The compassionate clinician: Attending to the spiritual needs of self and others*

The heightened appreciation of the importance of spirituality is reflected in the growing number of medical schools offering courses that either focus on or include as a topic spirituality in medicine (1). Physicians are being encouraged to incorporate a spiritual history into their clinical practice to identify religious or spiritual needs and then coordinate resources to meet those needs (2–4). The majority of adult patients want physicians to inquire about spiritual beliefs, especially when facing serious or life-threatening conditions or death. An often significant minority, however, would not welcome such a discussion (5, 6). Practical guidelines have been published to assist physicians in discussing religious and spiritual issues with their patients (7).

Nevertheless, the association between spirituality or religious practices and improved health outcomes is the focus of ongoing research and debate (8–10). The distinction between religious practices and spirituality is often conflated, with empirical findings specific to one set of religious practices inappropriately generalized to all religions or to a broader spirituality as "the search for ultimate meaning." (11) Regardless, spirituality can be viewed usefully as the search for or experience of a transcendent meaning and purpose to life apart from any specific set of religious beliefs and practices. As such, spirituality plays an important role in how patients, families, and clinicians cope with the experience of suffering and death (4, 12).

Reporting on their experience with a modified program of clinical pastoral education (CPE), Dr. Todres and colleagues (13), in this issue of *Critical Care Medicine*, present one model for training clinicians in spiritual assessment and the recognition and management of spiritual distress. The program involves three general areas of instruction, including didactic sessions about the diversity of religious and spiritual beliefs, practical tools for spiritual assessment, and reflective exercises fostering personal growth and spiritual awareness. The goals of the program range from providing the "skills and literacy to explore religious and spiritual beliefs. . .in a manner that is focused and respectful" to the more ambitious incorporation of "spiritual care. . .into clinical practice" (13). The personal impact and power of the CPE experience center around the supervised provision of pastoral care and structured individual and group reflection on that clinical experience. As such, the strength of the CPE model becomes a weakness when considering whether this intensive experience *could* be adapted to other educational programs (such as critical care fellowship training) or whether physicians *should* be trained to provide pastoral care.

Dr. Todres and colleagues (13) clearly assert that physicians should provide pastoral care as part of clinical practice. In a 2002 letter written in response to the recommendation that the role of the physician and pastoral counselor be kept separate (7), Catlin and Todres (14) advocated that these two roles can be fused as the physician-patient relationship develops. The supporting evidence is their 5-month training experience in the modified CPE program (13, 14). Whether this amount of pastoral care training is sufficient remains unanswered, with the prevailing view remaining that physicians should not provide "in-depth religious counseling to patients" (4, 10, 11). An important distinction, however, should be made between providing "in-depth" pastoral care as a calling or vocation and being attentive to the spiritual needs of the patient and family. Although eschewing the role of spiritual counselor, "physicians and other health care professionals [should] be compassionate and attentive to patients' spiritual needs and know how to address those needs" (4).

Compassion, or suffering with, requires us to "risk lifting the barrier of clinical distance to become a partner with the patient in his or her human journey." Thus, CPE training focuses on the spiritual experience of the clinician so that she may "accompany" patients and family on their human journey with "similar spiritual integrity" (13). "What compassionate care asks us to do is be present to our patients fully as they suffer and to partner with them in the midst of their pain" (4). This language of "presence" reflects the insight that spiritual care is fundamentally relational (4, 12). Being fully present to our patients in the midst of their suffering requires "an attentiveness to one's own spiritual and values framework" (4). Thus, being attentive to the spiritual needs of our patients requires being attentive to our own spiritual needs. Rather than teaching technical "skills in the diagnosis and management of spiritual distress," the modified CPE program may provide clinicians the opportunity to address their own spiritual needs as they accompany patients and families who are suffering (13). Fusing the role of clinician and pastoral counselor may not be necessary or even desirable, as "the only requirement of compassionate dialog with one's patients is our humanity" (4).

Should we address spirituality with patients, families, and other clinicians in the intensive care unit? Yes. Are we ready and able to do this (15)? Over time, our "exposure to suffering and the existential questions that arise from suffering may lead to a spiritual or philosophical growth, or it may result in 'gradual wearing down of the spirit'" (4). Thus, attending to the spiritual needs of others requires that we first attend to our own spiritual distress (i.e., jading or burnout) that may manifest itself by a lack of moral or spiritual responsiveness (16, 17). Our

*See also p. 2733.

Key Words: spirituality; pastoral care; critical care; burnout; professional; professional-family relations; religion and medicine; physician-patient relations

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ability to attend to spiritual and religious needs in the intensive care unit does not require fusing the roles of pastoral counselor and physician. Rather, it requires self-reflective attention to our own feelings, values, and beliefs as we struggle to make sense of the suffering we witness. Drawing on the Buddhist tradition, Epstein presents the concept of "mindfulness" as "a quality of the physician as person" engaged in self-awareness and critical reflection, in being "present in everyday experience, in all its manifestations," enabling "compassionate informed action" (18). As presented by Dr. Todres and colleagues (13), the intensity and focus on the CPE program modified for clinicians make it difficult if not impossible to adapt it to existing training programs. However, we need to find ways to nurture among critical care clinicians the spiritual awareness (or mindfulness) necessary to accompany our patients and families compassionately on their journey of suffering. We owe it to our patients and families and, more important, we owe it to ourselves.

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The swinging pendulum of corticosteroid use in the intensive care unit: Has it swung too far or not far enough?*

Although unequivocally disproved by several large prospective trials <20 yrs ago, steroid use in the critically ill has now come back into vogue. Now it appears that steroids are used in shock, sepsis, stress, systemic inflammatory response syndrome, and trauma. Is emerging steroid use in all these patient populations a fad or is it the beginning of a sustainable trend? Either way, without doubt, the way steroids are used have changed since the 1980s, when high-dose, short-term steroids were shown to be of no benefit for the treatment of septic shock and possibly even harmful (1). Since then, some (2, 3) but not all (4) recent prospective randomized double-blinded studies have shown that low-dose (200–300 mg/day), longer-term (~7 day) corticosteroid therapy improves survival in vasopressor-dependent patients with septic shock. Additionally, regardless of its effect on survival, in all these studies, the time on vasopressors was significantly reduced and essentially all clinicians who have used corticosterone in vasopressor-dependent patients can recall patients whose response to the steroids was almost miraculous. These beneficial effects of corticosterone on the vasculature are not surprising, since beginning with physiologic studies carried out in patients with Addison's disease, it became clear that cortisol has important actions on the circulation, including the maintenance of vascular tone as well as the ability to potentiate the vasomotor actions of catecholamines. However, what is surprising is the fact that these almost physiologic doses of steroids were effective even though the cortisol levels in these patients were generally elevated many-fold higher than normal. This led to the notion that certain patients may have "relative" or "functional" adrenal insufficiency even though their basal cortisol levels were supranormal. The mechanism of this relative cortisol resistance remains to be fully determined but may involve the effects of circulating proinflammatory factors, such as cytokines and nitric oxide, as well as catecholamine receptor densensitization and down-regulation. Nonetheless, at this point, based on encouraging clinical studies and the concept of relative adrenal insufficiency, the notion of low-dose, longer term steroid therapy in vasopressor-

*See also p. 2737.

