Echoes of the past?*

The hemodynamic abnormalities of sepsis, and their appropriate treatment, are familiar to caregivers in the intensive care unit (ICU) and the emergency department. The key is early recognition, resuscitation with fluids and vasopressors if required, and treatment of the underlying cause. This approach is the basis of the hemodynamic management guidelines of the Surviving Sepsis Campaign (1), and of the campaign's 6-hr resuscitation care bundle. Yet, this consensus hides fundamental difficulties that bedevil our ability to improve care, especially for patients who do not stabilize or reverse their shock after initial resuscitation and require more advanced and prolonged support. Once into this second phase, agreement disappears as to the most appropriate hemodynamic monitoring techniques, the correct targets and end points of treatment, and even which fluids and vasoactive drugs to give. Practice varies internationally, with a preference for crystalloid resuscitation in the United States, and greater use of artificial colloids in Europe, although the results of recent large studies (2, 3) mean that these patterns are in a state of flux. There are also differences in the hemodynamic monitoring used to guide therapy, and therefore the paradigms of care. In general terms, there is a greater reliance on filling pressures in the United States, and a more "mixed economy" in Europe, with various flow and volume measurement techniques (transpulmonary thermodilution, arterial pulse wave analysis, esophageal Doppler) more widely employed. There is general agreement about the importance of using volume challenges and demonstrating volume responsiveness, but less clarity about the best way of doing this. This variation in practice possibly is due to the gaps that still exist in our fundamental understanding of the pathophysiology of sepsis, because accurate description of complex physiology in the ICU remains a challenge.

It is against this challenging background that Dr. Viellard-Baron and colleagues (4) publish their intriguing study of the incidence of left ventricular hypokinesia in septic shock in this issue of *Critical Care Medicine*. They assessed 67 patients with septic shock on a daily basis for the first 3 days of ICU admission using echocardiography and again after weaning from vasoactive support in those who recovered. Patients were treated with standard supportive therapies, with fluid resuscitation being guided echocardiographically using the pattern of respiratory cycle flow variation in the superior vena cava during mechanical ventilation, an approach that the authors have previously validated, and initial vasopressor support with norepinephrine. They found that primary global hypokinesia (defined as a left ventricular ejection fraction derived from the long axis view of $<45\%$) was present in 26 patients (39%), and that secondary global hypokinesia (defined similarly, but occurring in patients whose initial study was within the normal range) developed in a further 14 patients (21%). In these patients, dobutamine was added and the norepinephrine dosage reduced, with epinephrine also used if hypotension persisted. Nonsurvivors had a significantly higher cardiac index on day 1 than survivors (3.8 ± 1.3 vs. 3.1 ± 0.9, $p = .017$), although this difference disappeared subsequently, but the authors found no convincing evidence of differences between ejection fraction, left ventricular (LV) end-diastolic volume (EDV), or ventricular elastance (estimated by the relationship between systolic arterial pressure and left ventricular end-systolic volume). The authors therefore conclude that left ventricular global hypokinesia is common in severe sepsis, that its presence does not discriminate between survivors and nonsurvivors, that its development may be influenced by the use of norepinephrine via an increase in left ventricular afterload, and that it responds to and is a possible indication for an inotrope such as dobutamine.

Why are these findings important? Certainly, this is not the first paper to describe the high incidence of global LV dysfunction in severe sepsis; indeed, the same authors do exactly this in their larger previous series (5), reporting broadly similar hemodynamic patterns to those that they document on this occasion. What is different is the lower mortality in their current series, which may be expected given the general improvements in supportive care that have occurred over the last decade, and the fact that they no longer observe the pattern of higher LVEDV and lower LV ejection fraction in nonsurvivors as compared with survivors that they saw in their first study. The association between severe sepsis and LV dysfunction characterized by ventricular dilation has been known since the work of two pioneering critical care research groups in the 1980s. Dr. Calvin and colleagues (6) demonstrated decreased ejection fraction and increased LVEDV using electrocardiogram-gated radionuclide cineangiography in 1982. Dr. Parker and colleagues (7) expanded this work in 1984 to demonstrate that the pattern of LV dilation and decreased ejection fraction was characteristic of survivors recovering after several days and introduced the concept of adaptive LV dilation as a mechanism by which a heart with a reduced ejection fraction could still maintain an adequate stroke volume. It is this later concept that Dr. Viellard-Baron and colleagues are now challenging.

Were the early radionuclide studies wrong? Certainly, technology has moved on considerably since that time, and high quality bedside echocardiography is now available in most ICUs, although usually for traditional diagnostic assessment rather than as a bedside monitor to guide treatment. This latter approach is becoming more common as more ICUs acquire the technology, and as training schemes for ICU physicians develop, and the authors' unit is a pioneer of this approach. There are also doubts as to the accuracy of the method used by Dr. Parker and

***See also p. 1701.**

Key Words: septic shock; echocardiography; cardiac function; myocardial depression; hemodynamics

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colleagues for generating absolute values for LVEDV, because they derived stroke volume from thermodilution cardiac output studies using a pulmonary artery catheter and ejection fraction from the radionuclide studies, then combined the two to back-calculate end-diastolic and end-systolic volumes. However, even with high-quality modern echocardiographic equipment, Doppler flow estimates from the LV outflow tract and the difference in ventricular volumes in systole and diastole give different values for stroke volume, and these inconsistencies raise doubts about the conclusions of echo-based studies such as this in the minds of non–echocardiography intensivists more used to conceptualizing hemodynamics using standard ICU monitoring technologies. In any event, unlike the current study, the authors' prior study did find a higher LVEDV in nonsurvivors. Just to confound the situation further, a recent study of patients with severe sepsis presenting to the emergency room (8) found that a hyperdynamic left ventricle, as evidenced by an increased ejection fraction, was highly specific for severe sepsis, although the degree of echocardiographic detail provided is limited. So what is the hemodynamic truth in severe sepsis—hyperkinetic (usually associated with vasodilatation) or hypokinetic? Indeed, is there a single characteristic pattern, or is the situation more complex?

There is another fundamental problem with studies that characterize sepsis in terms of a specific hemodynamic profile. This is the idea that there are dichotomous categories that patients with severe sepsis can be classified into; in this instance, either ventricular hypokinesia or not. In fact, the examinations within the authors' current paper are point assessments in time along a physiologic continuum, when "time zero" is often unclear. The more extreme disease manifestations, perhaps including adaptive ventricular dilation, probably only occur in some patients some of the time, so applying group analysis to these physiologic phenomena risks missing individual events, and also losing the opportunity to understand them. Furthermore, in severe sepsis hemodynamics also are influenced by fluid loading, vasopressor and inotrope use, and host response. Weaknesses in all our current monitoring technologies make it impossible to be certain that patients have been treated precisely the same, however hard the authors try to standardize these factors. So whether adaptive LV dilation really does occur, how often and in whom, and what it means is less important than recognizing that ventricular hypokinesia is commonplace and knowing when it is present. This means using a bedside monitoring technology that allows its detection; i.e., making echocardiography much more readily available in the ICU.

The other issue is the potential therapeutic consequence of this study's findings. The Surviving Sepsis Campaign guidelines recommend the use of dobutamine as an inotrope in severe sepsis (grade 1C) in the presence of myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output (1). Unfortunately, in their current study, the authors do not provide any filling pressure data, and it is not clear if they used the central venous pressure at all in the management of this patient group, although in their previous study that found differential ventricular kinetics between survivors and nonsurvivors they fluid-loaded patients to a central venous pressure of 12 mm Hg. There has been debate as to the value of filling pressures as a reliable guide to fluid therapy in sepsis, and this area remains highly controversial. All patients in the current study also showed relative preservation of cardiac index, with values of at least about 3 L/min/m^2, so would not necessarily have qualified for dobutamine therapy according to Surviving Sepsis Campaign criteria. When they were given dobutamine at 5.4 $\pm$ 1.7 μg/kg/min, patients demonstrated significant increases in ejection fraction, but not in cardiac index or changes in LVEDV. The situation was made more complex by a concomitant reduction in norepinephrine dose from 0.8 $\pm$ 0.7 μg/kg/min to 0.5 $\pm$ 0.5 μg/kg/min. These are high doses of norepinephrine, and a relatively low dose of dobutamine, and it is impossible to know whether the hemodynamic changes are due to dobutamine, or to norepinephrine reduction, or their influence on outcome, which the authors acknowledge. Even if these data are interpreted as suggesting that inotropic therapy should be used more widely in severe sepsis, other data suggest that dobutamine may not necessarily be the optimum inotrope (9).

What does this study mean for routine practice? Ventricular hypokinesia is a frequent phenomenon in severe sepsis, but requires bedside echocardiography in the ICU to be readily detected and quantified. Filling pressures or volumes and cardiac output measurement alone are not adequate to describe fully the hemodynamic defects of sepsis. Nor is echocardiography, in spite of the authors' enthusiasm, because it is not a continuous monitoring technique but an intermittent measurement technique with a degree of subjectivity. It does, however, provide direct visualization of the response to therapy that no other technology allows. Perhaps it is time for us to learn from neurosurgical critical care, and make a virtue of the individual shortcomings of specific monitoring approaches by actively favoring a multimodal approach that combines the different technologies to allow us to describe and ultimately treat these complex patients more effectively than we manage to do at present.

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REFERENCES

1. Dellinger RP, Levy MM, Carlet JM, et al: Surviving Sepsis Campaign: International guidelines for the management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36:296–327
2. The SAFE Study Investigators. A Comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350:2247–2256
3. Brunkhorst FM, Engel C, Bloos F, et al: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; 358:125–139
4. Viellard-Baron A, Caille V, Charron C, et al: Actual incidence of global left ventricular hypokinesia in adult septic shock. *Crit Care Med* 2008; 36:1701–1706
5. Jardin F, Fourme T, Page B, et al: Persistent preload defect in severe sepsis despite fluid loading. A longitudinal echocardiographic study in patients with septic shock. *Chest* 1999; 116:1354–1359
6. Calvin JE, Driedger AA, Sibbald WJ: An assessment of myocardial function in human sepsis utilizing ECG-gated cardiac scintigraphy. *Chest* 1981; 80:579–586
7. Parker MP, Shelhamer JH, Bacharach SL, et al: Profound but reversible myocardial depression in patients with septic shock. *Ann Intern Med* 1984; 100:483–490
8. Jones AE, Craddock PA, Tiyal VS, et al: Diagnostic accuracy of left ventricular function for identifying sepsis among emergency department patients with nontraumatic symptomatic undifferentiated hypotension. *Shock* 2005; 24:513–517
9. Morelli A, De Casto S, Teboul JL, et al: Effects of levosimendan on systemic and regional haemodynamics in septic myocardial depression. *Intensive Care Med* 2005; 31:639–644

Growth hormone to catabolic patients revisited*

The muscle protein depletion associated with critical illness and in particular multiple organ failure is one of the major challenges in intensive care medicine. Adequate nutrition attenuates the depletion, but nutrition is not sufficient to counteract the catabolic processes. Despite nutritional support, the protein loss from leg muscle amounts to 10% per week (1). In parallel to the protein losses, there is a free glutamine depletion (2, 3), although the efflux of free glutamine from skeletal muscle is moderately increased (4). The low plasma concentration of glutamine is an independent predictor for mortality in septic shock patients (5), and an extra supply of glutamine has been demonstrated to decrease mortality in multiple organ failure patients requiring parenteral nutrition (6–8).

The well-known anabolic effect of growth hormone was recognized previously (9) as a potential agent to counteract muscle protein depletion in critical illness. Shortage of growth hormone limited the exploration of this possibility, but when recombinant growth hormone became available, a number of encouraging case reports were published (10, 11). In mechanistic studies, a stimulation of skeletal muscle protein synthesis rate and an attenuation of muscle free glutamine depletion were reported (12–14). A considerable optimism arose, although concerns were raised about the potential danger of suppressing endogenous glutamine production (15) as well as the insufficient knowledge of the effects of the pharmacologic doses of growth hormone that were used (16). A phase III multicenter study treating mechanically ventilated intensive care unit (ICU) patients with pharmacologic doses of growth hormone was launched (17). At an interim safety control, an elevated mortality rate in the treated patients was found. Overnight the enthusiasm was gone and ongoing studies were stopped.

A number of possible explanations for the disastrous result of the phase III trial were suggested, such as elevation of the concentration of free fatty acids in plasma resulting in cardiac toxicity and arrhythmias, shortage of glutamine as indicated previously, and immunodepressive effects. Thorough scrutiny of the clinical report forms from the phase III study does not provide any clear-cut clues to the mechanism behind the excess mortality rate. The mortality was evenly distributed over time related to the initiation of therapy as well as in relation to the total length of ICU stay. Cause of death was not different between the controls and the treatment group.

Following the publication of the phase III study, there has virtually been a total absence of clinical studies involving growth hormone in catabolic patients. Therefore, it is extremely welcome that investigators have come back to the idea of growth hormone substitution as a possible mechanism to overcome the depletion of muscle proteins in critical illness. A working group from the Czech Republic has chosen an approach with which they mimic the physiologic endogenous secretion pattern for growth hormone using intravenous pulses (18). Furthermore, in the experimental setup the investigators supplement their patients with exogenous glutamine intravenously, to compensate for any decrease in endogenous glutamine production. As a result, Dr. Duška and colleagues (19) were able to demonstrate an improved nitrogen retention in a model study involving mechanically ventilated trauma patients in the ICU, published in this issue of *Critical Care Medicine*.

This study represents an important revival of the idea that hormonal stimulation of muscle protein metabolism may be a possibility in the future when the risks involved with growth hormone therapy are identified and controlled. The effects of growth hormone on glucose hemostasis necessitate a close surveillance of blood glucose. Furthermore, the effect of growth hormone on endogenous glutamine production should be separately elucidated, and it is recommended that in clinical studies plasma glutamine concentration be normalized (to >0.5 mmol/L) by exogenous supplementation. In the present study the exogenous supplementation was only sufficient to prevent a further decrease in plasma glutamine concentration. It is even possible that a normalization of plasma glutamine concentration will facilitate blood glucose control, as it is reported that exogenous glutamine supplementation decreases insulin resistance (20).

The study by Dr. Duška and colleagues (19) is an important step forward after the total silence in the field of clinical research over the effects of growth hormone as a possible therapeutic agent in catabolic states.

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REFERENCES

1. Gamrin L, Essen P, Forsberg AM, et al: A descriptive study of skeletal muscle metabolism in critically ill patients: Free amino acids, energy-rich phosphates, protein, nucleic acids, fat, water, and electrolytes. *Crit Care Med* 1996; 24:575–583
2. Roth E, Funovics J, Muhlbacher F, et al: Metabolic disorders in severe abdominal sepsis: Glutamine deficiency in skeletal muscle. *Clin Nutr* 1982; 1:25–41
3. Tjader I, Rooyackers O, Forsberg AM, et al: Effects on skeletal muscle of intravenous glutamine supplementation to ICU patients. *Intensive Care Med* 2004; 30:266–275
4. Vesali RF, Klaude M, Rooyackers OE, et al: Longitudinal pattern of glutamine/glutamate balance across the leg in long-stay intensive care unit patients. *Clin Nutr* 2002; 21: 505–514
5. Oudemans-van Straaten HM, Bosman RJ, Treskes M, et al: Plasma glutamine depletion and patient outcome in acute ICU admissions. *Intensive Care Med* 2001; 27:84–90
6. Griffiths RD, Jones C, Palmer TE: Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition* 1997; 13:295–302

*See also p. 1707.

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7. Goeters C, Wenn A, Mertes N, et al: Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. *Crit Care Med* 2002; 30:2032–2037
8. Novak F, Heyland DK, Avenell A, et al: Glutamine supplementation in serious illness: A systematic review of the evidence. *Crit Care Med* 2002; 30:2022–2029
9. Dahn MS, Lange P: Hormonal changes and their influence on metabolism and nutrition in the critically ill. *Intensive Care Med* 1982; 8:209–213
10. Ziegler TR, Young LS, Ferrari-Baliviera E, et al: Use of human growth hormone combined with nutritional support in a critical care unit. *JPEN J Parenter Enteral Nutr* 1990; 14: 574–581
11. Herndon DN, Barrow RE, Kunkel KR, et al: Effects of recombinant human growth hormone on donor-site healing in severely burned children. *Ann Surg* 1990; 212:424–429
12. Gamrin L, Essén P, Hultman E, et al: Protein-sparing effect in skeletal muscle of growth hormone treatment in critically ill patients. *Ann Surg* 2000; 231:577–586
13. Biolo G, Iscra F, Bosutti A, et al: Growth hormone decreases muscle glutamine production and stimulates protein synthesis in hypercatabolic patients. *Am J Physiol Metab* 2000; 279:E323–E332
14. Carroll PV, Jackson NC, Russell-Jones DL, et al: Combined growth hormone/insulin-like growth factor I in addition to glutamine-supplemented TPN results in net protein anabolism in critical illness. *Am J Physiol Endocrinol Metab* 2004; 286:E151–E157
15. Wernerman J: Protein wasting in severe illness: Pathogenesis and therapy. *Diabetes Nutr Metab* 2000; 13:21–24
16. Van den Berghe G: Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* 2000; 342: 134–135
17. Takala J, Ruokonen E, Webster NR, et al: Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* 1999; 341:785–792
18. Duška F, Fric M, Pažout J, et al: Frequent intravenous pulses of growth hormone together with alanylglutamine supplementation in prolonged critical illness after multiple trauma: Effects on glucose control, plasma IGF-I and glutamine. *Growth Horm IGF Res* 2008; 18:82–87
19. Duška F, Fric M, Waldauf P, et al: Frequent intravenous pulses of growth hormone together with glutamine supplementation in prolonged critical illness after multiple trauma: Effects on nitrogen balance, insulin resistance, and substrate oxidation. *Crit Care Med* 2008; 36:1707–1713
20. Dechelotte P, Hasselmann M, Cynober L, et al: L-alanyl-L-glutamine dipeptide-supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in critically ill patients: The French controlled, randomized, double-blind, multicenter study. *Crit Care Med* 2006; 34:598–604

Insights from PAC-Man on flow-monitoring devices: Curb your enthusiasm*

In the past few years, a number of large, well-conducted, clinical trials have cast doubt on or disproved the effectiveness of commonly employed interventions for critically ill patients, each of which was supported by strong physiologic rationale and investigation. Examples include the use of albumin for resuscitation (1), corticosteroids for traumatic brain injury (2) or septic shock (3), and nitric oxide for hypoxemic respiratory failure (4). The precise benefit of intensive insulin control in a heterogeneous population of critically ill patients is uncertain (5), and the use of activated protein C in severe sepsis is being reevaluated in another large multicenter trial (6).

Perhaps the mother of all controversies in critical care over the past 2 decades has revolved around goal-directed therapy and the role of the pulmonary artery catheter (PAC). A number of randomized controlled trials and observational studies have not found a benefit in clinical outcomes when pulmonary catheters have been used to direct intravenous fluid and hemodynamic support among high-risk surgical patients or those with acute lung injury or sepsis (7–11). Accordingly, we have seen a dramatic decrease in pulmonary artery catheter use in the United States over the past 15 yrs (12). Adding insult to injury is the potential for increasing risk of misuse, side effects, and harm if the skill of pulmonary artery catheter insertion and data interpretation is lost through waning experience (13).

The PAC-Man study was a large pragmatic trial of pulmonary artery catheterization or not for critically ill patients that took place in 65 intensive care units (ICUs) in the United Kingdom. Unlike the ARDS Network Fluid and Catheter Treatment Trial (FACTT), PAC-Man did not use prescribed management algorithms in the treatment or control arm of the trial. The primary objective was to compare hospital mortality and pulmonary artery catheter use. However, nearly 80% of ICUs enrolling patients decided, *a priori*, to use an alternative cardiac output measurement device in the control arm, such as Doppler ultrasonography, or indicator dilution techniques of PiCCO and LiDCO. Hence, PAC-Man did not compare pulmonary artery catheter-derived cardiac output and vascular pressure measurement with no cardiac output measurement but rather compared pulmonary artery catheter use vs. a frequently less invasive flow measurement strategy (11).

In this issue of *Critical Care Medicine*, Dr. Harvey and colleagues (14) present a *post hoc* analysis of the PAC-Man trial, providing descriptive information on patients and exploring important subgroups that were considered for management with a pulmonary artery catheter or alternative flow-measuring device. The authors specified these subgroups and the analytic method after initial trial results were known. Cox proportional hazards modeling was used for time-to-event analyses and multilevel logistic regression was used for other evaluations to make comparisons between groups receiving different flow-monitoring strategies or not and to adjust for differences in measured potential confounders.

After stratifying for time from ICU admission to randomization, age, severity of

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Key Words: heart catheterization; critical care; clinical trial; mortality; cardiac output

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illness, surgical status, the use of other flow-monitoring devices, and ICU and hospital characteristics, the authors found no difference in hospital survival among patients managed with a pulmonary artery catheter compared with another cardiac output monitoring device. The only exception was among scheduled postoperative patients admitted to ICU within whom pulmonary artery catheterization had a significant hospital survival benefit. However, we should be cautious in the interpretation of results from one small subgroup among a large number of comparisons, on which no adjustments in the required *p* value to denote significance have been made. It is difficult to imagine the mechanism that would underlie this benefit.

The main strength of the current study is that it addresses a very important comparison not extensively examined in the main PAC-Man publication. Because use of an alternative flow-measuring device may have been a postrandomization decision for patients enrolled in PAC-Man, the benefits of randomization in allocating nonintervention characteristics equally among the two groups is lost, and the authors must therefore rely on multivariable modeling to adjust for the recognized and measured potential confounding variables. Although the authors did their best to remove the influence of such variables from their analysis, it is possible that unrecognized or unmeasured confounders still conspire to make the two patient groups different and thus the comparisons inconclusive. The other chief limitation of this study is its *post hoc* nature and the risk that in asking a number of questions, associations will be found, or not, by chance alone.

Should we be surprised that the PAC-Man investigators did not find benefit in use of either pulmonary artery catheter or other flow-measuring devices? In the absence of an incrementally effective treatment strategy that is aided by flow-measuring device information, it is difficult to believe that such devices should affect outcome. For example, if we did not have effective medications, such as β-blockers, angiotensin-converting enzyme inhibitors, and receptor blockers, to treat congestive heart failure, would the use of echocardiography alone to diagnose left ventricular function be associated with improved patient outcomes? It is unlikely that other devices, providing similar (or less) physiologic information about cardiac output and vascular pressures than do pulmonary artery catheters, will prove more effective. We should be prudent in employing expensive diagnostic-therapeutic strategies without documented clinical benefit. We should also likely temper our enthusiasm for repeating such difficult, expensive, and important trials, using end points of mortality, with each next generation of similar technology in the absence of advances in therapy.

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REFERENCES

1. The SAFE Study Investigators: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350:2247–2256
2. Edwards P, Arango M, Balica L, et al, and the CRASH trial collaborators: Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury—Outcomes at 6 months. *Lancet* 2005; 365:1957–1959
3. Sprung CL, Annane D, Keh D, et al, and the CORTICUS Study Group: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111–124
4. Adhikari NK, Burns KE, Friedrich JO, et al: Effect of nitric oxide on oxygenation and mortality in acute lung injury: Systematic review and meta-analysis. *BMJ* 2007; 334:779
5. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449–461
6. Efficacy and Safety of Drotrecogin Alfa (Activated) in Adult Patients With Septic Shock. NCT00604214. http:// www.clinicaltrials.gov. Accessed February 22, 2008
7. Connors AF Jr, Speroff T, Dawson NV, et al, SUPPORT Investigators: The effectiveness of right heart catheterization in the initial care of critically ill patients. *JAMA* 1996; 276: 889–897
8. Sandham JD, Hull RD, Brant RF, et al, for the Canadian Critical Care Clinical Trials Group: A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003; 348:5–14
9. Richard C, Warszawski J, Anguel N, et al, French Pulmonary Artery Catheter Study Group: Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2003; 290:2713–2720
10. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354: 2564–2575
11. Harvey S, Harrison DA, Singer M, et al, PAC-Man study collaboration: Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): A randomised controlled trial. *Lancet* 2005; 366:472–477
12. Wiener RS, Welch HG: Trends in the use of the pulmonary artery catheter in the United States, 1993–2004. *JAMA* 2007; 298:423–429
13. Rubenfeld GD, McNamara-Aslin E, Rubinson L: The pulmonary artery catheter, 1967–2007: Rest in peace? *JAMA* 2007; 298: 458–461
14. Harvey SE, Welch CA, Harrison DA, et al: *Post hoc* insights from PAC-Man—The U.K. pulmonary artery catheter trial. *Crit Care Med* 2008; 36:1714–1721

Burden of psychological symptoms and illness in family of critically ill patients: What is the relevance for critical care clinicians?*

In this issue of *Critical Care Medicine*, Dr. Seigel and colleagues (1) describe a high prevalence of psychological illness among family members whose loved one died in the intensive care unit (ICU). This study is unique, as the first of its kind from North America. The burden of psychological symptoms has previously been described among family members of ICU patients in France. Pochard et al. (2) found that 73% of family members had a significant level of symptoms of anxiety and 35% had significant levels of symptoms of depression 3–5 days after a loved one was admitted to the ICU. Another French study, by Azoulay et al. (3), found the prevalence of a significant burden of anxiety symptoms among 49% and of depression symptoms among 20% of family members of patients in the ICU when measuring symptoms 3 months after ICU stay. A recent intervention study, also from France, examined psychological symptoms among family members whose loved one had died in the ICU 3 months prior. In their control group, the prevalence of a significant level of depression symptoms was 67% and the prevalence of a significant level of anxiety symptoms was 56% (4). For each of these French studies, a "significant level" of symptoms was the level previously defined in studies of survey-based screening measures that were associated with a high risk for a clinical diagnosis of anxiety or depression, although these measures have not been validated specifically among family members of critically ill patients.

