dium or a more lipid-rich environment in the vascular compartment with consequent reduction of tissue distribution of lipophilic medications is still unknown. However, the experimental data reviewed above strongly support its possible value in the resuscitation of patients with cardiotoxic drug-induced cardiac arrest.

The human experience with lipid resuscitation is impressive, although sporadic. Multiple case reports tout its efficacy even after prolonged periods of resuscitation (chronicled on www.lipidrescue.org). However, these suffer from the inevitable anecdotal nature of such reports and the almost certain publication bias resulting in nonresuscitated cases not being published. Thus, at the present time it is unknown whether lipid resuscitation is truly beneficial in the real world of human cardiac arrest.

The Resuscitation Council of the United Kingdom published guidelines in July 2008 endorsing lipid therapy for the treatment of cardiac arrest or cardiovascular collapse caused by local anesthetic toxicity (8). Similarly, in 2007, the Association of Anaesthetists of Great Britain and Ireland published guidelines for its use in the management of severe local anesthetic toxicity (9). Despite these guidelines, presently there is no consensus in the critical care or medical toxicology community regarding the benefit of lipid resuscitation for the treatment of cardiac arrest by such cardiotoxic agents as tricyclic antidepressants, beta-receptor blockers, or calcium channel antagonists. Importantly, there is a notable lack of safety data with lipid resuscitation. For example, does it interfere with the action of therapeutically administered agents such as amiodarone? The development of lipid rescue therapy is, therefore, more of an evolution than a revolution. The current state of knowledge dictates that the initial approaches to patients with cardiac arrest due to cardiotoxic drugs follow standard resuscitation guidelines. However, in the absence of expeditious and sustained resuscitation it is reasonable to then quickly move to a trial of lipid therapy. It is fair to say that based on what we know so far, no patient dying of cardiotoxic drug poisoning should do so without a trail of lipid rescue. Although there is no validated protocol for the use of this treatment, the one advocated by Weinberg (Fig. 1) is appropriately based on the experimental data to date.

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The red blood cell: An underestimated actor in alterations of the microcirculation*

The microcirculation (vessels with a diameter below 100 μm) provides transport of oxygen to meet tissue metabolic needs (1). The microcirculation can be influenced not only by endothelial cell function and smooth muscle tone (mostly in arterioles), but also by blood components, including red blood cells (RBC), white blood cells, platelets, and plasma (1).

Alterations of the microcirculation are common in critically ill patients (2), especially in sepsis, and persistence of these alterations is associated with a poor outcome (2). Although many studies investigating alterations of the microcirculation have focused on the role of white blood cells (3), the role of rheologic changes in RBCs has only recently been investigated. RBCs are now considered as a primordial actor in oxygen delivery, more than just an oxygen transporter. Indeed, when oxygen content falls, RBCs can liberate, by a complex signal transduction pathway, mediators like nitric oxide and adenosine-5′-triphosphate, that can induce local vasodilatation (4). Figure 1 summarizes some of the new areas of investigation into the role of RBCs in the pathophysiology of oxygen transport.

To move within the microcirculation, RBCs can pass through capillaries with smaller diameters than their own. This property is a result of their capacity to deform due to specific characteristics of the components of the RBC membrane (carbohydrates, proteins, and lipids). In critically ill patients, especially in sepsis, RBC rheology (deformability, ag-

*See also p. 1000.

Key Words: microcirculation; red blood cell; oxygen transport; rheology; erythrophagocytosis