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dependent patients in septic shock seems established.

Because trauma (tissue injury), hemorrhage, surgery, and severe illness, just like septic shock, are all accompanied by activation of the hypothalamic-pituitary-adrenal axis and increased serum corticotrophin and cortisol concentrations, patients in these populations may also be at risk of developing relative adrenal insufficiency. Consequently, it is not unreasonable to speculate that individuals in these patient populations might be at risk of developing relative adrenal insufficiency and hence might also benefit from low-dose steroid therapy, especially if they are vasopressor dependent. Now comes a problem, which is how to define the condition of relative adrenal insufficiency. Identifying patients likely to have relative adrenal insufficiency is necessary unless one wishes to empirically treat large numbers of patients hoping some respond. Since some of the potentially beneficial effects of steroids, such as limiting the immuno-inflammatory response (5, 6), may cause harm in infected patients with an adequate adrenal response, the indiscriminate use of steroids in intensive care unit (ICU) patients is potentially hazardous. To this end, several operational definitions of relative adrenal insufficiency have been proposed. These include a failure to increase total plasma cortisol >9 μg/dL after stimulation with corticotrophin (2), a basal cortisol level <15 μg/dL (5), or failure to have a cortisol level >20 μg/dL after stimulation (7). However, based on which definition of relatively adrenal insufficiency was used, one prospective study of ICU patients with severe sepsis found that the incidence of adrenal insufficiency would vary from 9% to 50% of the patients (7). The fact that the adrenal cortisol response increases as the magnitude of the stress increases and that the highest levels of plasma cortisol are found in moribund patients (5) further compounds the utility of defining relative adrenal insufficiency based on assays of plasma cortisol. Furthermore, in contrast to the study of Annane et al. (2) in patients with septic shock, other studies have not documented a differential response to low-dose steroid treatment between those patients who met the operational definition of relative adrenal insufficiency and those who did not (3, 8). In trying to resolve this issue it is important to keep certain physiologic principles related to cortisol bioactivity in mind. First, only free and non-protein-bound cortisol is active, and second, approximately 90% of cortisol is protein bound. To date, only one large study has measured the levels of free plasma cortisol in ICU patients (9). This study found that although basal total plasma cortisol was lower in hypoproteinemic patients (albumin ≤2.5 g/dL) than patients with higher albumin levels, there was no difference in their free cortisol concentrations (5.1 vs. 5.2 μg/dL) (9). Furthermore, the free cortisol levels of these patients were almost nine-fold higher than those observed in normal volunteers (0.6 μg/dL). Thus, at present the definition of relative adrenal insufficiency in the critically ill appears to be at least somewhat arbitrary, making it somewhat difficult to decide which patients would or should be candidates for steroid therapy.

With this background, I would like to consider the study by Dr. Hoen and colleagues in this issue of *Critical Care Medicine* (10). In this study, the authors documented that cortisol administration increased the sensitivity to phenylephrine in 23 trauma patients. With the exception of the use of etomidate in half of their patients (which inhibits cortisol synthesis), the study is very well done. Nonetheless, my bias is that this is a study where the pendulum of steroid therapy may have swung too far. First, I see no clinical rationale for giving cortisol to trauma patients at the end of the resuscitation period, since these patients are at increased risk for future infection, hydrocortisone is immunosuppressive, and there are no prospective randomized trials, outside of patients in septic shock, showing that steroid therapy improves survival in trauma patients or the critically ill. Second, the authors did not find a difference in the pressor response to cortisol between patients who did or did not respond to a corticotrophin stimulation test, indicating that this effect of steroids was not likely related to an "adrenal insufficiency state." Additionally, since the pressor response to catecholamines is increased by cortisol even in healthy volunteers, what is the clinical significance of this observation? In fact, in an earlier publication studying a similar trauma population (11), this group found that there was no difference in morbidity or mortality between trauma patients who did and did not respond to a corticotrophin stimulation test.

Thus, what might we learn from this study? To me it indicates that the pressor response to cortisol does not correlate with the results of cortisol stimulation tests, further bringing the reliability of the corticotrophin stimulation test as an indicator of adrenal insufficiency into question. Second, it re-raises the important issue of considering the potential risk-benefit ratio of steroid therapy in the critically ill. Third, it highlights the notion that although it is critical to move forward in this area, we must move forward with caution.

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Refrigerated intravenous fluids: Kick-starting the cooling process*

Hypothermia is often referred to as "nature's gold standard" for neuroprotection. Over the past decade, an overwhelming collection of experimental evidence has established that even small fluctuations in brain temperature can profoundly influence the extent and severity of ischemic neuronal injury (1). After being used for decades in the operating room to provide neuroprotection during cardiac and neurologic surgery, more recently therapeutic temperature modulation has entered clinical practice in the intensive care unit and emergency department. In the intensive care unit, the most common indication for lowering body temperature is to control fever in neurologic patients (2). Taking it one step further, induced mild to moderate (33°C) hypothermia has been shown to be effective for lowering intracranial pressure in patients refractory to conventional therapy (3) and has been tested as an acute neuroprotective intervention for traumatic brain injury, cerebral infarction, and global hypoxic-ischemic injury after cardiac arrest (4–7).