There have been few studies in North America that similarly document the prevalence and risk factors of psychological symptoms among family members of critically ill patients. The North American experience may be different from that reported by French investigators because families' preferences for care and clinicians' delivery of care are affected by regional, racial, religious, and cultural influences (5). This study by Dr. Seigel and colleagues (1) finds the overall prevalence of one of four psychiatric illnesses (major depressive disorder, generalized anxiety disorder, panic disorder or complicated grief disorder) to be 34%, with the most common single disorder being major depressive disorder, with a prevalence of 27%. Symptoms were assessed 3 to 12 months after the patient's death. Given the differences in study design, it is difficult to directly compare the current study with the French studies, but this new study shows that this problem is not confined to France.

The study by Dr. Seigel and colleagues (1) is unique in the authors' use of Structured Clinical Interviews for DSM-IV (SCID) rather than screening survey measures to assess symptoms of psychiatric illness. The SCID allows not only the assessment of symptoms of psychiatric illness but also a sensitive and specific diagnosis of psychiatric illness by DSM-IV criteria. This is clearly a strength of this study; by contrast, the studies from France all used the Hospital Anxiety and Depression Scale (HADS) as a screening tool. A formal structured clinical interview, while it provides more reliable diagnostic information than screening tools, is more time and resource intensive. Therefore, screening tools like the Hospital Anxiety and Depression Scale and other psychological symptom measures are more feasible for large research studies, and many of these survey tools have been shown to provide reliable and valid assessment of the burden of psychological symptoms (6, 7).

Particularly interesting findings of this new study are the risk factors that were associated with psychiatric illness, including being the patient's spouse, experiencing an additional major stressor after the patient's death, and the patient's illness lasting <5 yrs (1). These risk factors are important to elucidate to better understand the process behind development of psychiatric illness in this group and to identify a subgroup of family members who may be at increased risk for psychiatric illness. Additionally, family members who did not consider the critical care physician a source of comfort were more likely to have psychiatric illness. In this retrospective study, it is not possible to determine whether physician behavior or communication caused family distress, but in the context of other studies this seems to be a likely explanation and it seems likely that improving physician communication will reduce the burden on the family (4, 8).

The study by Dr. Seigel and colleagues (1) included only family members of patients who died in the ICU. There is evidence that these family members are at increased risk for psychological symptoms compared with the families of patients who survive (3). However, even though patient death is a risk factor for psychological symptoms among family members, families of patients who survive are also at increased risk of these symptoms compared with the general population (3). There are two other important reasons for focusing on the families of all critically ill patients, not only the families of those patients whom we expect to die. First, it is generally not clear whether critically ill patients will survive at the time when most clinician-family communication is occurring. Second, there is evidence that family members of patients who survive are actually

*See also p. 1722.

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less satisfied with communication from ICU clinicians than are family members of patients who die (9). If we are to be truly effective in minimizing the long-term effects of critical illness and critical care on family members, we must focus on our communication with the families of all critically ill patients.

As Dr. Seigel and colleagues (1) discuss, the major limitations of their study are the small sample size and a single-center study design; nonetheless, this study highlights an important phenomenon. It is important for critical care clinicians to understand and address psychological morbidity among family members for several reasons. First, care provided by critical care clinicians has been associated with these symptoms (4, 8). Second, because families often serve as surrogate decision makers for critically ill patients (10), communication with and care for family members of critically ill patients are important components of the quality of care delivered to critically ill patients. Third, the family's experience in the ICU is a high priority for most critically ill patients. Fourth, psychological morbidity among family members of critically ill patients is likely to have important long-term consequences in many domains, including future health care, employment, and quality of life. Studies like this one will be critical in both defining the scope of the problem and understanding risk factors and mechanisms for development of these symptoms. This information will be necessary to develop interventions that assist family through the difficult experience of having a critically ill loved one and also enhance the quality of care we provide to critically ill patients.

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REFERENCES

1. Seigel MD, Hayes E, Vanderwerker LC, et al: Psychiatric illness in the next of kin of patients who die in the intensive care unit. *Crit Care Med* 2008; 36:1722–1728
2. Pochard F, Azoulay E, Chevret S, et al: Symptoms of anxiety and depression in family members of intensive care unit patients: Ethical hypothesis regarding decision-making capacity. *Crit Care Med* 2001; 29: 1893–1897
3. Azoulay E, Pochard F, Kentish-Barnes N, et al: Risk of post-traumatic stress symptoms in family members of intensive care unit patients. *Am J Respir Crit Care Med* 2005; 171: 987–994
4. Lautrette A, Darmon M, Megarbane B, et al: A communication strategy and brochure for relatives of patients dying in the ICU. *N Engl J Med* 2007; 356:469–478
5. Vincent JL: Cultural differences in end-of-life care. *Crit Care Med* 2001; 29(2 Suppl): N52–N55
6. Lowe B, Spitzer RL, Grafe K, et al: Comparative validity of three screening questionnaires for DSM-IV depressive disorders and physicians' diagnoses. *J Affect Disord* 2004; 78:131–140
7. Kroenke K, Spitzer RL, Williams JB, et al: Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med* 2007; 146:317–325
8. Tilden VP, Tolle SW, Garland MJ, et al: Decisions about life-sustaining treatment: Impact of physicians' behaviors on the family. *Arch Intern Med* 1995; 155: 633–638
9. Wall RJ, Curtis JR, Cooke CR, et al: Family satisfaction in the ICU: Differences between families of survivors and non-survivors. *Chest* 2007; 132:1425–1433
10. Prendergast TJ, Luce JM: Increasing incidence of withholding and withdrawal of life support from the critically ill. *Am J Respir Crit Care Med* 1997; 155:15–20

Pediatric organ donation after cardiac death—Still in its infancy*

Organ donation after cardiac death (DCD) has been identified as an important tool in the struggle to close the gap between the number of organ donors and the nearly 100,000 individuals in the United States who currently are waiting for lifesaving organs. An important goal of the National Organ Donation Breakthrough Collaborative, launched in 2003, has been to increase the percentage of DCD donors from approximately 5% to ≥10% of all donors. Significant progress has been made nationally, with the total number of DCD donors steadily increasing each year and 26 of 59 organ procurement organizations (OPOs) reporting that >10% of their total donors were DCD donors in 2007 (1).

Despite this overall progress, the story is quite different when the focus is shifted to pediatric DCD. While DCD donors >18 yrs old accounted for 10.2% of total adult deceased donors nationally in 2007, only 7.3% of deceased donors under <18 yrs old were DCD donors. Since 1995, three OPOs have accounted for 27% of the national pediatric DCD donor activity. During the same time period, 34 OPOs reported fewer than five pediatric DCD donor recoveries, and ten OPOs reported no pediatric DCD donor activity whatsoever (2). A qualitative study by Curley et al. (3) may offer some clues as to why DCD in pediatrics is lagging behind. In this study of hospital staff involved in organ donation at a large children's hospital, respondents reported concerns regarding DCD that may be particularly salient with pediatric patients. These concerns included: 1) questions regarding the legitimacy of parental consent for DCD, since DCD is not strictly in the dying child's best interests; 2) worries that DCD, even if done well, might negatively affect the dying experience for patients and families; and 3) concern that public trust in the hospital might erode if a perception grew that dying children were being "used" for their organs (3).

Another likely barrier to the development of pediatric DCD programs is the lack of published clinical research as well as the striking lack of formal guidance from professional organizations specifically with regard to pediatric DCD. The

*See also p. 1729.

Key Words: organ donation; donation after cardiac death; non-heart-beating organ donation; cardiorespiratory death; pediatrics; ethics

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Institute of Medicine's reports on DCD do not address the issue of DCD in children (4). The Society of Critical Care Medicine's position paper on DCD briefly addresses pediatric DCD and concludes that it is ethically reasonable to perform DCD on children, although the report gives scant attention to the specifics and subtleties of developing pediatric DCD programs (5).

This is the milieu in which Dr. Naim and colleagues (6), in this issue of *Critical Care Medicine*, present their 11-yr experience with pediatric DCD. They report the DCD experience at Children's Hospital of Philadelphia over an 11-yr period from 1995 to 2005. While there were 14 pediatric DCD cases during this period, charts were only available for 12. The donors in all 12 cases were <18 yrs of age. All donors had suffered severe neurologic injury but did not meet brain death criteria. Death was declared after 2 mins of acirculation, and organ procurement began after an additional 5-min waiting period. Overall graft survival at 1 yr was excellent, and all 12 donors successfully donated at least one lifesaving organ. Despite this relatively small series of cases, this experience actually accounts for 6% of the total national pediatric DCD donor activity during this time period (2). Hospitals across the country that are interested in considering, developing, or improving a pediatric DCD program will be able to use this relatively rich descriptive study to move toward their goals.

While the reader is likely to see in this study a variety of findings that advance his or her knowledge of the subject, several observations merit discussion here. In 1998, authors from the same institution published a study intended to explore the potential impact of pediatric DCD on overall deceased organ donation and determined that 6.9 patients per year would qualify for DCD and four patients per year would donate through DCD (7). This estimate contrasts sharply with the actual rate of pediatric DCD of 1.3 DCD donors per year observed by Dr. Naim and colleagues (6). The findings of the current study are more in line with other studies from large intensive care units that have attempted to estimate the impact of pediatric and adult DCD on procurement rates (8, 9). While a number of potential explanations for these discrepancies have been offered, one factor that may have significantly reduced the observed rate of DCD donation from that predicted is the dominant practice during the study period of family-initiated donation. If all potential DCD donor families had been approached during the period of observation, it is possible that DCD procurement rates might have been higher. This experience, while primarily reflective of the preceding decade, should give pause to those who would argue that pediatric DCD has the potential to dramatically increase pediatric organ donation rates.

Another notable aspect of this case series relates to the waiting period between the development of acirculation and the start of organ procurement. An adequate time interval is essential to ensure that death has occurred before organ removal begins, but as the time interval increases, the viability of the donated organs diminishes. Addressing this critical element, the Institute of Medicine recommended that "an interval of at least 5 mins elapse after complete cessation of circulatory function . . . before death is pronounced and organ perfusion or donation begins" (4). While this recommendation has been widely adopted in the United States, some American hospitals continue to use a 2-min interval and others (particularly in Europe) use a 10-min time interval (10). Lingering questions remain about the effect of the duration of the time interval on graft function, and few data are available to guide the way that children's hospitals approach this critical component of the DCD protocol. While the experience offered by Dr. Naim and colleagues (6) is small, the authors show that excellent graft function can result from a total interval of 7 mins in a pediatric population.

This article brings into focus, but does not answer, many of the most difficult questions regarding the development of pediatric DCD programs. As a rich descriptive study of a single center's successful pediatric DCD program, the article will illuminate the challenging and controversial aspects of pediatric DCD and provide guidance to the national debate. Future research should address the biological, psychological, emotional, ethical, and social particularities of pediatric organ donation after cardiac death. The concerns voiced by Curley et al. (3) will be addressed and overcome only after considerable dialogue, reflection, and deliberation on the part of hospital communities across the country, informed by the pediatric community at large and by work like that of Dr. Naim and colleagues (6).

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REFERENCES

1. Organ Procurement and Transplantation Network. www.optn.org. Accessed February 11, 2008
2. United Network for Organ Sharing. www.unos.org. Accessed February 11, 2008
3. Curley MA, Harrison CH, Craig N, et al: Pediatric staff perspectives on organ donation after cardiac death in children. *Pediatr Crit Care Med* 2007; 8:212–219
4. Institute of Medicine: Non-Heart-Beating Organ Transplantation: Medical and Ethical Issues in Procurement. Washington, DC, National Academy Press, 1997
5. Recommendations for nonheartbeating organ donation: A position paper by the Ethics Committee, American College of Critical Care Medicine, Society of Critical Care Medicine. *Crit Care Med* 2001; 29:1826–1831
6. Naim MY, Hoehn KS, Wertlieb S, et al: The Children's Hospital of Philadelphia's experience with donation after cardiac death. *Crit Care Med* 2008; 36:1729–1733
7. Koogler T, Costarino AT: The potential benefits of the pediatric nonheartbeating donor. *Pediatrics* 1998; 101:1049–1052
8. Lacroix JD, Mahoney JE, Knoll GA: Renal transplantation using non-heart-beating donors: A potential solution to the organ donor shortage in Canada. *Can J Surg* 2004; 47: 10–14
9. Durall AL, Laussen PC, Randolph AG: Potential for donation after cardiac death in a children's hospital. *Pediatrics* 2007; 119: e219–e224
10. Shemie SD, Baker AJ, Knoll G, et al: National recommendations for donation after cardiocirculatory death in Canada: Donation after cardiocirculatory death in Canada. *Can Med Assoc J* 2006; 175:S1

The curse of the drinking class*

Work is the curse of the drinking class—Oscar Wilde

The adage that the definition of an alcoholic is someone who drinks more than his doctor turns on the truth that one often has a blind spot to one's own weaknesses. In this issue of *Critical Care Medicine*, Dr. Gacouin and colleagues (1) have unveiled another blind spot related to prior alcohol consumption in intensive care unit (ICU) patients, putting them at increased risk of developing bacterial infections and ventilator-associated pneumonia (VAP) during their ICU stays. Heavy drinkers also had almost twice the rate of death compared with those who abstained from alcohol or those who were moderate drinkers.

The study is a prospective, observational study of 358 patients admitted for >3 days to a 21-bed ICU at a French university medical center over a 1-yr period. The preadmission alcohol drinking habits of patients were evaluated using two tools: the National Institute of Alcohol Abuse and Alcoholism criteria for at-risk drinkers and the Simplified Michigan Alcohol Short Test (SMAST). To improve the accuracy of the diagnosis, the determination of being at-risk was made, whenever possible, by interviewing both patients and family. The at-risk group was further subdivided into a high-dose group (five or more drinks per day) and a low-dose group (fewer than five drinks per day). The at-risk group was compared with a larger group (n = 247) who either were abstinent (74%) or were moderate drinkers (37%).

These results confirm those seen previously in trauma and postoperative patients where alcohol consumption was significantly associated with excess morbidity and mortality during their ICU stays (2–4). At-risk drinkers had higher rates of acquired bacterial infection (36% vs. 19%), VAP (27% vs. 16%), and septic shock (18% vs. 8%). The effect of drinking also appears dose-related, as the group of drinkers consuming five or more drinks per day had higher acquired bacterial and VAP infection rates than drinkers consuming fewer than five drinks per day. The length of time of heavy drinking was also important: Acquired bacterial infection occurred in only 5% of at-risk drinkers for <5 yrs, rose to 17% for those drinking 5–10 yrs, and reached 78% for those drinking >10 yrs.

The risk of developing VAP in at-risk drinkers was increased by 70% in this study. The baseline rate of VAP in this unit is within the typical range reported for ICUs in the United States and Europe. What could cause such an increase? Barring some difference in how at-risk patients were provided with measures for preventing VAP, these data imply intrinsic factors at work. Could high daily alcohol consumption cause a delay in seeking medical attention, so that patients were sicker and more likely infected before admission? A higher but not significantly different neutrophil count suggests this. It is well established that the progression of head and neck cancers is more advanced in patients with high alcohol consumption, related to delay in seeking attention for an incipient problem (5). Furthermore, it has been suggested that excessive alcohol consumption leads to a relative immunodeficient state. Tonnesen et al. (2) found that delayed hypersensitivity reactions were depressed in postoperative patients with high alcohol consumption (>60 g of ethanol alcohol per day = five drinks) compared with a matched group of low alcohol consumption.

One question about the study concerns the accuracy of the ethanol consumption history. How reliable is self-reporting of alcohol consumption? Studies from the United States, the United Kingdom, and Denmark have addressed this question and surprisingly have found that underreporting or forgetting is not usually present (6–8). Others have found that the interviewing technique is important for avoiding underreporting and that the quantity-frequency approach, as used in this study, is better than a graduated frequency approach (9). In addition, the authors sought to improve accuracy by interviewing family to confirm the two reports. So although the authors did not provide evidence of the accuracy of their history taking, we can be fairly confident that the data on alcohol consumption were accurate in this study.

There are two other aspects of the study that deserve consideration. First, to what extent was treatment for ethanol withdrawal applied in the at-risk patient group? These patients were consuming enough ethanol regularly to manifest signs and symptoms of ethanol withdrawal and thus were probably treated with benzodiazepines or other agents to ameliorate the withdrawal syndrome. Although the proportions of patients who required intubation and ventilation were not different between the two groups, the length of time patients required mechanical ventilation is not reported. It is known that excessive alcohol use increases the need for and duration of mechanical ventilation in medical patients and may have contributed to the increased VAP rates seen in this study (10). In addition, many physicians treat patients at risk for alcohol withdrawal with prophylactic doses of benzodiazepines. If the at-risk group received additional sedatives, whether or not they were mechanically ventilated, they would be expected to have a higher rate of complications.

Another aspect that is not well characterized is the severity of liver impairment in the at-risk group. The authors state that only eight of 111 patients had cirrhosis, based on a diagnosis made be-

***See also p. 1735.**

Key Words: alcohol; nosocomial infection; sepsis; infection; liver; cirrhosis

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fore entry into the study. However, more than three fourths of the at-risk group had been drinking >10 yrs. With this amount of alcohol consumption in the at-risk group, there may be more patients with end-stage liver disease. Why is this important? Chronic liver injury secondary to chronic ethanol ingestion causes impaired clearance of intestinal bacteria that enter the portal circulation. Impaired hepatic filtering function of gut flora could be a mechanism for the increased infection rate in at-risk drinkers and may explain higher rates of septic shock (11).

So what is the take-home message from the findings of Dr. Gacouin and colleagues (1)? It is essential to take a detailed alcohol ingestion history in patients admitted to the ICU. This history is important not only for the prediction of well-recognized complications, such as liver dysfunction and alcohol withdrawal syndrome, but also to recognize that these patients are at increased risk for severe infection.

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REFERENCES

1. Gacouin A, Legay F, Camus C, et al: At-risk drinkers are at higher risk to acquire a bacterial infection during an intensive care unit stay than abstinent or moderate drinkers. *Crit Care Med* 2008; 36:1735–1741
2. Tonnesen H, Petersen KR, Hojgaard L, et al: Postoperative morbidity among symptom-free alcohol misusers. *Lancet* 1992; 340:334–337
3. Jurkovich GJ, Rivara FP, Gurney JG, et al: The effect of acute alcohol intoxication and chronic alcohol abuse on outcome from trauma. *JAMA* 1993; 270:51–56
4. Spies CD, Neuner B, Neumann T, et al: Intercurrent complications in chronic alcoholic men admitted to the intensive care unit following trauma. *Intensive Care Med* 1996; 22:286–293
5. Tromp DM, Brouha XD, De Leeuw JR, et al: Psychological factors and patient delay in patients with head and neck cancer. *Eur J Cancer* 2004; 40:1509–1516
6. Crawford A: Bias in a survey of drinking habits. *Alcohol* 1987; 22:167–179
7. Grant KA, Arciniega LT, Tonigan JS, et al: Are reconstructed self-reports of drinking reliable? *Addiction* 1997; 92:601–606
8. Stockwell T, Donath S, Cooper-Stanbury M, et al: Under-reporting of alcohol consumption in household surveys: A comparison of quantity-frequency, graduated-frequency and recent recall. *Addiction* 2004; 99:1024–1033
9. Gronbaek M, Heitmann BL: Validity of self-reported intakes of wine, beer and spirits in population studies. *Eur J Clin Nutr* 1996; 50:487–490
10. de Wit M, Best AM, Gennings C, et al: Alcohol use disorders increase the risk for mechanical ventilation in medical patients. *Alcohol Clin Exp Res* 2007; 31:1224–1230
11. Balzan S, de Almeidaq Uadros C, de Cleva R, et al: Bacterial translocation: Overview of mechanisms and clinical impact. *J Gastroenterol Hepatol* 2007; 22:464–471

Tracheostomy protocol compliance: Herding cats?*

Tracheostomies are common procedures in the intensive care unit (ICU), occurring in about 10% of critically ill patients who require mechanical ventilation (1). A tracheostomy is reported to allow a more secure airway, earlier and safer enteral feeding, easier oral care, and enhanced patient comfort while reducing sedation needs. However, the benefits of tracheostomy have to be weighed against potential complications, which include infections, hemorrhage, pneumothorax, pneumomediastium, and tracheal stenosis (2).

A review published in 1998 concluded that there was insufficient evidence to support the view that timing of a tracheostomy can alter the duration of mechanical ventilation or prevent airway injury in the critically ill patient (3). Since then, many other studies have reported decreased days of mechanical ventilation (4), decreased duration of ICU and hospital length of stay (5), and less damage to the upper airway (4) with early tracheostomies. A meta-analysis attempted to answer this question definitively in 2005. Griffiths et al. (6) reported that early tracheostomy (<7 days) may lead to reduced duration of mechanical ventilation and shorter ICU stays, but the timing of tracheostomies did not alter mortality or increase the risk of developing hospital-acquired pneumonia. Unfortunately, this meta-analysis only included a limited number of studies (five trials) and a small number of patients (406 patients). Heterogeneity was also high in the meta-analysis due to variability of inclusion and exclusion criteria, definitions of *early* and *late* tracheostomy, characteristics of enrolled patients, and diagnostic criteria for hospital-acquired pneumonia.

Part of the difficulty in designing studies to address the timing of tracheostomy lies in identifying patients who may have a simple subsequent weaning process after failing the first attempt at extubation. Tracheostomies should be performed in those patients who will encounter a difficult or prolonged wean. Unfortunately, no validated specific and sensitive test or scoring system is available that predicts the need for prolonged ventilation, so the selection of patients for tracheostomy remains a subjective, arbitrary decision due to the lack of solid data.

In this issue of *Critical Care Medicine*, Dr. Freeman and colleagues (7) undertake the task of developing a standardized approach to tracheostomy selection and timing. The authors felt that one way to decrease arbitrary choices would be to integrate the decision-making process into a standard ventilator weaning protocol. The primary purpose of the study was to determine the feasibility of developing such a protocol. In their pilot implementation group of 125 patients, patients, who met criteria for tracheostomy, failed the preliminary weaning assessment (PWA) or spontaneous breathing trial (SBT) for two successive days after either 5 days of mechanical ventilation if they had not been reintubated or 3 days of mechanical ventilation if they had been reintubated.

***See also p. 1742.**

Key Words: tracheostomy; mechanical ventilation; protocol; quality improvement; critical care; sedation

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The article by Dr. Freeman and colleagues (7) has certain limitations that the authors readily acknowledge. Despite focused educational sessions for physicians, nurses, and ancillary staff, visible protocols posted at each bedside, and extensive discussions on ICU rounds, only 45% of the patients underwent tracheostomy consistent with the protocol. Thirty-three percent of the patients underwent tracheostomy earlier than dictated by protocol, and 22% of the patients, despite passing one or more SBTs, continued to tracheostomy.

The fact that the majority of physicians did not follow the study protocol reflects the experience with other clinical protocols (e.g., daily sedation cessation protocol) (8). As anyone who has tried to implement a protocol into widespread clinical practice knows, this can be a difficult feat. Implementation of clinical practice guidelines is often slow to nonexistent. Lack of physician buy-in to protocols is attributed to physicians' underlying knowledge and attitudes, the culture in which they practice, minimal incentive to change, and lack of time or staff support (9).

The study was preliminary and therefore could not be extrapolated to all critical care patients, such as those on noninvasive ventilation. The study could not evaluate other questions related to tracheostomy, such as technique, patient comfort, and reintubation rates. Another study designed to look at tracheostomy protocol efficacy compared with standard practice will have to be completed, but in the meantime, this introduction of a standardized approach to tracheostomy based on weaning performance may be just the breakthrough we need to use tracheostomy in a more consistent and effective fashion. This protocol may not be perfect, but one logical approach must be chosen to promote consistent clinical decisions. The consistency then allows for the rigorous evaluation of the intervention, which in this instance is the timing of tracheostomy placement (10).