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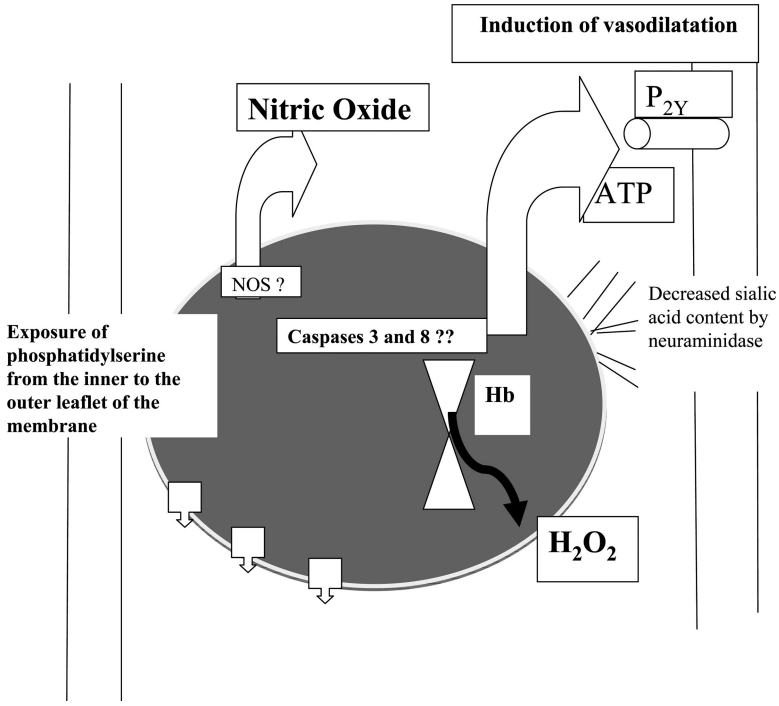

Figure 1. In hypoxic conditions, the red blood cell (*RBC*, *in red*) releases adenosine 5′-triphosphate (*ATP*), which can bind the receptor, P_{2y}, on the vascular endothelium and induces vasodilatation. RBCs are probably able to synthesis nitric oxide (*NO*) by a membrane and cytoplasmic NO synthase (*NOS*), which can also induce vasodilatation. Alterations in the RBC membrane have been described in critically ill patients with decreased sialic acid content by circulating neuraminidase, and increased phosphatidylserine exposure. RBCs contain caspases 3 and 8 and their activation induces eryptosis, i.e., RBC apoptosis. Hemoglobin located on the RBC membrane induces synthesis of H_2O_2 by autoxidation, which could participate in oxidation injuries.

gregation, adhesion, and shape) is rapidly altered (5–8) and all membrane components are modified with decreased RBC membrane surface carbohydrate content (6), increased phosphatidylserine exposure from the inner to the outer leaflet of the membrane (9), increased phosphorylation status, and reorganization of the membrane proteins, i.e., band 3 (10).

In this issue of *Critical Care Medicine*, Machiedo et al (11) observed in naïve rats that underwent exchange transfusion with altered RBCs withdrawn from rats subjected to hemorrhagic shock, that these altered RBCs induced a decrease in cardiac output and blood flow to the different organs (lungs, spleen, distal small bowel, terminal ileum, and cecum) with increased trapping of these altered RBCs in these particular organs. *Ex vivo* studies of these altered RBCs showed decreased deformability only for a shear stress of 0.3 Pa, and increased aggregation and static adhesion on endothelial cells. The important contributing role of RBCs on these blood flow abnormalities was suggested by the fact that these alterations were absent when the naïve rats were transfused with trauma/hemorrhagic shock RBC-depleted blood, without modifications of the plasma fibrinogen concentrations. As reported by Machiedo et al (11), other studies have also reported, *in vitro* or *in vivo*, increased adhesion of altered RBCs on endothelial cells in dynamic conditions, depending on the type and the speed of the flow (7), and decreased RBC deformability (8). Twenty years ago, Simchon et al (12) had already observed the same alterations in blood flow in several organs after reinfusion of neuraminidase-treated RBCs. This enzyme induces a decreased RBC membrane sialic acid content as observed in RBCs from critically ill patients (6). Furthermore, the RBC membrane sialic acid content is correlated with a more spherical shape and a decreased capacity of spherical change in hypo-osmolar environments (6). Modifications of the RBC membrane could also modify RBC biochemistry (synthesis of 2,3-diphosphoglycerate, adenosine-5′-triphosphate) because the majority of the glycolytic enzymes are located in the RBC membrane (13).

Interestingly, the organs in which RBC trapping was noted the most (spleen, lungs, and intestine) are known to contain the reticuloendothelial system and to participate in erythrophagocytosis (14). Further studies are needed to investigate the link between altered RBCs, blood flow, erythrophagocytosis, and development of anemia in critically ill patients.