Although the jury is still out on whether hypothermia is beneficial when given acutely for ischemic stroke and trauma, two trials have shown impressive results in comatose survivors of cardiac arrest. In the larger of these studies (n = 273), conducted by Fritz Sterz and colleagues (6), patients cooled to 33°C within 8 hrs of the arrest were 40% more likely to be independent with a mild or moderate disability at 6 months than those treated with standard supportive care (55% vs. 39%; $p = .009$). Reinforcing the notion that hypothermia is a real and credible method for reducing global hypoxic-ischemic injury was a similar study by Bernard and colleagues (7), published in the same issue of the *New England Journal of Medicine*. These investigators randomly assigned 77 patients to normothermia or mild hypothermia for 12 hrs after return of spontaneous circulation and found that the proportion with a good outcome (discharge to home or a rehabilitation facility) in the hypothermia group was nearly twice that in the normothermia group (49% vs. 26%; $p = .046$). In both studies, adverse events (most notably, infectious complications) occurred more frequently with hypothermia, but these differences were not significant.

Perhaps the most surprising aspect of these trials is the fact that the clinical benefits associated with hypothermia occurred despite long delays in attaining target body temperature. In the study of Sterz et al., the median interval from return of spontaneous circulation to attaining a temperature below 34°C was 8 hrs. Part of the difficulty in cooling these patients may have resulted from the use of a cooled-air convection cooling system, which has been shown to be less effective than conduction cooling (8). Cooling was faster in the trial of Bernard and colleagues because surface cooling with ice packs began in the ambulance: mean core body temperature was 33.5°C just 2 hrs after the return of spontaneous circulation. The long delay in attaining target temperature raises an important question: Would the results have been even better with more rapid cooling?

In this issue of *Critical Care Medicine*, Polderman and colleagues (9) present safety and efficacy data for a simple and efficient method for accelerating the cooling process when mild to moderate hypothermia (target temperature, 33°C) is the goal. When used in combination with a water-circulating cooling blanket, an average volume of 2.3 L of refrigerated (4°C) saline, with or without the addition of colloids, infused over 50 mins led to a mean reduction in core body temperature from 36.9°C at baseline to 32.9°C at 1 hr. Remarkably, even with the relatively large volumes administered, there were no episodes of pulmonary edema, cardiac arrhythmia, or other serious adverse events in the 134 patients who were studied.

This study confirms the results of several smaller studies evaluating the use of refrigerated Ringer's lactate or normal saline (10, 11) and should encourage clinicians to begin to apply this practice. Until better evidence is available to support the use of early mild to moderate hypothermia for acute ischemic stroke or traumatic brain injury, for now this protocol should probably be applied only to mechanically ventilated survivors of out-of-hospital cardiac arrest. The protocol as described calls for infusion of 1500 mL of chilled saline over the first 30 mins, followed by additional 500-mL boluses every 10 mins as needed until a temperature of <33.5°C is attained. Central venous pressure monitoring is desirable; the infusions were temporarily stopped if central venous pressure increased more than 5 mm Hg over 5 mins. Continuous temperature monitoring with a rectal probe or bladder catheter probably represents the simplest and most accurate way to measure core temperature during the infusion. Finally, one must be vigilant to avoid potassium, magnesium, and phosphate depletion during and immediately after the infusion, particularly given the increased risk of cardiac arrhythmia that occurs with induced hypothermia. Careful attention to all of these details on the part of the investigators may explain in part the low complication rate in this study.

In summary, the infusion of refrigerated fluids seems to be a viable adjunct to either surface or endovascular cooling for the rapid induction and maintenance of therapeutic hypothermia. However, it remains to be seen whether "kick-starting" the cooling process in this way can positively influence outcome. Now that we know that such infusion is feasible, placebo-controlled clinical trials are needed to determine whether cooled-fluid infusion should become a standard of care for survivors of out-of-hospital cardiac

*See also p. 2744.

Key Words: intravenous fluids; hypothermia; cooled-fluid infusion

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arrest in ambulances and emergency departments around the world.

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Reversible myocardial dysfunction in sepsis and ischemia*

The provocative paper by Dr. Levy and colleagues (1) in this issue of *Critical Care Medicine* provides elegant *in vivo* data comparing the metabolic effects of infection and ischemia in a well-defined murine model. The authors enthusiastically state, "Our findings represent the first demonstration of hibernation in a nonischemic disease state." The authors may have unintentionally left the impression that the similarities between the myocardial effects of ischemia and infection have not been previously appreciated. A brief review of some pertinent basic and clinical studies should help to provide a context within which the reader can appreciate both the implications and limitations of the authors' contribution. These studies focus on the molecular mechanisms responsible for reversible myocardial dysfunction observed in a variety of clinical and experimental conditions, including, but not limited to, hibernating myocardium and sepsis.

Reversible myocardial dysfunction was first identified in the opened chest dog model when myocardial ischemia followed by reperfusion was shown to be associated with a transient period of depressed contractility (2). The clinical implications of these experimental observations were not fully appreciated until sophisticated imaging techniques enabled clinicians to assess myocardial contractility and viability noninvasively in patients (3). This phenomenon is generally referred to as myocardial "stunning" and contrasts with myocardial "hibernation" that results from chronic ischemia (4). Hibernating myocardium also contrasts with stunned myocardium in that it was first described clinically and later studied experimentally (5). A clinically important feature of hibernating myocardium is that revascularization by catheter and/or bypass surgery restores cardiac function. Another strength of the contribution by Dr. Levy and colleagues (1) is that the *in vivo* imaging techniques used in their murine model are clinically employed to distinguish between reversibly depressed, hibernating myocardium and permanently damaged, infracted myocardium.

A number of nonischemic conditions have also been shown to be associated with reversible myocardial depression in animal models and humans. The systemic inflammatory response syndrome seen in sepsis is one such condition that may serve as a paradigm for reversible myocardial depression associated with both ischemic and nonischemic etiologies. The myocardial effects of sepsis have three characteristics shared by myocardial ischemia and chronic heart failure: a) activation of inflammatory mediators; b) reversible myocardial depression; and c) β-adrenergic desensitization (6–10). These observations and others have led us to propose that activation of inflammatory mediators contributes to the reversible myocardial depression and β-adrenergic desensitization reported in such disparate clinical and experimental conditions as *s*epsis, *t*rauma, *i*schemia, *t*ransplant rejection, myocarditis, and *h*eart failure ("STITCH syndrome") (11–13). This brings us to the next question: Just how similar are the molecular mechanisms involved in the host responses to ischemia and infection? An answer to this question may be provided from insights derived from elegant parallel studies into the mechanisms responsible for ischemic preconditioning and LPS cross-tolerance.