Although it is too early to recommend widespread implementation of tracheostomy protocols, perhaps someday a patient admitted to the ICU with severe sepsis will be enrolled in an early resuscitation protocol, a low tidal volume ventilation protocol, a daily sedation cessation protocol, a spontaneous breathing trial protocol, a glucose control protocol, and an assessment for tracheostomy protocol. The ultimate success of this protocol-based care may well hinge on our ability to "herd the cats" (ourselves) into following our own recommendations.

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REFERENCES

1. Esteban A, Anzueto A, Frutos F, et al: Characteristics and outcomes in adult patients receiving mechanical ventilation: A 28-day international study. *JAMA* 2002; 287: 345–355
2. Stauffer JL, Olson DE, Petty TL: Complications and consequences of endotracheal intubation and tracheotomy: A prospective study of 150 critically ill adult patients. *Am J Med* 1981; 70:65–76
3. Maziak DE, Meade MO, Todd TR: The timing of tracheotomy: A systematic review. *Chest* 1998; 114:605–609
4. Rumbak MJ, Newton M, Truncale T, et al: A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients. *Crit Care Med* 2004; 32:1689–1694
5. Rodriguez JL, Steinberg SM, Luchetti FA, et al: Early tracheostomy for primary airway management in the surgical critical care setting. *Surgery* 1990; 108:655–659
6. Griffiths J, Barber VS, Morgan L, et al: Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation. *BMJ* 2005; 330:1243
7. Freeman BD, Kennedy C, Robertson TE, et al: Tracheostomy protocol: Experience with development and potential utility. *Crit Care Med* 2008; 36:1742–1748
8. Mehta S, Burry L, Fischer S, et al: Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. *Crit Care Med* 2006; 34:374–380
9. Cabana MD, Rand CS, Powe NR, et al: Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999; 282:1458–1465
10. Morris AH: Developing and implementing computerized protocols for standardization of clinical decisions. *Ann Intern Med* 2000; 132:373–383

Sleep and breathing: The impact of mechanical ventilation on the quality of sleep*

The field of sleep medicine has rapidly expanded in the last 10 yrs. Although sleep disturbances have received much attention in the medical community and the outpatient setting, sleep disturbances have not been a focus in the hospital setting, particularly the intensive care unit (ICU). Patients admitted to intensive care are critically ill with multiple organ system dysfunctions. Studies have consistently demonstrated that sleep disturbances are a common and significant concern for these patients. Patients in the ICU have poor sleep efficiency with fragmented sleep, increased arousals resulting in awakenings, and a low percentage of time spent in rapid eye movement (REM) sleep (1–4). Few studies have undertaken the task of evaluating the physiologic, neurocognitive, and psychological consequences of poor sleep in this patient population. Also, how sleep contributes to the recovery of illness has not been evaluated.

Sleep disturbances in the ICU are multifactorial. Some of these factors include the ICU environment, medications, noise, pain, illness, frequent care-related interruptions by nurses and physicians, and mechanical ventilation (5, 6). Cooper et al. (2) evaluated sleep architecture in 20 critically ill patients requiring me-

*See also p. 1749.

Key Words: sleep; respiration; artificial respiration; critical illness

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chanical ventilation and found that all patients had abnormal sleep with severely reduced sleep efficiency and REM sleep. Severe sleep fragmentation was reflected by a high frequency of arousals and awakenings. The mode of mechanical ventilation used may contribute to sleep disturbance. The study by Meza et al. (7) showed that pressure support ventilation (PSV) caused arousals and awakenings due to central apneas in healthy subjects. Parthasarathy and Tobin (4) evaluated the relationship between the mode of mechanical ventilation and sleep disruption by comparing assist control ventilation (ACV) with pressure support in 11 mechanically ventilated patients. Five patients (with congestive heart failure and ejection fraction $<50\%$) developed central apneas on PSV leading to arousals and increased sleep fragmentation compared with subjects on ACV.

Problems associated with mechanical ventilation, such as dyssynchrony of breathing, endotracheal tube discomfort, and increased patient effort, can contribute to frequent arousals and fragmented sleep. Bosma et al. (3) looked at the relationship between patient-ventilator interaction and sleep quality in 13 mechanically ventilated patients by comparing pressure support to proportional assist ventilation. The overall sleep quality was better on proportional assist ventilation due to fewer arousals, fewer awakenings, a greater proportion of REM and slow-wave sleep, and less patient-ventilator asynchrony. Toublanc et al. (1) conducted a recent study comparing assist-control ventilation to low levels of PSV (at 6 cm H_2O) on sleep quality in intubated patients. Consistent with previous findings, regardless of the mode of mechanical ventilation used, sleep architecture was abnormal, with up to 40% of the night spent in wakefulness. There was a predominance of stages 1 and 2, while slow-wave sleep and REM periods were significantly reduced. However, ACV compared with PSV reduced wakefulness during the first part of the night and increased slow-wave sleep during the second part of the night. These studies raised the possibility that there could be an optimal mode of mechanical ventilation that provides good-quality sleep in patients requiring support from a mechanical ventilator.

In this issue of *Critical Care Medicine*, the interesting although small study by Dr. Cabello and colleagues (8) addressed sleep quality on three different modes of mechanical ventilation. Fifteen patients requiring ventilatory support were placed on assist ACV, clinically adjusted PSV (cPSV), and automatically adjusted PSV (aPSV). Consistent with previous studies, the authors found reduced REM sleep and a high frequency of arousals and awakenings. However, unlike previous studies by Parthasarathy and Tobin (4) and Toublanc et al. (1), where ACV seemed to be the superior mode, Dr. Cabello and colleagues found that none of the three ventilatory modes were superior to the others. Sleep architecture and quality were equally affected in all three modes of mechanical ventilation. The reduced amount of REM sleep, increased arousals and awakenings, and high sleep fragmentation were similar in all three modes. Central apneas were present during pressure support ventilation but occurred much less frequently compared with the study by Parthasarathy and Tobin, accounting for $<10\%$ of sleep fragmentation. This may be explained in part by a lower amount of pressure delivered during this study. Using more sensitive indicators for respiratory effort would be helpful, such as the esophageal pressure monitor. In this study, respiratory efforts were measured by chest and abdominal inductance plethysmography. Esophageal pressure monitoring is invasive, and in the case of patients requiring ventilatory support, it measures diaphragmatic excursions. Stoohs et al. (9) evaluated noninvasive estimation of esophageal pressure based on intercostal electromyography in patients with sleep-disordered breathing and found that this method can be used to estimate esophageal pressure with sufficient accuracy. Increased respiratory effort causing arousals may be better quantified using more sensitive monitoring, such as the technique described by Stoohs and colleagues.

Based on studies by Toublanc et al. (1) and Parthasarathy and Tobin (4), pressure support ventilation is an inferior mode of maintaining good-quality sleep. Fanfulla et al. (10) reported that the type of ventilator mode might have a major influence on sleep quality and neuromuscular function in patients with known neuromuscular disease. Chen and Tang (11) showed that sleep loss might impair inspiratory muscle endurance in intubated patients. Muscle strength is a significant determinant of successful weaning, and therefore the quality of sleep should be an important focus for physicians. It is a common practice in the intensive care setting to maintain or increase ventilatory support for intubated patients during nocturnal hours. Toublanc et al. suggested that PSV may not be the optimal mode to ensure adequate ventilatory support while patients are rested during nocturnal hours of sleep. The study by Dr. Cabello and colleagues (8) highlights the importance of an appropriate amount of pressure delivered to prevent the occurrence of central apneas leading to sleep fragmentation. If pressure support ventilation is to be used, then perhaps it is important to define the correct pressure to avoid central apneas leading to arousals/awakenings and poor sleep efficiency.

Circadian rhythm disturbances can significantly affect sleep. Dr. Cabello and colleagues (8) determined sleep start at 2 p.m. with three 6-hr sessions ending at 8 a.m. the following day. Sleep start was determined at 2 p.m. because most routine ICU care was performed between 8 a.m. and 2 p.m. Patients in the ICU may not demonstrate normal circadian rhythm fluctuations as defined by daylight and night. Hardin et al. (12) demonstrated that 18 ICU patients monitored with 24-hr polysomnography displayed abnormal sleep/wake cycles with erratic progression through sleep stages. Patients were not quantitatively sleep deprived, but $>50\%$ of sleep occurred in daytime. Starting sleep time at 2 p.m. may contribute to the already present circadian disturbances in this population group. Rapid eye movement sleep is most difficult to achieve and is at its lowest in percentage of total sleep time during mid-afternoon. In Dr. Cabello and colleagues' study, REM sleep was nonexistent in the daytime period and the proportion of REM sleep progressively increased in the second nocturnal period. The authors should take into account the alteration of normal circadian rhythm in the intensive care setting and how it contributes to poor quality sleep.

Medications routinely used in the ICU commonly cause sleep disturbances, in particular benzodiazepines and opioids. In this study by Dr. Cabello and colleagues (8), the average duration of ventilatory support for a patient was 22 ± 17 days. These patients required prolonged ventilatory support and therefore likely required prolonged sedation and pain control. Although the patients had been off sedatives and opioids for $\geq$24 hrs, the effects of these medications may still be

clinically significant. The dose-dependent relationships of these medications are based on renal and hepatic metabolism, as well as the volume of distribution, all of which are abnormal in the critically ill patient. Benzodiazepines in particular are known to decrease REM sleep, and opioids have been shown to cause respiratory depression and induce central apneas. Allowing for a >24-hr benzodiazepine and opioid-free duration before the start of sleep time recording would be prudent.

Dr. Cabello and colleagues (8) address a difficult but important issue in the ICU. Sleep disturbances in the intensive care setting can bring about acute and long-term physiologic, psychological, and behavioral consequences for the patient. Physicians should pay closer attention to sleep-related issues in this patient population and attempt to find resolution. Many questions remain unanswered in regard to the topic of sleep in the intensive care environment. Much more is expected from the field of sleep research focusing on this patient population, and we hope that larger well-designed studies will answer our questions.

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REFERENCES

1. Toublanc B, Dominique R, Jean-Charles G, et al: Assist-control ventilation vs. low levels of pressure support ventilation on sleep quality in intubated ICU patients. *Intensive Care Med* 2007; 33:1148–1154
2. Cooper A, Thornley K, Young B, et al: Sleep in critically ill patients requiring mechanical ventilation. *Chest* 2000; 117:809–818
3. Bosma K, Ferreyra G, Ambrogio C, et al: Patient-ventilator interaction and sleep in mechanically ventilated patients: Pressure support versus proportional assist ventilation. *Crit Care Med* 2007; 35:1048–1054
4. Parthasarathy S, Tobin M: Effect of ventilator mode on sleep quality in critically ill patients. *Am J Respir Crit Care* Med 2002; 166: 1423–1429
5. Gabor J, Cooper A, Crombach S, et al: Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. *Am J Respir Crit Care Med* 2003; 167: 708–715
6. Freedman N, Gazendam J, Levan L, et al: Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *Am J Respir Crit Care Med* 2001; 163:451–457
7. Meza S, Mendez M, Ostrowski M, et al: Susceptibility to periodic breathing with assisted ventilation during sleep in normal subjects. *J Appl Physiol* 1998; 85:1929–1940
8. Cabello B, Thille AW, Drouot X, et al: Sleep quality in mechanically ventilated patients: Comparison of three ventilatory modes. *Crit Care Med* 2008; 36:1749–1755
9. Stoohs RA, Blum HC, Knaack L, et al: Noninvasive estimation of esophageal pressure based on intercostal EMG monitoring. In: Proceedings of the 26th Annual International Conference of the IEEE EMBS, September 2004, San Francisco, CA
10. Fanfulla F, Delmastro M, Berardinelli A, et al: Effects of different ventilator settings on sleep and inspiratory effort in neuromuscular patients. *Am J Respir Crit Care* Med 2005; 172:619–624
11. Chen HI, Tang YR: Sleep loss impairs inspiratory muscle endurance. *Am Rev Respir Dis* 1989; 140:907–909
12. Hardin K, Seyal M, Stewart T, et al: Sleep in critically ill chemically paralyzed patients requiring mechanical ventilation. *Chest* 2006; 129:1468–1477

Acute compartment syndrome: Are we close to making an early diagnosis?*

Compartment syndrome, an orthopedic emergency, is the condition of increased pressure within a limited anatomical space that compromises tissue perfusion and, ultimately, causes tissue necrosis, rhabdomyolysis, renal failure, and even death (1). Compartment syndrome can develop anywhere skeletal muscle is surrounded by substantial fascia and most commonly is caused by fractures, soft tissue trauma, arterial injury, burns, and strenuous physical exertion (2–5).

Timely diagnosis is important to avoid irreversible consequences of compartment syndrome. Although time of injury or ischemia to tissue necrosis can vary, currently the upper limit of accepted tissue viability is 6 hrs (6). Diagnosis can be challenging even for those who are aware of the possibility of compartment syndrome in certain clinical settings due to lack of a definitive diagnostic measure. Moreover, frequent evaluations of patients may be needed if clinical findings are not clear. Relevant history and classic clinical symptoms of pain, paresthesia, palor, and pulselessness may be enough for diagnosis, whereas early cases or unconscious trauma patients may not have typical presentation. In those instances, laboratory tests (serum creatine phosphokinase, serum and urine myoglobin), radiography, and ultrasound/Doppler of the extremity may give additional information. A number of commercially available tonometers (i.e., Stryker, ACE) can be used to measure the compartment pressures. While pressures of 0–15 mm Hg are considered normal, pressure ≥30 mm Hg in the presence of appropriate clinical signs is diagnostic for compartment syndrome (7). While investigators have studied methods of diagnosing chronic exertional compartment syndrome with newer noninvasive tools, such as using magnetic resonance imaging at 0.1 T (8) or near-infrared spectroscopy to measure hemoglobin saturation of deep tissues as an indicator of blood flow (9), the diagnosis of acute compartment syndrome relies on conventional methods.

*See also p. 1756.

Key Words: acute compartment syndrome; extremity; leg; diagnosis; infrared

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In this issue of *Critical Care Medicine*, Dr. Katz and colleagues (10) describe early detection of acute compartment syndrome in trauma patients by using a novel technique of infrared imaging. This technique is proposed to provide an early diagnosis of acute compartment syndrome by using thermographic images of extremities to detect lower surface temperatures, which can be seen in compartment syndrome due to decreased blood flow in the affected extremities. In this observational study, the authors measured the average temperature of the anterior surface of the proximal and distal region of each leg, termed the *thigh-foot index*, with an uncooled microbolometer infrared camera in 164 patients who presented to a level I trauma center with trauma. Research assistants obtained the thermographic images using the same angle and distance (90 cm) in patients who presented within 4 hrs of trauma. Eleven of 164 analyzed patients developed compartment syndrome. Those with acute leg compartment syndrome (unilateral or bilateral) had significantly lower anterior leg surface temperatures than did the patients with contralateral leg syndrome (unilateral compartment syndrome) and the control group (bilateral compartment syndrome). Similarly, thigh-foot index was greater in the legs with compartment syndrome. Analysis of covariance revealed no significance in the surface temperature measurements for the variables of blood pressure, presence of shock, body temperature, ambient temperature, and lower extremity fractures.

Although this is a unique method and holds promise as a noninvasive diagnostic tool for acute compartment syndrome, future studies are needed to eliminate the limitations of the current study and validate its clinical utility. As noted by the authors, the study has numerous limitations. First, this was an observational study based on retrospective chart review for final diagnosis of compartment syndrome. Therefore, clinical utility, especially the decision for fasciotomy, cannot be drawn from the current data. Second, no correlation with conventional diagnostic methods (clinical symptoms, physical examination, measurements of compartment pressures) was performed prospectively. Therefore, we have no data regarding whether this new technique would provide an early and accurate diagnosis of acute compartment syndrome. Moreover, no data were provided regarding whether a diagnosis of compartment syndrome was missed based on chart review and thermographic measurements. Third, most patients diagnosed with acute compartment syndrome had sustained blunt extremity trauma and fracture. We have no data as to whether infrared imaging would help determine compartment syndrome from other causes. Fourth, the study had technical limitations: Technical skills are required to properly calibrate the camera and use it to collect data. As mentioned in the article, images from seven patients could not be used due to poor quality. Fifth, the cost of equipment and having readily available personnel who can operate the system can be problematic in the emergency department.

Once these limitations are addressed in future studies, infrared imaging may potentially provide a supportive measure to diagnose acute compartment syndrome. Until then, clinical judgment and conventional diagnostic measures must be used to diagnose acute compartment syndromes.

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REFERENCES

1. Matsen FA: Compartmental Syndrome. New York, Grune and Stratton, 1980
2. Tornetta P, Templeman D: Compartment syndrome associated with tibial fracture. *Instr Course Lect* 1997; 46:303–308
3. Roberge RJ, McLane M: Compartment syndrome after simple venipuncture in an anticoagulated patient. *J Emerg Med* 1999; 17: 647–649
4. Mubarak SJ, Hargens AR: Acute compartment syndromes. *Surg Clin North Am* 1983; 63:539–565
5. Berlemann U, Al-Momani Z, Hertel R: Exercise-induced compartment syndrome in the flexor-pronator muscle group. *Am J Sports Med* 1998; 26439–441
6. Matsen FA, Winquist RA, Krugmire RB: Diagnosis and management of compartmental syndromes. *J Bone Joint Surg Am* 1980; 62: 200–203
7. Heppenstall RB, Sepega AA, Scott R, et al: The compartment syndrome: An experimental and clinical study of muscular energy metabolism using phosphorous nuclear magnetic resonance spectroscopy. *Clin Orthop* 1988; 226:138
8. Eskelin MK, Lotjonen JM, Mantysaari MJ: Chronic exertional compartment syndrome: MR imaging at 0.1 T compared with tissue pressure measurement. *Radiology* 1998; 206: 333–337
9. van Den Brand JG, Verleisdank EJ: Near infrared spectroscopy in the diagnosis of chronic exertional compartment syndrome. *Am J Sports Med* 2004; 32:452–457
10. Katz LM, Nauriyal V, Nagaraj S, et al: Infrared imaging of trauma patients for detection of acute compartment syndrome of the leg. *Crit Care Med* 2008; 36:1756–1761

Death by TPN . . . the final chapter?*

It seems obvious that the human body was designed to receive nourishment and hydration via the gastrointestinal route; this model of nourishment is found throughout the animal kingdom. It is now widely accepted that the gastrointestinal tract is the preferred route of delivering nutritional support even in hospitalized patients (1). Furthermore, consensus guidelines strongly recommend enteral over parenteral nutrition in critically ill patients (2, 3). Indeed, for patients in whom enteral nutrition is possible (i.e., who have a functional gastrointestinal tract), there is no disease state that is known to benefit from parenteral nutrition (1). The institution of early enteral nutrition in critically ill medical and postoperative patients has been demonstrated to improve outcome (4, 5). Yet parenteral nutrition continues to be widely used in patients who can be fed enterally. The results from the German Competence Network Sepsis (SepNet) study by Dr. Schmitz and colleagues (6) in this issue of *Critical Care Medicine* confirm this observation; only 20.1% of intensive care unit (ICU) patients with severe sepsis/septic shock received exclusively enteral feeding during their ICU stay. In addition, these authors confirm what should be no surprise; parenteral nutrition was an independent predictor of death (odds ratio of 2.09). The adverse sequelae associated with parenteral nutrition result from 1) not directly feeding the bowel; 2) the metabolic, immunologic, endocrine, and infective complications associated with parenteral nutrition; and 3) the fact that parenteral nutrition is infused into the patient's systemic venous system, bypassing the liver. This latter concept is supported by the recent study by Grau et al. (7), who in a large cohort of critically ill patients demonstrated that parenteral nutrition was strongly associated with the development of liver dysfunction, while early enteral nutrition was protective. The hepatotoxicity of parenteral nutrition may partly explain the perniciousness of this admixture, considering the central role the liver plays in metabolism and homeostasis.

The findings of the SepNet study are all the more important as the study took place in the era of "tight glycemic control" and the mean blood glucose concentration was similar between enterally and parenterally fed patients. It has previously been argued that the increased risk of infections and death associated with parenteral nutrition is due to poor glycemic control and that with adequate glucose control parenteral nutrition is safe (8, 9). Clearly, this is not the case! Furthermore, it is likely that the parenteral nutrition admixtures in the United States are more deadly than those available in Europe, because intravenous glutamine solutions and non-soy-based lipid emulations, which have been demonstrated to reduce the toxicity of parenteral nutrition, are not available in the United States (10).

Why would clinicians purposefully harm their patients with a toxic solution that would certainly not meet current safety standards? Again, the article by Dr. Schmitz and colleagues (6) may shed some light on this question. Mechanical ventilation, intra-abdominal disease, and the presence of shock were independently associated with the failure to feed enterally. These exclusions are clearly contrary to current evidence, which suggests that early enteral nutrition improves outcomes in these patient groups and that enteral nutrition may protect the gastrointestinal tract from vasopressor-induced ischemia (4, 11, 12). In addition, many clinicians are still under the misguided impression that enteral nutrition and parenteral nutrition are equivalent. This myth (9, 13) is unfortunately propagated by experts who contend that "appropriately administered parenteral nutrition may provide similar or more benefit than enteral (nutrition) and clearly needs more widespread acceptance" (9). Enteral nutritional support may not be possible in patients with intestinal failure, such as short-gut syndromes, and in those with high-output small-bowel fistulas. However, these patients are uncommon in clinical practice. Almost all patients who receive parenteral nutrition in the ICU have a functional gastrointestinal tract and can be fed enterally.

The risk of pulmonary aspiration and ventilator-associated pneumonia (VAP) is often cited as a reason to delay enteral feeding. Feeding mechanically ventilated patients with a nasogastric tube in the supine position is clearly a risk factor for VAP (14). However, it is unclear whether early enteral nutrition increases the risk of VAP when measures to prevent VAP are systematically applied and patients are fed slowly (15). Data from the Project Impact Data System suggested that early (as opposed to delayed) enteral nutrition was associated with a small but nonsignificant increase in the risk of VAP. However, overall mortality was lower in the "early enteral group," with both groups having an equivalent number of ventilator-free days (4). This suggests that despite a possible increase in the risk of VAP, early enteral feeding has an overall benefit. In addition, it is unclear whether small-bowel feeding decreases the risk of VAP (16, 17). Therefore, I recommend that an orogastric tube be placed in all ventilated patients on admission to the ICU and tube feeding be started within 12 hrs (except when extubation within 24 hrs is planned). Tube feeding should be initiated slowly (20 mL/hr) with permissive underfeeding for the first 3–5 days (15–20 kcal/kg/day) and then advanced to a goal of 20–25 kcal/kg/day as the patient's condition improves. In patients with gastric intolerance, promotility agents (such as erythromycin, 100 mg intravenously every 8 hrs) and small-bowel feeding should be considered. With this approach, almost 100% of ICU patients can be nourished in the way that nature intended.

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*See also p. 1762.