Nevertheless, the study by Machiedo et al (11) has some limitations. First, RBCs are species dependent. RBC rheology, due to differences in membrane proteins, is completely different in rats and humans (15), limiting the extrapolation of these results to humans. Second, the alterations in rheology should be interpreted with caution. Indeed, the assessment of RBC deformability depends on the technique used. In this study, alterations were only present for the lower shear stress (0.3 Pa) and not for the other shear-stressed studied. Nevertheless, the K_{ei}, defined as the shear stress that causes half-maximal deformation was significantly increased. Third, adhesion was only studied in static conditions, and we know how important flow is to the study of adhesion. Eichelbronner et al (7) have demonstrated that adhesion of RBCs to stimulated endothelial cells by lipopolysaccharides was dependent on the type (continuous and intermittent) and the speed of the flow (7).

Nevertheless, this study by Machiedo et al (11) confirms that RBCs play a major role in the alterations of microcirculation and are much more than just a "dead" cell composed only of a membrane and hemoglobin.

A better understanding of the mechanisms of RBC rheologic alterations in critically ill patients and the effects of these alterations on blood flow and on oxygen transport may be important to improve outcomes.

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Hyperglycemia: Breaking the barriers?*

We have come a long way, since sugar was celebrated as a luxury product and was worth its weight in gold in the 17th century. Equally, the notion that stress-induced hyperglycemia during critical illness is essential to provide fuel for vital organ systems and thus is a beneficial adaptation has been challenged over recent years. A plethora of studies point at hyperglycemia as an independent risk factor for poor outcome in a diversity of intensive care populations. Consecutively, multiple studies into possible mechanisms, explanations, and treatments have been conducted (1).

A frequently returning matter in both laboratory and clinical investigations is the striking association of hyperglycemia with infectious complications and hyperinflammation, and as the case may be, the prevention of wound healing problems, bloodstream infections, and inflammatory syndromes when hyperglycemia is strictly prevented during critical illness by means of continuous insulin infusions. Several pathophysiologic explanations have been brought forward. Most likely, preventing hyperglycemia is doing most of the job by, for example, preserving physiologic endothelial function and preventing excessive systemic nitric oxide release and leukocyte dysfunction, whereas insulin, although anti-inflammatory and immunomodulatory effects have been advocated, seems to play a minor role in this concept (2, 3).

The "gut origin of sepsis" hypothesis predicates that bacteria, normally resident in the lumen of the intestinal tract, translocate across the intestinal epithelial barrier and act as a source of sepsis at distant sites. The idea first gained ground in the 19th century and since then efforts have been undertaken to map the factors that influence the permeability of the gut barrier and potentially increase the translocation of bacteria (4).

In an attempt to investigate the association between these two possible attributing factors for the development of systemic inflammatory response syndrome, Yajima et al (5) performed an elaborate study on the relationship between hyperglycemia, gut barrier dysfunction and bacterial translocation, and inflammatory responses in endotoxemic rats, the results of which are published in this issue of *Critical Care Medicine*. As a second objective, they investigated the role of tumor necrosis factor-α in this interlinkage. They conducted a prospective randomized trial, studying three groups of endotoxemic rats: a hyperglycemic group (G), a saline (control) group (S), and a group kept normoglycemic with an insulin infusion (GI). They assessed gut permeability with an *in situ* loop preparation of gut with fluorescence-labeled dextran and bacterial translocation by counting the numbers of bacteria in mesenteric lymph nodes. The role of tumor necrosis factor-α was studied with the use of an inhibitor of the converting enzyme, thereby impairing the function of tumor necrosis factor-α. They found that hyperglycemia aggravates lipopolysaccharide-induced gut barrier dysfunction and bacterial translocation and that blocking tumor necrosis factor-α function counteracts this aggravation.

The investigation is well performed and the conclusions valid for the model studied, but what does this bring us for daily clinical intensive care unit practice? As usual, data from experimental animal studies should be interpreted with care with respect to applicability to the human situation, and the authors rightfully do not claim direct transferability. It is tempting, however, to consider the results of the above-mentioned study as one of many elements of a comprehensive explanation for the reduced infection rates observed when strict glycemic control is maintained. This, however, implies several assumptions, for which currently

***See also p. 1024.**

Key Words: intensive insulin therapy; sepsis; inflammation; hyperglycemia; gut barrier

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just indications, rather than evidence exist: intestinal permeability is increased in intensive care patients for several reasons and it is suggested that there is an association between bacterial translocation and systemic infection and inflammation in this population. Evidently, this association is not unidirectional. It would be an oversimplification to allege that increased gut permeability equals increased bacterial translocation equals increased infection and inflammation rates. For systemic infections caused by enteropathogens in intensive care patients, hand hygiene of caregivers seems at least as important (6). The induction of hyperglycemia by means of a high glucose load to values above 400 mg/dL might be justified in experimental settings to prove the concept and does not necessarily dismiss the conclusions. As the authors state correctly, such high glycemia values are seldom met and rarely left untreated in daily patient care.