Ischemic preconditioning was described by Murry et al. (14) as the phenomenon of myocardial protection that occurs following brief periods of ischemia with intermittent reperfusion. Astute clinicians appreciated from clinical trial data that patients who presented

***See also p. 2752.**

Key Words: hibernating myocardium; myocardial depression; nitric oxide; lipopolysaccharide tolerance; ischemic preconditioning; sepsis

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with a stuttering course of intermittent chest pain before their myocardial infarction fared better than those who did not (15). The molecular mechanisms responsible for the early and delayed protective effects are not fully understood. Ping et al. (16) reported that the nitric oxide (NO) donor, S-nitroso-N acetylpenicillamine, induced preconditioning via activation of protein kinase C in the rabbit heart. NO donors have also been shown to induce late preconditioning by generation of oxidant species, $ONOO^-$ and/or OH^- (17).

LPS cross-tolerance was identified when pretreatment with lipopolysaccharide (LPS) or monophosphoryl lipid A (a nontoxic analogue of endotoxin) was reported to induce a cardioprotective effect against subsequent ischemia (18). NO also appears to play an important role in LPS and monophosphoryl lipid A induced cardioprotection. Cytokines are well known to induce NO production following LPS exposure *in vivo* (11, 19). Thus, LPS and ischemia can each trigger a cytokine-mediated response to injury by cardiac myocytes or other resident intramyocardial cells to produce NO to protect the heart from subsequent potential insults such as ischemia or infection.

Mitogen activated protein (MAP) kinases are intracellular enzymes that phosphorylate proteins in response to inflammatory mediators (e.g., cytokines) and stress (e.g., ischemia/reperfusion) (20–24). Experimental evidence is accumulating supporting a role for p38 MAP kinase in ischemic preconditioning and in β-adrenergic receptor signaling in the heart (25–30). p38 MAP kinase has been reported to be activated by ischemia (23, 25, 31, 32). In particular, p38 MAP kinase activation has been reported to be associated with increased glucose transport (GLUT-4) and NO in hibernating myocardium (33). Inhibition of p38 MAP kinase activity has also been reported to block the cardioprotection conferred by ischemic preconditioning (34).

Sepsis has served as the paradigm for cytokine-induced expression of NO (35). Much unsuccessful effort has been invested in regulating the presumed exclusively deleterious effects of cytokine-induced NO production in sepsis. This view of cytokine-induced NO production appears to be too simplistic and avoids a truly important fundamental question: What is the biological advantage to cytokine-induced NO production? Evidence has already been provided that cytokine-induced NO production by inducible NO synthase plays an important role in the normal host response to infection (36). Intriguing reports by Badorff et al. (37, 38) shed additional light on these important questions by providing a potential molecular mechanism for a protective role for NO in viral infection. The authors demonstrated that coxsackie B3 virus possesses a protease (2A) that cleaves an integral membrane glycoprotein, dystrophin, in human and mouse cardiac membranes (37, 38). They next provided evidence that NO donors can s-nitrosylate a cysteine residue that is essential for catalytic activity of protease 2A. Thus, the elaboration of NO by cardiac myocytes may prevent dystrophin cleavage by inactivating viral protease 2A. These data help to explain previous reports that NO inhibits coxsackie B3 virus replication *in vitro* and the augmentation of coxsackie B3 virus infection in inducible NO synthase-deficient mice (39).

The rationale for exploring the effects of NO on dystrophin cleavage evolved from previous work by others demonstrating the presence of a dystrophin defect in genetic cardiomyopathy (37, 38). This illustrates the potential for evoking the same molecular mechanism for an acquired as well as a genetic defect. A genetic defect in dystrophin alone is sufficient to result in developing a rare cardiomyopathy. A virally acquired defect in a susceptible dystrophin isoform may also be sufficient to develop a relatively more common cardiomyopathy. This would further suggest that defects in this NO-mediated host response to viral infection could also contribute to some of the variability in the natural history of idiopathic cardiomyopathy. Too little NO could allow greater viral invasion. Too much NO in response to norepinephrine, angiotensin II, and/or tumor necrosis factor could depress mitochondrial activity and lead to apoptosis (40–42).

Dr. Levy and colleagues (1) also provide evidence that cytochrome oxidase plays a role in the reversible myocardial depression in their murine sepsis model. Interestingly, NO has also been shown to inhibit cytochrome oxidase (43, 44). Thus, the data from Dr. Levy and colleagues support the hypothesis that NO contributes to reversible myocardial depression through inhibition of cytochrome oxidase. Further support for a NO-mediated mitochondrial defect in sepsis can be found in a study showing that inhibition of NO synthase attenuated the impaired mitochondrial function induced by serum from septic patients (45).

The host responses to infection and ischemia are clearly essential for survival. It should not be surprising that the adaptations to these stresses would share common phenotypic features and signaling pathways. The article by Dr. Levy and colleagues (1) provides an opportunity to reflect on the elegance of nature in designing such a versatile and adaptive system for survival. Elucidating the molecular survival pathways activated by ischemia and infection is a public health imperative that promises to provide new therapeutic targets for the management of our most challenging patients.

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Admission hyperglycemia and outcome: The ongoing story*

In the late 19th century, Claude Bernard described for the first time that acute injury was associated with the development of hyperglycemia. One and a half century further, the hyperglycemia debate is still going on.

An increasing number of studies have examined the effect of admission hyperglycemia on outcome. Most of these studies focused on the association between hyperglycemia and increased risk of death in patients with myocardial infarction and stroke.

In this issue of *Critical Care Medicine*, Dr. Whitcomb and colleagues (1) describe the impact of admission hyperglycemia on hospital mortality rate in a mixed population of 2,713 critically ill patients. Higher mortality rate was observed in hyperglycemic nondiabetic patients admitted to the cardiac, cardiothoracic surgical, or neurosurgical intensive care unit (ICU) but not in hyperglycemic patients admitted to the medical or general surgical ICU or in diabetic patients.

This is the first article on the effect of admission hyperglycemia in a large and mixed population of critically ill patients. The results of Dr. Whitcomb and colleagues (1) are in line with the findings of studies in patients with myocardial infarction or with stroke. Capes et al. (2, 3) described in these patient groups an association between admission hyperglycemia and in-hospital mortality rate for nondiabetics, whereas this association was absent or weaker for diabetics. Norhammar (4) found that in nondiabetics with myocardial infarction, increased plasma glucose levels were associated with worse outcome. The impact of hyperglycemia for patients without diabetes has also been reported by Umpierrez et al. (5), who found that these patients had a more than six-fold increase in hospital mortality, were more often admitted to the ICU, and had a longer hospital stay compared with diabetic patients.