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REFERENCES

1. Zaloga GP: Parenteral nutrition in adult inpatients with functioning gastrointestinal tracts: Assessment of outcomes. *Lancet* 2006; 367:1101–1111
2. Heyland DK, Dhaliwal R, Drover JW, et al: Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr* 2003; 27:355–373
3. Kreymann KG, Berger MM, Deutz NE, et al: ESPEN guidelines on enteral nutrition: Intensive care. *Clin Nutr* 2006; 25:210–223
4. Artinian V, Krayem H, DiGiovine B: Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. *Chest* 2006; 129:960–967
5. Marik PE, Zaloga GP: Early enteral nutrition in acutely ill patients: A systematic review. *Crit Care Med* 2001; 29:2264–2270
6. Schmitz G, Schädler D, Engel C, et al: Current practice in nutritional support and its association with mortality in septic patients—Results from a national, prospective, multicenter study. *Crit Care Med* 2008; 36: 1762–1767
7. Grau T, Bonet A, Rubio M, et al: Liver dysfunction associated with artificial nutrition in critically ill patients. *Crit Care* 2007; 11: R10
8. Perioperative total parenteral nutrition in surgical patients. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. *N Engl J Med* 1991; 325:525–532
9. Bistrian BR, McCowen KC: Nutritional and metabolic support in the adult intensive care unit: Key controversies. *Crit Care Med* 2006; 34:1525–1531
10. Marik PE: Maximizing efficacy from parenteral nutrition in critical care: Appropriate patient populations, supplemental parenteral nutrition, glucose control, parenteral glutamine, and alternative fat sources. *Curr Gastroenterol Rep* 2007; 9:345–353
11. Marik PE, Zaloga GP: A meta-analysis of parenteral nutrition vs enteral nutrition in acute pancreatitis. *BMJ* 2004; 328:1407–1409
12. Zaloga GP, Roberts PR, Marik PE: Feeding the hemodynamically unstable patient: A critical evaluation of the evidence. *Nutr Clin Pract* 2003; 18:285–293
13. Jeejeebhoy KN: Total parenteral nutrition: potion or poison? *Am J Clin Nutr* 2001; 74: 160–163
14. Drakulovic MB, Torres A, Bauer TT, et al: Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: A randomised trial. *Lancet* 1999; 354:1851–1858
15. Collard HR, Saint S, Matthay MA: Prevention of ventilator-associated pneumonia: An evidence-based systematic review. *Ann Intern Med* 2003; 138:494–501
16. Goncalves RR, Leite HP, Nogueira PC: Does small bowel feeding decrease the risk of ventilator-associated pneumonia? *JPEN J Parenter Enteral Nutr* 2004; 28:60
17. Marik PE, Zaloga G: Gastric vs post-pyloric feeding? A systematic review. *Crit Care* 2003; 7:R46–R51

Glutamine and tight glycemic control: Chicken or egg?*

For a clinician striving to deliver the optimal nutrient regimen to the critically ill, it is a reassurance to learn that two of the most significant clinical developments in nutrition that impact on outcome are themselves intimately related. The glutamine story (1) is one of system failures arising as a consequence of a conditional deficiency due to a limited endogenous production in skeletal muscle failing to meet increased demands. The activation of muscle proteolysis with relative inhibition of protein synthesis leads to muscle wasting and release of amino acids, many of which are metabolized to glutamine. However, it is also recognized that part of the carbon used in glutamine production also is linked to the glucose delivered to muscle. This is optimal in hyperinsulinemic euglycemia and is impaired in hypoglycemia or when insulin resistant (2). Perhaps it may be possible to get an optimal glutamine supply without scavenging the body protein reserve by simply combining adequate nutrient provision with sufficient exogenous insulin to give tight glycemic control?

The elegant clinical research study by Dr. Gianni Biolo and colleagues (3) in this issue of *Critical Care Medicine* starts to suggest that this actually may be possible. They have studied a select group of cancer patients undergoing radical abdominal surgery. Using carefully controlled metabolic studies involving stable isotope tracers, they show that by maintaining strict euglycemia with insulin in company with good nutrient delivery, they were able to increase glucose uptake and increase protein synthesis with a more neutral protein balance indicative of less catabolism of muscle. This resulted in a higher glutamine synthesis and plasma glutamine concentration. This contrasts with their previous work on growth hormone (4), which showed that, although stimulating protein synthesis, it was associated with a reduction in glutamine availability.

Each patient provided his/her own control in a 24-hr crossover study in randomized order, once with moderate hyperglycemia (mean, 9.6 mmol) and the other with insulin-mediated tight euglycemia (mean blood glucose, 5.8 mmol) soon after surgery. They received continuous intravenous nutrition of glucose, lipids, and amino acids to a total energy of 28 kcal/kg/day for the 48 hrs of study. An interesting feature was that the increased endogenous insulin production during the hyperglycemic periods could be reduced (shown by lower C-peptide) during the tight euglycemia period and this was associated with improved insulin sensitivity. Are there limitations? Yes, these are stressed patients but not septic or critically ill with multiple organ failure. They only studied eight female patients for 48 hrs, so we do not know if the effect is sustained. However, their findings are consistent and the changes observed are of a magnitude to suggest clinical significance.

Does this seems too good to be true? Will using a tight glycemic protocol alone solve the glutamine issue as well? We must recognize that intensive insulin therapy in some hands appears problematic (5) with increased hypoglycemia, but then these workers did not follow a detailed nutrition protocol that prescribed a

***See also p. 1768.**

Key Words: glutamine; insulin; tight glycemic control; euglycemia; nutrition; glucose

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reasonable glucose load to avoid this risk. From the paper, it appears that in their moderately obese population (BMI of 27) over the first few days, they were delivering on average <1000 kcals per day in total. This is a period of great instability with considerable variability and inconsistency of nutrient delivery. This contrasts with the careful attention to consistent nutrient delivery shown in a paper from the Leuven group (6). Studies in septic critically ill patients show that glucose oxidation is not impaired; it is the nonoxidative disposal (e.g., into skeletal muscle) that accounts for reduced total utilization and appearance of hyperglycemia. Therefore, with physiologic levels of insulin, an optimal glucose utilization rate in sepsis (and hence safe delivery rate if not exceeded) is 4 mg/kg fat free mass/min (7). Contrary to what some appear to believe (5), it may be important to deliver glucose within this range of between 8 to 12 g/hr, which is precisely what was done in the original studies (6, 8).

But perhaps the glutamine deficiency that occurs plays a role in worsening insulin sensitivity? Glutamine, as a parenteral infusion, can favorably influence insulin-mediated glucose utilization (9) and in healthy adults can beneficially influence postprandial insulin action, glucose disposal, and fat oxidation (10). Clinical studies of glutamine (11), as well as showing a substantially reduced infection and pneumonia rate, demonstrate significant reduction of hyperglycemia and a significant reduction in the number of patients requiring insulin. As has been elegantly demonstrated, multiple-trauma patients (12) receiving parenteral glutamine show improved insulin sensitivity. This suggests that we cannot ignore exogenous glutamine provision, and that perhaps glutamine and tight glycemic control are complementary with each facilitating the other.

There is no doubt that tight glycemic control is not a simple therapy, but rather a complex integrated process of care that requires considerable attention to all details to be performed safely. Simply controlling glucose levels is not enough, because it masks the signs and therefore risks of overfeeding (13), which sadly appears endemic and cavalier with parenteral nutrition use (14). For tight glycemic control to work safely and effectively, making sure there is consistent nutrient delivery, neither overfeeding nor underfeeding, with attention to glucose and glutamine in the initial period may be the key.

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REFERENCES

1. Bongers T, Griffiths RD, McArdle A: Exogenous glutamine: The clinical evidence. *Crit Care Med* 2007; 35(Suppl 9):S545–S552
2. Meyer C, Woerle HJ, Gerich J: Paradoxical changes of glutamine release during hyperinsulinemia euglycemia and hypoglycaemia in humans: Further evidence for glucose–glutamine cycle. *Metabolism* 2004; 53: 1208–1214
3. Biolo G, De Cicco M, Lorenzon S, et al: Treating hyperglycaemic improves skeletal muscle protein metabolism in cancer patients after major surgery. *Crit Care Med* 2008; 36:1768–1775
4. Biolo G, Iscra F, Bosutti A, et al: Growth hormone decreases muscle glutamine production and stimulates protein synthesis in hypercatabolic patients. *Am J Physiol Endocrinol Metab* 2000; 279:E323–E332
5. Brunkhost FM, Engel C, Bloos F, et al: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; 358:125–139
6. Van den Berghe G, Wilmer A, Milants I, et al: Intensive insulin therapy in mixed medical/surgical intensive care unit: Benefits versus harm. *Diabetes* 2006; 55:3151–3159
7. Carlson G: Hunterian Lecture: Insulin resistance in human sepsis: Implications for the nutritional and metabolic care of the critically ill surgical patient. *Ann R Coll Surg Engl* 2004; 86:75–81
8. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449–461
9. Borel MJ, Williams PE, Jabbour K, et al: Parenteral glutamine infusion alters insulin-mediated glucose metabolism. *JPEN J Parenter Enteral Nutr* 1998; 22:280–285
10. Iwashita S, Mikus C, Baier S, et al: Glutamine supplementation increases postprandial energy expenditure and fat oxidation in humans. *JPEN J Parenter Enteral Nutr* 2006; 30:76–80
11. Déchelotte P, Hasselmann M, Cynober L, et al: L-alanyl-L-glutamine dipeptide–supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in critically ill patients: The French controlled, randomized, double-blind, multicenter study. *Crit Care Med* 2006; 34:598–604
12. Bakalar B, Duska F, Pachl J, et al: Parenterally administered dipeptide alanyl-glutamine prevents worsening of insulin sensitivity in multiple-trauma patients. *Crit Care Med* 2006; 34:381–386
13. Griffiths RD: Too much of a good thing: The curse of overfeeding. *Crit Care* 2007; 11:176
14. Dissanaike S, Shelton M, Warner K, et al: The risk for bloodstream infections is associated with increased parenteral caloric intake in patients receiving parenteral nutrition. *Crit Care* 2007; 11:R114

Hypothermia and coronary intervention after cardiac arrest: Thawing a cool relationship?*

Therapeutic hypothermia (TH) represents one of the most promising treatments for cardiac arrest victims since the introduction of defibrillation and cardiopulmonary resuscitation >50 yrs ago (1). Supported by two landmark randomized controlled trials (2, 3) as well as a number of smaller clinical and laboratory studies, current resuscitation guidelines recommend that comatose survivors of out-of-hospital ventricular fibrillation (VF) cardiac arrest be cooled to 32°C to 34°C for ≥12 hrs after return of spontaneous circulation (ROSC). This therapy has been shown to improve survival as well as neurologic outcomes among survivors. It is generally believed that the cooling process should be initiated as soon as possible after ROSC, based on animal investigations of postarrest TH (4, 5).

A large number of questions remain to be answered regarding the application of hypothermia, and such questions have contributed to the slow adoption of this crucial therapy (6). A number of hospitals elect to treat patients after cardiac arrest involving non-VF rhythms, such as asystole or pulseless electrical activity, or patients suffering in-hospital cardiac arrest (7); it remains to be definitively shown whether such patients benefit from cooling. In addition, the time-sensitivity of cooling initiation has not been clearly defined. This latter question is of great practical importance, as a number of post-VF survivors are found to have ST-segment elevation myocardial infarction (STEMI) requiring immediate percutaneous coronary intervention (PCI). Should cooling be started before PCI or can it wait until after this process, introducing a likely delay of several hours? Would hypothermia induction delay the time-sensitive intervention of PCI? TH carries a potential risk of increased bleeding; is it safe to perform PCI, with concomitant use of anticoagulants, such as heparin or glycoprotein IIb/IIIa inhibitors, while hypothermia is being induced? These concerns have created tension between two competing modalities that are essential treatments for survivors of cardiac arrest due to STEMI, which represents a sizable fraction of arrest patients.

The report by Dr. Wolfrum and colleagues (8) in this issue of *Critical Care Medicine* is a useful addition to the sparse literature addressing such practical questions of TH implementation. In the authors' observational study from one hospital, VF cardiac arrest patients achieving ROSC and found to have electrocardiographic evidence of STEMI were treated immediately with TH. They subsequently received PCI during hypothermia treatment. These patients were compared with historical controls, namely resuscitated STEMI patients who received PCI without cooling. The authors found that the process of TH implementation did not lengthen door-to-balloon times for PCI. They also found that while complications, such as bleeding or infection, appeared to be more common in the TH/PCI group, survival was not worse with the combination therapy; indeed, there was a trend toward improved survival. Finally, they showed that cooling can be quickly initiated with intravenous infusions of chilled saline and application of external ice packs, a cost-effective method that is practical for most settings.

While the investigation suffers from small sample size (n = 33 patients) and the likely confounders of patient selection bias and secular trend (door-to-balloon times may have improved over time independent of TH, especially given increased scrutiny of these patients by investigators), the finding that cooling and PCI are not incompatible lays important groundwork for collaboration between the emergency department and the catheterization laboratory. Emergency physicians and intensivists need not worry about delaying PCI to establish hypothermia induction if systems are appropriately established for rapid cooling. Although further study is required, cardiologists may be reassured that cooling can be initiated before PCI without significantly increased risks to the patient during catheterization. This work adds to several other publications that have shown the benefit of combined TH and PCI in postarrest patients (9–11); in one of these other studies, Sunde et al. (11) astutely suggest that cooling and PCI are necessary components of the larger suite of postresuscitation critical care, including careful glycemic control, neurologic monitoring, and appropriate hemodynamic support.

While a number of established protocols for hypothermia involve the use of chilled saline infusions or external ice packs, such as those described by Dr. Wolfrum and colleagues (8) (a compilation of hospital protocols can be found at http://www.med.upenn.edu/resuscitation/hypothermia/protocols.shtml), a note of caution should be given: These cooling methods depend on careful monitoring by operators, as there are no inherent thermostatic controls to prevent overcooling. Chilled saline and ice packs have been shown to be useful during cooling induction, but these are blunt and unwieldy tools that can overcool (12), with concomitant increased risk of bleeding and arrhythmia, and that fail to adequately maintain cooling over 12–24 hrs (13). Newer thermostatically controlled devices, while expensive, appear to induce and maintain cooling in a consistent fashion (14). Further investigations will be required to determine the utility of combined approaches, such as using chilled saline as a cooling "accelerant" in concert with a thermostatically controlled device.

*See also p. 1780.

Key Words: cardiac arrest; cardiopulmonary resuscitation; hypothermia; myocardial infarction; percutaneous coronary intervention

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Other important questions regarding PCI and cardiac arrest remain to be addressed. While PCI is clearly indicated for arrest survivors with STEMI, what about survivors of VF without STEMI? It is likely that a large fraction of VF patients have significant coronary disease or even acute coronary syndrome without electrocardiographic evidence of STEMI. Should the majority of post-VF arrest patients receive prompt coronary evaluation and possible intervention? In a provocative report, Grogaard et al. (15) describe successful PCI of two VF patients *before* ROSC, during active cardiopulmonary resuscitation. Should PCI be considered part of the Advanced Cardiovascular Life Support algorithm for VF patients? It is hoped that future investigations using cardiac arrest registry data and active clinical trial networks will elucidate further the boundaries and practical issues surrounding TH and postarrest care. These pragmatic advances in optimizing postarrest care will allow cardiac arrest patients to receive the best chance of returning home from the hospital alive and neurologically intact.

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REFERENCES

1. Safar PJ, Kochanek PM: Therapeutic hypothermia after cardiac arrest. *N Engl J Med* 2002; 346:612–613
2. Bernard SA, Gray TW, Buist MD, et al: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; 346:557–563
3. The Hypothermia After Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; 346:549–556
4. Kuboyama K, Safar P, Radovsky A, et al: Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: A prospective, randomized study. *Crit Care Med* 1993; 21: 1348–1358
5. Abella BS, Zhao D, Alvarado J, et al: Intra-arrest cooling improves outcomes in a murine cardiac arrest model. *Circulation* 2004; 109:2786–2791
6. Merchant RM, Soar J, Skrifvars MB, et al: Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest. *Crit Care Med* 2006; 34:1935–1940
7. Arrich J, European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group: Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med* 2007; 35:1041–1047
8. Wolfrum S, Pierau C, Radke PW, et al: Mild therapeutic hypothermia in patients after out-of-hospital cardiac arrest due to acute ST-segment elevation myocardial infarction undergoing immediate percutaneous coronary intervention. *Crit Care Med* 2008; 36:1780–1786
9. Hovdenes J, Laake JH, Aaberge L, et al: Therapeutic hypothermia after out-of-hospital cardiac arrest: Experiences with patients treated with percutaneous coronary intervention and cardiogenic shock. *Acta Anaesthesiol Scand* 2007; 51:137–142
10. Knafelj R, Radsel P, Ploj T, et al: Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. *Resuscitation* 2007; 74:227–234
11. Sunde K, Pytte M, Jacobsen D, et al: Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007; 73:29–39
12. Merchant RM, Abella BS, Peberdy MA, et al: Therapeutic hypothermia after cardiac arrest: Unintentional overcooling is common using ice packs and conventional cooling blankets. *Crit Care Med* 2006; 34:S490–S494
13. Kliegel A, Janata A, Wandaller C, et al: Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest. *Resuscitation* 2007; 73:46–53
14. Al-Senani FM, Graffagnino C, Grotta JC, et al: A prospective, multicenter pilot study to evaluate the feasibility and safety of using the CoolGard System and Icy catheter following cardiac arrest. *Resuscitation* 2004; 62: 143–150
15. Grogaard HK, Wik L, Eriksen M, et al: Continuous mechanical chest compressions during cardiac arrest to facilitate restoration of coronary circulation with percutaneous coronary intervention. *J Am Coll Cardiol* 2007; 50:1093–1094

Acute lung injury after blood product transfusion: Are the times changing?*

In this issue of *Critical Care Medicine*, Dr. Wright and colleagues (1) present a provocative study on the United Kingdom's experience with the frequency of acute lung injury (ALI) after ruptured abdominal aortic aneurysm repair. This study raises a number of interesting issues, including the gender selection of specific blood products and the pathogenesis of ALI in patients experiencing large amounts of blood loss.

Acute lung injury from blood transfusions has most commonly been referred to as *transfusion-related acute lung injury* (TRALI). TRALI is an underreported and underrecognized serious complication of transfusion therapy. TRALI is defined as acute lung injury that develops within 6 hrs (often within 30–60 mins) of a blood product transfusion (2). However, there is also a more general association with blood product transfusions and the development of ALI and an association with worse outcomes from ALI (3, 4). The exact mechanisms of these latter associations are unclear, but possibilities include cases of overt and subclinical TRALI, transfusion-related immunomodulation predisposing to infectious causes of ALI (5), misclassification of transfusion-associated circulatory overload cases (6), or even an immune priming effect of blood transfusions, predisposing the patient to a more robust reaction to a second, more common cause of ALI (i.e., neutrophil priming followed by pulmonary aspiration, pneumonia, sepsis).

***See also p. 1796.**

Key Words: acute lung injury; transfusion-related acute lung injury; fresh frozen plasma; aortic aneurysm; blood transfusion

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There has been a general association of TRALI with the transfusion of donor human leukocyte antigen (HLA) or neutrophil antibodies that recognize the cognate antigen in the recipient. Many of the donors implicated in TRALI cases are alloimmunized women who harbor HLA antibodies. The U.K. National Blood Service, though monitoring from its Serious Hazards of Transfusion (SHOT) database, and the American Red Cross have identified that donors from reported TRALI cases are commonly female and that the blood products implicated in these TRALI cases often contained HLA antibodies (7, 8). There appears to be a dose-dependent effect of the number of pregnancies on HLA alloimmunization (9), with >20% of multiparous women harboring HLA antibodies. Plasma from multiparous donors was even shown previously in a randomized, controlled trial to produce more hypoxemia in critically ill patients (10). Recently, it has been reported that intensive care patients who received high plasma volume blood products (fresh frozen plasma [FFP] or platelets) from female donors vs. male donors developed worsened oxygenation (11). Given the association of female donors with TRALI cases, the U.K. National Blood Service initiated in 2003 the diversion of female blood donations away from FFP and platelet concentrates. Is this regulation of blood products misogyny or prescient policy?

The current study by Wright and colleagues may yield valuable insight into transfusion policy and important clinical outcomes (1). The investigators capitalized on the U.K. policy change to ask the following important question: In a critically ill patient population requiring multiple blood product transfusions, will male-only FFP lead to a decreased frequency of postoperative ALI? The investigation was a retrospective, before/after observational trial at a single center that cares for a large number of patients with ruptured abdominal aortic aneurysms. Despite the overall limitations of the study design, interesting conclusions can be made due to the large sample size (211 patients over 7.5 yrs), reasonable matching of the two groups, and the before/after FFP policy. The authors should also be commended for using a sham study protocol to blind the data extractors and expert radiologists to the working hypothesis. The primary outcome was the frequency of ALI in the first 6 postoperative hours, a time course similar to clinical TRALI. Importantly, the patients receiving male-only FFP for resuscitation had a lower occurrence rate of postoperative ALI (21% vs. 36%). This was upheld by a multivariable logistic regression analysis controlling for potential confounding variables. The patients receiving male-only FFP also had a lower frequency of postoperative hypoxemia (Pao_2/Fio_2 <300 cutoff) and a trend for a higher mean Pao_2/Fio_2 ratio. Given the trial design, confounders that could bias the conclusions (and would not be controlled by the multivariate logistic regression analysis) include potential unmeasured imbalances in the two patient groups and the general improvement in intensive care over time. In addition, the contribution of male vs. female platelet transfusions was not specifically addressed in this study, although platelet transfusions (or the plasma fraction of the platelet pool) are directed to be male-only in the United Kingdom. Also, even though there was a lower frequency of ALI in the male-only FFP group, it is curious that the overall mortality in the female vs. male FFP groups was unchanged.

Nevertheless, these results are provocative for a protective effect of male-only FFP in the resuscitation of these surgical patients. So, what exactly was the cause of ALI in this patient population? As acknowledged by the authors, the pathogenesis of ALI in patients with large amounts of blood loss is probably multifactorial, with contributions from shock, ischemia-reperfusion of the lungs, and possibly the blood products themselves (TRALI). Importantly, only one case of postoperative ALI in this study was reported to the blood bank as possibly being transfusion-related, which highlights the underrecognition and underreporting of potential TRALI cases.

Data are still being collected in the United Kingdom on how the change in donor allocation of blood products has affected the frequency of TRALI, although there may be a trend for fewer referred cases (12). There are several other blood-banking policy initiatives that could potentially decrease the risk of TRALI (13). The American Association of Blood Banks has made similar recommendations to divert potentially alloimmunized donors from FFP and eventually from platelet donations (14). Time will tell if the occurrence rate of TRALI, or perhaps even ALI, will change with these new recommendations. Prospective clinical trials of ALI and TRALI that do not rely on passive reporting may be helpful in detecting changes in lung injury after blood product transfusion. For now, gender-specific blood product selection seems like a reasonable approach to improve the safety of allogeic blood transfusions.

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REFERENCES

1. Wright SE, Snowden CP, Athey SC, et al: Acute lung injury after ruptured abdominal aortic aneurysm repair: The effect of excluding donations from females from the production of fresh frozen plasma. *Crit Care Med* 2008; 36:1796–1802
2. Toy P, Popovsky MA, Abraham E, et al: Transfusion-related acute lung injury: Definition and review. *Crit Care Med* 2005; 33:721–726
3. Netzer G, Shah CV, Iwashyna TJ, et al: Association of RBC transfusion with mortality in patients with acute lung injury. *Chest* 2007; 132:1116–1123
4. Gong MN, Thompson BT, Williams P, et al: Clinical predictors of and mortality in acute respiratory distress syndrome: Potential role of red cell transfusion. *Crit Care Med* 2005; 33:1191–1198
5. Vamvakas EC: Pneumonia as a complication of blood product transfusion in the critically ill: Transfusion-related immunomodulation (TRIM). *Crit Care Med* 2006; 34:S151–S159
6. Skeate RC, Eastlund T: Distinguishing between transfusion related acute lung injury and transfusion associated circulatory overload. *Curr Opin Hematol* 2007; 14: 682–687
7. Stainsby D, Jones H, Asher D, et al: Serious hazards of transfusion: A decade of hemovigilance in the UK. *Transfus Med Rev* 2006; 20:273–282
8. Eder AF, Herron R, Strupp A, et al: Transfusion-related acute lung injury surveillance (2003–2005) and the potential impact of the selective use of plasma from male donors in the American Red Cross. *Transfusion* 2007; 47:599–607
9. Densmore TL, Goodnough LT, Ali S, et al: Prevalence of HLA sensitization in female apheresis donors. *Transfusion* 1999; 39: 103–106
10. Palfi M, Berg S, Ernerudh J, et al: A randomized controlled trial of transfusion-related acute lung injury: Is plasma from multiparous blood donors dangerous? *Transfusion* 2001; 41:317–322

11. Gajic O, Yilmaz M, Iscimen R, et al: Transfusion from male-only vs. female donors in critically ill recipients of high plasma volume components. *Crit Care Med* 2007; 35: 1645–1648
12. Serious Hazards of Transfusion Annual Report 2006. Available at: http://www.shotuk.org/SHOT%20report%202005.pdf. Accessed March 25, 2008
13. Mair DC, Hirschler N, Eastlund T: Blood donor and component management strategies to prevent transfusion-related acute lung injury (TRALI). *Crit Care Med* 2006; 34: S137–S143
14. Strong DM, Lipton KS: American Association of Blood Banks Association Bulletin 06–07. http://www.nibb.org/pdf/ab06–07.pdf. Accessed February 25, 2008

Is extravascular lung water measurement in acute respiratory distress syndrome worth the effort?*

Since it was first described by Lyman Brewer et al. (1) in World War II as "wet lung" and named by Ashbaugh et al. in 1967 (2), acute respiratory distress in adults or adult respiratory distress syndrome (ARDS) has remained a "syndrome" and not a specific disease that can be easily characterized or diagnosed. In 1994, the American-European Consensus Conference determined specific criteria based on chest radiograph (a gross exam), Pao_2/Fio_2 ratio (a gross physiologic variable), and absence of left atrial hypertension (to rule out cardiogenic edema) (3). The search for a more reliable, reproducible, and measurable variable continues.

