potential deleterious consequences is systemic anticoagulation. Although anticoagulation exposes patients to the risk of bleeding, its absence may result in clotting of the circuit and less effective treatment. Worldwide, systemic unfractionated heparin is the most common anticoagulant (1). In the last two decades, various methods of regional anticoagulation using citrate (RCA) have been described (2, 3); however, its use worldwide is limited. Several factors are responsible for this, including concerns about the safety of RCA, the metabolic complexity, the costs and logistics of obtaining custom-made solutions, and the lack of uniformity in therapeutic approaches.

Citrate causes anticoagulation in the extracorporeal circuit by chelating ionized calcium (iCa). The citrate–calcium complex is partly filtered and partly diluted by the total blood volume. In the systemic circulation, citrate is rapidly metabolized via the Krebs cycle in the liver and other tissues yielding bicarbonate and releasing iCa. The extracorporeal loss of calcium is substituted. Citrate possibly also inhibits the calcium-mediated activation of inflammatory cells in the extracorporeal circulation (4, 5). A potential safety risk with RCA is the occurrence of metabolic disturbances, entailing the frequent monitoring of acid–base status, plasma electrolytes, and calcium levels. The infusion of hypertonic trisodium citrate may lead to hypernatremia and/or alkalosis, unless adapted replacement solutions are used. Citrate toxicity may occur in patients insufficiently metabolizing citrate (e.g., severe liver failure, decreased muscle perfusion). Systemic citrate levels are not routinely measured in clinical practice, but accumulation is easily detected by an increased total calcium concentration/iCa ratio (6).

In this edition of Critical Care Medicine, Oudemans-van Straaten et al compare the safety and efficacy of RCA with the systemic low-molecular weight heparin nadroparin (7). To date, this is the largest randomized controlled trial on RCA. Patients with acute kidney injury requiring RRT and no contraindications for systemic nadroparin and/or RCA were included. Of the 215 randomized patients, 200 patients received continuous veno-venous hemofiltration (CVVH) per protocol (97 RCA and 103 nadroparin). The study was powered on adverse events necessitating discontinuation of study medication. Primary outcomes were safety and efficacy. Discontinuation was required in two patients of the RCA group (citrate accumulation, clotting) and in 20 patients in the nadroparin group (bleeding, thrombocytopenia) (p < 0.001). Unfortunately, anti-Xa levels were not measured and this might have reduced bleeding. Nevertheless, the differences in bleeding and transfusion were not statistically significant between the groups, possibly because nadroparin was discontinued when bleeding occurred, and patients with a high risk of bleeding were excluded. Circuit survival was not significantly different between groups. These results contrast with the findings of previous randomized controlled trials (Table 1). Although previous studies were small and underpowered, some differences among studies are noteworthy. The present study infused fixed doses of nadroparin and citrate, whereas previous studies titrated unfractionated heparin and citrate to achieve a doubling of the activated partial thromboplastin time and a circuit iCa of <0.35 mmol/L. Routine circuit disconnection affects circuit survival. Circuits were routinely disconnected after 72 hours in the studies by Oudemans-van Straaten et al and Betjes et al (8), but not in the studies by Monchi et al (9) and Kutsgaard-Petersen et al (10). Notably, in the present study RCA did not result in serious metabolic disturbances confirming previous findings (2, 3, 8–12). In the present study, RCA even resulted in less metabolic alkalosis (p = 0.001) compared with nadroparin; however, the RCA protocol aimed at normal pH using two replacement fluids, and this was not the case in the nadroparin group.

A remarkable finding in the present study is the survival benefit of the RCA group. Three-month mortality on intention-to-treat was 48% (RCA) and 63% (nadroparin) (p = 0.03). Three-month mortality per protocol was 45% (RCA) and 62% (nadroparin) (p = 0.02). There were no significant differences in CVVH-timing and CVVH-dose between groups. Post hoc analysis showed that RCA was particularly beneficial in surgical patients, patients with sepsis, patients with severe organ failure, and relatively younger patients. As suggested by the authors, one can hypothesize that RCA is favorable, nadroparin unfavorable, or both. Although the patients in the nadroparin group tended to bleed more, the differences in bleeding and transfusion between groups were not statistically significant and could not explain the RCA survival benefit. The incidence of metabolic alkalosis was higher in the nadroparin group. Alkalemia has hemodynamic consequences as a result of direct effect and by means of reducing iCa. In the present study, however, iCa was lower in the RCA group. Furthermore, metabolic alkalosis during CVVH was not related to mortality at univariate analysis, supporting the recent findings of Demirjian et al (13). The authors speculate that this reduction in mortality is from RCA blocking inflammation. This is certainly a plausible explanation based on the results of previous studies on patients undergoing chronic dialysis (4, 5, 14). These studies demonstrated that dialysis-induced polymorphonuclear cell degranulation is primarily iCa dependent and is abolished during RCA dialysis (4, 5). In addition, Gabetti et al (14) showed that RCA dialysis had a favorable effect on inter-

*See also p. 545.

Key Words: citrate; heparin; acute kidney injury; continuous renal replacement therapy.

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leukin-1β release. Unfortunately, the present study does not provide data concerning biocompatibility and inflammatory markers to support the theory.

In summary, the study of Oudemans-van Straaten et al provides convincing evidence that RCA is as effective as, yet safer than nadroparin. The study has some limitations, including being a single-center study and using low-molecular weight heparin instead of unfractionated heparin. Furthermore, it is clear that the study was designed to evaluate the safety and efficacy of RCA and not survival. Another large Dutch multicenter study is underway, randomizing patients into CVVH with RCA or unfractionated heparin (www.clinicaltrials.gov/ct2/show/NCT00209378). Primary outcome measures of this study are mortality, circuit survival, and bleeding complications, whereas laboratory markers of inflammation, endothelial dysfunction, and coagulation parameters are secondary end points. If this upcoming study confirms the results of Oudemans-van Straaten et al, RCA will definitely be the number one anticoagulation for continuous RRT.

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Table 1. Randomized controlled trials comparing the safety and efficacy of regional citrate anticoagulation and systemic heparins

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Anticoagulation Monitoring</th>
<th>CRRT Modality</th>
<th>Filter</th>
<th>Qn (mL/min)</th>
<th>Qpr (mL/hr)</th>
<th>Citrate (mmol/L)</th>
<th>Quf (mmol/L)</th>
<th>Qd (mL/hr)</th>
<th>Median Circuit Survival (hr)</th>
<th>Major Bleeding Events</th>
<th>Units of PRC per Day of CRRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oudemans-van Straaten et al (7)</td>
<td>RCA 97, LMWH and RCA</td>
<td>Fixed dose LMWH and RCA</td>
<td>Postdilution CVVH</td>
<td>CTA 1.9 m²</td>
<td>220</td>
<td>2000–4000</td>
<td>3</td>
<td>RCA 27, LMWH 26</td>
<td>(p = 0.68)</td>
<td>RCA 6, LMWH 16</td>
<td>(p = 0.08)</td>
<td>RCA 0.27, LMWH 0.36</td>
</tr>
<tr>
<td>Monchi et al (9)</td>
<td>RCA-UFH 8, UFH-RCA 12</td>
<td>Circuit iCa 0.3 mmol/L, APTT 60–80 sec</td>
<td>Postdilution CVVH</td>
<td>PS 1.9 m²</td>
<td>150</td>
<td>35 mL/kg/hr</td>
<td>4.3</td>
<td>RCA 70, UFH 40</td>
<td>(p = 0.007)</td>
<td>RCA 0, UFH 1</td>
<td>(p = 0.01)</td>
<td>RCA 0.43, UFH 0.88</td>
</tr>
<tr>
<td>Betjes et al (8)</td>
<td>RCA 21, UFH</td>
<td>Circuit iCa 0.25–0.3 mmol/L, APTT 50–70 sec</td>
<td>Postdilution CVVH</td>
<td>CTA 1.9 m²</td>
<td>150</td>
<td>1500</td>
<td>3</td>
<td>RCA 36, UFH 38.4</td>
<td>(p = 0.01)</td>
<td>RCA 0, UFH 10</td>
<td>(p &lt; 0.01)</td>
<td>RCA 0.17, UFH 0.33</td>
</tr>
<tr>
<td>Kutsogiannis et al (10)</td>
<td>RCA 16, UFH</td>
<td>Circuit iCa 0.25–0.35 mmol/L, PTT 45–65 sec</td>
<td>Predilution CVVHDF</td>
<td>AN 69 1.0 m²</td>
<td>125</td>
<td>1000, QD</td>
<td>3.3</td>
<td>RCA 124.5, UFH 38.3</td>
<td>(p = 0.001)</td>
<td>RCA 0, UFH 7</td>
<td>(p = NR)</td>
<td>RCA 0.17, UFH 0.33</td>
</tr>
</tbody>
</table>

RCA, regional citrate anticoagulation; LMWH, low molecular weight heparin; UFH, unfractionated heparin; iCa, ionized calcium; APTT, (activated) partial thromboplastin time; CVVH, continuous veno-venous hemofiltration; CVVHDF, continuous veno-venous hemodiafiltration; CTA, cellulose triacetate; PS, polysulfone; AN69, polyacrylonitrile; Qb, blood flow; Qpr, ultrafiltrate flow; Qd, dialysate flow; NS, not significant; NR, not reported; PRC, packed red cell; CRRT, continuous renal replacement therapy.

aInclusion criteria, patients without contraindications for citrate or systemic heparin; bRoutine circuit disconnection after 72 hrs.
New biomarkers of acute kidney injury: Promise for the future but beware the lure of novelty*

A t last, a much needed consensus definition of acute kidney injury (AKI) has emerged, which should not only facilitate comparative research and audit but also recognize the adverse impact of even modest disease (1). However, its reliance on rises in serum creatinine—the traditional biomarker of renal dysfunction—does carry the risk of missed therapeutic opportunity because of the time lag between the initiating insult and the diagnostic elevation (2). The interpretation of changes in serum creatinine is also complicated by factors such as diet, muscle mass, and the use of certain drugs and supplements, as well as by the presence of prerenal dysfunction when no cellular injury has actually occurred. It is these limitations that have stimulated an ongoing and intensive evaluation of a variety of alternative early biomarkers of AKI.

When examining the evolving literature, it is crucial to bear in mind what the potential candidate biomarker is actually reflecting; cystatin C, for instance, is a measure of renal functional status (a “quick creatinine”) whereas others, such as neutrophil gelatinase–associated lipocalin (NGAL) and urinary interleukin-18, are products of the pathophysiologic processes that underlie AKI (3) and indicate active renal damage (a “troponin of the kidney”).

In human studies, cystatin C can predict the development of AKI (4) and the requirement for renal replacement therapy (5), although its superiority over serum creatinine has not been a universal finding (6). Serum and/or urine NGAL levels have been shown to be accurate predictors of AKI in settings as diverse as percutaneous coronary intervention (7), pediatric (8) and adult (9) cardiac surgery, and septic (10) and nonseptic (11) critically ill children. Rising urinary interleukin-18 levels have proved similarly predictive in a nonseptic critically ill pediatric population (12), in critically ill patients with acute respiratory distress syndrome (13), and after adult and pediatric cardiac surgery (14). As well as predicting AKI, there may be an additional prognostic role for novel biomarkers (12, 13).

The article by Haase-Fielitz et al (15), published in this issue of Critical Care Medicine, adds to the existing literature. They are the first to study the early use of serum biomarkers in adult cardiac surgical patients (urine NGAL having already been studied in this setting [9]). Compared to the intensive care unit admission creatinine, the contemporaneous serum NGAL and serum cystatin C were found to have good predictive value for the subsequent development of AKI. The accuracy of cystatin C diminished after patients with preexisting renal impairment were excluded from analysis, suggesting that it did not only indicate evolving AKI but was also an independent risk factor for it, being a reflection of the strong, predisposing effects of chronic renal dysfunction. Beyond AKI, both serum NGAL and cystatin C carried excellent prognostic value for the composite outcome of renal replacement therapy or hospital mortality.

Taken in the context of the current literature, the study has added further evidence of potential value of the novel biomarkers of AKI but its weaknesses should be borne in mind: it was small (only 23 of 100 subjects developed AKI), confidence intervals of the area under the receiver operating characteristic curves were wide (in part, a reflection of the former), and an absolute intensive care unit admission serum creatinine was used (a more valid comparison might have been a Δ creatinine that would have helped correct for the confounding effects of preexisting abnormalities).

What seems to be evident from the literature as a whole is that no one biomarker fulfils all the desirable features of early detection of active renal damage, of rapid reflection of changes in renal function, of risk stratification, or of differential diagnosis. It is entirely possible that different panels of biomarkers will be required to meet different needs (16). Exploration of this is currently the focus on significant, multicentered effort.

If novel biomarkers of AKI are to be of potential value, can we speculate about how they might be utilized?

They have clear roles as research tools. An early diagnosis of AKI may allow timely experimental intervention—a major deficiency of previous human studies (17) in which the initiating insult may have been long over by the time AKI was actually diagnosed. Close linkage between the index insult and time of diagnosis may be particularly important if other, confounding insults are likely, as is clearly the case in the critical care setting.

Beyond research, the actual clinical utility of these early biomarkers remains untested with a key question being whether they would add anything to management beyond the information provided using conventional, creatinine-based diagnosis.