However, the study of Dr. Whitcomb and colleagues (1) has some weaknesses. The use of a single blood glucose value to define if a patient is hyperglycemic may be problematic. It is hard to believe that hyperglycemia on admission can predict outcome in such a diverse cohort of patients. Although the authors corrected for severity of illness, admission blood glucose levels may have been simply collinear with other covariates with an important impact on outcome such as sepsis, shock, and the likely use of steroids, vasoactive agents, or immunosuppressants. Multiple measurements may improve accuracy of the effect of hyperglycemia on outcome.

Another flaw may be the use of a threshold value of >200 mg/dL blood glucose to classify patients as being hyperglycemic. Previous studies on admission hyperglycemia have used blood glucose levels far below this value (2, 3, 6, 7). The authors noted that their findings were the same when ≥150 mg/dL was used as the cutoff for defining hyperglycemia, but this analysis was not reported in detail, although it may have been quite interesting.

Due to the lack of glycosylated hemoglobin and the unclear definition of diabetes, it is likely that dysglycemic patients or patients with undiagnosed diabetes were classified in the hyperglycemic nondiabetic group, and this may have biased the results.

Finally, there might be a power issue. Only 21.2% of the patients had a history of diabetes. This could imply that the study lacked power to find a significant effect on mortality in diabetic patients.

Questions may arise involving clinical implications of this article. The first to be answered is whether aggressive therapy of high admission blood glucose can affect outcome. Although large trials are still ongoing, at this moment there is no evidence that strict metabolic care improves prognosis in a general ICU population, as it has been demonstrated to do in diabetics with acute myocardial infarction (8) and in postsurgical critically ill patients (9). This study (1) adds to the increasing evidence that hyperglycemia negatively affects outcome. However, because Dr. Whitcomb and colleagues (1) did not mention it, it is unlikely that the patients were treated according to a "tight glycemic control" protocol. Will a single admission glycemia measurement be as predictive for mortality in patients if tight glycemia protocols are used? Anyway, the introduction of insulin protocols to target glycemia in specific ranges has become a new standard of care in a lot of ICUs. Of 36 ICUs screened in Europe, >80% used intravenous insulin protocols (10). Protocols are not selected for specific patient groups. Although target glycemia varied largely, half of these ICUs tried to maintain blood glucose <150 mg/dL according to the Surviving Sepsis Campaign guidelines (11).

The second question to be considered is the possible positive role of insulin in diabetic patients as assumed by the authors. The findings of Van den Berghe et al. (12) and Finney et al. (13) suggest that lowering blood glucose rather than insulin therapy was the primary factor in lowering mortality rate in their studies. Insulin is known to have anti-inflammatory, vasodilatory, and antiplatelet effects (14). In septic patients, insulin may act as an inflammatory modulator that can prevent and possibly stop undesirable activation (15) of the inflammatory cascade. The finding that hyperglycemia is at least as, or even more, deleterious in nondiabetic patients as it is in diabetic patients can partly be explained by the fact that nondiabetics are less likely to receive therapy to control glycemia. Unfortunately, data about insulin therapy in the diabetic patients are missing. Further trials are warranted to disclose the exact role of insulin in critically ill patients.

The role of admission blood glucose on outcome is an interesting issue because blood glucose is measured easily and can be influenced readily. Screening patients at admission for hyperglycemia and diabetes is a relatively simple and inexpensive procedure that may increase the likelihood of further glucose control during hospitalization. This study (1), al-

*See also p. 2772.

Key Words: hyperglycemia; diabetes; insulin; outcome; nondiabetic patients

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though retrospective and observational, has the potential to give additional information about the impact of admission hyperglycemia on hospital mortality rate. It should therefore attract attention to the heavily debated problem of hyperglycemia in a mixed population of critically ill patients.

"A fact in itself is nothing. It is valuable only for the ideas attached to it, or for the proof which it furnishes." Claude Bernard (1813–1878)

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How accurate are currently used methods of determining glycemia in critically ill patients, and do they affect their clinical course?*

In this issue of *Critical Care Medicine*, Kanji et al. have examined the accuracy of different methods of determining circulating glucose levels in critically ill patients, which is crucial for monitoring glucose levels and, hence, for adjusting therapies to obtain and maintain euglycemia (1). Patients requiring prolonged intensive care have varying degrees of insulin resistance and hyperglycemia, the severity of which reflects the course of the illness and the risk of death (2, 3). Following a number of publications demonstrating a substantial morbidity and mortality benefit when glucose levels were maintained within a strictly defined normal range with insulin administration, this approach has been incorporated into the clinical management of critical illness in many intensive care units around the world (4, 5).

Post hoc analysis of a seminal study by Van den Berghe et al. revealed a linear correlation between the degree of hyperglycemia and the risk of death, which persisted after correction for insulin dose and severity-of-illness scores (3). Indeed, even patients who had only moderate hyperglycemia (110–150 mg/dL, or 6.1–8.3 mmol/L) had a higher risk of death than those who were intensively treated with insulin to restore blood glucose levels to <110 mg/dL (6.1 mmol/L). Multivariate logistic regression analysis confirmed the independent role of blood glucose control in achieving most of the clinical benefits of intensive insulin therapy and underlined the importance of lowering the blood glucose level to strict normoglycemia. Cellular glucose overload and/or potentially toxic effects of altered glycolysis and/or oxidative phosphorylation were proposed as possible mechanisms to explain the deleterious effects of hyperglycemia in intensive care patients (2). More recently, it was shown that insulin infusion to restore euglycemia was associated with a marked reduction in many inflammatory indices, such as adhesion molecules, hepatic inducible nitric oxide synthase, and plasma nitric oxide metabolites, suggesting that the reduction in inflammatory mediators may be responsible for the impressive improvement in clinical outcomes observed with insulin therapy (6).

These findings suggested a new paradigm in which glucose and insulin influence the organism not only through their crucial roles in metabolism but also through their respectively stimulatory and inhibitory effects on inflammation

*See also p. 2778.