In this issue of *Critical Care Medicine*, Dr. Berkowitz and colleagues (4) reintroduce the use of extravascular lung water (EVLW) to help in the diagnosis and treatment of the "noncardiogenic pulmonary edema" subset of acute lung injury. This is a technique first described using two indicators (indocyanine green dye and chilled saline) in 1951 by Newman et al (5). In the late 1970s and early 1980s, Elings et al. (6) perfected the technique and were able to use a single-indicator technique to estimate EVLW.

The twist that Dr. Berkowitz and colleagues (4) add to this technique is the use of predicted body weight (PBW) and adjusted body weight (AdjBW) based on height, instead of actual body weight or an index based on height and weight (body surface area).

The authors propose that indexing to PBW or AdjBW increases the proportion of ARDS patients with elevated EVLW (defined as >10 mL/kg) and may help differentiate them from patients without ARDS. By adjusting for PBW, the authors created a situation in which all but one of the ARDS patients had at least one elevated measurement of EVLW. The number of septic patients without clinical ARDS and an elevated EVLW decreased to 50%.

This is a novel approach, because all previous data, including animal data, have been expressed in mL/kg units. The original studies correlated EVLW via dye dilution technique to wet weight/dry weight lung changes in animals (6). The formulas were not ideal-weight adjusted. The formula for EVLW uses cardiac output, which can be indexed by body surface area as a means of eliminating differences in size. All the authors' hemodynamic measures (cardiac index, as shown in their Table 2) were indexed. Using a new measurement (AdjBW or PBW) that is not used to normalize other variables will need validation in future studies.

The use of EVLW as a tool to diagnose and treat ARDS has drawbacks: It requires a pulmonary artery catheter, a 5-Fr femoral artery catheter, and multiple measurements. EVLW should not be used at a single point in time but rather as a method to follow the physiologic changes of the capillary leak in ARDS and identify the point at which the leak improves. This is labor intensive at present. Other physiologic, less invasive techniques, such as pulmonary leak scans (7, 8), may be more useful to diagnose ARDS.

On the positive side, EVLW might be a better determinant of the onset and resolution of the acute phase of ARDS than the presently used criteria. Perhaps the patients who had sepsis and elevated EVLW but did not meet strict ARDS clinical criteria actually had subclinical ARDS. If this is the case, changing variables, such as adjusting weight, would not be necessary to make the patient fit the technology. Instead, we believe that the technology improves the diagnosis of the patient's disease. We need a better way to diagnose ARDS, and the article by Dr. Berkowitz and colleagues (4) reinforces our desire to continue to search for an objective measure to identify this entity.

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REFERENCES

1. Brewer LA, Burbank BB, Samson PC, et al: The wet lung in war casualties. *Ann Surg* 1946; 123:343–362
2. Ashbaugh DG, Bigelow DB, Petty TL, et al: Acute respiratory distress in adults. *Lancet* 1967; 2:319–323
3. Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS. *Am J Respir Crit Care Med* 1994; 149:818–824
4. Berkowitz DM, Danai PA, Eaton S, et al: Accurate characterization of extravascular lung water in acute respiratory distress syndrome. *Crit Care Med* 2008; 36:1803–1809
5. Newman EV, Merrell M, Genecin A, et al: The dye dilution method for describing the central circulation: An analysis of factors shaping the time-concentration curves. *Circulation* 1951; 4:735–742
6. Elings VB, Lewis FR: A single indicator technique to estimate extravascular lung water. *J Surg Res* 1982; 33:375–385
7. Spicer KM, Reines HD, Frey GD: Diagnosis of adult respiratory distress syndrome with Tc-99m human serum albumin and portable probe. *Crit Care Med* 1986; 14:669–676
8. Groenevald AB, Verheij: Extravascular lung water to blood volume ratios as measures of permeability in sepsis induced ALI/ARDS. *Intensive Care Med* 2006; 32:1315–1321

***See also p. 1803.**

Key Words: acute respiratory distress syndrome; extravascular lung water; noncardiogenic edema; sepsis

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Interleukin-6 plasma level in organ donors influences outcome for recipients of organ transplantation: Is it clinically relevant?*

Organ shortage is a well-known and well-substantiated fact. In the United States in 2007, >26,000 patients received organ transplantations from >13,000 donors. However, the number of patients waiting for an organ is still >98,000 (1). Based on the continuous increased gap between available organs for transplantation and patients waiting on the list for organ transplantation, in >70,000 patients (1), different strategies have been developed to increase organ transplantation. The application of "expanded donor" criteria, the use of organs that in the past were not considered for transplantation, has been successful for this purpose. Expanded donor criteria include use of donors of older age, donors who were exposed to hepatitis B and C viruses, grafts infiltrated with fat, non-heart-beating donors, donors with hypernatremia, or donors with multiple comorbidities (2). Another approach used to address the increased demand in organ transplantation has been the introduction of live donor transplantation, which in 2001 exceeded transplantation from cadaveric donors (1). However, live donor transplantation is not applicable to every solid organ, and not every program has the required expertise and infrastructure to run this type of program (3). Living donor transplant poses complex ethical challenges in part due to widespread altruistic donation in the United States and due to the monetary exchange known to take place in countries different from the United States (4).

In this issue of *Critical Care Medicine*, Dr. Murugan and colleagues (5) describe the correlation between cadaveric donor plasma level of interleukin (IL)-6 and the recipient's outcome after transplantation. It is known that brain death is accompanied by a "cytokine storm," which in turns creates donor instability and organ damage (6–8); however, this is the first study that correlates the plasma level of a cytokine in the donor to the recipient's 6-month hospital-free survival. The authors demonstrated with an elegant method that higher levels of IL-6 in the donor are associated with a worse outcome in the recipient. This article introduces a novel and somewhat substantiated approach to predict the recipient's outcome; nevertheless, the study raises many questions. First, it is difficult to introduce the measurement of cytokine plasma level on a routine basis as one of the screening tests to be performed on every cadaveric donor. Time and cost are two important factors that drive decisions of organ procurement organizations around the country, and a future feasibility study might help in determining if the benefit of this data can overcome the burden of time and cost involved with the acquisition of this information. Second, there is not an accepted standardized protocol for the maintenance of cadaveric donors in the United States. Therefore, what the authors observed in their cohort of donors and recipients might not reflect the implications of IL-6 plasma levels in the rest of the country. Third, there is conflicting evidence in the medical literature about the effect of IL-6 on different types of cells. As an example, Bin Gao (9) described a protective effect of this cytokine on hepatocytes. Finally, based on the evidence that corticosteroids decrease plasma levels of IL-6 (10), it might have been interesting to know the outcomes of the recipients of the eight donors who received corticosteroids.

Recently only a few articles about transplantation have caught my interest as much as this one. The results of this research, although difficult to apply clinically, open up a new way of assessing outcomes in organ transplantation, and while we are not at the point where organs will be declined from donors solely based on elevated IL-6 level, this may become an important factor in evaluating donors, especially in a time when expanded donors are increasingly evaluated and used in transplantation.

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REFERENCES

1. United Network for Organ Sharing Web site. Available at: http://www.unos.org. Accessed December 31, 2007
2. Cameron A, Busuttil RW: AASLD/ILTS transplant course: Is there an extended donor suitable for everyone? *Liver Transpl* 2005; 11(Suppl 1):S2–S5
3. Berg CL, Gillespie BW, Merion RM, et al: Improvement in survival associated with adult-to-adult living donor liver transplantation. *Gastroenterology* 2007; 133:1806–1813
4. Aulisio MP, DeVita M, Luebke D: Taking values seriously: Ethical challenges in organ donation and transplantation for critical care professionals. *Crit Care Med* 2007; 35:S95–S101
5. Murugan R, Venkataraman R, Wahed AS, et al: Increased plasma interleukin-6 in donors is associated with lower recipient hospital-free survival after cadaveric organ transplantation. *Crit Care Med* 2008; 36: 1810–1816
6. Nijboer WN, Schuurs TA, van der Hoeven JAB, et al: Effect of brain death on stress and inflammatory response in the human donor kidney. *Transplant Proc* 2005; 37:367–369
7. Avlonitis VS, Wigfield CH, Golledge HDR, et al: Early hemodynamic injury during donor brain death determines the severity of primary dysfunction after lung transplantation. *Am J Transplant* 2006; 7:83–90
8. Weiss S, Kotsch K, Francuski M, et al: Brain death activates donor organs and is associated with a worse I/R injury after liver transplantation. *Am J Transplant* 2007; 7:1584–1593
9. Gao B: Therapeutic potential of interleukin-6 in preventing obesity- and alcohol-associated fatty liver transplant failure. *Alcohol* 2004; 34:59–65
10. Kuecuek O, Mantouvalou L, Klemz R, et al: Significant reduction of proinflammatory cytokines by treatment of the brain-dead donor. *Transplant Proc* 2005; 37:387–388

*See also p. 1810.

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Epidemiology on intra-abdominal hypertension: An urgent call for multicenter trials*

In this issue of *Critical Care Medicine*, Dr. Vidal and colleagues (1) report the results of a study entitled "Incidence and Clinical Effects of Intra-abdominal Hypertension in Critically Ill Patients." On first sight, it looks as if this study just repeats the previously performed multicenter studies on prevalence and incidence of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) (2, 3). Is this really the case? Dr. Vidal and colleagues (1) collected prospective data on 83 critically ill patients in a sample of 153. They found that IAH (sustained increase in intra-abdominal pressure [IAP] of ≥12 mm Hg) was present at admission in 23–31% of cases (depending on whether mean or maximal IAP values were used), whereas 12% developed ACS. Primary IAH was seen in 32% of patients with IAH. Patients with IAH were sicker, had more organ failure, and a higher hospital mortality (53% vs. 27%) than patients with a normal IAP. Risk factors for IAH were fluid resuscitation, acidosis, hypotension, ileus, mechanical ventilation, and acute respiratory distress syndrome. The most important message is that in critically ill patients with capillary leak or sepsis, futile resuscitation may lead to positive daily and cumulative fluid balance, IAH, and subsequent morbidity (organ failure) and mortality. Therefore, intensive care unit (ICU) physicians no longer have an excuse not to obtain a baseline IAP value in patients with two or more risk factors for IAH (4, 5).

This epidemiologic study has a lot of similarities with previous multicenter studies, in which multiple logistic regression analysis showed that the occurrence of IAH during the first week of ICU stay is an independent outcome predictor, whereas the mean IAP at admission is not. In the present study, Dr. Vidal and colleagues (1) showed that maximal IAP was also identified as an independent predictor of mortality. This is a new finding, as is the association of IAH with the Sequential Organ Failure Assessment score, and more particular, renal and respiratory subscores, abdominal perfusion pressure (APP = mean arterial pressure − IAP), and the filtration gradient (FG = mean arterial pressure − 2 × IAP). The authors are the first to have successfully incorporated the new consensus definitions recently published by the World Society of the Abdominal Compartment Syndrome (WSACS, www.wsacs.org), confirming the results from previous studies (4, 6, 7). They also looked at differences in the prognostic ability of IAP-mean vs. IAPmax and performed the proper analysis identifying thresholds for IAP and APP with receiver operating characteristic curves. The authors found no significant difference between mean or maximal IAP at admission (days 1 and 2) between survivors and nonsurvivors, whereas APP was significantly lower in nonsurvivors already from day 2 onwards, suggesting that APP could be a better outcome predictor or resuscitation target than IAP. This is an interesting point that could have been stressed more because it has only been studied retrospectively so far (8). Another good point is that prognostic markers were not based on single IAP measurements but on the mean of two IAP measurements with 3-min intervals, so as to rule out possible measurement outliers (7). The study also tackles the issue of the ideal frequency of IAP monitoring. The article stresses again the importance of measuring IAP in the ICU on a daily basis and the implications IAH and ACS can have on mortality.

To play the devil's advocate, one could argue that the questions that Dr. Vidal and colleagues (1) tried to answer have already been addressed. From the introduction, it is unclear why yet another similar study is needed. Patients with IAH are sicker than those without, and this is associated with morbidity and mortality. Although this is certainly true, it is nothing new: reading the conclusions about the relationship between IAH/ACS and morbidity and mortality brings to mind a number of similar articles that have reached the same conclusions again and again. Open questions related to risk stratification, early diagnosis, and innovative preventive or treatment methods were not addressed in this article.

Does this study really add to the growing body of evidence showing that increased IAP has a negative effect on organ function and patient outcome? This question is difficult to answer because data on only 83 patients can hardly be extrapolated to the general ICU population, especially because 60 patients (or 39.2%) of the initial sample were excluded from the final analysis. The authors conducted a prospective 9-month study but only included 83 patients? How many beds has the ICU under study? What was the body mass index in the study population? Were obese patients excluded? Was this really a cohort study or a random sample? Epidemiologic conclusions can only be drawn if the collected data are complete and of good quality; was this the case? Furthermore, the results reported are difficult to interpret because Table 1 contains data collected at admission and during the ICU stay (64% of patients developed IAH but only 31% presented with IAH at admission). The authors could also have done a better job on other points, as we will demonstrate below.

Dr. Vidal and colleagues (1) used the old-fashioned Kron technique for IAP measurement, which is probably inferior to other techniques. Recently, standardized IAP measurement kits to avoid inter-observer and intra-observer variability

***See also p. 1823.**

Key Words: abdominal pressure; abdominal compartment; epidemiology; risk factors

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have become available, such as the Foley-Manometer (www.holtech-medical.com), the AbViser valve (www.wolfetory.com), or even a fully automated continuous technique by means of a balloon-tipped nasogastric tube (www.spiegelberg.de or www.pulsion.com) (9–14). It is important that a good IAP measurement technique is used for study purposes because definitions of IAH and ACS (and thus the epidemiologic prevalence and incidence data) stand or fall with the accuracy and reproducibility of the method used.

Another major drawback is that a volume of 50 mL was used to prime the bladder before IAP measurement, whereas the World Society of the Abdominal Compartment Syndrome advocates the instillation of a maximal amount of 25 mL (6, 7). Recent studies have shown that instilling even a relatively small volume into the bladder may increase intrinsic intravesical pressure 1 to 2 mm Hg. With a mean IAP of around 10 mm Hg, this would produce a 10–20% error (15–17). The authors also used the wrong zero reference point, namely, the symphysis pubis. The consensus definitions advocate the use of the midaxillary line at the level of the iliac crest (6). This has recently been studied in a multicenter fashion (18, 19). The authors state the number of patients who were mechanically ventilated but failed to mention if they were under sedation or curarization, which can also affect baseline IAP values.

Finally, the authors looked at the effect of IAH on organ function and found an inverse relation with renal function (as expressed by the Sequential Organ Failure Assessment renal subscore and filtration gradient). However, it is unfortunate that they did not look at the acute kidney injury and RIFLE criteria for their study population, which would have given extra and new value to the results (20).

The data presented in this issue of *Critical Care Medicine* may raise even more questions than they answer, and this may also hold true for the majority of the available literature data available because of the previous lack of standardized IAP pressure measurement methods and good consensus definitions.

Currently, no multicenter, randomized, interventional, controlled clinical trial is available to tackle the question of whether an increase in IAP is a phenomenon or an epiphenomenon and whether any intervention to normalize IAP or APP will eventually affect patient outcome. Until that study exists, there will always be believers and nonbelievers (21).

The development of a management algorithm for IAH/ACS compares with the multifaceted approach emerging for early goal-directed therapy in sepsis (22). Indeed, these two syndromes overlap, and the 2004 Surviving Sepsis Campaign guidelines call for careful fluid management to prevent IAH (23). To survive sepsis, consensus campaigns have called for vigilance in diagnosis, careful monitoring during goal-directed resuscitation, and multifaceted early interventions, including antibiotics, vasopressors, inotropes, steroids, activated protein C, and tight glucose control, along with other general ICU standards of care (24–26). With these bundles of evidence-based recommendations, small supportive studies have been completed and large multicenter trials are underway (27). Clinicians and researchers interested in IAH/ACS must tread the same path. In many ways, we have already started down this path (21). In general, we understand who is at risk, how to monitor them, and we have numerous preventive and therapeutic interventions for IAH/ACS (4, 7). Similar to early goal-directed therapy in sepsis, few of these interventions are based on level 1 evidence (4). However, at least some evidence exists for many of these therapies, thus providing us with a start for an IAH/ACS therapeutic bundle. The urgency for progress is real. The prevalence and incidence data for IAH/ACS demonstrate that IAH and ACS are real and do exist, not only in surgical, trauma, or burn patients, but also in patients admitted to a medical ICU. The prevalence and incidence data show that at a minimum, IAH and sepsis go hand in hand (2, 3). It is also not unrealistic to suggest that IAH/ACS may affect an even greater number of ICU patients than those affected by sepsis (2).

Considerable progress has been made over the past decade, but significant work still needs to be done. We must study and learn from the past and, at the same time, proactively "invent" the future. As aptly described by Ivatury and Sugerman (28), IAH/ACS is ". . . a clinical entity that had been ignored for far too long . . . . . the mystery of IAH and ACS continues to unfold, transgressing the boundaries of acute and chronic illness and medical and surgical specialities." Recently, Sugrue (29) asked for practice guidelines, and Malbrain (30) questioned whether it would be wise not to think about IAP. The future of patients with IAH and ACS is in our hands, and the results of the present study and other recent multicenter studies confirm the importance of IAH and ACS on patient outcome (1–3, 31). For those who carry the mandate to future IAH/ACS research, the path ahead is clear. Using available evidence, we must develop an IAH/ACS therapeutic bundle and apply it in a multicenter, prospective, outcome trial.

We invite others to join the World Society of the Abdominal Compartment Syndrome, to adhere to the consensus definitions posted at the Web site, and to submit some prospective data for the next world congress (www.wcacs.org) to be held in Dublin, Ireland, June 24–27, 2009.

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REFERENCES

1. Vidal M, Ruiz Weisser J, Gonzalez F, et al: Incidence and clinical effects of intra-abdominal hypertension in critically ill patients. *Crit Care Med* 2008; 36:1823–1831
2. Malbrain ML, Chiumello D, Pelosi P, et al: Prevalence of intra-abdominal hypertension in critically ill patients: A multicentre epidemiological study. *Intensive Care Med* 2004; 30:822–829
3. Malbrain ML, Chiumello D, Pelosi P, et al: Incidence and prognosis of intra-abdominal hypertension in a mixed population of critically ill patients: A multiple-center epidemiological study. *Crit Care Med* 2005; 33:315–322
4. Cheatham ML, Malbrain ML, Kirkpatrick A, et al: Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome: II. Recommendations. *Intensive Care Med* 2007; 33:951–962
5. Malbrain ML: You don't have any excuse, just start measuring abdominal pressure and act upon it! *Minerva Anestesiol* 2008; 74:1–2
6. Malbrain ML, Cheatham ML, Kirkpatrick A, et al: Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome: I. Definitions. *Intensive Care Med* 2006; 32:1722–1732
7. Malbrain ML, De laet I, Cheatham M: Consensus conference definitions and recommendations on intra-abdominal hypertension (IAH) and the abdominal compartment

syndrome (ACS): The long road to the final publications, how did we get there? *Acta Clin Belg Suppl* 2007; 62:44–59
8. Cheatham ML, White MW, Sagraves SG, et al: Abdominal perfusion pressure: A superior parameter in the assessment of intra-abdominal hypertension. *J Trauma* 2000; 49:621–626
9. De Potter TJ, Dits H, Malbrain ML: Intra- and interobserver variability during in vitro validation of two novel methods for intra-abdominal pressure monitoring. *Intensive Care Med* 2005; 31:747–751
10. Balogh Z, De Waele JJ, Malbrain ML: Continuous intra-abdominal pressure monitoring. *Acta Clin Belg Suppl* 2007; 62:26–32
11. De Waele JJ, De laet I, Malbrain ML: Rational intra-abdominal pressure monitoring: How to do it? *Acta Clin Belg Suppl* 2007; 62:16–25
12. Malbrain ML, De laet I, De Waele JJ: Continuous intra-abdominal pressure monitoring: This is the way to go! *Int J Clin Pract* 2008; 62:359–362
13. Malbrain ML, De Laet I, Viaene D, et al: In vitro validation of a novel method for continuous intra-abdominal pressure monitoring. *Intensive Care Med* 2008; 34:740–745
14. Malbrain ML: Different techniques to measure intra-abdominal pressure (IAP): Time for a critical re-appraisal. *Intensive Care Med* 2004; 30:357–371
15. De Waele J, Pletinckx P, Blot S, et al: Saline volume in transvesical intra-abdominal pressure measurement: Enough is enough. *Intensive Care Med* 2006; 32:455–459
16. Malbrain ML, Deeren DH: Effect of bladder volume on measured intravesical pressure: A prospective cohort study. *Crit Care* 2006; 10:R98
17. Chiumello D, Tallarini F, Chierichetti M, et al: The effect of different volumes and temperatures of saline on the bladder pressure measurement in critically ill patients. *Crit Care* 2007; 11:R82
18. Cheatham ML, De Waele J, De Keulenaer B, et al: The effect of body position on intra-abdominal pressure measurement: A multicenter analysis. *Acta Clin Belg Suppl* 2007; 62:246
19. De Waele J, Cheatham ML, De Keulenaer B, et al: The optimal zero reference transducer position for intra-abdominal pressure measurement: A multicenter analysis. *Acta Clin Belg Suppl* 2007; 62:247
20. Bellomo R, Kellum JA, Ronco C: Defining and classifying acute renal failure: From advocacy to consensus and validation of the RIFLE criteria. *Intensive Care Med* 2007; 33: 409–413
21. Kimball EJ, Kim W, Cheatham ML, et al: Clinical awareness of intra-abdominal hypertension and abdominal compartment syndrome in 2007. *Acta Clin Belg Suppl* 2007; 62:66–73
22. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
23. Dellinger RP, Carlet JM, Masur H, et al: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Intensive Care Med* 2004; 30:536–555
24. Annane D, Sebille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288: 862–871
25. van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; 345: 1359–1367
26. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699–709
27. Otero RM, Nguyen HB, Huang DT, et al: Early goal-directed therapy in severe sepsis and septic shock revisited: Concepts, controversies, and contemporary findings. *Chest* 2006; 130:1579–1595
28. Ivatury RR, Sugerman HJ: Abdominal compartment syndrome: A century later, isn't it time to pay attention? *Crit Care Med* 2000; 28:2137–2138
29. Sugrue M: Intra-abdominal pressure: Time for clinical practice guidelines? *Intensive Care Med* 2002; 28:389–391
30. Malbrain ML: Is it wise not to think about intra-abdominal hypertension in the ICU? *Curr Opin Crit Care* 2004; 10:132–145
31. Malbrain ML: Incidence of intra-abdominal hypertension in the intensive care unit: For the Critically Ill and Abdominal Hypertension (CIAH) Study Group. *Crit Care Med* 2005; 33:2150–2153

The ups and downs of a good idea: Phased chest and abdominal compression–decompression cardiopulmonary resuscitation in cardiac arrest*

Approximately 166,000 out-of-hospital cardiac arrests occur annually in North America, with a median reported survival to discharge of 6.4% (1, 2). Despite advances in the delivery of care and innovations in cardiopulmonary resuscitation (CPR), prognosis remains poor. Improving outcome from sudden cardiac arrest is a healthcare urgency, but clinical human research is very difficult secondary to ethical concerns over informed consent and poor funding (3). Innovations to improve vital organ blood flow were introduced into the 2005 American Heart Association CPR guidelines, which attempted to maximize coronary and cerebral perfusion pressures and minimize their loss from excessive ventilation during the hemodynamic phase of cardiac arrest (4, 5). Nevertheless, disappointment with outcomes from conventional CPR has prompted researchers to investigate alternative methods to improve vital organ blood flow and postresuscitation survival.

Active phased compression–decompression resuscitation (APCDR) is an alternative to standard CPR that traces its origins from computer-based analog modeling designed to optimize coronary and cerebral perfusion (6). It is performed by a hand-held seesaw-like device that delivers coincident positive intrathoracic pressure and abdominal decompression, followed by negative intrathoracic pressure and abdominal compression. During the chest compression phase, the positive intrathoracic pressure is thought to augment cerebral perfusion pressure with coincident decompression of the abdomen, which reduces ventricular afterload. Active chest decompression with abdominal compression increases venous

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return and augments coronary perfusion pressure (7). Adequate coronary and cerebral perfusion pressures after prolonged cardiac arrest but before defibrillation are the main determinants of survivability and neurologic outcome (8).

Early animal studies with APCDR suggested improved survival with increased coronary and cerebral perfusion pressures when compared with standard CPR. Tang et al. (9) induced ventricular fibrillation in a porcine model of cardiac arrest. Animals were randomized to either Lifestick (Datascope Corporation, Fairfield, NJ) APCDR or standard CPR. Significant improvements in coronary perfusion pressure, aortic pressure, end-tidal CO_2, 48-hr survival, and neurologic recovery over standard CPR were demonstrated. Wenzel et al. (10) performed a confirmatory study of the hemodynamic effects of Lifestick APCDR relative to standard CPR, also in the porcine model. Lifestick APCDR animals again demonstrated improved coronary and cerebral perfusion, mean arterial pressure, and end-tidal CO_2 compared with standard CPR. More significantly, Wenzel et al. (10) were able show that the survival and neurologic improvements from earlier animal studies were associated with improved coronary and cerebral perfusion pressures compared with standard CPR.