One area of possible use is to identify groups of patients who have undergone a discrete renal “hit” and who require subsequent, augmented monitoring. High-risk outpatients undergoing contrast-enhanced radiography might fall into this category but would require a threshold biomarker level of sufficient negative predictive value to definitively exclude evolving AKI.

Conversely, the utility of biomarkers as a less targeted, sequential screening tool, unlinked to a specific renal event, is less clear although the results of large-scale population studies are outstanding and definitive therapeutic interventions.

*See also p. 553.

Key Words: acute renal failure; acute kidney injury; neutrophil gelatinase–associated lipocalin; cystatin; interleukin 18; biomarkers; creatinine

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are lacking. Although a case could be made that early detection of AKI could encourage the avoidance of harm (e.g., aminoglycoside antibiotics or premature intensive care unit step down), this approach of risk stratification is also, as yet, untested in the clinical environment.

In summary, it is increasingly evident that a variety of novel biomarkers are predictive of overt AKI in a range of different settings. Although holding promise for the future, the lure of their novelty does not remove the need for a clear and guarded appraisal of their potential.

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Improving function following cardiopulmonary bypass in children: Digging deeper than steroids*

In the United States alone, approximately 400,000 cardiac surgical operations are performed using cardiopulmonary bypass (CPB) each year, of which approximately 20,000 are performed on children. This volume of pediatric cardiac surgical procedures is, partly, because of the fact that progress in corrective and palliative surgery for congenital heart disease means that most lesions are now operable. Although overall perioperative mortality has declined considerably in the past two decades, short- and long-term morbidity remains a significant healthcare burden. Mortality and morbidity following cardiac surgery is multifactorial, including changes in the inflammatory response, disordered hemostasis, reduced cardiac output, and multiorgan dysfunction. Most corrective procedures require the use of CPB, which invariably activates the inflammatory system. Frequently, this leads to the development of a systemic inflammatory response syndrome, which is characterized by alterations in cardiopulmonary function, coagulopathy, and multiorgan system dysfunction/failure (1). Although cardiac surgery may be technically successful, children are at risk of harm both in terms of increased risk of death and of long-term disability, as a consequence of these CPB-related dysfunctions. This response is predictably more severe in neonates and small infants because of the relatively high exposure of the child’s blood (small volume) to the relatively large volume of the cardiac bypass circuit.

The etiology of the inflammatory response is thought to include activation of blood components by the bypass apparatus, ischemia with subsequent reperfusion injury, and endothelial damage. This leads to reversible contractile dysfunction and impairment to flow at the microvascular level secondary to neutrophil plugging and vasoconstriction. Once inflammation is initiated in response to CPB, it is maintained and amplified by cytokine production. Clinical indicators of organ injury and dysfunction, and worse clinical outcome, are associated with increased levels of certain cytokines (inter-
leukin [IL]-6, IL-8) following CPB. The pattern and magnitude of elevations have been routinely associated with post-CPB morbidity in both animal models and human investigations (2).

Nuclear factor-(NF-kB) is a ubiquitous inducible transcription factor involved in the regulation of transcription of many proinflammatory genes. It is activated by stimuli such as IL-1, tumor necrosis factor-α, and oxygen-free radicals (3). Normally, NF-kB is bound to the inhibitory protein of NF-kB (inhibitory kappa-B alpha [IkBa]) (4). Triggered by ischemia and reperfusion, and proinflammatory cytokines themselves, phosphorylation of IkBa and p38 MAPK promotes gene expression of potential myocardial damaging mediators such as tumor necrosis factor-α, IL-β, and IL-6 (5). NF-kB translocates to the nucleus where, binding to DNA, it is able to induce the expression of several inflammatory mediators. This pathway plays an important role in both the inflammatory response triggered by CPB and the ischemia and reperfusion associated with circulatory arrest. In fact, the proposed mechanisms for the local anti-inflammatory glucocorticoid’s actions inhibition of IkBa degradation resulting in decreased NF-kB activation and inhibition of p38 MAPK through induction of the mitogen-activated protein kinase phosphatase-1 (6).

Understanding the triggers, timing, and pattern of the complex inflammatory cascade associated with CPB is essential for modifying or arresting it. Unlike other triggers associated with whole-body inflammatory reactions such as trauma or sepsis, cardiac surgical teams have the advantage of knowing when the trigger will occur (i.e., during CPB), and hence have an opportunity for preemptive intervention in an effort to attenuate or minimize the response. Current strategies involve modulation of the inflammatory response and include the use of corticosteroids (7, 8), coated circuits, (9), and aprotinin (10). These interventions have thus far focused on large-scale interference with inflammation rather than a specific, tailored therapy. Additionally, specific data examining the efficacy of these therapies in various age populations are not available, leaving open the possibility of tailored therapies based on age. Although steroids have gained widespread use in this setting in pediatric cardiac surgery (11), they have potential detrimental effects on neonates (12).

In this issue of Critical Care Medicine, Duffy et al (13) examine NF-kB and its role in the inflammatory response associated with CPB. Their hypothesis is that partial inhibition of NF-kB can alleviate cardiopulmonary dysfunction associated with ischemia and reperfusion injury CPB. The article describes the effects of SN50, an inhibitor of NF-kB translocation on hemodynamic and pulmonary function. Specifically, SN50 was administered 1 hour before CPB with subsequent measurement of NF-kB activity, endothelin-1, troponin I degradation, and cardiopulmonary function. Their results indicate that the administration of SN50 decreased NF-kB activity levels in nuclear extracts from left ventricular myocardium. Additionally, SN50 treatment maintained IkBa protein at higher levels and lower total troponin I degradation than in untreated animals. This resulted in preservation of myocardial contractile function and prevented the increase in pulmonary vascular resistance.

Their findings are consistent with previous reports that NF-kB inhibition protects the myocardium from ischemic injury. By inhibition of NF-kB with the compound curcumin, Yeh et al (14) ameliorated the surge of proinflammatory cytokines during CPB and decreased the occurrence of cardiomyocyte apoptosis after global cardiac ischemia and reperfusion. This previous report, however, did not measure a clinical effect. Additionally, work by Schwartz et al (15) examined the relationship among glucocorticoid administration, decreased NF-kB activity in the heart, and improved cardiopulmonary function. Finally, inhibition of NF-kB has been demonstrated to play a role in injury following circulatory arrest (16).

The findings of Duffy et al are important in two fundamental aspects. First, they give insight into a potential mechanism of action of corticosteroid administration in the modulation of CPB-associated inflammation. As previously stated, the local anti-inflammatory action of glucocorticosteroids maybe, partly, due to the NF-kB pathway (6). Additionally, Duffy et al have proposed the development of a clinically useful, more specific agent that avoids the potential negative effects found with steroids. Because administration of corticosteroids during CPB remains controversial, the goal of therapies targeted at the beneficial aspects of the mechanism of action of steroids would be welcome.

Those of us who work in the field of congenital heart disease and cardiac critical care medicine have a unique opportunity to modify or arrest an inflammatory process that contributes to the morbidity and mortality of children undergoing CPB and cardiac surgery. With clinical investigations, such as the study carried out by Duffy et al, the therapeutic strategies available to treat the postbypass inflammatory response will increase, potentially leading to improved outcomes. As the authors themselves state in their conclusion, targeting a specific activity level for NF-kB would be clinically challenging; yet, it may provide a mechanism to move beyond steroid administration.

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“Pas de DEux” for phosphodiesterase-2 in acute lung injury*

The phosphodiesterase (PDE)-2 isozyme was first discovered as a cyclic guanosine monophosphate (cGMP)-stimulated cyclic nucleotide PDE2 capable of hydrolyzing both cyclic adenosine monophosphate (cAMP) and cGMP (1). Three variants of the unique PDE2 gene have been described. All of them are specifically inhibited by 9-(2-hydroxy-3-nonyl) adenine monohydrochloride (EHNA) when PDE2 is activated by cGMP in vitro. PDE2 is expressed in both endothelial and pulmonary epithelial cells (2) and, beyond membrane receptors, this isozyme regulates cyclic nucleotide levels (cAMP and cGMP) and several highly localized intracellular signaling pathways such as cAMP dependent protein kinase and cGMP dependent protein kinase-dependent phosphorylation. Furthermore, when regulating local cAMP and cGMP, PDE2 controls the (adenosine triphosphate)/(cAMP) and (cAMP)/(cGMP) energetic ratio.

PDEs are ubiquitous enzymes constituted by a multigenic super family (PDE1–11) (3). They have been involved in various feedback processes, and PDE inhibitors have been developed and used as bronchorelaxant (theophylline), cardioactive (milrinone), anti-inflammatory (rolipram), and vasodilating drugs (such as sildenafil). The putative role of PDE2 in inflammatory processes or infectious diseases has been evoked, although evidences have been somewhat scant. Hence, the classic PDE2 inhibitor EHNA has been mainly used in in vitro assays, because its poor specificity has precluded its use in in vivo studies.

PDE2s, which are mainly cytosolic as well as particulate (membrane attached) enzymes, are likely surrounded by a complex microenvironment in vivo, according to intracellular molecular crowding. Consequently, it would not be surprising that PDE2s are associated with specific transmembrane receptors within specific microdomains. Such intracellular location would facilitate the control of local concentrations of cAMP (or cGMP) in the vicinity of the molecular complexes. Conversely, since PDE2 hydrolyzing activity is stimulated by cGMP (5 μM) via an allosterically regulated site, the presence of a guanylate cyclase in contiguity with the signaling complex could also represent a hypothesis to be ascertained.

Using combined classic methodologic approaches and an array of pharmacologic conditions involving two new PDE2 inhibitors, namely PDP and hydroxyl-PDP, Witzenrath et al in this issue of Critical Care Medicine (4) demonstrated that prophyllactic and systemic infusion of these specific PDE2 inhibitors reduced acute lung injury (ALI) in a mice model of pneumococcal infection. This noteworthy observation was also supported by a constellation of preliminary and original results obtained in endothelial cell monolayers (5). Hence, both PDE inhibitors were able to oppose the electrophysiologic effects of pneumococcal pneumonia in endothelial cell (human umbilical venous endothelial cells [HUVEC]) monolayers. Thus, PDE2 appears as a key target in this process, since the contribution of other PDE isozymes was elegantly ruled out in control experiments.

Despite a relevant set of preliminary data gained on endothelial cell monolayers in which PDE2 expression was stimulated by exogenous tumor necrosis factor-α (4), this study partially performed in a murine model and in isolated lungs did not allow to pinpoint the precise location of the inhibited PDE2. In addition, other more specific types of endothelial cell cultures, such as lung microvascular-derived cells, should have been favorably compared with HUVEC. Furthermore, although endothelial cells are likely candidates, the effect of PDE2 inhibitors on epithelial cell layers at the infection site (nasal mucosa) or within the respiratory track may have been underestimated (6). In this respect, although the selection of electrical resistance of endothelial cell (HUVEC) and human serum albumin leakage certainly represented a sound choice, other tools were not considered such as small molecular weight molecule (e.g., Evans blue, fluorescein) or microprotein (e.g., Clara cell protein 16) leakages (7), for assessing epithelial damage. Histopathologic examination of lung tissues should have also served for analysis of interstitial edema analysis to further consolidate PDE2 inhibition-induced decreased permeability.

Sepsis-induced tissue and lung hyperpermeability is the “underdog” in terms of research on mechanistic events leading to ALI/acute respiratory distress syndrome.

**See also p. 584.

Key Words: phosphodiesterases; inhibitors; acute lung injury; lung; permeability; pneumonia

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Indeed, hyperpermeability is a neglected but important event leading to sepsis-induced organ disability, due to a lack of specific tools to assess this particular phenomenon. However, it is a potentially leading cause of organ dysfunction/failure, either by impairing exchange ability (e.g., lung, kidney) or by compromising organ perfusion, especially for capsule- or membrane-bearing tissues or those exhibiting bone-limited compliances (e.g., kidney, adrenal gland, liver, brain) (8). However, as stated above, microvascular permeability is likely only half of the story, especially with regard to organ exchanges such as in lung or kidney. Indeed, the epithelium should be considered as the other side of the coin, since it is clearly committed in lung barrier considered as the other side of the coin, or kidney. Indeed, the epithelium should be likely only half of the story, especially with lung barrier or kidney. Indeed, the epithelium should be considered as the other side of the coin, with regard to organ exchanges such as in lung or kidney. Indeed, the epithelium should be considered as the other side of the coin, since it is clearly committed in lung barrier permeability (9). Water and solutes (i.e., sodium), through aquaporins and Na+/K+ pumps (in conjunction with Na+/K+ -adenosine triphosphatase basal pumps), are able to clear excess permeability in lung distal airspaces in ALI (10, 11), and therefore have to be taken into account together with endothelial impairment. Finding inhibitors of tissue permeability is a challenging issue requiring extensive research, which in return could yield invaluable applications at least for combination therapies for ALI at the bedside. This issue should have been explored in the study by Witzenrath et al (4), at least by specific in vitro lung epithelial cultures or optimally by epithelial-endothelial cocultures.