Key Words: glycemia; critical illness; insulin infusion; intensive care unit

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(7). Thus, glucose appears to act as a proinflammatory agent, with insulin being antiinflammatory indirectly through normalization of plasma glucose concentrations and directly through antiinflammatory actions on several target tissues. In addition, insulin, as an anabolic hormone, could help reduce the catabolic state induced by severe inflammation (6, 7). Thus, insulin infusion could be of potential benefit in conditions characterized by severe systemic inflammation, such as major surgery, septic shock, and the acute respiratory distress syndrome. The use of insulin infusions to maintain normoglycemia has already been shown to be of benefit during cardiac surgery (8) and in medical intensive care unit patients (5). Furthermore, the antiinflammatory effect of insulin was confirmed in rats injected with endotoxin (9) and in patients with severe forms of hyperglycemia, including diabetic ketoacidosis (10). Similarly, insulin infusion was antiinflammatory and cardioprotective in acute myocardial infarction (5).

Achieving and maintaining strict glucose control with use of insulin infusions is not without hazards. Similarly to previous studies, where optimal glucose control with intensified insulin treatment was accompanied by side effects, intensive insulin therapy in critically ill patients was also associated with a higher incidence of hypoglycemia than in patients treated conventionally (4). It was believed, however, that such episodes did not lead to clinically relevant consequences, as the use of an insulin titration algorithm guaranteed that when hypoglycemia did occur, it was always quickly resolved (2, 4).

To initiate and maintain a continuous insulin infusion, frequent glucose measurements, which traditionally have been determined with capillary blood, are required. This approach is safe and cost-effective for adjusting insulin requirements and to achieve appropriate target glucose values. Although several studies have questioned the accuracy of the glucose concentrations obtained with this method in relation to a reference standard for critically ill patients, several limitations in the design of these studies may have affected their clinical significance (11–13). The study by Kanji et al. (1) is unique in that it demonstrates relatively poor agreement between methods of glucose estimation of capillary and/or arterial/gas blood and the method of the central laboratory. This agreement was as low as 26.3% with glucose meter analysis of capillary blood when glucose values within the defined hypoglycemic range < 4 mmol/L (72 mg/dL) were considered (1). In addition, this study provides useful evidence that no differences of glucose estimations exist when these are applied to patients with different pathologies, clinical signs, and/or treatment (1).

A major point of the Kanji et al. study is that it raises further concerns that the accuracy of glucose measurement from capillary samples may not be acceptable for critically ill patients (1, 14). The risks of failure to detect a hypoglycemic episode or a spurious detection of such an episode were 11% and 3%, respectively, with use of capillary blood vs. either the standard laboratory or arterial/gas analysis reading (1). As the authors state, disagreement during periods of normoglycemia or hyperglycemia is less likely to be associated with an adverse clinical outcome (the latter has now become a rare event with the use of insulin infusions); however, this may not be the case during periods of hypoglycemia, where the presence of true low glucose concentrations could be missed and the low circulating glucose might not be adequately and rapidly corrected (1). This raises some questions regarding the safety of this approach, as even moderate hypoglycemia is associated with a significant stress response, behavioral changes, and alterations in cerebral blood flow and metabolism (15). It is unclear what effect prolonged or repeated episodes of moderate hypoglycemia may have on patient outcome. Depending on its severity and duration, hypoglycemia has varying influences on neurologic function, and this should be taken into account (15).

The limitations of insulin infusion titration to maintain euglycemia, based on the widely used capillary blood analysis outlined in this study, may have important clinical implications, particularly in the subgroup of patients in whom alterations of insulin infusion rates are made on the basis of low capillary blood glucose level. It is not known whether extremely low glucose levels may induce a "stress reaction" and/or promote a proinflammatory response similar to that noted with hyperglycemia (6). However, in order to suggest that the maintenance of euglycemia in critically ill patients could, particularly with respect to low glucose estimations, affect their long-term outcome, a controlled, prospective study must be performed. In such a study, the outcomes for carefully selected patients need to be analyzed according to the alterations of insulin infusion rates made on the basis of glucose readings from capillary, arterial, and/or reference laboratory analyses.

Although the design of the Kanji et al. study was sufficient to identify disagreements between the different methods used to estimate glucose levels, a larger-scale study could possibly identify a "correction factor" that might help adjust critical glucose values obtained from capillary glucose analysis according to reference values, leading to appropriate changes in insulin infusion rates. Similarly, a study comparing patient outcome on the basis of capillary glucose vs. arterial/gas analysis measurements—as the latter exhibits a better correlation with the reference laboratory analysis—will provide further supporting evidence. Until such results become available and in order to maintain cost-effectiveness, use of capillary glucose measurements as a guide for adjusting insulin infusion rates in critically ill patients should remain the method of choice. When low glucose readings are obtained that could indicate alterations of the insulin infusion rate, confirmation of such values by arterial/gas analysis and/or central laboratory measurements may be required.

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Nitric oxide and inflammatory cytokines in the heart: The presence of positive feedback loops*

Since the discovery of nitric oxide (NO) in the late 1980s, its role in the regulation of the cardiovascular system has gradually expanded to the point that it is now considered a key modulator of cardiovascular function in physiologic and pathophysiologic conditions (1). Initially described as "endothelium-derived relaxing factor," NO generated by a constitutive NO synthetase (cNOS) in endothelial cells was shown to effect vascular smooth muscle relaxation in intact vascular rings exposed to acetylcholine (2). Subsequent studies implicated NO as the end-effector of vasorelaxation in response to a variety of intermediary stimuli including bradykinin, substance P, histamine, and shear stress (1, 3, 4). Later, NO produced by an inducible NO synthetase (iNOS) was also found to be responsible for vasorelaxation and vascular collapse in septic shock and related conditions (1, 5).

With respect to the heart, the role of cNOS-generated NO was initially extended to regulation of normal cardiac contractility in a series of *in vitro* and *in vivo* studies (1, 6, 7). Nitric oxide donors were found to directly modulate myocardial contractility and relaxation by generation of cyclic guanosine monophosphate (cGMP) *in vitro* and *in vivo* (8–10). Later studies also implicated NO (produced by both cNOS and iNOS) as a key mediator of inflammatory cytokine and sepsis-associated myocardial dysfunction (11, 12). Inflammatory cytokines (including tumor necrosis factor-α, interleukin-1β, interleukin-6) alone and in synergistic combinations, supernatants of activated macrophages, and serum from patients with acute septic shock were found in several studies to induce both early and late depressant effects on isolated cardiomyocytes through NO and cGMP-dependent mechanisms (11, 13).