Arntz et al. (11) performed a prospective, blinded feasibility and safety study of 50 patients randomized to Lifestick APCDR (n = 24) or conventional CPR (n = 26) in patients with nontraumatic out-of-hospital cardiac arrest. Although no improvement in outcome was demonstrated, Lifestick APCDR demonstrated no significant chest or abdominal complications. Rescue personnel considered application of the Lifestick device practical and relatively easy to fixate to the chest. Notably absent was any objective hemodynamic assessment of Lifestick or conventional CPR. Overall, Lifestick application seemed feasible and safe, but the small sample size and variability in presenting rhythms between the groups limited any assessment of hemodynamic efficacy.

In the current issue of *Critical Care Medicine*, Dr. Havel and colleagues (12) examine the safety, feasibility, and hemodynamic consequences of Lifestick APCDR compared with mechanical chest compression (Thumper device, Michigan Instruments, Grand Rapids, MI) in a prospective, case-control, clinical study of prolonged cardiac arrest.

Caveats that are appropriately noted by the authors at the outset are that the experimental and control groups were not randomized, physicians were not blinded to the interventions, and the small sample sizes (Lifestick, 20; Thumper, 11) preclude any definitive commentary on efficacy or safety. Nevertheless, the article by Dr. Havel and colleagues (12) provides interesting and valuable commentary on the hemodynamic and echocardiographic changes associated with APCDR in humans.

In five patients, direct measurements revealed increased coronary perfusion pressures and, in 15 patients, increases in end-tidal CO_2 during Lifestick APCDR relative to mechanical precordial compression, supportive of preserved and possibly improved coronary perfusion pressures and cardiac output.

Transesophageal echocardiography was performed in a limited number of Lifestick and Thumper patients, revealing that likely both thoracic and cardiac pump mechanisms are mutually operative to maintain blood flow during CPR (13).

At this time, Lifestick resuscitation cannot be recommended in cardiac arrest because of the lack of any objective benefit and limited human studies. Nevertheless, Dr. Havel and colleagues (12) should be congratulated on moving forward an adjunctive resuscitation technique that remains promising. Future studies should be directed to further clarify the hemodynamic consequences of Lifestick resuscitation earlier in cardiac arrest, with higher compression and lower ventilation ratios to be consistent with current American Heart Association CPR guidelines.

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REFERENCES

1. Rea TD, Eisenberg MS, Sinibaldi G, et al: Incidence of EMS-treated out of hospital cardiac arrest in the United States. *Resuscitation* 2004; 63:17–24
2. Nichol G, Stiell IG, Laupacis A, et al: A cumulative meta-analysis of the effectiveness of defibrillator-capable emergency medical services for victims of out-of-hospital cardiac arrest. *Ann Emerg Med* 1999; 34:517–525
3. Halperin H, Paradis N, Mosesso V, et al: Recommendations for implementation of community consultation and public disclosure under the Food and Drug Administration's "Exception From Informed Consent Requirements for Emergency Research": A special report from the American Heart Association Emergency Cardiovascular Committee and Council on Cardiopulmonary, Perioperative and Critical Care. Endorsed by the American College of Emergency Physicians and the Society for Academic Emergency Medicine. *Circulation* 2007; 116:1855–1863
4. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005; 112(Suppl 1)IV-1–IV-211
5. Ewy GA: Cardiocerebral resuscitation: The new cardiopulmonary resuscitation. *Circulation* 2005; 111:2134–2142
6. Babbs CF, Weaver C, Ralston S, et al: Cardiac, thoracic, and abdominal pump mechanisms in cardiopulmonary resuscitation: Studies in an electrical model of the circulation. *Am J Emerg Med* 1984; 2:299–308
7. Babbs CF: CPR techniques that combine chest and abdominal compression and decompression: Hemodynamic insights from a spreadsheet model. *Circulation* 1999; 100:2146–2152
8. Ewy GA, Kern KB, Sanders AB, et al: Cardiocerebral resuscitation for cardiac arrest. *Am J Med* 2006; 119:6–9
9. Tang W, Weil MH, Schock RB, et al: Phased chest and abdominal compression-decompression: A new option for cardiopulmonary resuscitation. *Circulation* 1997; 95:1335–1340
10. Wenzel V, Lindner KH, Prengel AW, et al: Effect of phased chest and abdominal compression-decompression cardiopulmonary resuscitation on myocardial and cerebral blood flow in pigs. *Crit Care Med* 2000; 28: 1107–1112
11. Arntz HR, Agrawal R, Richter H, et al: Phased chest and abdominal compression-decompression versus conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest. *Circulation* 2001; 104:768–772
12. Havel C, Berzlanovich A, Sterz F, et al: Safety, feasibility, and hemodynamic and blood flow effects of active compression–decompression of thorax and abdomen in patients with cardiac arrest. *Crit Care Med* 2008; 36:1832–1837
13. Andreka P, Frenneaux MP: Haemodynamics of cardiac arrest and resuscitation. *Curr Opin Crit Care* 2006; 12:198–203

Gender differences after hemorrhagic shock from blunt trauma: What is helping the women?*

A great debate has been surfacing in intensive care units in recent years. At stake in this debate is the validity of the notion that gender-differentiated outcomes are unequal for similar disease entities. The majority of investigators interested in this topic seem to think that women appear more physiologically positioned to withstand a septic challenge. This stance is more clearly defensible for female rats than female humans, as human studies have yielded conflicting gender-stratified results, depending on the population and disease studied (1).

A less-debated aspect of the argument is the mechanism by which women may theoretically gain their advantage over their male counterparts in the aforesaid septic challenge. The exact mechanism for the protection is unclear, but the stance by the pro-female advocates has always been initiated by the most fundamental of the difference between the sexes: the female sex hormones. They reason that because female sex hormones in the studied populations are the only discernible differences among the groups, these entities must contain the elixir that staves off the woes of sepsis. Which sex hormones is less clear, but what else could women have in sufficient quantities over men to create a physiologic difference in a given clinical setting?

The recent study by Dr. Sperry and colleagues (2) in this issue of *Critical Care Medicine* gives some much needed support for the first debate of whether any gender-differentiated outcomes between men and women exist (they do). However, in attempting to authenticate the purported superiority of their female patients, the authors have also thrown the proverbial monkey wrench into the basis for this advantage. These investigators found that adult female patients after severe blunt trauma complicated by hemorrhagic shock fared better in regard to multiple organ failure and nosocomial infection rates. However, these advantages occurred in both premenopausal and postmenopausal women, indicating that the effects of sex hormones were unlikely to be a valid mechanism.

On further analysis of these intriguing results, several observations require rumination. First, this retrospective study, gleaned from the data of The Inflammation and Host Response to Injury grant, was not designed to solve the gender-protection question. Next, the reader sees that questions arise concerning the baseline equality between the male and female groups. The Injury Severity Scores for men and women are identical, but the initial resuscitation and initial Acute Physiology and Chronic Health Evaluation II scores differ significantly between the groups. The transfusion requirements for the initial 12 hrs also differ between the two groups, but not significantly, and the authors did not report their 24- or 48-hr transfusion requirements. In addition, the men in this study did have a higher rate of alcoholism compared with their female counterparts. Most importantly, however, the need for initial laparotomy and thoracotomy *did* differ between the two groups, implying that the men were more severely injured than their female counterparts, even if this feature was not demonstrated by the Injury Severity Scores.

Whether these aforementioned observations indeed explain the subsequent differences in nosocomial infection or organ dysfunction rates in men over women is a matter for conjecture. Plausibility and common sense would claim that the summation of these baseline differences, rather than sex hormones or unidentified elusive female-specific factors, would bear the burden for creating the adverse secondary outcomes for the male patients reported herein. Nonetheless, in this retrospective blunt trauma study evaluating the host response to hemorrhagic shock, Dr. Sperry and colleagues (2) have contributed more valuable data for all sides of the ignited outcome debates regarding gender and sepsis.

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REFERENCES

1. Eachempati SR, Hydo L, Barie P: Gender-based differences in outcome for septic patients admitted to the surgical intensive care unit. *Arch Surg* 1999; 134:1342–1347
2. Sperry JL, Nathens AB, Frankel HL, et al: Characterization of the gender dimorphism after injury and hemorrhagic shock: Are hormonal differences responsible? *Crit Care Med* 2008; 36:1838–1845

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Critical illness myopathy: Deeper insights*

Acutely acquired neuromuscular dysfunction occurs in >50% of intensive care unit patients with sepsis for a duration of >1 wk (1). Often, this involves neuropathy and myopathy together, but these entities can occur independently in many patients (2, 3). The pathogenesis of critical illness neuropathy and myopathy is not known, but recent research is providing promising insights.

In this issue of *Critical Care Medicine*, Dr. Rossignol and colleagues (4) report their study of skeletal muscle taken from septic rats (cecal perforation model) in which they found reduced force of contraction but faster contraction and relaxation times compared with controls. Furthermore, they found that the muscle fatigued more quickly, despite reaching maximal tetanic force more quickly. In examining the molecular mechanisms underlying these phenomena, they discovered an increase in the ryanodine receptor expression, which related to increased messenger RNA activity responsible for its synthesis. As a separate issue, they observed increased sensitivity to the neuromuscular blocking agent atracurium. What does it all mean?

The increased sensitivity to neuromuscular blockade suggests a problem with neuromuscular transmission (in the sense of reduced acetylcholine from nerve terminals or a decrease in receptors at the endplate), but this has never been demonstrated in critical illness neuromyopathy. Indeed, the problem seems to be dissociable from neuropathy. It could well relate to the diminished activity of sodium channels, including the endplate region, which Dr. Rossignol and colleagues have also described (5).

The most intriguing aspect of this article is the potential insight into altered cytoplasmic ionized calcium homeostasis in skeletal muscle, which may play a role in some of the myopathies of critical illness (6, 7). To activate muscle contraction, ionized calcium must be released from the sarcoplasmic reticulum within the muscle cells. Sarcoplasmic reticulum calcium release (ion) channels are governed by the large macromolecular complex known as the *ryanodine receptor* (RyR1). The activity of the receptor, and therefore, the release of ionized calcium into the cytoplasm, is affected by numerous factors that phosphorylate its regulatory subunits or nitrosylate-free sulfhydryl groups on its cysteine residues (8). These include calmodulin, calstabin-1, and others that can, in turn, be influenced by various "stressors," including catecholamines, ischemia, acidosis, and possibly, inflammatory mediators. Excessive cytoplasmic calcium can cause much mischief within the muscle cell, including oxidation of myofibrillar proteins (9). This might explain the observations of Dr. Rossignol and colleagues (4). The large muscle slow-twitch fibers are higher in oxidative reserves than the type 2, rapid-twitch fibers; selective dysfunction or loss of the larger, slow-twitch fibers might then allow for the more rapid onset, but less tetanic strength, of contraction that they observed.

Further research is clearly needed to substantiate these findings and to explore the mechanisms in more detail. Dr. Rossignol and colleagues (4) are to be commended for their continued pursuit of muscular weakness in critically ill/sepsis models.

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REFERENCES

1. Khan J, Harrison TB, Rich MM, et al: Early development of critical illness myopathy and neuropathy in patients with severe sepsis. *Neurology* 2006; 67:1421–1425
2. Visser LH: Critical illness polyneuropathy and myopathy: Clinical features, risk factors and prognosis. *Eur J Neurol* 2006; 13:1203–1212
3. Bolton CF: Neuromuscular manifestations of critical illness. *Muscle Nerve* 2005; 32: 140–163
4. Rossignol B, Gueret G, Pennec JP, et al: Effects of chronic sepsis on contractile properties of fast-twitch muscle in an experimental model of critical illness neuromyopathy in the rat. *Crit Care Med* 2008; 36:1855–1863
5. Rossignol B, Gueret G, Pennec JP, et al: Effects of chronic sepsis on the voltage-gated sodium channel in isolated rat muscle fibers. *Crit Care Med* 2007; 35:351–357
6. Larsson L: Experimental animal models of muscle wasting in intensive care unit patients. *Crit Care Med* 2007; 35(9 Suppl):S484–S487
7. Schweickert WD, Hall J: ICU-acquired weakness. *Chest* 2007; 131:1273–1274
8. Bellinger AM, Mongillo M, Marks AR: Stressed out: The skeletal muscle ryanodine receptor as a target of stress. *J Clin Invest* 2008; 118: 445–453
9. Dalla Libera L, Ravara B, Gobbo V, et al: Skeletal muscle myofibrillar protein oxidation in heart failure and the protective effect of Carvedilol. *J Mol Cell Cardiol* 2005; 38:803–807

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A treatment worth its salt?*

A new era in the treatment of shock began with the 1980 report that hypertonic (7.5%) saline (HS) could resuscitate dogs in hemorrhagic shock (1). This study sparked numerous investigations into the benefits of HS either alone or with dextran or hetastarch to resuscitate experimental animals from hemorrhagic hypotension (cited in Ref. 2) and led to several clinical trials in patients with traumatic hypotension (3–5). Other studies investigated the efficacy of these fluids in traumatic brain injury or intracranial hemorrhage (5, 6). These studies provided solid evidence for the physiologic effects of hypertonic fluids on expanding plasma volume and improving cardiac output, regional blood flows, and the microcirculation.

Sprinkled among the earlier studies were a few from the 1980s and early 1990s that investigated whether the hemodynamic effects of HS would be useful as supportive therapy in the treatment of sepsis in experimental animals (7–9). However, in the past decade recognition of possible immunomodulating effects of HS has opened new possibilities that the benefits of HS could extend beyond its hemodynamic effects. Hypertonicity was shown to inhibit leukocyte adherence and activation. Subsequent to improved microcirculatory flow, use of hypertonic fluids was associated with a reduction of neutrophils rolling and sticking to the endothelial cells of blood vessels (10–12). In addition, in isolated neutrophils from healthy human volunteers, it was observed that HS alone or with dextran inhibited their respiratory burst and decreased β_2-integrin expression, superoxide production, and elastase release, but only if HS was added before neutrophils became primed or activated (10–14). However, if HS was added after neutrophil priming or activation, superoxide production and elastase release were actually enhanced (13). Immunomodulatory effects of HS have since been investigated in animal models of hemorrhage. Pascual et al. (12) observed that infusion of HS reduced neutrophil adherence to pulmonary endothelium and reduced lung myeloperoxidase activity compared with infusion of lactated Ringer's solution. These authors also reported that the susceptibility to sepsis after hemorrhage was diminished, possibly due to inhibition of sepsis-induced P-selectin expression or to bacterial challenge. Taken together, these data suggested that modulation of immune function by HS could possibly reduce secondary complications of infection and that initial or early hypertonic saline resuscitation would be of greater benefit than infusion after administration of conventional fluids. A similar conclusion that hypertonic fluids should be the initial resuscitation fluid was also drawn from the hemorrhage studies in experimental animals (2).

In this issue of *Critical Care Medicine*, Dr. Shih and colleagues (15) present a well-designed, comprehensive investigation of the use of HS vs. normal saline in a peritonitis-induced (cecal ligation and puncture [CLP]) septic shock model in rats. HS was infused 3 hrs after CLP. The investigators monitored standard hemodynamics and the systemic pressor response to norepinephrine over an 18-hr period. In addition, they measured blood glucose, indices of hepatic and renal function, lactate dehydrogenase as a general index of cellular injury, and plasma interleukin-1β and nitric oxide levels. Upon euthanasia, thoracic aorta, lung, liver, and kidney were assayed for superoxide levels and lung and liver for expression of inducible nitric oxide synthase. Histology was performed on lung, liver, kidney, and aorta for evidence of neutrophil infiltration, and survival rates at 9 and 18 hrs were quantified. The investigators observed that HS infusion maintained mean arterial pressure in CLP rats with no effect on heart rate. In addition, HS infusion in these rats improved systemic vascular reactivity and indices of organ and general cellular injury. Mechanistically, the investigators reported that HS attenuated the elevated levels of several mediators in both plasma (interleukin-1β and nitric oxide) and tissues (superoxide). This translated into reduced neutrophil infiltration in lung and liver and 27% and 47% higher survival rates at 9 hrs and 18 hr, respectively, in CLP rats that received HS compared with normal saline. This study shows that in an animal model that may be the closest mimic available to human septic shock, 4 mL/kg HS was able to prevent hypotension, reduce organ dysfunction, and improve survival, possibly through its actions on hemodynamics and the inflammatory response.

Although this study has limitations regarding the clinical significance of the level of improvement seen with HS over normal saline, as well as the relevance of the results to human sepsis and septic shock, it does expand the therapeutic potential of HS in this field. Currently, a multicenter trauma trial sponsored by the U.S. National Institutes of Health and the U.S. Army is underway evaluating HS alone or with dextran compared with normal saline. Some of the enrolling centers are investigating the potential benefit of these hypertonic fluids on immune function and their ability to reduce multiorgan failure. The results of these studies are highly anticipated. Perhaps this study by Dr. Shih and colleagues (15) will encourage the planning of similar clinical studies to evaluate HS as the initial resuscitation fluid in the therapy of sepsis and septic shock, beyond its typical physiologic effects.

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REFERENCES

1. Velasco IT, Pontieri V, Rocha e Silva M Jr, et al: Hyperosmotic NaCl and severe hemorrhagic shock. *Am J Physiol* 1980; 239: H664–H673
2. Dubick MA, Bruttig SP, Wade CE: Issues of concern regarding the use of hypertonic/

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hyperoncotic fluid resuscitation of hemorrhagic hypotension. *Shock* 2006; 25:321–328
3. Wade CE, Kramer GC, Grady JJ, et al: Efficacy of hypertonic 7.5% saline and 6% dextran-70 in treating trauma: A meta-analysis of controlled clinical studies. *Surgery* 1997; 122:609–616
4. Olsson JSC: The use of hypertonic solutions in prehospital care in Scandinavia. *Scand J Trauma Resusc Emerg Med* 2004; 12:78–85
5. Wade CE, Grady JJ, Kramer GC, et al: Individual patient cohort analysis of the efficacy of hypertonic saline/dextran in patients with traumatic brain injury and hypotension. *J Trauma* 1997; 42(5 Suppl):S61–S65
6. Himmelseher S: Hypertonic saline solutions for treatment of intracranial hypertension. *Curr Opin Anaesthesiol* 2007; 20:414–426
7. Luypaert P, Vincent JL, Domb M, et al: Fluid resuscitation with hypertonic saline in endotoxic shock. *Circ Shock* 1986; 20:311–320
8. Kreimeier U, Frey L, Dentz J, et al: Hypertonic saline dextran resuscitation during the initial phase of acute endotoxemia: Effect on regional blood flow. *Crit Care Med* 1991; 19:801–809
9. Horton JW, Walker PB: Small-volume hypertonic saline dextran resuscitation from canine endotoxin shock. *Ann Surg* 1991; 214:64–73
10. Angle N, Hoyt DB, Coimbra R, et al: Hypertonic saline resuscitation diminishes lung injury by suppressing neutrophil activation after hemorrhagic shock. *Shock* 1998; 9:164–170
11. Pascual JL, Ferri LE, Seely AJ, et al: Hypertonic saline resuscitation of hemorrhagic shock diminishes neutrophil rolling and adherence to endothelium and reduces in vivo vascular leakage. *Ann Surg* 2002; 236:634–642
12. Pascual JL, Khwaja KA, Ferri LE, et al: Hypertonic saline resuscitation attenuates neutrophil lung sequestration and transmigration by diminishing leukocyte-endothelial interactions in a two-hit model of hemorrhagic shock and infection. *J Trauma* 2003; 54:121–130
13. Ciesla DJ, Moore EE, Zallen G, et al: Hypertonic saline attenuation of polymorphonuclear neutrophil cytotoxicity: Timing is everything. *J Trauma* 2000; 48:388–395
14. Junger WG, Liu FC, Loomis WH, et al: Hypertonic saline enhances cellular immune function. *Circ Shock* 1994; 42:190–196
15. Shih CC, Chen SJ, Chen A, et al: Therapeutic effects of hypertonic saline on peritonitis-induced septic shock with multiple organ dysfunction syndrome in rats. *Crit Care Med* 2008; 36:1864–1872

Levo is in the air: Take a deep breath!*

Mrs. Fictive-Fitness is a 40-yr-old "healthy" woman who underwent a laparoscopic cholecystectomy that was complicated by iatrogenic intestinal perforation, necessitating a 10-cm bowel resection with end-to-end anastomosis. On the second postoperative day, she developed septic shock and required high doses of norepinephrine to maintain a sufficient mean arterial blood pressure. Despite a hemoglobin value of 10 g/dL and appropriate intravascular volume replacement, her central venous oxygen saturation was unacceptably low, so incremental doses of dobutamine were continuously infused with the aim to achieve threshold values of ≈70%. Although the surgical focus had been eliminated and antibiotic therapy was judged as appropriate, septic shock progressed. Probably due to adrenergic receptor down-regulation, excessive catecholamine doses were needed to maintain at least a minimal circulation. In the meantime, Mrs. Fictive-Fitness had undergone metamorphosis and converted into Mrs. Ultra-Weakness. As she suffered from multiple organ failure despite (or because of?) having received 1 μg/kg/min norepinephrine and 25 μg/kg/min dobutamine, the intensive care physicians in charge considered administering levosimendan as drug of last resort, hoping that a somewhat "magic bullet" could revive her. Because she had severe myocardial insufficiency with a cardiac index of 1.5 L/min/m^2 and a central venous oxygen saturation of only 45%, the team decided to give a bolus dose of 24 μg/kg body weight. Some minutes later, her mean arterial blood pressure dropped dramatically, and a couple of hours thereafter she was dead. What went wrong with this case?

In the last years, levosimendan has emerged as a promising agent in the management of reversible cardiovascular dysfunction. Levosimendan is a calcium sensitizer that reliably increases cardiac output at low energetic costs. Due to simultaneous activation of adenosine triphosphate-sensitive potassium channels, levosimendan contributes to global vasodilatation within the systemic and pulmonary circulation (1). Whereas the decrease in afterload may be desirable, the subsequent decrease in systemic vascular resistance may threaten organ perfusion. Therefore, it is important to guarantee both appropriate vascular filling and tone before levosimendan infusion. Since the vasodilatory properties are dose dependent, vasodilation is most pronounced if a bolus is given (without preceding volume loading and coadministration of a vasoconstrictor agent). But what do we do if the patient suffers from systemic inflammation, associated with pronounced vasodilatation in conjunction with pulmonary hypertension and right heart failure? In this life-threatening condition, it would be smart to administer an anti-inflammatory agent that ameliorates cardiopulmonary dysfunction without further deteriorating systemic hemodynamics and tissue perfusion.

In this issue of *Critical Care Medicine*, Dr. Boost and colleagues (2) report the results of a timely and carefully conducted study investigating the role of aerosolized levosimendan in the experimental setting of ventilator-induced lung injury (VILI) in rats. The authors demonstrated that nebulization of levosimendan, when applied preinjury, reduced the release of inflammatory mediators and improved survival. The data support the concept that prophylactic inhalation of levosimendan may be a useful option to prevent pulmonary derangement in ventilated subjects.

Previous studies provided evidence that among the factors involved in the pathogenesis of VILI, overdistension and collapse of distal bronchioli and alveoli during mechanical ventilation, as well as activation and release of proinflammatory mediators, play a pivotal role. In addition, increased expression of intercellular adhesion molecule-1, cytokine-induced neutrophil chemoattractant-1, and

***See also p. 1873.**

Key Words: levosimendan; acute lung injury; ventilator-induced lung injury; sepsis; septic shock; hemodynamics

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monocyte chemoattractant protein-1 is implicated in the inflammatory orchestration (3–6).

Levosimendan has proven to inhibit the expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 on the surface of endothelial cells (7) and to reduce the release of endothelin-1 (8). Additional anti-inflammatory properties of levosimendan have been reported during ischemia and reperfusion, acute heart failure, and experimental sepsis (9–11). Pharmacologic preconditioning with levosimendan is currently known to represent a powerful cell-protective mechanism conferring relative resistance against cell death. Finally, an improvement in myocardial performance associated with a decrease in pulmonary vascular resistance (1) might also contribute to an increase in tissue perfusion and oxygenation.

In the study by Dr. Boost and colleagues (2), levosimendan exerted anti-inflammatory properties, as indicated by a decrease in proinflammatory cytokines (i.e., macrophage inhibitory protein-2 and interleukin 1β) as well as a reduction in nitric oxide release and matrix metalloproteinase-9 expression. The present study confirms the notion that calcium sensitizing may be a promising therapeutic option in a condition in which the right ventricle is acutely overloaded (1) and suggests that levosimendan attenuates the degree of inflammation in the setting of mechanical ventilation (2).