In summary, the data described by Witzenrath et al (4) undoubtedly provide an important addition to our current knowledge on the role of PDE2 in host infection by Streptococcus pneumoniae. This isozyme may indeed regulate key cell signaling processes, whose activation would be required to facilitate the early steps directly involved in the infectious cascade triggered by S. pneumoniae strains. In an explosion of interest for this concept, a rapid succession of studies will likely identify the missing links, the next step being the identification of the membrane receptor upstream (such as toll-like receptor) and the cyclic nucleotide-sensitive effectors, downstream of PDE2 in either endothelial or epithelial cell layers. An alternative issue would be that low levels of cAMP would facilitate interaction of S. pneumoniae exotoxin proteins with specific membrane receptors, whereas highly localized increases in cAMP levels (on PDE2 inhibition) would abolish this early step. Despite the fact that the role of proinflammatory cytokines cannot be ruled out, clinical teams will likely focus on the ability of new specific PDE2 inhibitors to decrease morbidity in ALI-related conditions to sever S. pneumoniae in curative protocols.

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Hemorrhagic shock and reperfusion injury: The critical interplay of fibrin fragments, leukocytes, and vascular endothelial-cadherin*

Reperfusion, the restoration of blood flow after a period of ischemia, can place ischemic organs at risk of further cellular necrosis and thereby limit the recovery of function. In particular, the microvasculature is vulnerable to the deleterious consequences of ischemia and reperfusion (I/R). The underlying pathophysiology of I/R injury is not fully understood, but several mechanisms are involved such as membrane damage inflicted by oxygen radicals, intracellular calcium overload, and tissue damage caused by infiltration and activation of white blood cells (1, 2). Reperfusion of ischemic tissues is often associated with microvascular dysfunction that is manifested as impaired endothelium-dependent dilation in arterioles, enhanced fluid filtration, leukocyte plugging in capillaries, and the trafficking of leukocytes and plasma protein extravasation in postcapillary venules. The resulting imbalance between superoxide and nitric oxide in endothelial cells leads to the production of reactive oxygen species, which can cause endothelial dysfunction and inflammation. The magnitude of albumin leakage in postischemic venules is highly correlated with the number of adherent and migrated leukocytes. Adhesion molecule-directed antibodies that effectively blunt leukocyte adherence/emigration also exert an attenuating action on I/R-induced albumin leakage (5). Leukocytes attach to the blood vessel wall via interaction of selectins and integrins with their respective receptors, and become progressively activated. To accomplish the final step of transmigration the endothelial layer, leukocytes must cross a multilayered molecular zipper of cell–cell junctions. Leukocyte transmigration is critically controlled by fibrin fragments. These short-lived intermediates engage leukocytes to the endothelial cell junction, which breaks up the VE-cadherin interaction between neighboring endothelial cells, allowing the leukocytes to pass through into the tissue (diapedesis).

In myocardial infarction, about 50% of overall tissue damage is caused by reperfusion injury. For several decades, it has been known that the inflammatory response during reperfusion is the major cause of myocardial I/R injury. If uncontrolled, the inflammation results in irreversible damage of the heart muscle, limiting the success of reperfusion procedures. The inflammatory reaction can be mitigated by application of Bβ15-42, also called FX06, concomitant with reperfusion (6–9). FX06, is a polypeptide, derived from the neo-N-terminus of fibrin, being the natural cleavage product of fibrin after being exposed to plasmin. FX06 targets an endothelial adherens junction protein, VE-cadherin, and reduces leucocyte transmigration across endothelial junctions and the release of proinflammatory cytokines (6–9). Therefore, FX06 prohibits the emigration of all leucocyte subtypes into myocardial tissue by preventing the critical interaction between fibrin fragments and VE-cadherin, which is rate limiting and irreversible.

Previous data on acute and chronic myocardial I/R models were promising and appeared to reduce myocardial inflammation and infarct size (6–9). In occlusion–reperfusion studies in rats, FX06 (2.4 mg/kg optimal dose) caused 40% reduction in infarct size (6). The positive effects of FX06 on the inflammatory response were reflected by a decrease in cytokines (interleukin [IL]-6, troponin). The safety and tolerability of FX06 has been demonstrated in a phase I trial in 30 healthy male volunteers, as no significant toxicity and adverse events were observed (7). A phase II trial on the treatment with FX06 for reperfusion injury in myocardial infarction (F.I.R.E. trial) has been completed recently and is designed to clinically evaluate infarct size at 5–7 days post-percutaneous coronary intervention (www.clinicaltrial.gov) (10).

In this issue of Critical Care Medicine, Roevers et al (11) report on the beneficial effects of this novel endogenous polypeptide FX06 in a hemorrhagic shock model. Hemorrhagic shock followed by volume resuscitation largely resembles the state of myocardial I/R. The key treatment of hemorrhagic shock involves early hemorrhage control, aggressive resuscitation, and the prevention and correction of coagulopathy (12). The current management of hemorrhagic shock relies heavily on transfusion of red blood cells that are associated with the development of multiple organ failure, increased intensive care unit admissions and length of stay, increased hospital length of stay, and mortality (13). Other therapeutic options are limited because of lack of understanding the pathophysiological mechanisms and lack of a specific target. Some novel
(experimental) interventions to limit reperfusion damage have some promise such as sodium/hydrogen exchange suppression (14), melatonin (15), IL-11 (16), or selectin inhibition (17), but failed to reach the clinical stage. In this context, the salutary effects of the compound FX06 on hemorrhagic shock-induced organ injury are potentially important and clinically relevant (11). The controlled-shock model was characterized by rather severe tissue damage (I/R and laparotomy), a long (5 hours) reperfusion time, and adequate volume resuscitation guided by volumetric preload parameters. FX06-treated animals showed a reduction in myocardial damage and leukocyte infiltration in the heart, as well as less liver/intestinal damage. The effects on lung filtration seem to be most prominent. Albertus Beishuizen, MD
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Peroxisome proliferator-activated receptor-gamma agonists, control of bacterial outgrowth, and inflammation*

In the 1980s, at a time when few cytokines were described, a new paradigm emerged that sepsis may be a syndrome that consists of an inappropriate and maladaptive systemic inflammatory response induced in response to infection. Numerous attempts were made to treat sepsis in the clinic using immune modulators that block proinflammatory cytokine mediators such as tumor necrosis factor or interleukin-1, or other components of innate immunity. Ultimately, all of these down-regulating immune modulators failed in clinical trials to treat sepsis.

Despite their failure in the acute setting of infection, many of the same anti-inflammatory treatments are now proven to be effective treatments for chronic inflammatory conditions such as rheumatoid arthritis and Crohn’s disease. Ironically, many of the treatments that were initially developed to treat sepsis have, in fact, turned out to predispose to infection and sepsis (1). This finding, coupled with data in animal experiments, suggests that blocking even single components of the innate immune system runs the risk of altering host defense sufficiently to compromise the elimination of microorganisms. For this reason, agents that suppress the inflammatory response in the setting of infection have traditionally been studied for use as adjuvant treatment in addition to primary antimicrobial treatment.

Peroxisome proliferator-activated receptor-gamma (PPARγ) is a member of the nuclear receptor family of transcription factors that mediates transcriptional activation or repression of genes related to lipid metabolism, cell proliferation, angiogenesis, and inflammation. PPARγ agonist ligands diminish insulin resistance and are used to help treat type 2 diabetes. PPARγ ligands also repress the gene for nitric oxide synthase, as well as tumor necrosis factor, interleukin-6, and interleukin-1 (2, 3). Because of these and other anti-inflammatory activities, it seems reasonable to study their potential use as an anti-inflammatory agent in the setting of infection.

In this issue of Critical Care Medicine, Stegenga et al (4) report a study in which a synthetic PPARγ ligand, ciglitazone, was evaluated in an established mouse model of pneumonia with Streptococcus pneumoniae. The drug was administered to groups of mice either once at the start of the infectious challenge or twice with the first dose at challenge and a second dose at 24 hrs. The mice were evaluated at 24 and 48 hrs after infectious challenge. Mice that received ciglitazone had decreased bacterial counts in the lungs compared with controls; in addition, there were decreased inflammatory cytokines in lung tissues at 24 hrs and decreased inflammation on histopathology at 48 hrs. There was also a trend toward a decreased mortality in the group.

It seems remarkable that a drug that possesses anti-inflammatory effects would decrease bacterial outgrowth. Because the innate immune system presumably evolved to control infection, one might expect the opposite effect. Indeed specific inhibition of the interleukin-1 or tumor necrosis factor in a similar model has been reported to lead to increased bacterial loads and decreased survival (5, 6). Therefore, the results reported in the current study in this model with the PPARγ ligand ciglitazone seem the best of all situations for an anti-inflammatory drug—decreased inflammation and at the same time, decreased bacteria.

The mechanism of the drug’s effect is not clear. There are several possibilities that the authors have addressed. First, there could be some sort of direct antibacterial action if the drug was acting as an antibiotic. There was apparently no antibacterial effect when the authors tested the drug in vitro at 5 μg/mL. However, ciglitazone was administered to the mice at 5 mg/kg; depending on the pharmacokinetics, it is possible that drug levels could have exceeded 5 μg/mL for some period of time. Second, a decrease in bacterial proliferation could be explained if ciglitazone had stimulated bacterial clearance in some way. PPARγ ligands have been reported to increase phagocytosis through increasing expression of CD36 (7), as well as through Fcy (8). The authors did not detect an effect of the drug using a murine alveolar cell line to assess phagocytosis of S. pneumoniae labeled with fluorescein isothiocyanate, and did not detect increased killing in these cells using a capsule-deficient strain of S. pneumoniae. It is unclear, however, how well this in vitro system with a cell line reflects the in vivo situation in the mouse model using an encapsulated strain of S. pneumoniae.

The results of Stegenga et al with S. pneumoniae are consistent with two other publications that reported that ciglitazone decreased inflammation without an increase in bacterial counts. One of these used the cecal ligation and puncture model (9), and the other a model of brain abscess with Staphylococcus aureus (10). Thus, the results may extend to organisms other than S. pneumoniae.

Interpretation of decreased inflammation in the setting of decreased bacterial load is complex. It is not clear from the present study if the antibacterial effect and the decreased inflammation stem from two different activities of the drug, one leading to decreased inflammation and the other to decreased bacterial counts. An alternative and simpler explanation is that the decreased inflammation may follow simply from the presence of fewer bacteria in tissues leading to less of a stimulus to the host.

*See also p. 614.

Key Words: peroxisome proliferator-activated receptor-γ; inflammation; bacteria; mouse model; pneumonia

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As always, there are many cautions in extrapolating results of animal models to human disease. Mice are much more resistant than humans to most forms of induced inflammation. It will be essential to determine the mechanism of the antibacterial effect and to determine whether there is any additional advantage when ciglitazone is used as adjuvant treatment in addition to simultaneous traditional antibiotics. Regardless, this study is provocative and raises some hope that PPARγ ligands could be a new approach to an area that could use a breakthrough in treatment.

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Look on the “air side” in pneumonia*

Pneumonia is the leading cause of acute lung injury (ALI) (1). The pathophysiology of ALI involves an uncontrolled host defense response, with a malignant alveolar cross talk between inflammation and hemostasis activation (2), which further propagates as the natural anticoagulant axis is disrupted (3).

Despite the use of early broad-spectrum antibiotics, the mortality of pneumonia is still high with an “attributable mortality” from hospital-acquired Gram-positive and Gram-negative pneumonia of 33% to 50% (4). One explanation is that the mortality is not only attributed to the infection per se but also to the antigens of the bacteria.

In this issue of Critical Care Medicine, Hoogerwerf et al (5) shows for the first time that antigens from cell walls of both Gram-positive and Gram-negative bacteria have the same effect in humans. Furthermore, they also showed that alveolar levels of antithrombin and activated protein C (APC) concentrations were reduced. This was meticulously documented by this randomized study of instillation of saline, lipoteichoic acid, or lipopolysaccharide, i.e., applying the antigens from the “air side.” Their findings are not self-explanatory in as much as Gram-positive and Gram-negative pathogens actuate immune and procoagulant responses in the lung via different recognition receptors, i.e., via toll-like receptors 2 and 4, respectively.

Severe pneumonia in hospitals has still a high mortality despite applying evidence-based early use of broad-spectrum antibiotics. As documented by Hoogerwerf et al, the problem is that the pulmonary dysfunction in pneumonia is further aggravated by the antigens of the bacterial cell walls.

How do we then offset the changes induced from the air side, and, further does pharmacotherapy with natural anticoagulants and fibrinolytics have a role in the treatment of ALI? It is logical to introduce such a therapy using natural anticoagulants because the intra-alveolar hemostasis activation is not sufficiently counterbalanced by natural inhibitors, such as tissue factor pathway inhibitor (6) and APC (7, 8).

Tissue factor pathway inhibitor was shown to reduce lung injury and systemic levels of inflammatory cytokines in an animal study (9), and, further, in a subsequent phase II trial, the results were promising. However, this benefit was lost in a subsequent phase III trial (10). At present, we are awaiting the results from a placebo-controlled trial in community-acquired pneumonia using intravenous tissue factor pathway inhibitor (11).