In their elegant study in this issue of *Critical Care Medicine*, Dr. Maas and colleagues (14) bring the story full circle. They again demonstrate that NO donors induce contractile depression of isolated myocytes by a cGMP-dependent mechanism. They also make the startling observation that both NO donors and a membrane-permeable cGMP analogue, in addition to inducing myocyte contractile depression, provide a positive feedback stimulus for generation of proinflammatory cytokines by cardiomyocytes.

Although cardiomyocyte generation of cytokines has clearly been demonstrated in various models of myocardial injury (e.g., myocardial ischemia/reperfusion injury, inflammatory cardiomyopathy, septic myocardial dysfunction) (15–17), the suggestion that NO and cGMP may provide positive feedback stimulus to help generate proinflammatory cytokines within the heart is novel. This observation has significant implications, particularly regarding further research in the field.

If a positive feedback mechanism involving NO stimulation of myocardial proinflammatory cytokine production plays a significant pathophysiologic role in inflammatory cardiac dysfunction, one important question that is arises is the underlying signaling pathways. As the authors suggest, one possibility is direct myocardial injury from peroxynitrite formed by NO interaction with oxygen radicals. However, other possibilities will need to be examined.

Perhaps the most intriguing aspect of this observation relates to potential therapeutic approaches to inflammatory myocardial dysfunction. The existence of positive feedback loops suggests that interruption of this loop at any one of several points could have broader salutary effects than might be immediately apparent. For example, cardiac-specific neutralization of NO activity could reduce injury in myocardial inflammatory states by attenuating direct NO-mediated depression of myocyte contraction, limiting NO-associated peroxynitrite generation, and reducing local proinflammatory cytokine production within the myocardium. Approaches involving targeted interruption of multiple points within the feedback loop might also be envisioned as one way to focus therapy on inflamma-

***See also p. 2794.**

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tory cardiac dysfunction while limiting adverse effects elsewhere.

This study by Dr Maas and colleagues (14) opens an important new window into how inflammatory myocardial damage associated with septic myocardial depression, myocardial ischemia/reperfusion injury, and inflammatory cardiomyopathies develops and propagates. Further research into this question is clearly required to bring the clinical and therapeutic implications of these observations to fruition.

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Ventilator-induced diaphragmatic dysfunction: Keep working*

Although mechanical ventilation is essential to support acutely ill patients, it is associated with complications such as barotrauma, ventilator-associated pneumonia, cardiovascular collapse, tracheal injuries, and ventilator-associated lung injury. Ventilation-induced diaphragm dysfunction (VIDD) is a subtle complication and has been detected more recently than other complications (1). VIDD was described in rats, rabbits, piglets, and baboons. Owing to the use of different animal species, mechanical ventilation durations and protocols, some results are still controversial, in particular the myosin type modification and fatigue resistance. On the other hand, animal studies consistently found that controlled mechanical ventilation leads to a decrease in the force-generating capacity of diaphragm in a time-dependent manner. This decrease in diaphragm force was associated with atrophy and increased MAFbox gene expression, structural abnormalities of diaphragm muscle fibers, oxidative injury, increased 20S proteasome-mediated proteolysis, and decreased diaphragmatic protein synthesis. The basic mechanisms leading to VIDD seem to be disuse and passive shortening of the diaphragm.

Although the evidence for VIDD in animals is convincing, conclusive proof for the existence of VIDD in humans is missing. Indirect evidence showing that VIDD could affect humans includes the demonstration of VIDD in baboons (2) and in rats, a species that have similar diaphragms to humans in fiber-type composition, gross anatomical features, and function (3). In addition, in humans, many weaning failure patients displayed diaphragmatic weakness (4), and clinically stable mechanically ventilated patients had a reduced twitch transdiaphragmatic pressure elicited by supramaximal magnetics of the phrenic nerves compared with normal subjects (5).

Considering that human diaphragm may be susceptible to VIDD, the next question should be, Is VIDD clinically relevant? Taking into account that around 20% of mechanically ventilated patients are difficult to wean, that the imbalance between increased workload

***See also p. 2804.**

Key Words: mechanical ventilation; myogenic regulatory factors; diaphragm; intermittent spontaneous breathing; adverse effects; respiratory muscle

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and inspiratory muscle endurance is an important determinant of ventilator dependence (6), and that twitch pressure revealed considerable diaphragmatic weakness in many weaning failure patients (4), we could picture VIDD as a relevant phenomenon. Again, the importance of VIDD in difficult to wean patients is not easy to prove due to many confounding factors (i.e., corticosteroid use, sepsis, neuromuscular blockage). Moreover, in rabbits the diaphragm force required to sustain spontaneous breathing was only around 11% of its maximum (7), and extrapolating this finding to humans, VIDD would be a determinant of weaning failure only in the presence of elevated respiratory system impedance, a fact expected if the condition that brought the patient to mechanical ventilation was not completely reversed or if a new respiratory system disturbance developed during mechanical ventilation.

If we consider VIDD as a major or minor factor leading to ventilator dependence, we will be interested in avoiding or attenuating VIDD. In rabbits it was recently demonstrated that partial muscle activation associated with assist-control mechanical ventilation attenuated the profound diaphragm force reduction associated with fully controlled mechanical ventilation (8). However, a previously formulated question (9) still persisted: What is the optimal degree of respiratory muscle effort that should be targeted during mechanical ventilation, to either prevent or reverse VIDD? In this issue of *Critical Care Medicine*, Dr. Gayan-Ramirez and colleagues (10) address this question. In their study, five groups of rats (control, spontaneously breathing, 24 hrs of continuous mechanical ventilation, 24 hrs of controlled mechanical ventilation with 20 mins of spontaneous breathing, and 20 hrs of controlled mechanical ventilation with 4 hrs of spontaneous breathing) were compared using diaphragm contractile properties, histologic analysis, and expression of myogenic transcription factors (MyoD and myogenin). These authors showed that even a short period of spontaneous breathing (20 mins in 24 hrs) was as effective as a 12 times longer period (4 hrs in 24 hrs) to lessen the deleterious effect of controlled mechanical ventilation on diaphragm force. Another relevant result was the demonstration that intermittent spontaneous breathing during controlled MV attenuated VIDD but did not prevent it. A similar result was obtained comparing controlled mechanical ventilation and assisted mechanical ventilation with a control group (8). The relevance of these findings is that not only fully controlled mechanical ventilation leads to VIDD. This is a fundamental concept because if VIDD were restricted to controlled mechanical ventilation, it would not be a clinical problem, since controlled mechanical ventilation is not a frequent mechanical ventilation mode (11).