Another important aspect of the current study is that levosimendan has been administered preventively. During the last years, it has become more and more obvious that the efficacy of goal-directed therapies—whether the approach focuses on balanced oxygen demand-supply relationship (12), hemodynamic stabilization (13), or appropriate antimicrobial therapy (14)—critically depends on early institution of therapy. In this regard, it is especially noteworthy that even a powerful therapeutic agent may result in unchanged or even increased mortality if administration is delayed (14). In clinical practice, however, levosimendan is commonly used as last resort, when conventional (less expensive) inotropes have failed to improve hemodynamics. This may result in clinicians' biased impression that many patients die after having been treated with levosimendan. The major question that needs to be addressed is why we are not using levosimendan early in the stage of the disease. In this regard, it may be of relevance that physicians more and more are forced to work as economically as possible. Therefore, it sometimes happens that potentially promising therapeutic options are withheld because of their considerable price compared with standard therapy, which may be less effective. Of course, it makes no sense to break a fly on the wheel. However, it is important to figure out whether, when, and how potentially effective compounds may be used under special circumstances. Although the results of the current study strengthen the hypothesis that levosimendan confers organ protection and reduces mortality in the experimental setting, it needs to be taken into consideration that levosimendan was given preinjury and that no randomized clinical trials have shown that calcium sensitizing reduces mortality in patients suffering from VILI and right ventricular overload.

Nevertheless, the work by Dr. Boost and colleagues (2) is of special importance, since it demonstrated for the first time that levosimendan can be effectively aerosolized. Unfortunately, the study did not determine the effects of inhaled levosimendan on cardiac output and vascular resistance within the systemic and pulmonary circulation. Although it appears that this route of administration may be preferable compared with classic intravenous infusion, it needs to be taken into account that inhalation of 240 μg of levosimendan in 500-g rats corresponds to 30–40 mg (approximately three vials) in adult humans. In this context, it remains inconclusive a) which amount of the drug actually reached the alveolar and pulmonary microvascular compartment; b) whether innovative nebulization techniques may enable a more economic way of drug distribution within the airways; c) to what extent inhaled levosimendan exerts (possibly adverse) systemic hemodynamic effects; and d) whether the (potentially increased) costs associated with this innovative approach contribute to a better outcome compared with conventional inotropes or intravenous levosimendan infusion, respectively.

When we view the published studies on this topic together with the current work of Dr. Boost et al. (2), it appears reasonable to investigate the role of levosimendan in the early stage of the disease (without a loading bolus dose, if possible). Since levosimendan administration may contribute to arterial hypotension, invasive monitoring is desirable to detect and treat a relevant decrease in mean arterial blood pressure. Future clinical studies are needed to elucidate the safety, efficacy, and costs of inhaled vs. intravenous levosimendan. If the experimental results by the current authors (2) are replicable in humans, inhaled levosimendan may become an attractive approach, especially in hemodynamically unstable conditions, such as acute heart failure or sepsis-related myocardial depression (1). We hope that the near future will reveal whether our patients should take a deep breath, when there is levo in the air.

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REFERENCES

1. Morelli A, Teboul JL, Maggiore SM, et al: Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: A pilot study. *Crit Care Med* 2006; 34:2287–2293
2. Boost KA, Hoegl S, Hofstetter C, et al: Inhaled levosimendan reduces mortality and release of proinflammatory mediators in a rat model of experimental ventilator-induced lung injury. *Crit Care Med* 2008; 36: 1873–1879
3. Parker JC, Hernandez LA, Peevy KJ: Mechanisms of ventilator-induced lung injury. *Crit Care Med* 1993; 21:131–143
4. Li LF, Yu L, Quinn DA: Ventilation-induced neutrophil infiltration depends on c-Jun N-terminal kinase. *Am J Respir Crit Care Med* 2004; 169:518–524
5. Schmeck J, Janzen R, Munter K, et al: Endothelin-1 and thromboxane A2 increase pulmonary vascular resistance in granulocyte-mediated lung injury. *Crit Care Med* 1998; 26:1868–1874
6. Mendez MP, Morris SB, Wilcoxen S, et al: Shedding of soluble ICAM-1 into the alveolar space in murine models of acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 2006; 290:L962–L970
7. Parissis JT, Karavidas A, Bistola V, et al: Effects of levosimendan on flow-mediated vasodilation and soluble adhesion molecules in patients with advanced chronic heart failure. *Atherosclerosis* 2008;197:278–282
8. Gruhn N, Nielsen-Kudsk JE, Theilgaard S, et al: Coronary vasorelaxant effect of levosimendan, a new inodilator with calcium-

sensitizing properties. *J Cardiovasc Pharmacol* 1998; 31:741–749
9. Zager RA, Johnson AC, Lund S, et al: Levosimendan protects against experimental endotoxemic acute renal failure. *Am J Physiol Renal Physiol* 2006; 290:F1453–F1462
10. Lepran I, Pollesello P, Vajda S, et al: Preconditioning effects of levosimendan in a rabbit cardiac ischemia-reperfusion model. *J Cardiovasc Pharmacol* 2006; 48:148–152
11. Adamopoulos S, Parissis JT, Iliodromitis EK, et al: Effects of levosimendan versus dobutamine on inflammatory and apoptotic pathways in acutely decompensated chronic heart failure. *Am J Cardiol* 2006; 98:102–106
12. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
13. Morelli A, Ertmer C, Lange M, et al: Continuous terlipressin infusion in patients with septic shock: Less may be best, and the earlier the better? *Intensive Care Med* 2007; 33:1669–1670
14. Kumar A, Roberts D, Wood KE, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34:1589–1596

Calcium sensitizing in sepsis: Is levosimendan on the right path?*

Levosimendan is a triple-action compound exerting positive inotropic, vasodilatory, and anti-ischemic effects at the same time (1). Whereas the increase in myocardial contractility is primarily mediated by calcium sensitization, global vasodilation and anti-ischemic properties are ascribed to activation of adenosine triphosphate–sensitive potassium channels (K_{ATP}) in vascular smooth muscle cells and the mitochondria, respectively. By its unique mechanism, levosimendan may thus increase cardiac output and improve regional perfusion simultaneously. In this context, previous experimental and clinical studies demonstrated that levosimendan attenuates right and left ventricular dysfunction and increases both regional blood flow and global oxygen transport (2–4).

In addition to stimulation of K_{ATP} channels, levosimendan may contribute to vasodilation by blocking the release of endothelin-1 (5), a potent vasoconstrictive peptide involved in the pathophysiology of macro- and microvascular maldistribution seen in septic shock. Finally, levosimendan may beneficially affect endothelial dysfunction by inhibiting the expression of soluble adhesion molecules, such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 (6), thereby potentially attenuating sepsis-related microvascular dysfunction. Dr. Schwarte and colleagues (7) also performed experiments in this area and reported that levosimendan increases gastrointestinal mucosal oxygenation in healthy dogs, as determined by reflectance spectrophotometry. Interestingly, the latter authors demonstrated that the increase in gastrointestinal perfusion resulting from levosimendan infusion was not completely dependent on an increase in cardiac output, but was rather caused by redistribution of blood flow toward the gastrointestinal tract due to opening of vascular smooth muscle K_{ATP} channels (7). The fact that healthy animals were studied, however, raises the crucial question whether or not the beneficial microcirculatory effects caused by levosimendan may also be replicated in the presence of septic shock, a condition that is characterized by maldistribution of regional and microvascular blood flow.

In this issue of *Critical Care Medicine*, Dr. Fries and colleagues (8) report the results of a carefully conducted study designed to compare the effects of norepinephrine and levosimendan on microvascular perfusion and oxygenation in a rat model of septic shock. Using sidestream darkfield imaging and oxygen-dependent quenching of phosphorescence, the authors showed that both norepinephrine and levosimendan had comparable effects on the restoration of sepsis-induced alterations in systemic hemodynamics (i.e., cardiac output) with no significant impact on microvascular perfusion. Whereas levosimendan significantly improved microvascular oxygenation, norepinephrine contributed to a further impairment. Despite the restoration of cardiac output with both vasoactive agents, neither norepinephrine nor levosimendan improved microcirculatory blood flow. Unfortunately, it cannot be excluded that the uncoupling between unaffected microvascular oxygen delivery (microvascular blood flow) and increased microvascular oxygenation has to be attributed to the techniques adopted in this study. However, it appears that μPO_2 measurements are more sensitive than the semiquantitative measurements derived from the sidestream darkfield imaging. Whether a larger sample size would have yielded significant differences in terms of microvascular blood flow remains inconclusive.

It also may be critically discussed whether the animals have suffered from hypovolemia at the time of levosimendan administration (3, 4), as suggested by marked hemoconcentration. The finding that norepinephrine, an alpha-adrenergic vasoconstrictor with scarce inotropic effects, resulted in a similar increase in cardiac output when compared with levosimendan, a strong inodilator, is rather surprising and in contrast to clinical observations. A potential explanation may be that hypovolemia limited the increase in cardiac output in the levosimendan group, whereas the relatively high norepinephrine dose exerted positive inotropic effects by stimulation of beta-1 receptors. Unfortunately, the authors did not study an additional group treated with combined levosimendan and norepinephrine. Such an approach would have helped stabilize mean arterial pressure and increase cardiac output simultaneously, and potentially could have resulted in different microcirculatory effects.

Opening of K_{ATP} channels in response to levosimendan administration typically is associated with significant vasodilation. In the presence of an adequate volume status, the drop in blood pressure may be limited by a simultaneous in-

***See also p. 1886.**

Key Words: levosimendan; septic shock; norepinephrine

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crease in cardiac output. In this context, it is especially important to note that the vasodilatory effects of levosimendan are dose-dependent and most pronounced if a loading bolus is administered. In the presence of systemic inflammation and/or vasodilatory shock states, levosimendan should therefore only be given when adequate fluid resuscitation can be assured. In a condition in which a change in myocardial contractility is not required immediately (e.g., in sepsis), it may be reasonable to continuously infuse levosimendan without a preceding loading bolus dose (3, 4). Finally, we urgently recommend combining levosimendan with a vasopressor agent to circumvent a (further) decrease in perfusion pressure.

To explain the levosimendan-associated increase in μPO_2, Dr. Fries and colleagues (8) focused their attention on the possible effects on mitochondrial K_{ATP} channels and cellular mechanisms independent of microvascular perfusion. Under hemodynamic stress conditions associated with microcirculatory alterations, the opening of mitochondrial K_{ATP} channels may exert a positive effect on energy consumption, as recently demonstrated in the failing heart (9, 10). In this context, it may be important that in the presence of reduced oxygen delivery and cellular hypoxia, cells can adapt to maintain viability by down-regulating oxygen consumption, energy requirements, and ATP demand (11), an adaptive phenomenon often referred to as *hibernation-type response* (11). Whether this protective mechanism plays a similar role in sepsis-related dysfunction in organs other than the heart remains to be determined in future studies. However, because mitochondrial dysfunction is critically involved in the pathogenesis of multiple organ failure (11), a compound reducing oxygen consumption and preserving mitochondrial function represents an interesting therapeutic strategy in a state of reduced energy availability, such as sepsis. By opening mitochondrial K_{ATP} channels, levosimendan may contribute to maintenance of mitochondrial volume, to amelioration of Ca^{2+} overload during ischemia, and to preservation of mitochondrial function. Because these mechanisms are implicated in the prevention of apoptosis (12), it is conceivable that levosimendan likewise offers some degree of protection against programmed cell death.

The current literature on this topic, together with the work of Dr. Fries and colleagues (8), makes it appear very likely that besides its positive effect on myocardial contractility, levosimendan plays a pivotal role in cellular protection. However, although it appears that levosimendan is on the right path, future large-scale, randomized clinical trials are now needed to explicitly clarify whether or not calcium sensitizing represents a rational concept in patients suffering from septic shock. If it can be proven that the beneficial effects of levosimendan translate into a reduced length of hospital stay and a reduction in mortality, the discussion about initially increased costs (as compared with current standard therapy) would certainly change significantly.

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REFERENCES

1. Westphal M, Morelli A, Van Aken H: Dear Levosimendan, the right ventricle will thank you! *Crit Care Med* 2007; 35:952–953
2. Dubin A, Murias G, Sottile JP, et al: Effects of levosimendan and dobutamine in experimental acute endotoxemia: A preliminary controlled study. *Intensive Care Med* 2007; 33: 485–494
3. Morelli A, De Castro S, Teboul JL, et al: Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. *Intensive Care Med* 2005; 31: 638–644
4. Morelli A, Teboul JL, Maggiore SM, et al: Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: A pilot study. *Crit Care Med* 2006; 34:2287–2293
5. Gruhn N, Nielsen-Kudsk JE, Theilgaard S, et al: Coronary vasorelaxant effect of levosimendan, a new inodilator with calcium-sensitizing properties. *J Cardiovasc Pharmacol* 1998; 31:741–749
6. Parissis JT, Karavidas A, Bistola V, et al: Effects of levosimendan on flow-mediated vasodilation and soluble adhesion molecules in patient with advanced chronic heart failure. *Atherosclerosis* 2007; 197:278–282
7. Schwarte LA, Picker O, Bornstein SR, et al: Levosimendan is superior to milrinone and dobutamine in selectively increasing microvascular gastric mucosal oxygenation in dogs. *Crit Care Med* 2005; 33:135–142
8. Fries M, Ince C, Rossant R, et al: Levosimendan but not norepinephrine improves microvascular oxygenation during experimental septic shock. *Crit Care Med* 2008; 36:1886–1891
9. Kevelaitis E, Peynet J, Mouas C, et al: Opening of potassium channels: The common cardioprotective link between preconditioning and natural hibernation? *Circulation* 1999; 99:3079–3085
10. De Luca L, Colucci WS, Nieminem MS, et al: Evidence-based use of levosimendan in different clinical settings. *Eur Heart J* 2006; 27:1908–1920
11. Singer M: Mitochondrial function in sepsis: Acute phase versus multiple organ failure. *Crit Care Med* 2007; 35(Suppl 9):S441–S448
12. Buckley JF, Singer M, Clapp LH: Role of KATP channels in sepsis. *Cardiovasc Res* 2006; 72:220–230

Monitoring the brain: Lack of tools or lack of will?*

In this issue of *Critical Care Medicine*, Dr. Jia and colleagues (1) address the role of an electrophysiological marker to predict the neurologic functional outcome associated with temperature manipulations following cardiac arrest in rats. While hypothermia previously has been demonstrated to provide neuroprotection in rats, the important message of this article is that in using a quantified (q) electroencephalogram (EEG), the authors were able to predict the effect of various treatments on neurologic outcome. This marker was predictive at a time when the animal was in a coma and thus the clinical neurologic exam unrevealing.

Currently, imaging is the predominant mode of investigating the brain. However, it is not designed for continuous monitoring, only for point investigation, even with the advance of scanner technology allowing bedside imaging. Only a few techniques, such as positron emission tomography or single photon emission computed tomography, give information on metabolic state, and these types of investigations are not readily available (2). Jugular bulb oximetry, a global reflection of the brain metabolic status, cannot be maintained *in situ* for prolonged periods (3). More recently, brain cortical microdialysis techniques have become available and bring a vast array of information (4). However, this type of monitoring also is highly invasive, provides focal rather than global monitoring, and has yet to accumulate evidence that it improves outcome. Thus, we have no easily applied tools available for continuous cerebral monitoring.

The EEG always has been a staple of brain evaluation. However, it is not routinely utilized for brain-injured patients, owing to what is felt to be a necessity for skilled interpretation. Therefore, EEG data rarely are used in the acute setting for clinical decision-making. It is remarkable that intensive care personnel commonly employ continuous monitoring for organs such as the heart and lungs, but not the brain. A simple 5-lead EEG can now be displayed readily on most intensive care and operating room monitors with small computerized modules. Furthermore, qEEG facilitates the process of data interpretation. Commercially available qEEG monitors are used in the operating room setting, developed in response to demand by clinicians to quantify the effects of anesthetic drugs on the brain and to improve patient outcomes (5–6). These monitors, such as the bispectral index type, while far from perfect, have given clinicians a new tool to monitor their patients.

Information quantity (IQ) is derived through processing of hemispheric EEG recordings and represents the variability present in the tracings (7). Short windows at various time points after resuscitation from cardiac arrest are analyzed by computer algorithm. Discrete wavelet transform is first applied to remove redundancy after which Shannon's entropy is calculated (8). IQ is presented as a ratio comparing this measurement to the prearrest baseline. The qEEG is able to identify patterns associated with significant injury; burst suppression, generalized suppression, and seizure activity are all periodic patterns and score low by IQ. The authors demonstrate that early return of variability, as measured by higher IQ, is predictive of neurologic recovery. This correlation is shown to be significant as early as 30 mins postresuscitation.

IQ as described by Dr. Jia and colleagues (1), despite limitations, is a technology that could be adapted rapidly to bring EEG to the bedside. Further investigation must be made to translate IQ into clinical practice. IQ is expressed as a ratio, relative to a baseline measurement that one would not expect to be available for most patients. The authors suggest that IQ could be computed based on a standardized baseline. Clinicians could then follow a positive or negative trend, and possibly use this information to guide therapy. The absolute value may be predictive as well. IQ could be subject to pitfalls secondary to the effects of sedatives and anesthetics on human patients. In high doses, many of these lead to slowing and burst suppression, which would be expected to lower IQ (9). In this study, halothane did not appear to interfere with IQ. Furthermore, it is the unresponsive patient, in whom sedation is rarely required, where IQ would be most useful. Nevertheless, more work needs to be done to define the influence of anesthetics on qEEG. Technology to suppress artifact and improve signal–noise ratio also may be required to realize the full potential of quantitative EEG at the bedside.

IQ may be valuable clinically as an early predictive tool following neurologic injury, particularly in the setting of the comatose patient. As Dr. Jia and colleagues suggest, IQ could help predict outcome in patients resuscitated after cardiac arrest (10). Conceivably, IQ also could provide useful information in other types of brain injury, such as intracranial hemorrhage and traumatic brain injury. In addition to providing prognostic information, this tool possibly could monitor response to therapeutic interventions. In a more immediate translation to the clinical arena, the return of variability also could be monitored following major neurosurgical procedures when secondary brain injury may be expected and directly compared with a preanesthetic baseline. These data would help us to better follow our patients' evolution in case of poor outcome, in conjunction with imaging data and other tools.

In conclusion, Dr. Jia and colleagues demonstrate the validity of a novel method for continuous EEG monitoring to evaluate response to a guided therapy. At present, continuous cerebral monitoring in humans remains imprecise. This should not deter us from doing so. As evidenced in this work, new noninvasive monitoring is on the horizon. The brain should be monitored, especially in acute situations. Only in doing so routinely will

***See also p. 1909.**

Key Words: brain monitoring; electroencephalography; quantified EEG, information quantity; entropy; cardiac arrest

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we learn from experience and stimulate new ideas and technology. In this sense, the work of Dr. Jia and colleagues points the way forward.

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REFERENCES

1. Jia X, Koenig MA, Nickl R, et al: Early electrophysiologic markers predict functional outcome associated with temperature manipulation after cardiac arrest in rats. *Crit Care Med* 2008; 36:1909–1916
2. Wartenberg KE, Schmidt JM, Mayer SA: Multimodality monitoring in neurocritical care. *Crit Care Clin* 2007; 23:507–538
3. Feldman Z, Robertson CS: Monitoring of cerebral hemodynamics with jugular bulb catheters. *Crit Care Clin* 1997; 13:51–77
4. Tisdall MM, Smith M: Cerebral microdialysis: Research technique or clinical tool. *Br J Anaesth* 2006; 97:18–25
5. Tempelhoff R, Modica PA, Rich KM, et al: Use of computerized electroencephalographic monitoring during aneurysm surgery. *J Neurosurg* 1989; 71:24–31
6. Modica PA, Tempelhoff R: A comparison of computerized EEG with internal carotid artery stump pressure for detection of ischemia during carotid endarterectomy. *J Neurosurg Anesthesiol* 1989; 1:211–218
7. Jia X, Koenig MA, Shin HC, et al: Quantitative EEG and neurological recovery with therapeutic hypothermia after asphyxial cardiac arrest in rats. *Brain Res* 2006; 1111: 166–175
8. Shin HC, Tong S, Yamashita S, et al: Quantitative EEG assessment of brain injury and hypothermic neuroprotection after cardiac arrest. *Conf Proc IEEE Eng Med Biol Soc* 2006; 1:6229–6232
9. Sleigh J, Voss L, Bernard J: What are electroencephalogram entropies really measuring? *Int Congr Ser* 2005; 1283:231–234
10. Bernard SA, Gray TW, Buist MD, et al: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; 346:557–563

Brain tissue oxygen monitors: More than an ischemia monitor*

Brain cells need a constant supply of oxygen and glucose for normal energy metabolism. Therefore, continuous cerebral blood flow (CBF) and cerebral oxygen tension and delivery are essential to brain function. In the absence of effective neuroprotective treatments, clinical management of patients with severe traumatic brain injury (TBI) tries to maintain adequate cerebral perfusion pressure (CPP) and control intracranial pressure (ICP). Recent studies, however, have failed to demonstrate that adequate CPP improves patient outcome (1). This raises the possibility that there may be additional mechanisms of tissue hypoxia, and so the interstitial partial pressure of oxygen in brain tissue ($P_{bt}O_2$) is emerging as an additional complementary therapeutic target in TBI. This issue is important since brain tissue hypoxia is associated with worse outcome after severe TBI (2).

Direct $P_{bt}O_2$ monitors have been available for clinical use in the United States for several years. Despite this, there remain several unanswered questions: In particular, what are the determinants of $P_{bt}O_2$? In this issue of *Critical Care Medicine*, Dr. Rosenthal and colleagues (3) try to answer this question. The authors examined 14 patients with severe TBI and challenged them with an increase in FIO_2 to 1.0 (oxygen reactivity), an increase in mean arterial blood pressure by 10 mm Hg (cerebral autoregulation), and a decrease in $PaCO_2$ of 10 mm Hg (CO_2 cerebral vascular reactivity). The study has several limitations; for example, some physiologic responses were measured using local monitors (Licox and Hemedex), the challenges were administered in a consecutive manner, hyperoxygenation was maintained during the CO_2 and mean arterial blood pressure challenges, and information from the challenges was used to guide therapy. Nevertheless, the data are robust (119 data points) and suggest that $P_{bt}O_2$ reflects the product of cerebral blood flow and the arteriovenous difference in oxygen tension, that is, $P_{bt}O_2 = CBF \times AVTO_2$. This finding is consistent with experimental studies which suggest that $P_{bt}O_2$ does not simply mirror CBF (4), positron emission tomography studies in humans after TBI which show that diffusion rather than perfusion-limited ischemia may be responsible for cerebral hypoxia (5), and microdialysis studies which indicate that increases in the lactate-pyruvate ratio, a marker of anaerobic metabolism, can occur independently from CPP (6). The findings of Dr. Rosenthal and colleagues (3) may apply only to normal-appearing tissue and to patients with preserved cerebral autoregulation after TBI. Additional studies are needed to further explore the determinants of $P_{bt}O_2$ in pericontusional brain tissue, where cerebral metabolism and tissue oxygenation may behave differently, in TBI patients with impaired autoregulation, or in conditions such as subarachnoid hemorrhage.

While earlier studies using xenon computed tomography suggested that $P_{bt}O_2$ reflects regional CBF, the finding that $P_{bt}O_2 = CBF \times AVTO_2$ implies a relationship between the amount of dissolved plasma oxygen passing through a given volume of brain per unit time and the steady-state oxygen concentration in brain tissue. This is important in TBI since magnetic resonance imaging studies demonstrate that cytotoxic edema is the predominant edema after TBI and so may limit diffusion of needed metabolites and oxygen to and from the cell (7). In these situations, the brain might require higher tissue oxygen tensions to maintain sufficient tissue oxygenation. Furthermore, the results imply that a $P_{bt}O_2$ monitor is not simply an ischemia monitor or a measure of CBF. While reduced CBF (ischemia) is a cause of cellular hypoxia, there are other potential causes of reduced oxygen. This is relevant since positron emission tomography studies in normal volunteers during visual activation and hypoxia suggest that adequate levels of tissue oxygenation can be maintained without an increase in CBF (8). In

*See also p. 1917.