Since the introduction of the recombinant APC for the treatment of severe sepsis (Drotrecogin alpha activated) (12), several studies have used APC intravenously to counteract the hemostatic changes in ALI (8). Recently, a controlled trial using intravenous APC in patients with acute lung injury was published (13). The study revealed that APC did not improve outcomes of acute lung injury and concluded that the results “do not support a large clinical trial of APC in acute lung injury.” Furthermore, intrave-
nous APC has been shown to result in noteworthy bleeding as alluded to in two recent articles (14, 15). The adverse effects of systemic bleeding may be avoided if APC is inhaled and provided that there is no spillover from the alveoli to the systemic circulation (16).

From a theoretical viewpoint, inhaled APC has all the essential properties to counteract the pathophysiologic changes seen in ALI. In an animal study by Slofstra et al (17), the lipopolysaccharide-induced inflammation was reduced after inhalation of APC. A human experience with inhaled APC has been reported in a patient with ALI (16), with an important improvement in pulmonary gas exchange concomitant with a noteworthy clearing of the pulmonary opacities.

There is thus a good reason to “look at the pneumonia from the air side” not only with respect to explaining the acute pathophysiologic changes ensuing pneumonia, but also treating the condition from the same side by inhaling a natural anticoagulant, such as APC. APC may be an important adjunctive intervention in severe pneumonia caused by both Gram-positive and Gram-negative bacteria. There is, however, only sparse information to substantiate such a new treatment paradigm. The next step, therefore, is to conduct controlled trials with inhaled APC because the intravenous intervention has already proved ineffective.

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The role of angiotensin-converting enzyme inhibition in endotoxin-induced lung injury in rats*

The renin-angiotensin system (RAS) plays an important role in the homeostasis of systemic blood pressure, but it can also regulate inflammation. RAS consists of the renin protease that cleaves angiotensinogen into angiotensin I (Ang I). Angiotensin-converting enzyme (ACE) is primarily expressed on the surface of pulmonary microvascular endothelial cells and cleaves Ang I into angiotensin II (Ang II) (1). ACE also inactivates the vasodilator bradykinins. The biological effects of the RAS system are mediated by Ang II on its specific receptors, Ang II receptor type 1 and Ang II receptor type 2. Production of Ang II and stimulation of Ang II receptor type 1 are responsible for vasoconstriction and endothelial dysfunction in models of systemic inflammation with endotoxin. Together with the observation that pulmonary Ang II was up-regulated in patients with acute respiratory distress syndrome (ARDS), inhibition of RAS became a potential treatment for these acute inflammatory disorders (2, 3). The discovery of a new homolog termed angiotensin-converting enzyme 2 (ACE2) revived interest and supported a potential role for RAS in the pathogenesis of lung inflammation. By counterbalancing ACE and reducing Ang II levels, ACE2 can play a protective role in sepsis-induced ARDS (4). These pathways are shown in Figure 1. Polymorphisms of the ACE gene were also the first to be associated with susceptibility and outcome of ARDS (5).

In this issue of *Critical Care Medicine*, Haqiwara et al (6) report a beneficial role for ACE inhibition with enalapril on systemic inflammation and pulmonary injury using a rat model of intraperitoneal endotoxin-induced inflammation. Enalapril was administered before endotoxin exposure. The findings in this study agree with the protective role of ACE inhibition reported in models of ventilator-associated and oleic acid-induced lung injury. In these models, ACE inhibition attenuated pulmonary Ang II production with a reduction of 1) inflammatory cytokines; 2) procoagulant effects; and 3) endothelial and epithelial apoptosis (7, 8).

After endotoxin administration in the study by Haqiwara et al, the investigators measured increased systemic levels of Ang II that were attenuated by ACE inhibition with enalapril. However, there was no measure of systemic or local pulmonary ACE activity. In the study by Idell et al (9), ACE levels were increased in bronchoalveolar lavage fluid from patients with sepsis-associated ARDS, and plasma ACE activity was decreased in these patients. Animal models (10) of ventilator induced lung injury also demonstrated increased ACE activity in bronchoalveolar lavage fluid. However, in other models of lung injury, pulmonary endothelial ACE activity (assessed by *in vivo* dilution methods) was reduced as a result of enzyme downregulation caused by reactive oxygen species, as reported by Orfanos et al (11) in patients with ARDS. These findings indicate that it might be important to consider compartmentalization of RAS to understand its pathophysiology.

To identify the cellular and molecular mechanisms of ACE inhibition in their model of systemic inflammation, the authors focused on the role of macrophages. Besides endothelial cells, inflammatory cells are equipped with all the components of RAS and can produce Ang II. The key finding that enalapril sup-

*See also p. 626.*

Key Words: angiotensin; angiotensin-converting enzyme; angiotensin-converting enzyme inhibitor; acute lung injury; acute respiratory distress syndrome; sepsis; inflammation

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Figure 1. The pathways by which angiotensinogen system can participate in the regulation of vascular permeability, vasoconstriction, inflammation, remodeling, and vasodilation. As described in the text of the editorial, Ang II receptor type 1 (AT1R) and Ang II receptor type 2 (AT2R) identify the known receptors for angiotensin II (Ang II). ACE, angiotensin-converting enzyme; Ang I, angiotensin I.
presses nuclear factor kappa B activation is important, given the central role of nuclear factor kappa B in the regulation of proinflammatory and proapoptotic genes. This finding is supported by the systemic reduction of tumor necrosis factor-α and interleukin-6 with enalapril treatment. The reduction in high mobility group box protein 1 in serum, lung tissue, and macrophage supernatant was also associated with enalapril treatment.

The mechanistic insights in this study are not complete because the investigators did not study the effect of ACE inhibition on other cell types in this model. Others have provided in vitro evidence that Ang II induces apoptosis in alveolar epithelial cells (12). Altered myeloperoxidase activity suggests effects on endothelial cell adhesion molecules and/or direct neutrophil effects. Also, transcription factors such as activation protein-1 and the production of proinflammatory mediators might provide additional insights into the role of RAS during acute inflammatory changes. The primary site of action of Ang II in this model is still unclear. Exploration of specific interactions with Ang II receptor type 1, as has been done in other injury models (13), or receptors of the bradykinin system, might be necessary.

A role for Ang II in acute lung injury (ALI) may not be limited to the acute phase. Locally produced Ang II also plays a potential role in the fibroproliferative phase of the disease. Inhibition of the RAS system reduces procollagen production and transforming growth factor-β expression in human lung fibroblasts (14). It would be interesting to study the effect of early or late ACE inhibition on the fibroproliferative response in ALI.

Additional preclinical animal studies will be necessary to evaluate the potential clinical value of ACE inhibition in sepsis and ALI/ARDS. The potential systemic side effects of vasodilation and systemic hypotension need to be investigated, and dose–response effects and drug admission after exposure to the insult will need to be tested. One clinical study that reported outpatient use of ACE inhibitors reduced 30-day mortality for patients with community-acquired pneumonia (15).

In summary, the findings of this experimental study should stimulate further preclinical studies to test the potential value of ACE inhibition as a treatment in infectious and noninfectious models of ALI (16, 17). If the results of these experimental studies continue to be promising, then a phase II clinical trial may be warranted with ACE inhibition for early ALI/ARDS.

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A new approach to step on the vagal anti-inflammatory gas pedal*

In response to infection, the central nervous system initiates several anti-inflammatory pathways, designed to prevent the detrimental effects of the uncontrolled release of inflammatory mediators. One of these pathways involves an increased activity in the efferent vagus nerve, called the “nicotinic anti-inflammatory pathway,” which reflexively modifies the inflammatory response (1, 2). The most compelling evidence for role of the cholinergic nervous system in the regulation of inflammation is derived from studies on rodents challenged with endotoxin, the proinflammatory component of the outer membrane of Gram-negative bacteria (3, 4). In these studies, vagotomy led to enhanced systemic tumor necrosis factor-α production and accelerated the development of shock; in turn, electrical stimulation of the efferent vagus nerve down-regulated tumor necrosis factor-α production and protected animals from hypotension (3). These findings were later confirmed and expanded in animal models of sepsis, pneumonia, and pancreatitis (5–9). Further studies showed that the anti-inflammatory properties of the efferent vagus nerve are mediated through its major neurotransmitter acetylcholine (Ach), which interacts with nicotinic Ach receptors on macrophages resulting in inhibition of endotoxin-induced responses (3, 4), showing that the nicotinic Ach receptor (and not the muscarinic Ach receptor) and, specifically, the alpha7 subunit are required for this effect (4). The molecular target for this pathway has been identified as it has been shown that the vagal anti-inflammatory pathway acts by alpha7 subunit-mediated Jak2-STAT3 activation in macrophages (10). On the basis of these studies, it has been suggested that stimulation of nicotinic acetylcholine receptors might be beneficial in clinical syndromes involving overshoot inflammation such as septic shock, inflammatory bowel disease, or rheumatoid arthritis. Indeed in several studies, administration of nicotine or specific nicotinic Ach agonists, such as GTS-21, have been shown to reduce inflammation in various animal models (4, 5, 7).

In this issue of Critical Care Medicine, Liu et al (11) evaluated the effect of pretreatment with anisodamine, a muscarinic receptor antagonist, in rodent models of endotoxic shock. This is a surprising approach because, as stated above, all reported studies on anti-inflammatory compounds derived from the theory of the vagal anti-inflammatory reflex have involved ligands for nicotinic Ach receptors. Anisodamine is a compound that is derived from a Chinese medicinal herb and is chemically related to atropine. The authors state that anisodamine is widely used in the treatment of septic shock in China, although evidence from clinical studies is lacking. However, on the basis of their results there might be some truth and rationale behind the myth.

In their report, Liu et al (11) show that blockade of muscarinic receptors using anisodamine results in an anti-inflammatory phenotype in endotoxin shock. Furthermore, they show that this anti-inflammatory phenotype can be reversed when nicotinic receptors are blocked concurrently with muscarinic blockade. The authors hypothesize that muscarinic receptor blockade results in rerouting of Ach to nicotinic receptors resulting in increased Ach-mediated activation of nicotinic receptors and activation of the nicotinic anti-inflammatory pathway. These results are strengthened by studies involving vagotomy as well as alpha7 knockout mice because the beneficial effects of anisodamine are absent in vagotomized mice as well as alpha7 knockout mice. Using in vitro studies, the authors show that indeed the binding of the selective alpha7 selective agonist bungarotoxin is increased in anisodamine-treated macrophages.

Taken together, the authors demonstrate that pretreatment with anisodamine results in an anti-inflammatory phenotype, decreases shock, and increases survival. The observed effects of anisodamine are probably unrelated to muscarinic receptors per se but intimately linked to an alpha7 nicotine receptor-dependent pathway suggesting that a secondary enhanced activation of this pathway is a result of blockade of muscarinic receptors. The exact mechanism, however, can only be suggested based on the presented data and, therefore, remains to be elucidated. The study confirms the potential beneficial effects of anisodamine in the treatment of shock. However, an endotoxin model was used, and in the intensive care setting, septic shock is a different ballgame because it involves systemic circulation of live bacteria. An anti-inflammatory phenotype in genuine sepsis might result in enhanced bacterial load that may be clinically relevant. Although this study suggests that anisodamine might be of use in clinical sepsis, one should be very cautious and remember that no anti-inflammatory intervention has been shown to be beneficial in human studies. Therefore, I strongly feel that the use of this compound in septic shock, which as the authors state, is quite a common practice in China, cannot be recommended. To evaluate the clinical potential in sepsis, I would be interested in the phenotype of anisodamine treatment observed in animal models of sepsis such as cecal ligation and puncture. The most important question in studies involving the vagal anti-inflammatory reflex and pertaining to the location of the “immune synapse” remains. The exact location where the physiologic interaction between vagus nerve, derived acetylcholine and immune cells takes place has not been elucidated so far, although the spleen has been suggested (12, 13). Finally, this study suggests that activation of the vagal immune reflex can not only be pursued by stimulation of the vagus nerve or nicotinic receptors but also by inhibition of muscarinic receptors, which results in secondary activation of the pathway. The au-

*See also p. 634.

Key Words: vagus nerve; sepsis; endotoxin shock; anti-inflammatory; anisodamine

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The discovery of penicillin and the rise of antibiotic drugs changed the nature of medicine. Antibiotics, which actually killed bacteria, were hailed as “miracle drugs” (1), able to strike at the “root” cause of diseases like pneumonia, tuberculosis, malaria, syphilis, and gonorrhea. Unfortunately, bacteria soon demonstrated that they were able to become resistant to different antibiotics and, in turn, to pass their resistance genes onto their descendants, eventually producing populations of bacteria that could survive even the strongest drugs. As a consequence, pneumonia that was once thought could be eradicated remained a persistent problem.