On the basis of currently available data from experimental and clinical trials, assisted mechanical ventilation seems to be better than controlled mechanical ventilation in acute respiratory failure (12). The advantages of assisted mechanical ventilation are a) a better gas exchange, probably as a consequence of recruitment of collapsed lung, especially in the juxtadiaphragmatic region; b) improvement in the hemodynamic status because of lower sedation and positive end-expiratory pressure requirements; and c) abbreviation of the mechanical ventilation duration due to less sedative use. In case VIDD is proven in humans, an additional advantage of intermittent diaphragmatic contractions will be the prevention or attenuation of diaphragm dysfunction and weaning failure.

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Pediatric extracorporeal life support and central nervous system injury*

Since the first successful use of extracorporeal life support (ECLS) in an adult in 1972 and in a neonatal patient in 1976, the use of ECLS systems has dramatically increased (1–3). ECLS offers temporary cardiorespiratory support when conservative treatment modalities fail to do so. According to the Extracorporeal Life Support Organization (ELSO), as of July 2005 more than 31,000 patients had been treated with ECLS. Survival rates varied, depending on age and indication for ECLS, between 44% and 85% (3).

ECLS is a complex technique applied in patients who are, because of their severe underlying disease, at risk for adverse outcomes. Cerebral complications are amongst the most important complications of ECLS treatment, because they determine survival rates and can have great impact on the quality of life. Brain death, brain infarction and cerebral hemorrhage occur in 1.3–9.3 %, 1.8–3.6%, and 2.6–9.6% of all patients, depending on age and ECLS indication (3).

Several studies have tried to identify risk factors for cerebral complications. These studies mainly involved neonates (4, 5). Dela Cruz et al. (6), in a case-control study of infants on ECLS, found that acidosis and the need for cardiopulmonary resuscitation correlated with the development of intracranial hemorrhages.

In this issue of *Critical Care Medicine*, Cengliz and colleagues report about the incidence and risk factors for central nervous system complications during pediatric ECLS (7). The current, extensive study used the pooled data of almost 5,000 patients in the ELSO registry. Complications were categorized as brain death, brain infarction, and intracranial hemorrhage. Both pre-ECLS risk factors and ECLS events and complications were studied in relation to central nervous system complications. They found a high incidence of central nervous system complications (12.9%), with brain death being the most frequent one (7.7%) (7). Extracorporeal cardiopulmonary resuscitation increased the risk of central nervous system complications. In general, it seemed that sicker patients had a higher risk for central nervous system complications. This can be concluded from the fact that certain pre-ECLS parameters (bicarbonate level, inotrope/vasopressor requirement, acidosis) and complications during ECLS (renal failure, use of inotropes, acidosis), likely to arise in patients with more severe disease states, increased the risk for central nervous system damage.

In their discussion the authors mention certain limitations of their (retrospective) study with use of the ELSO registry. A few more comments can be made. Data submitted to ELSO depend upon the quality of single-center administrations. From the ELSO data, one cannot determine the number of patients for whom no computed tomography or magnetic resonance imaging was performed. Also, as the authors have stated themselves, scans might have been missing for patients who died, causing underreporting of central nervous system complications. There will be differences in the numbers of patients reported by the 115 centers involved in the ELSO registry, with the result that a single center's experience can have great influence on the data.

The timing of central nervous system complications in relation to ECLS initiation is unknown but important. Some complications may already have occurred before the start of ECLS and not be related to ECLS itself. Knowledge about the timing is also important in order to understand the pathophysiologic mechanisms behind the development of these complications.

Some findings of the current study are difficult to interpret. Ventilation mode (conventional ventilation vs. high-frequency ventilation) or ECLS technique used (venovenous vs. venoarterial) had an effect on the incidence of central nervous system complications. Patients were not randomized to either treatment modality; thus, it cannot be concluded from this study that one is superior to the other. This issue needs to be addressed in a prospective randomized study. However, in a neonatal animal model, Walker et al. demonstrated that autoregulation was less disturbed in venovenous ECLS than in venoarterial ECLS, pointing to a factor that could eventually explain the differences in central nervous system complications between the two techniques (8).

Finally, like the authors themselves conclude, certain statistically significant differences in parameters between patients with and without central nervous system complications are not very important clinically (PEEP and blood pressure values).

The content in the article by Cengiz et al. is of great value. Its major importance is not that central nervous system complications can be avoided easily now but that it offers a good analytical look at ELSO data pertaining to the use of pediatric ECLS and risk factors contributing to central nervous system injury. Furthermore, it makes us all, again, aware of the high incidence of central nervous system injury in ECLS patients and it identifies patients at risk for the development of neurologic damage. What should we think about the 53.3% and 85.7% of patients with respective sepsis and near-drowning who underwent ECLS for extracorporeal cardiopulmonary resuscitation and developed central nervous system complications (6)? In the latter group, no patient survived. Finally, this article can also be used as a reference for pediatric intensive care centers with ECLS units to evaluate their performance with that recorded by the ELSO registry.

Registration of central nervous system complications and understanding the risk factors are just a start. We need to understand

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the pathophysiologic mechanisms that cause central nervous system injury in infants treated with ECLS to be able to prevent them. The fact that severity of illness is an important factor for the development of central nervous system complications and mirrors the risk factors found in neonates treated with ECLS can give some direction for research topics. The group of Short in Washington has studied autoregulation in a neonatal lamb model and showed an abnormal autoregulation response (9, 10). (Animal) models for pediatric ECLS, like for neonatal ECLS, could help to translate the presence of a risk factor for central nervous system injury into an understanding of the pathophysiologic mechanism that causes this and are therefore urgently needed (9–11). This is underlined by the fact that, although the experience with ECLS has dramatically increased over the years, the incidence of central nervous system complications did not decrease as demonstrated in this study by Cengiz et al. (6).

Patients in need of ECLS are very sick and likely to die if not offered ECLS. It must be realized that central nervous system complications can occur before ECLS is initiated but can remain undetected until after its initiation. Therefore, it is likely that even a better understanding of the specific effects of ECLS on the brain will not enable us to avoid all neurologic complications in this group of patients.

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