Key Words: brain oxygen; cerebral blood flow; cerebral metabolism; traumatic brain injury

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animal and clinical studies of TBI, variables such as hemoglobin and lung function influence $P_{bt}O_2$ independent of CBF (9–11), and cellular distress may be observed in the absence of ischemia (12). Certainly CBF is important, and how oxygenation of the brain responds to various therapies depends in part on CBF (13, 14). However, knowing what is in the blood vessels of the brain (CPP and CBF) is only part of the information needed to prevent cellular dysfunction. While $P_{bt}O_2$ it is not a measure of supply and metabolism, the findings of Dr. Rosenthal and colleagues (3) suggest that at the very least, since $P_{bt}O_2$ reflects diffusion of dissolved plasma oxygen, we now know what is getting out of the blood vessels and into the brain tissue.

There are other important observations from the study. First, hyperoxygenation decreased CBF. In some circumstances this may be dangerous, but as Dr. Rosenthal and colleagues (3) found, CPP increased in part because ICP is reduced, likely through hyperoxic induced vasoconstriction. Similarly, hyperoxia can improve cellular metabolism because of greater oxygen availability (15), suggesting that the reduced CBF may not always be deleterious. However, Dr. Rosenthal and colleagues did not address the safety, feasibility, or efficacy of normobaric hyperoxygenation. This topic remains controversial, since some studies suggest a benefit while others do not (14, 16). However, hyperoxygenation (an F_{IO_2} of 1.0) may miss the point, since Dr. Rosenthal and colleagues also observed that the mean ratio of tissue to arterial or venous oxygen concentration is very small. This is consistent with Kety Schmidt's original hypothesis that the concentration of oxygen in brain tissue is very small relative to the oxygen content of arterial and venous blood. While the minimum tissue P_{O_2} required to provide sufficient intracellular oxygen is unknown, neuronal mitochondria require an intracellular P_{O_2} of 1.5 mm Hg to maintain aerobic metabolism. Together, these data suggest that small changes in brain oxygen tension to correct compromised brain oxygen may be all that is necessary to maintain cellular health. A $P_{bt}O_2$ monitor therefore may help identify the cause for cellular distress and so tailor therapy to the individual patient. In this way, a $P_{bt}O_2$ monitor is more than an ischemia monitor. Whether this knowledge can be used to improve patient outcome after TBI will need to be studied (17). Knowing what $P_{bt}O_2$ represents is the first step in that direction.

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REFERENCES

1. Robertson CS, Valadka AB, Hannay HJ, et al: Prevention of secondary ischemic insults after severe head injury. *Crit Care Med* 1999; 27:2086–2095
2. van den Brink WA, van Santbrink H, Steyerberg EW, et al: Brain oxygen tension in severe head injury. *Neurosurgery* 2000; 46: 868–876
3. Rosenthal G, Hemphill JC III, Sorani M, et al: Brain tissue oxygen tension is more indicative of oxygen diffusion than oxygen delivery and metabolism in patients with traumatic brain injury. *Crit Care Med* 2008; 36:1917–1924
4. Scheufler K-M, Lehnert A, Rohrborn H-J, et al: Individual values of brain tissue oxygen pressure, microvascular oxygen saturation, cytochrome redox level and energy metabolites in detecting critically reduced cerebral energy state during acute changes in global cerebral perfusion. *J Neurosurg Anesthesiol* 2004; 16:210–219
5. Menon DK, Coles JP, Gupta AK, et al: Diffusion limited oxygen delivery following head injury. *Crit Care Med* 2004; 32:1384–1390
6. Vespa PM, O'Phelan K, McArthur D, et al: Pericontusional brain tissue exhibits persistent elevation of lactate/pyruvate ratio independent of cerebral perfusion pressure. *Crit Care Med* 2007; 35:1153–1160
7. Marmarou A, Signoretti S, Fatouros PP, et al: Predominance of cellular edema in traumatic brain swelling in patients with severe head injuries. *J Neurosurg* 2006; 104:720–730
8. Mintun MA, Lundstrom BN, Snyder AZ, et al: Blood flow and oxygen delivery to human brain during functional activity: Theoretical modeling and experimental data. *Proc Natl Acad Sci U S A* 2001; 98:6859–6864
9. Rosenthal G, Hemphill JC, Sorani M, et al: The role of lung function in brain tissue oxygenation following traumatic brain injury. *J Neurosurg* 2008; 108:59–65
10. Smith MJ, Stiefel MF, Magge S, et al: Packed red blood cell transfusion increases local cerebral oxygenation. *Crit Care Med* 2005; 33: 1104–1108
11. Hare GM, Mazer CD, Hutchison JS, et al: Severe hemodilutional anemia increases cerebral tissue injury following acute neurotrauma. *J Appl Physiol* 2007; 103:1021–1029
12. Vespa P, Bergsneider M, Hattori N, et al: Metabolic crisis without brain ischemia is common after traumatic brain injury: A combined microdialysis and positron emission tomography study. *J Cereb Blood Flow Metab* 2005; 25:763–774
13. Hlatky R, Valadka AB, Gopinath SP, et al: Brain tissue oxygen tension response to induced hyperoxia reduced in hypoperfused brain. *J Neurosurg* 2008; 108:53–58
14. Nortje J, Coles JP, Timofeev I, et al: Effect of hyperoxia on regional oxygenation and metabolism after severe traumatic brain injury: Preliminary findings. *Crit Care Med* 2008; 36:273–281
15. Tolias CM, Reinert M, Seiler R, et al: Normobaric hyperoxia-induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: A prospective historical cohort-matched study. *J Neurosurg* 2004; 101: 435–444
16. Diringer MN, Aiyagari V, Zazulia AR, et al: Effect of hyperoxia on cerebral metabolic rate for oxygen measured using positron emission tomography in patients with acute severe head injury. *J Neurosurg* 2007; 106:526–529
17. Stiefel MF, Spiotta A, Gracias VH, et al: Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. *J Neurosurg* 2005; 103:805–811

Pediatric delirium: A new diagnostic challenge of which to be aware*

Probably one of the most frequent behavioral symptoms of acute brain dysfunction among pediatric patients is delirium, which is a complex neuropsychiatric syndrome that complicates physical illness, negatively impacting prognosis (1).

Delirium is a particularly derelict area, although it seems associated with longer hospital stay and higher mortality among hospitalized pediatric patients (2).

The delirium evaluation is a multiprofessional issue, and all professionals involved in the treatment of a hospitalized child—pediatricians, nurses, respiratory therapists, etc.—should be aware of the potential for this diagnosis and should be qualified to assess it. Though these professionals in pediatric intensive care units are used to monitoring end organ dysfunction, they often do not seem to recognize delirium (3).

The 2002 guidelines of the Society of Critical Care Medicine for sedation and analgesia published the parameters for the use of sedatives and analgesics in the critically ill adult, which also included the evaluation of delirium, clearly recommending the routine assessment of delirium (grade B recommendation) and the treatment of delirium with haloperidol (grade C recommendation) (4). As long as there is no similar guideline for pediatric patients, these adult recommendations can be followed.

There are two basic neurologic assessment steps to evaluate sedation and delirium. These involve evaluating the patient's level of consciousness/sedation and the brain's function directed to the level of arousal. This is where the big challenge begins, because in pediatric patients there is absence of a clear definition of delirium, the lack of a reliable and validated assessment tool, and great difficulty in distinguishing pain from delirium.

Delirium physiopathology remains a matter of intense research, but an important role seems to be played by the alteration of neuronal activity due to local brain production of cytokines, cell infiltration and tissue injury in response to systemic infections, and inflammatory injuries of the central nervous system. The inflammatory injuries that affect the brain include those induced by endotoxin, cytokines, and hypoxemia (5).

There also is evidence that three neurotransmitter systems are involved in the development of delirium: Dopamine increases neuronal excitability, while acetylcholine and gamma-aminobutyric acid decrease the excitability of neurons. An imbalance of one or more of these neurotransmitter systems in their synthesis, release, and inactivation results in neuronal instability and erratic neurotransmission, impairing an adequate control of cognitive function, behavior, and mood. Serotonin imbalance, increased central noradrenergic activity, and endorphin hyperfunction also may be involved in the development of delirium (6). Inadequate cerebral blood flow caused by shock and coagulopathies and metabolic disturbances also can be the source of delirium.

Among all the causes that may influence delirium, medical therapies, such as mechanical ventilation and sedative and analgesic drug use, should also be mentioned.

These lead us to the risk factors, which can be split in five categories (7, 8):

- Host factors: Age, baseline comorbidities, surgical procedure, pain;
- Acute illness itself: Sepsis, hypoxemia, disease severity score, stroke;
- Psychological: Difficult temperament, separation anxiety, premorbid psychiatric condition, pain;
- Social: Anxious caregiver, caregiver presence/absence, caregiver pain perceptions;
- Environmental or iatrogenic: Pediatric intensive care unit admission, metabolic derangements, anticholinergic medications, use of sedative and analgesic medications, noise, cool temperature, light, high number of hospital procedures, and pain.

Therefore, in the clinical setting, several aspects of delirium—such as the use of sedatives and analgesics, sepsis, and surgery and postoperative cognitive dysfunction—should be taken into account, because they are potentially modifiable factors. Given this approach, pain, anxiety, agitation, and of course delirium cannot be managed through trial and error drug administration, as has been done in the past.

We also can look at the risk factors for delirium from another point of view, that of predisposing and precipitating factors (9). For instance, age would be a predisposing factor and a metabolic disturbance a precipitating factor. It is interesting to note that using disease severity scores may lead one to look mainly at the precipitating factors and overlook the predisposing ones.

For these reasons, we should aim toward the prevention of delirium, given the inherent diagnostic and treatment complexity, the uncertainty about the clinical significance of delirium in children in the short and long term, the fact that it is biologically plausible that delirium is not only a marker of end organ damage but also a promoter of other organ system dysfunction (7), and the trend of intensivists to diagnose delirium only upon the presence or absence of an obvious medical etiology (10).

In this issue of *Critical Care Medicine*, Dr. Schieveld and colleagues (11) present two pediatric illness severity measures—Pediatric Index of Mortality (PIM) and Pediatric Risk of Mortality (PRISM) II—as possible means to assess the risk of pediatric delirium in pediatric intensive care units. The authors acknowledge the difficulty of diagnosing pediatric delirium, so they took extra care in presenting their data and in concluding that it is "worthwhile to employ PIM and PRISM II

*See also p. 1933.

Key Words: delirium; critical care; pediatrics; risk assessment mechanical ventilation

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in the risk assessment of pediatric delirium." We could not agree more, mainly when we take into account the difficulty in correctly and quickly diagnosing and treating delirium in the pediatric patient. Let's prevent it rather than manage it.

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REFERENCES

1. Leentjens AF, Schieveld JN, Leonard M, et al: A comparison of the phenomenology of pediatric, adult, and geriatric delirium. *J Psychosom Res* 2008; 64:219–223
2. Turkel SB, Tavaré CJ: Delirium in children and adolescents. *J Neuropsychiatry Clin Neurosci* 2003; 15:431–435
3. Pandharipande P, Jackson J, Ely EW: Delirium: Acute cognitive dysfunction in the critically ill. *Curr Opin Crit Care* 2005; 11: 360–368
4. Jacobi J, Fraser GL, Coursin DB, et al: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002; 30:119–141
5. Gunther ML, Morandi A, Ely EW: Pathophysiology of delirium in the intensive care unit. *Crit Care Clin* 2008; 24:45–65
6. Webb JM, Carlton EF, Geehan DM: Delirium in the intensive care unit: Are we helping the patient? *Crit Care Nurs Q* 2000; 22:47–60
7. Scott GM, Gold JI: Emergence delirium: A re-emerging interest. *Semin Anesth Perioper Med Pain* 2006; 25:100–104
8. Devlin JW, Fong JJ, Fraser GL, et al: Delirium assessment in the critically ill. *Intensive Care Med* 2007; 33:929–940
9. Burns A, Gallagley A, Byrne J: Delirium. *J Neurol Neurosurg Psychiatry* 2004; 75: 362–367
10. Cheung CZ, Alibhai SM, Robinson M, et al: Recognition and labeling of delirium symptoms by intensivists: Does it matter? *Intensive Care Med* 2008; 34:437–446
11. Schieveld J, Lousberg R, Berghmans E, et al: Pediatric illness severity measures predict delirium in a pediatric intensive care unit. *Crit Care Med* 2008; 36:1933–1936

Steroid therapy of septic shock: The decision is in the eye of the beholder

In 1911 Rupert Waterhouse reported a case of cardiovascular collapse in a septic infant with bilateral adrenal hemorrhage noted at autopsy, calling the condition "suprarenal apoplexy." This likely represented the peak of clarity to date on adrenal insufficiency in sepsis (Fig. 1; 1–15).

In this issue of *Critical Care Medicine,* Marik and colleagues, representing an international task force, publish clinical practice guidelines (SCPG) for the diagnosis and management of corticosteroid insufficiency in critical illness (16). The authors are to be congratulated for this very timely and clinically relevant publication. The recommendations are evidence based and in general on target and useful for the bedside clinician. They coin a new term, *critical illness related corticosteroid insufficiency* (CIRCI), defined as inadequate cellular corticosteroid (steroid) activity for the severity of the patient's illness. CIRCI occurs as a result of either a decrease in adrenal steroid production (adrenal insufficiency) or tissue resistance to glucocorticoids (with or without adrenal insufficiency). Although recommending that adrenal insufficiency in critical illness is best diagnosed by a delta cortisol following 250 mg cosyntropin of $\leq$9 μg/dL or random total cortisol of $<$10 μg/dL, the authors recommend using clinical assessment and not the ACTH (corticotropin) stimulation test to identify patients with septic shock or acute respiratory distress syndrome (ARDS) who should receive steroid therapy for CIRCI. The document does point to the potential for free cortisol measurement, not currently available at most centers, as having promise for decisions on steroid therapy in the future. The SCPG document recommendation for septic shock states "hydrocortisone should be considered in the management strategy of patients with septic shock, particularly those patients who have responded poorly to fluid resuscitation and vasopressor agents." This is a 2B (weak strength with moderate level of evidence support in a three-tiered quality of evidence grading system) recommendation. This recommendation is similar to that of the recently published Surviving Sepsis Campaign (SSC) recommendation that states "we suggest that intravenous hydrocortisone be given only to adult septic shock patients after it has been confirmed that their blood pressure is poorly responsive to fluid resuscitation and vasopressor therapy" (17). The SSC recommendation is graded 2C (weak strength with a four-tiered quality of evidence grading system). Discussion in both sets of guidelines point to the difference in patient populations enrolled in the French trial (which showed benefit of stress-dose steroids in septic shock) and the CORTICUS trial (which showed no survival benefit with a similar treatment strategy). The septic shock patients enrolled in the French trial were (1) more critically ill by severity scores, (2) more unstable from a blood pressure standpoint, and (3) enrolled earlier in septic shock. Any or all of these characteristics could lead to the difference in the outcome as far as survival advantage between the two studies. As the authors point out, in addition, steroids were available and widely used throughout the countries participating in the CORTICUS trial. Although there are no data to allow ascertainment for or against selection bias, this remains a potential concern. It should also be recognized that all four of the randomized trials of stress-dose steroid therapy of septic shock (including two single center studies) support the capability of steroids to reverse septic shock (11, 12, 14, 15). In the CORTICUS trial the dif-

***See also p. 1937.**

Key Words: corticosteroid; sepsis; intensive care; critical care; acute respiratory distress syndrome

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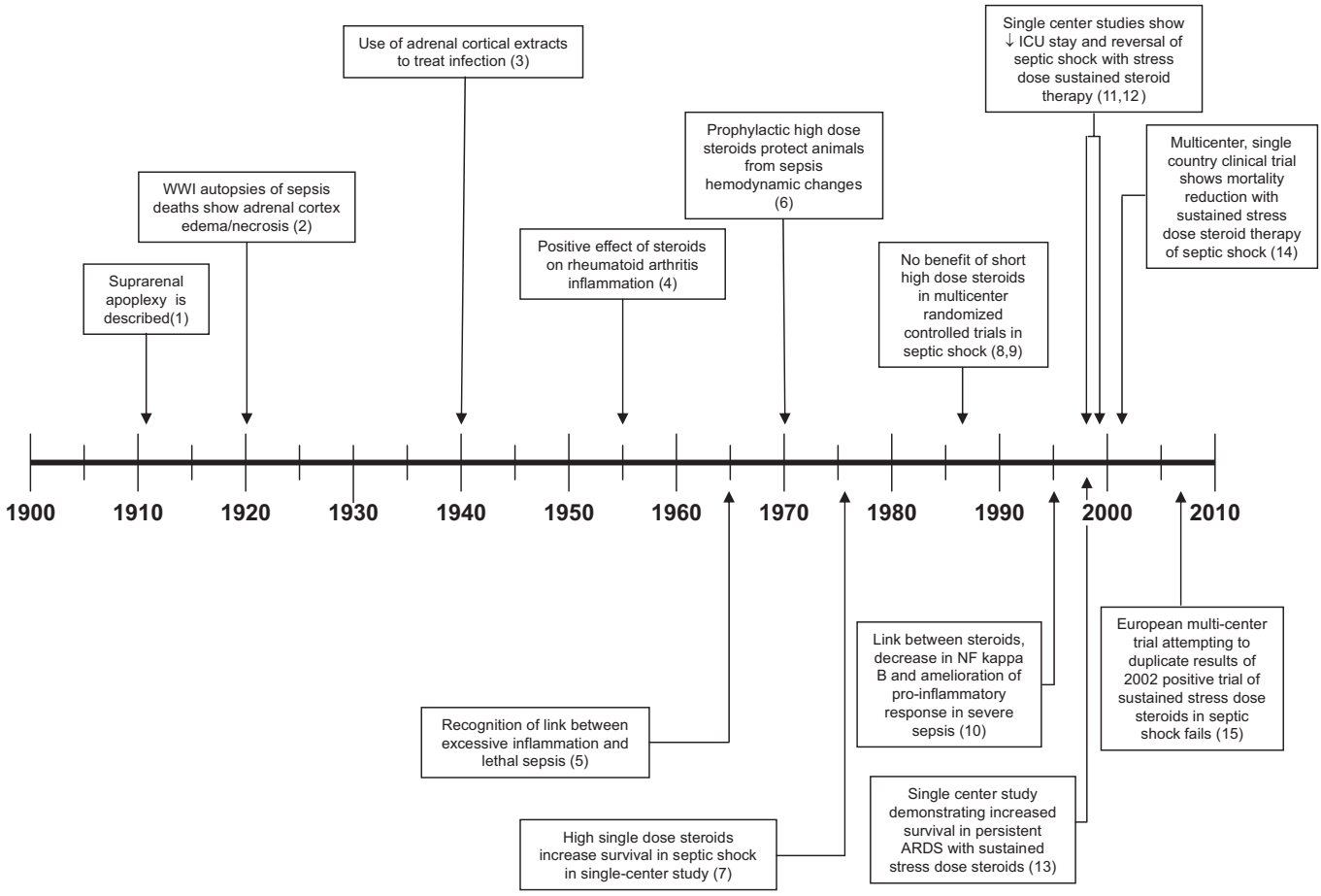

Figure 1. A history of the literature that has influenced our thought process concerning utility of steroid therapy of septic shock and acute respiratory distress syndrome.

Table 1. Steroid therapy of acute respiratory distress syndrome (ARDS)

	Early/Severe ARDS	Late/Persistent ARDS
Short duration high-dose steroids	No	Not studied. Would not be expected to work
Low-dose (stress-dose) sustained steroids	Potential. Needs further study	Improves oxygenation and patients off mechanical ventilation quicker, but no difference in outcome Select patients might benefit. Controversial

Table 2. Steroid therapy of septic shock

	Septic Shock with Blood Pressure Poorly Responsive to Fluids and Vasopressors (high dose/multiple agents)	Septic Shock Requiring Vasopressors but Single Pressor/ Lower Dose Range
Short duration high-dose steroids	No	No
Low-dose (stress-dose) sustained steroids	Yes for shock reversal; more controversial for survival but probably should be given with lower level of evidence than shock reversal.	No

ference in number of patients who had shock reversal did not reach statistical significance but a trend was present as it was in the single-center studies. More rapid reversal of shock in those patients who had shock reversal was demonstrated in the CORTICUS trial. A similar finding was present in the ARDSnet trial studying stress-dose steroids in persistent ARDS, where a decreased incidence of development of septic shock occurred in the steroid-treated group (18). So in the end as to steroid therapy of septic shock, it appears to be all about patient selection with a lingering question of survival advantage. Unfortunately, but out of necessity, both the SCPG recommendation and the SSC recommendation for septic shock are based on bedside clinician judgment of "poor" response of blood pressure to fluid resuscitation and vasopressor agents without any specific defined thresholds for this situation. There is no literature evidence that would allow specific threshold selection, i.e., "vaso-

pressors greater than ? with adequate fluid resuscitation judged by ?" My own personal bias is that following adequate (optimal?) fluid resuscitation, patients receiving two vasopressors or high-dose norepinephrine (or equivalent vasopressor) or increasing moderate doses of norepinephrine (or equivalent) would qualify for steroid treatment. Earlier is likely better. Comparing the SCPG and SSC document concerning stress-dose steroid therapy of septic shock, the recommendations for use of ACTH stimulation test, tapering of steroids with resolution of shock, and preference for hydrocortisone are essentially identical.

Concerning ARDS, it is recommended in the SCPG document that steroids be considered in patients with early severe ARDS (Pa_{O_2}:F_{IO_2} <200) and in addition before day 14 in patients with unresolving ARDS. Again the strength of recommendation is 2B. The data for decision making in acute early severe ARDS are less robust than the data for decision making in unresolving ARDS (18–20). The current data on steroids for acute severe ARDS, although encouraging, needs further validation in larger randomized trials before this therapy should be considered for general use in clinical practice. As to use of steroids in persistent (unresolving) ARDS, the authors of the SCPG document draw different conclusions than those of the ARDSnet investigators who carried out the trial of steroids in unresolving ARDS, despite that study contributing the majority of evidence for the SCPG guidelines recommendation (16, 18). The ARDSnet investigators concluded that there was no clinical benefit from use of stress-dose steroids in unresolving ARDS. Decisions for steroid use in the circumstance of unresolving ARDS need to be individualized and steroids should not routinely be used in this circumstance as no survival advantage was demonstrated in the ARDSnet trial (18). Tables 1 and 2 provide my current opinions on use of steroid therapy in ARDS and septic shock, respectively.

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REFERENCES

1. Waterhouse R: A case of suprarenal apoplexy. *Lancet* 1911; I:577–578
2. Meduri GU: An historical review of glucocorticoid treatment in sepsis. Disease pathophysiology and the design of treatment investigation. *Sepsis* 1999; 3:21–38
3. Perla D, Marmorston J: Suprarenal cortical hormone and salt in the treatment of pneumonia and other severe infections. *Endocrinology* 1940; 27:367–374
4. Kinsell LW, Jahn JP: The use of corticoids in association with antibiotics in the management of unusually severe infections. *Ann NY Acad Sci* 1955; 61:397–407
5. Breen GE, Talukdar PK: Corticosteroids in acute infections. *Lancet* 1965; 1:158–160
6. Motsay GJ, Alho A, Jaeger T, et al: Effects of corticosteroids on the circulation in shock: experimental and clinical results. *Fed Proc* 1970; 29:1861–1873
7. Schumer W: Steroids in the treatment of clinical septic shock. *Ann Surg* 1976; 184:333–339
8. Bone RC, Fisher CJ, Clemmer TP, et al: A controlled clinical trial of high dose methyl prednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987; 317:653–658
9. The Veterans Administration Systemic Sepsis Cooperative Study Group: Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. *N Engl J Med* 1987; 317:659–665
10. Scheinman RI, Cogswell PC, Lofquist AK, et al: Role of transcriptional activation of IkBa in medication of immunosuppression by glucocorticoids. *Science* 1995; 270:283–290
11. Bollaert PE, Charpentier C, Levy B, et al: Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med* 1998; 26:645–650
12. Briegel J, Forst H, Haller M, et al: Stress doses of hydrocortisone reverse hyperdynamic septic shock: A perspective, randomized, double-blind, single-center study. *Crit Care Med* 1999; 27:723–732
13. Meduri GU, Headley S, Golden E, et al: Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome. A randomized controlled trial. *JAMA* 1998; 280:159–165
14. Annane D, Sebille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288: 862–871
15. Sprung CL, Annane D, Briegel J, et al: Corticosteroid therapy of septic shock (CORTICUS). Abstr. *Am Rev Respir Crit Care Med* 2007; 175:A507
16. Marik PE, Pastores SM, Annane D, et al: Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: Consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med* 2008; 36:1937–1949
17. Dellinger RP, Levy MM, Carlet JM, et al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2008; 36: 296–327
18. The Acute Respiratory Distress Syndrome Network: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; 354: 1671–1684
19. Confalonieri M, Urbino R, Potena A, et al: Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med* 2005; 171:242–248
20. Meduri GU, Golden E, Freire AX, et al: Methylprednisolone infusion in patients with early severe ARDS: results of randomized trial. *Chest* 2007; 131:954–963