Pneumonia is a leading cause of death, particularly in children and elderly. The use of antibiotics and advances in health care lessened the risk; however, pneumonia remained the first cause of death among respiratory and infectious diseases globally. Streptococcus pneumoniae is the commonest etiology of mild, moderate, and severe community-acquired pneumonia. There is an increase in antibiotic resistance of pneumococci limiting the number of antimicrobial agents that produce reliable treatment results for these infections. Other microorganisms producing community-acquired or nosocomial pneumonia show the same resistance acquisition problem. Newer antimicrobials and combination therapy by antimicrobials with different mechanisms of action have been used to treat infections for decades with the goal of producing a wider spectrum of action, preventing the emergence of drug-resistant subpopulations, reducing the dose of a single agent, or achieving a synergistic effect; however, this use of antibiotics promoted the development of increasing resistance. This phenomenon has been named the antibiotic paradox—miracle drugs are destroying the miracle (2). The ways to face the antimicrobials resistance challenge include the increase of our efforts to preserve the activity of available antibiotics, or at least expand, as much as possible, the period of their use, while intense research efforts should be focused on the development and introduction of new antimicrobial agents into clinical practice. However, the problem generated with the evolving antimicrobial resistance in Pseudomonas aeruginosa, Acinetobacter baumannii, Staphylococcus aureus, and Klebsiella pneumoniae has led to the emergence of clinical isolates susceptible to only one class of antimicrobial agents and eventually to pandrug-resistant (i.e., resistant to all available antibiotics) isolates.

Bacteriophages or phages, so called bacteria-killing viruses, described at the beginning of the 20th century and characterized by Delbrück, Luria, and Hershey who were awarded the novel prize in 1969 for their discoveries (3), have been
used successfully in treatments against antibiotic-resistant bacteria in various infections, including pneumonia. These data have come from clinical trials in Eastern Europe, mostly uncontrolled. However, recent findings in well-controlled animal models demonstrating that phages can rescue animals from a variety of fatal infections produced by S. pneumoniae, S. aureus, and P. aeruginosa are encouraging (4–6). Therapeutic phages appear to kill their target bacteria by replicating inside and lysing the host cell via a lytic cycle; endolysins are lytic enzymes that ensure phages’ progeny survival, by selecting essential cell wall components as target for destruction to avoid phages’ breed from being locked up inside the bacteria (7, 8). However, lysis of host bacteria by a lytic phage is a complex process consisting of a cascade of events involving several structural and regulatory genes, and it is possible that some therapeutic phages have some unique yet unidentified genes or mechanisms responsible for their ability to effectively lyse their target bacteria (9). The therapeutic and prophylactic application of phages is now experiencing a renaissance of interest.

In this issue of Critical Care Medicine, Witzenrath et al (10) explored, in an experimental study on a mouse model of severe pneumococcal pneumonia, the therapeutic potential of Cpl-1, a purified bacteriophage endolysin, which specifically kills pneumococci on contact. They observed that when treatment was commenced 24 hours after experimental infection, 100% Cpl-1-treated mice survived the otherwise fatal pneumonia and showed rapid recovery. When treatment was started 48 hours after infection, mice had developed bacteremia, and three of seven Cpl-1-treated animals (42%) survived. Cpl-1 dramatically reduced pulmonary bacterial counts, and prevented bacteremia, systemic hypotension, and lactate increase when treatment commenced at 24 hours. In vivo, treatment with Cpl-1 effectively reduced counts of penicillin-susceptible pneumococci. The inflammatory response in Cpl-1-treated mice, as determined by multiplex cytokine assay of lung and blood samples, was lower than in untreated mice. They concluded that Cpl-1 may provide a new therapeutic option in the treatment of pneumococcal pneumonia.

This study adds new information about the effectiveness of purified recombinant bacteriophage lytic enzymes, and specifically on the role of Cpl-1 for the control of diseases caused by S. pneumoniae. These findings warrant research into further therapeutic uses of this novel technology to advance its application in the clinical setting.

Unfortunately, from the microbiological standpoint, pneumonia is a complex problem that cannot be immediately derived from an animal model to the patients’ presentation in the real world. Cpl-1, as most of the lytic enzymes, are targeted to specific pathogenic bacteria. It is difficult to ascertain, based on clinical or rapid microbiological techniques, which is the etiology of pneumonia; additionally, if more than one pathogen is involved, as happen, in about 10% to 50% of pneumonias, it is not clear if in these cases a “cocktail” of different lytic enzymes or bacteriophages could be used (11).

The postantibiotic era is more than a hypothesis; actually, pandrug-resistant bacteria are among us, producing severe nosocomial pneumonia and other kinds of infections in the healthcare setting. The strategies to face this problem include the use of novel therapies to fight against bacterial infections including phage therapy, immunomodulation, non-bacterial killing effects of antibiotics, and improved preventive measures. There is still a great lack of formal large, scale clinical-studies on bacteriophages safety and effectiveness; the lack of newer antimicrobials is essential; studies exploring newer ways to struggle against bacterial infections, like the original investigation presented by Witzenrath et al, should be encouraged.

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Functional hemodynamics and increased intra-abdominal pressure: Same thresholds for different conditions . . .?*

What this study tells us . . .

In this issue of Critical Care Medicine, Renner et al (1) report the results of a study entitled “Influence of increased intra-abdominal pressure on fluid responsiveness predicted by pulse pressure variation and stroke volume variation (SVV) in a porcine model.” On first sight, it looks as if this study just repeats previous studies on SVV and pulse pressure variation (PPV) during intra-abdominal hypertension (IAH) (2–5). Is this really the case? The authors collected prospective data on 14 domestic pigs during loading conditions and increased intra-abdominal pressure (IAP) up to 25 mm Hg via CO₂ pneumoperitoneum (PP). The application of PP increased the baseline values for SVV (from 9.6% ± 3.2% to 16.3% ± 5.9%) and PPV (from 12.8% ± 3.5% to 22% ± 8.2%), whereas global end-diastolic volume (GEDV) decreased (from 836 ± 210 mL to 788 ± 198 mL). After fluid loading, PP still increased SVV (from 6.4% ± 2.7% to 13.2% ± 4.7%) and PPV (from 7.4% ± 1.6% to 15.7% ± 4.5%). These changes were correlated with changes in esophageal or intrathoracic pressure (ITP). They also found that changes in PPV, SVV, and GEDV showed significant correlations with changes in SV after volume loading, independent of IAP. The ability of PPV and GEDV to predict fluid responsiveness remained unchanged during PP, whereas SVV lost this ability when IAP was increased up to 25 mm Hg. The bottom line is that in conditions of increased ITP, as is the case with IAH, different SVV and PPV thresholds should be used to predict fluid responsiveness.

What previous studies have shown . . .

Duperret et al (3) found similar results in a pig model of abdominal banding with IAP up to 30 mm Hg. A dose-related IAP effect was suspected. In their model, the systolic pressure variations (SPV), PPV, and inferior vena cava flow fluctuations were dependent on IAP values, which caused changes in pleural pressure swings, and this dependency was more marked during hypovolemia. Although the application of PP increased both PPV and SPV, a statistical significant effect was only observed for SPV. The increase in SPV was mainly related to the Δp component. Duperret et al (3) also looked at left ventricular end-diastolic pressure and left ventricular end-diastolic area and found that the increase in the IAP induced a progressive increase in ITP and, therefore, a relative hypovolemia owing to a redistribution of blood volume. Although this factor is likely to play a role at the highest values of IAP, a moderate value of IAP was associated with an increase in thoracic blood volume, left ventricular end-diastolic area, and transmural left ventricular end-diastolic pressure, suggesting an auto-transfusion effect.

Tournadre et al (5) found similar results for SPV in seven pigs undergoing CO₂ PP, but this time limited at 12 mm Hg. The SPV increased whereas central venous pressure remained unchanged and left ventricular end-diastolic area decreased. The 30% increase in SPV during elevated IAP was mainly because of an increase in Δp component from 3.8% ± 5.2% to 7.3% ± 5.5%. Volume loading with hydroxyethyl starch (10 mL/kg) during PP resulted in a decrease in SPV owing to a decrease in Δp up to 6% ± 3.1%.

In a similar study by Bliacheriene et al (2) in 11 rabbits undergoing CO₂ PP with IAP increase up to 10 mm Hg, SPV increased more than PPV. The PP in combination with hypovolemia induced by hemorrhage further increased SPV and PPV, confirming the superiority of PPV over SPV to predict “fluid responsiveness.” The increase in SPV by PP was also caused by an increase in Δp from 2% ± 1% to 6.7% ± 2%. This study had some limitations as discussed previously (4).

In a last study, Valenza et al (6) looked at the effects of Helium-PP up to 25 mm Hg in 15 rats. The PP increased SV from 8.7% ± 3% to 17.9% ± 8% together with the central venous pressure whereas GEDV decreased. Table 1 gives an overview of the different studies.

What this study adds . . .
The changes observed in SVV and PPV for a given IAP are the most important findings of this study. Together with the previously documented increases in SPV that were mainly related to the Δp component, possible mechanisms are suggested. First, a change in aortic compliance and an increase in aortic transmural pressure induced by increased IAP (either via direct compression or increased vasomotor tone). Second, errors in the measurement of dynamic indices in conditions of increased IAP, or, if we assume that no measurement errors are induced by IAP then this implies that these indices do not perform well during IAH (since SVV did not longer predict fluid responsiveness). Third, changes in extramural pressure, ITP, or chest wall compliance.

This study was one of the first looking at the abdominothoracic index of transmission (7). The authors found a 47% transmission of the ΔIAP to the lung and a 45% transmission to the thoracic compartment (Table 1). This is in accordance with previous studies showing on average an abdominothoracic index of transmission of 50% and confirms that traditional filling pressures are erroneously increased during increased ITP/IAP (7, 8). Interestingly, the abdominothoracic index of transmission was higher in nonresponders.

The authors also looked at receiver operating characteristic curves to identify the best thresholds for predicting fluid responsiveness at baseline and during PP. The results confirmed that GEDV is not

*See also p. 650.

Key Words: abdominal pressure; abdominal compartment; preload; fluid responsiveness; functional haemodynamics; stroke volume variation; pulse pressure variation

Dr. Malbrain has consulted for, received honoraria from, and holds stock in Pulsion Medical Systems. Dr. De laeët has not disclosed any potential conflicts of interest.

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Table 1. Overview of studies on functional hemodynamics during intra-abdominal hypertension

<table>
<thead>
<tr>
<th>Source</th>
<th>Stage</th>
<th>NormoV</th>
<th>HypoV</th>
<th>NormoV</th>
<th>HypoV</th>
<th>NormoV</th>
<th>NormoV</th>
<th>Fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tournadre et al (5)</td>
<td>Pig</td>
<td>7</td>
<td>11</td>
<td>7</td>
<td>15</td>
<td>14</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>Blacherine et al (2)</td>
<td>Co2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>6.5</td>
<td>2.0</td>
</tr>
<tr>
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<td>CO2</td>
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<td>10</td>
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<td>25</td>
<td>23</td>
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</tr>
<tr>
<td>Duperret et al (3)</td>
<td>Pig</td>
<td>12</td>
<td>10</td>
<td>10</td>
<td>25</td>
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<td>23</td>
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</tr>
<tr>
<td>Duperret et al (3)</td>
<td>Banding</td>
<td>7</td>
<td>12.7</td>
<td>11.1</td>
<td>14.4</td>
<td>14.4</td>
<td>13.3</td>
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</tr>
<tr>
<td>Valenza et al (6)</td>
<td>Bilat</td>
<td>7</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>11.2</td>
<td>12.2</td>
<td>13.5</td>
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<td>Rat</td>
<td>15</td>
<td>14</td>
<td>7</td>
<td>8.6</td>
<td>8.1</td>
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<td></td>
</tr>
<tr>
<td>Renner et al (1)</td>
<td>Pig</td>
<td>9.5</td>
<td>15</td>
<td>290.4</td>
<td>836</td>
<td>1069</td>
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<tr>
<td>Preload-BL</td>
<td>1</td>
<td>12.5</td>
<td>9.5</td>
<td>267.2</td>
<td>788</td>
<td>1034</td>
<td>496.4</td>
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<tr>
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<td>−0.4</td>
<td>−2.5</td>
<td>−2.5</td>
<td>16.9</td>
<td>21.4</td>
<td>21.1</td>
<td>18.7</td>
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<tr>
<td>Paw-BL (cmH2O)</td>
<td>26</td>
<td>13.4</td>
<td>13.4</td>
<td>28.1</td>
<td>33.6</td>
<td>34.6</td>
<td>30.0</td>
<td></td>
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<tr>
<td>Paw-Paw</td>
<td>11</td>
<td>10.1</td>
<td>10</td>
<td>11.2</td>
<td>12.2</td>
<td>13.5</td>
<td>11.3</td>
<td></td>
</tr>
<tr>
<td>Preload-BL</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>6.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Preload-Paw</td>
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<td>11.3</td>
<td>11.3</td>
<td>14.4</td>
<td>11.3</td>
<td>14.4</td>
<td>11.3</td>
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<tr>
<td>Preload-CVP</td>
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<td>13.8</td>
<td>12.4</td>
<td>5</td>
<td>161</td>
<td>3.2</td>
<td>48.8</td>
<td></td>
</tr>
</tbody>
</table>

ATI-car, abdomino-thoracic index of transmission to the cardiovascular compartment (calculated as ΔCVP divided by ΔIAP); ATI-res, abdomino-thoracic index of transmission to the lungs (calculated as ΔPaw divided by ΔIAP); ATI-thor, abdomino-thoracic index of transmission to the thoracic compartment (calculated as ΔITP divided by ΔIAP); BL, baseline values; CVP, central venous pressure; IAP, intra-abdominal pressure; ITP, intrathoracic pressure; Paw: peak airway pressure; PP, pneumoperitoneum; PPV, pulse pressure variation; SpV, systolic pressure variation; SVV, stroke volume variation.

Looking at the pooled data one can see that an increase in IAP (ΔIAP) of 17.9 mm Hg results in a ΔPaw of 3.8 mm Hg, a ΔITP of 10.5 mm Hg, and a ΔPaw of 11.3 cm H2O. The average abdomino-thoracic index of transmission was 47% to the thorax, 20% to the cardiovascular space, and 58% to the lungs (airway pressure). The bottom line is that dynamic indices like SpV, SVV, or PPV are not exclusively related to volemia in the presence of increased ITP or IAP; 5in the study by Tournadre data was given for pulmonary artery occlusion pressure instead of CVP.

Only a good static “volumetric” preload parameter (far more superior than the “barometric” indices of preload like central venous pressure or pulmonary artery occlusion pressure) but also a good indicator of fluid responsiveness (equal to PPV), regardless of IAP. In contrast to other studies, transmural filling pressures did not perform better than the central venous pressure and pulmonary artery occlusion pressure values taken at end-expiration (central venous pressure)." (9).

Interesting to see was that PPV (but not SVV) kept its ability to predict fluid responsiveness even at IAP levels of 25 mm Hg; however, receiver operating characteristic curve analysis identified 20.5% as the best threshold for fluid responsiveness (instead of the classic 12% and the 9.5% identified in this study at baseline). This is an important clinical message, meaning that we probably cannot use the same thresholds for different conditions. The threshold value will depend on the amount of tidal volume, positive end-expiratory pressure application, or increased ITP and consequent changes in pleural pressure and chest wall elastance, the presence of obesity, heart failure with changes in right and left ventricular preload and afterload, pulmonary hypertension, the use of a PP or increased IAP . . . and may also differ in children or neonates. However, it must be said that because of the limited sample size the cut-off values only give a rough estimation and need to be validated in a larger patient population.

This study showed that PPV performed better than SVV derived from pulse contour analysis based on a complex algorithm. This is a bit surprising because PPV is a surrogate of SVV and the latter should be less influenced by changes in vasomotor tone. The present study suggests that changes in pulse contour due to increased ITP may be more complex than previously thought.

The study also showed that ΔIAP correlates well with ΔITP and thus confirms the rule of thumb to calculate the transmural filling pressure: central venous pressure = central venous pressure − IAP/2 (10).

What this study does not tell us . . . To play the devil’s advocate one could argue that the questions that the authors tried to answer have been addressed previously. While the study was simple in its concept, it turned out to be complex in its execution and it may leave the average
modynamic parameters, and CO2 can cause argon has been observed to influence he-
effects. Although helium seems quite inert, results. Gases are likely to have systemic
levels (15–20 mm Hg) on dynamic indi-
hours) of IAH at clinically relevant IAP
look at the long-term effects (24 – 48
important and the authors have to be
relevant model therefore is one that mimics
quite short (only 15 minutes). The cur-
time-course between the different stages was
lack, resuscitation, and tissue edema.
Finally, the study period and the time-
course of fluid responsiveness implies even
change in vasomotor tone (aortic compli-
appearance, partly explaining the observations
11).
Third, this study was performed on
healthy pigs with normal cardiovascular
and respiratory function. Therefore, it re-
main questionable whether these results
be extrapolated to a pathologic con-
dition with a primary insult, capillary
leak, resuscitation, and tissue edema.
What future animal studies should
look at . . . Despite the fact that the data
raises a lot of questions, this study is
important and the authors have to be
congratulated. Future studies should
look at the long-term effects (24 – 48
hours) of IAH at clinically relevant IAP
levels (15–20 mm Hg) on dynamic indi-
ces of fluid responsiveness during PP,
with and without hemorrhage and before
and after fluid loading. Future studies
should try to integrate these results with
global indices of perfusion (lactate, base
deficit) and the presence of clinical overt
shock in animals and even better in pa-
tients who are critically ill. Furthermore,
they should also look at a good gold stan-
ard for SV measurement by means of an
ultrasonic flow probe in the aorta to ex-
clude the possibility for possible mathe-
matical coupling of data.
The results of this study confirm the
importance of IAH/abdominal compart-
ment syndrome (13). The world society of
the abdominal compartment syndrome
(www.wsacs.org) invites interested re-
searchers to join the society, to adhere to
the consensus definitions posted at the
Web site and to submit some prospective
data for the next world congress (www.
wacs.org), to be held in Dublin, Ireland,
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1565–1569
Designing clinical trials to improve neurobehavioral outcome after traumatic brain injury: From bench to bedside*

Traumatic brain injury (TBI), a physiologic disruption of brain structure and function resulting from the application of external physical force, is a problem of increasing concern within the medical community, among healthcare policymakers, and to the general public. Between one and two million persons in the United States suffer from TBI each year, of which ~230,000 are hospitalized. Improvements in prehospital care (1) and refinements in acute care management strategies (2) make survival after TBI more likely today than ever before. Despite improvements in survival after TBI, however, the Centers for Disease Control and Prevention estimate that >80,000 Americans develop long-term TBI-related disability each year and that about 3.2 million persons in the United States are living with such disabilities (3, 4).

Mitigating the neurologic, neurobehavioral, and functional sequelae of TBI, therefore, is an essential treatment goal at all stages of postinjury care. Unfortunately, the development of therapies that accomplish this goal has not kept pace with those that improve TBI survival. At least 21 multicentered randomized controlled trials of agents with potential neuroprotective properties, including N-methyl-D-aspartate receptor antagonists, calcium channel blockers, magnesium sulfate, cannabinoids, corticosteroids, aminosteroids, prostaglandin, cyclosporine, and inflammatory modulators, among others, have been conducted in the TBI population (5, 6). None of these studies convincingly demonstrated benefit.

Interpreting the failures of these randomized controlled trials is a complicated endeavor (6). The proportion of the variance in clinical outcome accounted for by any general neuroprotective intervention is likely to be relatively modest. When investigated in groups that are heterogeneous with respect to TBI characteristics—particularly the presence, type, severity of intracranial abnormalities, clinical severity, and baseline prognostic risk—the likelihood of effecting change through a single intervention is made more modest still. Additionally, when the outcome by which that intervention is assessed is a global measure (such as the Glasgow Outcome Scale [7]) dichotomized into “favorable” or “unfavorable” categories, statistical power to detect clinical neuroprotective effects is attenuated further.

The design of such randomized controlled trials and the selection of an outcome measure for use therein is more than a matter of statistics. Several decades of improvements in survival after TBI necessitate a shift, or at least an expansion, of focus from general measures of TBI outcome to the most enduring and difficult problem experienced by the majority of TBI survivors and their families: neurobehavioral disturbances (8, 9). These problems contribute substantially to postinjury disability (10, 11) and present major challenges for TBI survivors and their families: neurobehavioral disturbances (8, 9). These problems contribute substantially to postinjury disability (10, 11) and present major challenges for TBI survivors and their families throughout the postinjury period (12, 13). Despite the prevalence and functional relevance of posttraumatic neurobehavioral disturbances, their incorporation into the design of randomized controlled trials in TBI and stroke (14) is limited, if and when such problems are considered at all.

In this issue of *Critical Care Medicine*, Longhi et al (15) present findings from an experimental injury study in which neurobehavioral and neuropathological outcomes are afforded equal consideration. Recognizing the complement system as a contributor to the pathobiology of TBI, they investigated the effects of C1-inhibitor (C1-INH)—an endogenous serine-protease inhibitor of complement activation within the classic, alternative, and lectin pathways—given 10 minutes or 1 hour postinjury on neurobehavioral sequelae and histologic damage in a controlled cortical impact mouse model of TBI.

The selection of both this agent and this particular model of TBI are important initial considerations: the activation of complement and associated inflammatory responses are substantial contributors to brain injury in the setting of cerebral contusion, but are less relevant in the absence of such (i.e., in the setting of diffuse axonal injury alone). In addition to defining a subcategory of TBI in which the agent selected might be useful, the agent itself affects several elements of the complement cascade. Its multiplicity of effects increases the likelihood of attenuating injury with this single agent. Additionally, the authors anchor their investigation to outcomes that more readily model important clinical parameters than do histologic measures alone: they evaluate the effect of C1-INH on neurobehavioral function, including motor performance (as assessed by the Morris Water Maze) and cognitive ability (as assessed by the Morris Water Maze).

In this study, a single administration of C1-INH at 10 minutes following controlled cortical impact attenuated posttraumatic motor and cognitive impairments, and reduced histologic damage when assessed 4 weeks after injury. When this agent was administered 1 hour postinjury, motor deficits, but not cognitive function or histologic injury, were attenuated significantly. The efficacy of this agent and the timing of administration required to optimize its effects, if such are replicated in additional studies, remains uncertain. Nonetheless, the ability of a single administration of C1-INH—when given at any point postinjury—to attenuate motor, cognitive, and histologic abnormalities is noteworthy.

*See also p. 659.

Key Words: traumatic brain injury; neurobehavioral function; memory; outcome; clinical trials
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Also intriguing is the dissociation between motor, cognitive, and histologic outcomes following delayed C1-INH administration. The mechanism by which this dissociation developed is not clear. Nonetheless, its occurrence echoes the importance of expanding the concept of outcome beyond those used conventionally in experimental injury research: if only one of these outcomes was the sole subject of this investigation, then a very different set of the conclusions regarding the possible promise of this agent would be drawn.

Given the history of failed clinical investigations of neuroprotection in TBI, skepticism regarding the future of the line of investigation described by Longhi et al would not be unexpected. The most of which we can be certain is that replicating at the bedside the same types and magnitudes of neuroprotective effects observed in the laboratory is an uncertain endeavor, at best.

Independent of the future of the neuroprotective strategy described in this report, however, these investigators have provided the field with a model for future translational research in TBI. At the earliest stage of research, a subtype of injury is identified in the service of reducing heterogeneity and of developing a population-targeted therapy. An attempt is made to identify an intervention that might reasonably be expected to intervene on one or more aspects of the pathophysiology of that TBI subtype. If a single agent is used, then one with multiple mechanisms of action is selected to maximize the proportion of variance in outcome for which it might be expected account. Finally, neurobehavioral function, including both motor and cognitive performance, is incorporated into the research program at its earliest stages and is afforded the same level of attention and scrutiny as histopathology—an essential first step in the improvement of neurobehavioral and functional outcomes of persons with TBI and their families.

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Pediatric sepsis: Time is of the essence*

Clinical practice guidelines have been widely accepted as a tool to standardize care and improve outcomes in critically ill patients. Periodic revision of guidelines, especially those addressing clinical conditions for which a large number of new studies are published each year, is critical to keeping such guidelines up to date and relevant. Septic shock is one of the most common disorders managed in both adult and pediatric intensive care units, and one in which there is a rapidly growing body of literature. In 2002, the American College of Critical Care Medicine developed clinical practice parameters for hemodynamic support of children and neonates with septic shock (1). In this issue of Critical Care Medicine, the American College of Critical Care Medicine presents the 2007 revision of these clinical practice parameters, chaired by Dr. Joseph Carcillo (2). This revision of the 2002 guidelines incorporates data from new publications over the 5-yr interval. Thirty interested parties, many but not all of whom are recognized experts in the field, participated in the revision process. Recommendations included in the guidelines required that 90% of the committee members agreed with the recommendation. As with the 2002 guidelines, many of the recommendations have limited support in the literature, but the
A growing body of literature has reported improved outcomes with the implementation of the 2002 guidelines (3, 4). This finding is consistent with the current emphasis on standardization of care to improve outcomes in the critically ill. The 2007 revision includes new trials relevant to both the initial resuscitation and the ongoing hemodynamic management of children with septic shock. It also includes information on new and developing technologies for hemodynamic monitoring of these children. The rapid development of new therapeutics and technologies makes periodic revision of these guidelines essential.

The Task Force revising the 2002 guidelines completed a thorough literature review. Overall, there are relatively minor changes in the recommendations, but there is increasing emphasis on the importance of early rapid management. There is continued emphasis on the first hour fluid resuscitation and treatment with vasopressors/inotropes. Antibiotic administration within the first hour has been added to the revised guidelines. It is increasingly recognized that rapid early fluid resuscitation and antibiotic administration are critical elements in the management of the patient with septic shock. The Surviving Sepsis Campaign guidelines emphasize these points as well (5). Initial resuscitation goals for children and infants are clinical goals, aiming for normalization of the heart rate, blood pressure, capillary refill, and mental status. The age-old question of colloid vs. crystalloid for initial resuscitation remains unresolved; the clinician is free to select the fluid of his/her preference. The 2007 revision of the pediatric sepsis guidelines does depart from the conventional wisdom that catecholamines should only be infused through central venous catheters. As a practical matter, it can sometimes take a prolonged period of time to establish central venous access in a small child with shock. The 2007 guidelines include the recommendation from the American Heart Association Pediatric Advanced Life Support guidelines to administer vasoactive drugs through a peripheral intravenous catheter until central access is attained, monitoring the peripheral access site closely for infiltration (6).

The revised guidelines continue to recommend monitoring of cardiac index in children with catecholamine-resistant shock, and titrating therapy to a goal of 3.3–6 L/min/m². A new addition is that there are several new techniques that can be used instead of the pulmonary artery catheter, including Doppler echocardiography, the PICCO catheter, or femoral artery thermodilution catheter. Several new techniques are under investigation. None of these techniques, however, is possible in neonates and small infants, so the managing physician must continue to rely on clinical goals.

The role of corticosteroid therapy remains uncertain. Hydrocortisone is recommended for children with absolute adrenal insufficiency and catecholamine-resistant shock, but the doses used in the literature have varied enormously from 2 to 50 mg/kg/day; no specific dose recommendations can be made at this time. There continues to be clinical equipoise regarding the use of adjunctive steroid therapy for sepsis, outside the use in children with classic adrenal or known hypothalamic-pituitary-adrenal axis insufficiency.

The 2007 guidelines include stepwise algorithms for children and for neonates that will help the clinician at the bedside. Like many guidelines, the guidelines may not be as specific as some clinicians might like, but that is a reflection of the state of our knowledge, and not the quality of the guidelines. As we strive to decrease the mortality in children and infants with septic shock, we need to ensure that they receive early aggressive management with fluids, vasoactive agents, and antibiotics. This study provides a framework that each institution can use to develop its own specific guidelines to ensure this level of care.
Hypothermia has been demonstrated to reduce intracranial pressure, decrease excitotoxicity, attenuate oxidative stress, and limit the consumption of protective antioxidant agents. Moderate hypothermia has demonstrated benefit and has been specifically recommended in adults after cardiac arrest and in neonates who have sustained hypoxic-ischemic encephalopathy (1, 2). In children, moderate hypothermia has demonstrated efficacy in the control of intracranial pressure after traumatic brain injury (TBI), yet evidence of a survival or morbidity benefit has remained elusive (3, 4). The failure of a recent, large, multinational, randomized controlled trial to demonstrate the clinical benefit of hypothermia after TBI in children (5) has further diluted confidence that hypothermia may improve survival and neurologic outcome.

The brain is particularly sensitive to oxidative injury due to metabolic demands and high rate of oxygen consumption. Evidence of oxidative stress after TBI has been demonstrated via cerebrospinal fluid (CSF) analysis in animals (6), children (7, 8), and adults (9). Evidence of increased oxidative stress and disordered energy metabolism after TBI has preceded refractory increases in intracranial pressure (10). This latter finding suggests a role for the analysis of CSF biomarkers as potential predictors of clinical evolution and outcome and, in particular, elevated CSF markers of oxidative damage (11).

The article by Bayir et al (12) in this issue of Critical Care Medicine explored the effect of moderate hypothermia on markers of oxidative stress after TBI. A cohort of pediatric patients were recruited in a single center for inclusion in two larger multicenter studies investigating the role of therapeutic hypothermia after TBI. CSF was obtained via external ventricular drains and assayed for oxidative stress with measurements of antioxidant status, protein oxidation, and lipid peroxidation. Children who had been randomized to moderate hypothermia were shown to significantly preserve CSF antioxidant reserve, compared with children in the normothermic group. Analysis of the markers of free radical attack and lipid peroxidation did not demonstrate a similar beneficial profile in the hypothermic patients, although the authors do suggest a trend to decreased protein oxidation in the hypothermic group. The authors conclude that hypothermia attenuates brain oxidative stress after severe TBI in children. This reported investigation is intriguing because it demonstrates a potential mechanism for neuroprotection by therapeutic hypothermia. This study also demonstrates the utility of CSF analysis for TBI prognosis and provides measurable factors that could aid in identifying beneficial therapeutic interventions. Importantly, their work indicates that moderate hypothermia in the context of pediatric TBI is not yet a therapeutic dead end.

The study by Bayir et al (12) is, however, limited by a small sample size, a heterogeneous patient population, and limited study protocol information. The data presented also lack fidelity in a time course critical for understanding the pathophysiologic changes in oxidative state after TBI and for determining a potential optimal therapeutic window. It is also unclear if the preservation in oxidative state by therapeutic hypothermia reflects changes in compromised tissue, compared with areas of relatively uninjured brain. Finally, although antioxidant reserve is preserved by hypothermia, the significance of the improved oxidative profile is unclear. A causal relationship between oxidative stress and outcome has not been established. Despite these caveats, Bayir et al (12) should be commended for their reported investigation. Enrolling children with TBI in therapeutic trials is challenging, particularly when combined with external ventricular drain placement and regular CSF sampling for laboratory analysis (13). This report indicates that regular laboratory analysis of CSF obtained via external ventricular drains may offer valuable prognostic information and potentially guide future therapeutic interventions. Furthermore, this study is the first to demonstrate preserved antioxidant reserve in children with therapeutic hypothermia.

Hypothermia-induced preservation of the antioxidant profile may be beneficial in the prevention of delayed brain injury after TBI. Excessive oxidative stress damages lipids, proteins, and nucleic acids. Cytoskeleton and mitochondria disruption are consequences of oxidative stress, and, eventually, synaptic plasticity and cognitive function are impaired.

Similar to the action of therapeutic hypothermia reported by Bayir et al (12), anesthetic agents commonly administered after TBI may also provide protection against oxidative stress. Barbiturates and propofol limit oxidative stress by reducing the cerebral metabolic rate and decreasing glucose and oxygen consumption (14). Anesthetics also induce direct scavenging of reactive oxygen species and inhibit lipid peroxidation and excitotoxicity.

In conclusion, Bayir et al (12) who have previously identified the increased oxidative stress in the context of TBI now report a beneficial effect of therapeutic hypothermia on brain oxidative stress. Their work indicates a likely mode of secondary brain injury, and suggests that hypothermia may offer therapeutic benefit. Further, they offer CSF biomarker analyses as worthy of further evaluation not only as an aid in prognostication, but as an indicator of therapeutic efficacy. This work by Bayir et al (12) and others will fuel the emerging interest in drugs that have potent antioxidative effects, such as agonists of the nuclear peroxisome proliferator-activated receptors (15), and suggest that if therapeutic hypothermia has a role to play in the treatment of TBI, it is not as the magic bullet, but as one of a combina-
tion of therapies that act beneficially on brain oxidation status.

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How possibly are we to choose albumin or hydroxyethyl starch?*

Abumin treatment of hypovolemia has been shown to be superior to crystalloid solutions in virtually every pathologic condition, including its use as part of the pump prime for pediatric cardiopulmonary support. No known cases of infectious transmission have been reported and the incidence of either urticaria or anaphylactic shock is estimated at <1 per10,000 (1). Unit cost is high and shortages could occur. It is with these facts in mind that we evaluate the prospective, randomized, and quasi-blinded trial of albumin vs. hydroxyethyl starch (HES) 130/0.4 in the perioperative volume expansion during pediatric cardiac surgery requiring cardiopulmonary bypass (2). Hanart et al from Brussels, Belgium painstakingly evaluated perioperative fluid balance and blood loss in children who received 4% albumin (n = 59) or 6% HES 130/0.4 (n = 60). The volume of colloid used and recorded blood loss was similar between groups. Intraoperative fluid balance was more positive in the albumin group and the difference reached significance. In addition, more children in the albumin group received blood transfusions but less fresh frozen plasma. Taking the results at face value, equivalence of albumin and HES 130/0.4 was the conclusion. Factoring in the differential treatment cost, a recommendation to replace albumin with HES 130/0.4 for pediatric cardiac surgery seemed warranted. The authors were precise in the blinded quantification of fluid balance and the types of blood products used. However, there was less precision in the postoperative care protocols, in example, determining the need for ventilatory and inotropic support. I do not think this affects evaluation of the primary end point, but evaluation of safety is difficult.

Hanart et al, do discuss the possible complications of starch-based colloid solutions and discuss an evidence that the newer formulations, of which HES

*See also p. 696.

Key Words: albumin; hydroxyethyl starch; pediatric; volume expansion; cardiac surgery; editorial

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Central venous catheters (CVC) have become an essential and necessary component of the modern management of critically ill patients. However, the benefits of the CVC are often offset by the fact that such devices have now been recognized as the leading source of bloodstream infections in this critically ill patient population, which is associated with high morbidity and mortality (1).

For years, it has been recognized that catheter-related bloodstream infection (CRBSI) in critically ill patients is a preventable serious complication. In 1988, Maki et al (2) predicted that “binding an antimicrobial to the entire catheter surface may ultimately prove to be the most effective technological innovation for reducing the risk of device-related infections.” Subsequently, Maki et al have demonstrated that CVC impregnated with antimicrobial agents are the “most intensively studied technology for the prevention of CRBSI over the past 30 years” and have also shown that such anti-infective CVC (AI-CVC) are highly cost-effective, safe, and do not appear to select for resistance (3).

In the systematic review and meta-analysis by Hockenhull et al (4) published in this issue of Critical Care Medicine, 38 prospective randomized controlled trials of AI-CVC were evaluated. Meta-analysis data from 27 trials have demonstrated a strong treatment effect in favor of AI-CVC (odds ratio: 0.49; 95% confidence interval: 0.3–0.64). However, further subgroup analysis of different types of AI-CVC showed that the direction of the treatment effect favored the antimicrobial-coated catheters in all subgroups, except for the benzalkonium chloride–treated CVC. Further subanalysis demonstrated that the minocycline/rifampin coating was associated with the most significant treatment effect (odds ratio: 0.26; 95% confidence interval: 0.15–0.47), whereas other antimicrobial coatings varied as far as their efficacy with the second-generation chlorhexidine/silver sulfadiazine (CHSS+) “just failing to achieve statistical significance.”

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Making catheter-related bloodstream infections history: From the slogan to the serious strategy*

See also p. 702.

Key Words: catheter-related bloodstream infection; critically ill patients; anti-infective central venous catheters

*See also p. 702.

The author has received honoraria from Cook and royalties from Cook, AMX, Tyrx, and Horizon.

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The review and meta-analysis by Hockenhull et al also demonstrated that the AI-CVC is associated with a decrease in medical costs. They have estimated a cost savings in the United Kingdom for every patient who receives an AI-CVC to be equal to £138.2. This cost benefit is consistent with various analyses that have been demonstrated in multiple reviews conducted in the United States (5, 6).

During the last two decades, various infection control interventions have also been shown to be effective in reducing CRBSI, including the use of maximal sterile barrier precautions during insertion of the CVC and applying chlorhexidine at the insertion site (7, 8). More recently, Pronovost et al (9) have shown that when these effective infection control interventions are used concurrently as part of a “bundle” (that includes maximal sterile barrier precautions, hand washing, cleaning the insertion site with chlorhexidine, and avoidance of femoral vein insertion and unnecessary prolonged use of the catheter), a significant decrease in CRBSI is observed in critically ill patients. Despite the fact that the mean rate of CRBSI in the Pronovost et al study was reduced from 7.7 per 1000 catheter days to 1.4 per 1000 catheter days over a 6–18-month study with a reported median of zero, CRBSI continued to occur, despite the implementation of such infection control interventions.

Although the Pronovost et al study included a large number of intensive care unit and critically ill patients, it demonstrated a significant and prolonged reduction in CRBSI that persisted for an 18-month period. However, there were several limitations to the study. Among the limitations are the lack of assessment of compliance as far as the implementation of the infection control bundle, the crossover design of the study, the poor definitions of CRBSI included in the study, and the lack of assessment of confounding variables (such as the introduction of AI-CVC into the units being studied during the study period). Like Pronovost et al, other investigators have demonstrated that infection control interventions (such as the use of maximal sterile barriers) are associated with a decrease in CRBSI (7, 10). However, such measures on their own do not eliminate CRBSI completely. Although it is now well established that the infection control bundle is the mainstay of preventing CRBSI, it is also well recognized that these measures are often associated with high cost and poor compliance, are not very durable, and do not completely eliminate or prevent infections (10).

Hockenhull et al highlight the fact that “it is important to establish whether the strong treatment effect of AI-CVC remains after effective infection control bundles are established.” Two recent prospective randomized trials that are cited by Hockenhull et al could shed light on this issue (11, 12). In a multicenter prospective randomized study by Rupp et al (11), the second-generation CHSS+ was compared with uncoated CVC. During the trial, the infection control bundle was implemented into both arms of the study. In the uncoated CVC control arm, where such infection control bundle measures were implemented, the rate of CRBSI was 1.24 per 1000 catheter days. However, in the test arm, whereby the infection control bundles were implemented in addition to the use of AI-CVC (in this case CHSS+), the risk of CRBSI was decreased by more than three-fold to a level as low as 0.4 per 1000 catheter days (11). Another prospective randomized trial by Hanna et al (12) compared the use of an AI-CVC coated with minocycline and rifampin with uncoated CVC. Again, in this study, the elements of the infection control bundle were implemented, including the maximal sterile barrier precautions. In the uncoated CVC arm, the rate of CRBSI was 1.28 per 1000 catheter days, which was further reduced significantly with the use of the AI-CVC (coated with minocycline/ rifampin) to a low level of 0.25 per 1000 catheter days (12). Hence, the AI-CVC could complement the infection control bundle measures in further bringing the rate of CRBSI to a very low level approaching zero and, therefore, making CRBSI a very rare entity in high-risk patients.

Hockenhull et al also referred to as AI-CVC as a “safety net to prevent contaminated microorganisms from developing into CRBSI.” The referral of AI-CVC as a “safety net” is appropriate from several view points. First, it is well recognized that the absolute and complete compliance with all elements of the infection control bundle is never at a 100% level. The fact that the CVC is transformed into an anti-infective device that will prevent the microbial adherence of resistant pathogens represents another major barrier against biofilm colonization and, ultimately, CRBSI independent of human behavior and lack of compliance with infection control measures. Furthermore, the AI-CVC indeed serves as a safety net in that the infection control bundle, including maximal sterile barrier precautions and sterilization of the skin insertion site with chlorhexidine, do prevent contamination of the CVC during insertion. However, the AI-CVC do prevent biofilm colonization of the external and the internal surface not only during insertion but also subsequently during the dwell time of the catheter, where organisms could migrate from the external skin insertion site surface or from the hub into the lumen of the catheter.

In addition, impregnating the CVC with antimicrobial agents is very much similar to the concept of inoculating the patient with a modified attenuated microbial organism through vaccination. Whereas good infection control measures, including good hygiene, are important in preventing the transmission of various infections, such as polio, measles, and mumps, the use of effective vaccines does, indeed, represent an important safety net to further eliminate such infections (13). Appropriate infection control precautions do not substitute, but rather complement, vaccination as an intervention. The same is true for the AI-CVC.

In conclusion, the review and meta-analysis of Hockenhull et al does demonstrate the strong treatment effect that favors AI-CVC in the prevention of CRBSI, particularly in critically ill patients. Furthermore, the review demonstrates the cost effectiveness of such intervention, showing that such antimicrobial technology represents a safety net in the prevention of CRBSI. Given the new directives by the Central Medical Service System in the United States, including Medicare and Medicaid in not reimbursing hospitals for CRBSI, it is important to further press forward toward the elimination of such infections. To achieve such a zero end point and to realistically eliminate CRBSI, the use of AI-CVC in addition to effective infection control bundle should become the standard of care. Slogans such as “zero tolerance” will not achieve a zero end point of CRBSI and could not eliminate such preventable, serious infections unless they are associated with the implementation of a serious strategy that relies on evidence-based medicine. Using the combination of effective infection control measures with highly efficacious tech-
nologies, such as AI-CVC, is a solid foundation for this serious strategy. Issam Raad, MD, FACP, FIDSA
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The ethics of quality improvement research*

In December 2006, an article in the New England Journal of Medicine showed how a simple intervention virtually eliminated central venous catheter-related bloodstream infections at hospitals participating in the Michigan Keystone ICU Project (1). Lay and medical authors hailed the findings that suggested opportunities to save thousands of lives and billions of dollars (1–3).

Soon afterward, the Office for Human Research Protections (OHRP), responding to an anonymous complaint, launched an investigation culminating in Keystone’s suspension, citing the failure to obtain institutional review board (IRB) approval at participating hospitals and informed consent from patients (4). At first blush, the action seems absurd. The intervention studied was harmless—simply formal implementation of standard practice (1, 5). Outrage followed, fueled by concern that the OHRP’s action would discourage similar projects (2, 6–8). Leaders of professional organizations protested (6), whereas authors in the lay press labeled the action “bizarre and dangerous” (2). As one ethicist suggested, the government office responsible for protecting human subjects seemed to have taken action that would only increase harm (7).

In this issue of Critical Care Medicine, Savel et al (9) illuminate the factors precipitating the OHRP’s actions, particularly the lack of consensus regarding the relationship between quality improvement (QI) and human subjects research (HuSR). In advance of the project, the IRB at the lead investigator’s institution, Johns Hopkins, had exempted Keystone from review and waived the informed consent requirement (1). The OHRP disagreed with this exemption, believing the study constituted HuSR, thus mandating oversight from each participating hospital and informed consent (4). Months later, the OHRP seemed to modify its findings, indicating that research like Keystone that entailed negligible risk would qualify for expedited review and waiver of consent (10). Projects that were QI only would not need IRB oversight.

Although the OHRP’s final opinion may have closed this particular case, Savel et al (9) argue persuasively for more clarity regarding the oversight needed for work combining QI and HuSR. To prevent future uncertainty, they offer three recommendations. First, they suggest streamlining approval for QI/HuSR and clarifying the rules guiding the use of central IRBs and waiver of informed consent. Second, they suggest developing ways to make IRB approval less onerous. Third, they suggest that hospitals too small to have IRBs could use IRBs from “nearby regional centers of excellence.”

Several others have contributed to this debate (7, 8, 11, 12). Miller and Emanuel (12) believe three questions are key to evaluating projects like Keystone. First, does the project involve HuSR? Second, if yes, is expedited review appropriate? Third, is informed consent needed? At present, there is little controversy regarding questions two and three: expedited review and waived consent.
would be appropriate if the intervention entails minimal risk, obtaining formal consent is unfeasible, and the waiver will not adversely affect the rights and welfare of subjects (8–10, 12). However, the first question remains unanswered. Was Keystone HuSR or not? The question is important because HuSR, by definition, requires IRB review, and institutions engaged in federally funded research must file a Federalwide Assurance with the U.S. government (13). However, requiring IRB oversight for studies not involving human subjects could impose unnecessary barriers (7). Many small hospitals do not have IRBs (9). Central IRBs, which could streamline approval (8, 9), are not always available. Furthermore, institutions committed to using a central IRB still have to file a Federalwide Assurance, assuring compliance with HuSR regulations (13). Such documentation could overwhelm institutions lacking research infrastructures and discourage worthy projects.

In contrast, if QI projects like Keystone are not HuSR, then IRB oversight is unnecessary. The Code of Federal Regulations Common Rule, which governs human research activity in the United States, defines research as a “systematic investigation...designed to develop or contribute to generalizable knowledge (13).” By this definition, Keystone, and work like it, seems to constitute research. The Code of Federal Regulations goes on to define a human subject as “a living individual about whom an investigator...conducting research obtains 1) data through intervention or interaction with the individual or 2) identifiable private information.”

So was Keystone HuSR or something else? The technique used to reduce central venous catheter infections had already been proven effective; its value in individual patients was not being questioned (5). Rather, Keystone asked if the technique could reduce institutional infection rates (1). Thus, we agree with Baily (7) that the research did not meet the regulatory definition of HuSR. Instead, it seems to have been an example of QI coupled with research on organizations and did not require IRB oversight. In this view, the full implications of what is often perceived as an inflexible and burdensome system (IRB application, review, and approval; negotiation of a Federalwide Assurance for those without one; and continuing review and review of all changes before their implementation) need not be invoked.

Another ethical issue surrounds the notion of informed consent as it relates to this project. Savel et al state that the purpose of informed consent is to protect the subjects from whatever risks may be inherent in the research project. But, we would argue that informed consent flows more from the ethical principle of Respect for Persons, as described in the Belmont report (14). This principle relates to a respect for autonomy, allowing individuals to make their own decisions and accept whatever risks are inherent in the project. It reflects the concept of “voluntariness” in deciding to participate in research. This is in contrast to QI implementation, which explicitly is not done on a voluntary basis, but rather is an operational implementation on the part of healthcare organizations. Thus, it could be argued that the Keystone project did not invoke the need for informed consent for participation in research.

Research like the Keystone project offers useful guidance to healthcare institutions required to find ways to successfully implement recommended practices (1). Although unfortunate in many ways, the Keystone/OHRP saga has offered an opportunity to consider the ethical framework on which the nascent field of QI research is being built. The resulting discussion, including the contribution by Savel et al, should ensure that future work is performed both effectively and ethically.

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Refractory shock in the intensive care unit—Don’t fail to spot obstruction of the left ventricular outflow tract!

Left ventricular outflow tract obstruction (LVOTO) is a well-recognized feature of hypertrophic cardiomyopathy (1). The condition of LVOTO, in the absence of hypertrophic cardiomyopathy, has also been described in stress echocardiography with dobutamine (2–4) or exercise (5, 6) and after cardiac valve surgery (7–10). The main mechanisms behind the development of LVOTO, also referred to as dynamic LVOTO, are inotropic stimulation of left ventricles (LV) with higher than normal LV wall to lumen ratios such as in hypertensive heart disease. Thus, forceful contractions, particularly of the basal part of an LV with small dimensions and increased wall thickness in combination with peripheral vasodilation, may precipitate subaortic flow obstruction and a decline in cardiac output and hypotension. If the LVOTO is severe enough, blood will be ejected at a high velocity, which may cause the anterior mitral valve leaflet to be drawn to the septum by a Venturi effect, a so-called systolic anterior motion (SAM). Thus, parts of the anteriorly displaced mitral valve leaflet will extend beyond their coaptation point and protrude into the rapid flow velocity of the left ventricular outflow tract. This may result in a further LVOTO and a more or less pronounced mitral valve regurgitation and eventually cardiogenic shock.

In cardiac surgery, dynamic LVOTO is a well-recognized phenomenon, which may develop early after aortic valve replacement (7, 8) or mitral valve repair (9, 10) and may be totally reversible after correction of the precipitating factors such as high inotropic state, tachycardia, hypovolemia, and systemic vasodilation.

LVOTO with SAM may also occur in the perioperative setting of noncardiac surgery. Luckner et al (11) described two patients undergoing orthopedic surgery who developed cardiovascular collapse early after induction of anesthesia unresponsive to catecholamines and a third patient with severe intraoperative bleeding. LVOTO and SAM were diagnosed by transesophageal echocardiography, and hypotension was resolved by colloid infusion, phenylephrine, and β-blocker therapy. In these patients, LVOTO and SAM were triggered by hypovolemia and anesthetic drug–mediated vaso- and venodilation in conjunction with increased catecholamine concentrations.

In this issue of Critical Care Medicine, Chockalingam et al (12) describe the clinical recognition and management options of five patients (all women) presenting with unexplained hypotension and systolic murmur in the emergency/critical care setting. The underlying cause of their critical condition was dynamic LVOTO, with peak left ventricular outflow tract pressure gradients ranging from 60 to 150 mm Hg, diagnosed by echocardiography. The common clinical feature of all patients was hypertensive heart disease with more or less pronounced LV hypertrophy. Three patients presented in the emergency room with chest discomfort, anterior T-wave abnormalities, suggestive of myocardial ischemia, and mild to moderate troponin-I elevations. Two of these patients had a normal coronary angiogram, and one had a significant stenosis of the posterior (not anterior) descending artery. Dobutamine treatment was initiated in one patient because of shock. Severe LV apical dysfunction (apical ballooning syndrome) was confirmed in these three patients in association with LVOTO and SAM of the anterior mitral valve leaflet. Echocardiogram also revealed hypercontractility of the basal portions of the LV as a compensatory mechanism for the apical ballooning syndrome–related severe apical dysfunction, which resulted in LVOTO and SAM. The apical ballooning syndrome, also known as Takatsubo cardiomyopathy, is a reversible cardiomyopathy, which is triggered by severe psychological stress occurring in older women with normal coronary arteries, and may mimic evolving acute myocardial infarction and coronary syndrome (13). This condition is associated with a severe elevation of plasma catecholamines (14), which further strengthens the importance of cardiac sympathetic stimulation for the development of LVOTO and SAM in patients with aortic ballooning syndrome. Mild to moderate troponin elevations were observed in these patients with virtually normal coronary arteries. According to the authors, this may be explained by high levels of peak systolic subendocardial wall stress, which may considerably impair the oxygen demand–supply relationship of the subendocardial layers. These patients were successfully treated with β-blockers, and there was no evidence of LVOTO or SAM on repeat echocardiograms.

The authors also review two mechanically ventilated patients in the intensive care unit presenting with hypotension, tachycardia, systolic mural, and mild to moderate troponin elevations. In one of the patients, the clinical condition was not improved by dopamine treatment. Bedside echocardiograms revealed hyperdynamic LVs with hypertrophy and LVOTO in both cases, with or without SAM, which was fully resolved by vigorous fluid treatment in combination with a β-blocker. These two cases highlight the clinical problem one may encounter when inotropic treatment is instituted in volume-depleted, iatrogenically or not, patients in the intensive care unit with hypertrophied LVs, particularly when inotropic agents with vaso- and venodilating properties are used, e.g., dobutamine, low-dose dopamine, phosphodiesterase inhibitors, or levosimendan. Furthermore, this report emphasizes the importance of the use of echocardiography for early diagnosis of LVOTO in...
patients in the intensive care unit with refractory shock not responsive to “fluid challenge” and inotropic therapy. An echocardiogram in this situation may reveal that the fluid challenge was not vigorous enough and that inotropic support of the hypertrophied, hypovolemic, and hyperdynamic LV generated an LVOTO and caused a functional aortic stenosis in an LV not used to such high levels of afterload. The echocardiogram will also serve as a guide in the treatment of this critical condition consisting of blood volume expansion, β-blockers, and normalization of a low systemic vascular resistance with a vasocostructor, if necessary. This treatment strategy may completely resolve this clinical problem.

The authors of this interesting report conclude that dynamic LVOTO may occur in the emergency room and the critical care units more often than is recognized. To date, the true incidence of dynamic LVOTO as a cause of hypotension in the intensive care unit is not known, and most likely, this condition is underdiagnosed. The good news is that early recognition and appropriate medical management may dramatically improve the condition of these patients.

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