Despite these limitations, the authors have disclosed a piece of the large jigsaws of hyperglycemia and intensive insulin therapy in intensive care medicine. Eventually such pieces might help us in our understanding why sugar should no longer be considered "white gold," worth having as much as possible while you are in critical care.

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The role of positive end-expiratory pressure in modulating the apoptosis response during atelectasis-induced lung injury*

The acute respiratory distress syndrome is the most severe form of the acute lung injury and the prognosis of patients with acute respiratory distress syndrome still remains poor, with mortality in a range of 25% to 40% (1). Mechanical ventilation is delivered in patients with acute lung injury/acute respiratory distress syndrome to restore adequate gas exchange and, usually, these patients do not die of hypoxemia but rather of multiple organ dysfunction syndrome, which may be promoted paradoxically by the mechanical ventilation (2).

Intense researches during the last 20 years have clearly shown that mechanical ventilation itself can initiate or promote lung damage (ventilator-induced lung injury) and contributes to patient morbidity and mortality (3, 4).

The main mechanisms of ventilator-induced lung injury have been attributed to an excessive pressure (barotrauma) (5) or volume (volutrauma) (6) applied to open alveoli, to the shear stresses occurring at the interface of open and closed regions (atelectrauma) (7), and to an inflammatory response (8, 9).

Although there is a general consensus to limit the ventilator-induced lung injury by using a low tidal volume ventilatory strategy, at the present time, the selection of the "optimal positive end-expiratory pressure (PEEP)" remains controversial (10, 11). The application of a low tidal volume with an inadequate level of PEEP may induce lung atelectasis, as already shown in normal lungs during anesthesia several decades ago (12). The development of atelectasis is associated with several pathophysiologic effects, such as a decrease in lung compliance, an impairment of oxygenation, and a development of lung injury (13). The lung injury associated to atelectasis includes an increase in the alveolar–capillary protein leakage, which inhibits the surfactant function (14), a release of inflammatory mediators (8, 9), and an impairment of right ventricular function (14). This type of injury could be potentially avoided by the maintenance of lung recruitment by relatively high PEEP levels (10).

Apoptosis or programmed cell death, which is a biochemical adaptive–protective process, is triggered by several environmental conditions and regulates cell survival (15). With regard to the lung, apoptosis plays a role in the preservation of the normal epithelial structure (16, 17). Apoptosis is a process that can be modulated by the activation of the mitogen protein kinases (MAPKs) (18). The MAPKs are a family of kinases that are able to transduce the signals from cell membrane to the nucleus in response to a mechanical stress (18).

In this issue of *Critical Care Medicine*, Fanelli et al (19) present data from an experimental animal model of acute lung injury, which examined the role of lung atelectasis on apoptosis by applying three different ventilatory settings. An injurious setting "high stretch" (high tidal volume with no PEEP) and a protective setting "low stretch" (low tidal volume with a low and a high PEEP level, 8–10 vs. 14–16 cm H_2O) were applied. Both pro-

*See also p. 1046.

Key Words: ventilator-induced lung injury; positive end-expiratory pressure; acute lung injury; apoptosis; acute respiratory distress syndrome; atelectasis

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tective settings significantly reduced the MAPKs activation and the fragmentation of the alveolar epithelial cells, compared with the high stretch. In addition, the low stretch with high PEEP levels presented greater levels of apoptosis, a more uniform epithelial cell thickness, and a lower activation of MAPKs. Thus, the authors conclude that the atelectasis generated during a low stretch setting with inadequate PEEP levels may cause an inhibition of the apoptotic protective mechanism by an overexpression of the MAPKs signaling pathway in the lung. A major message from Fanelli et al is that in the presence of substantial lung edema, high PEEP levels, avoiding the lung derecruitment, can mitigate the alveolar cell damage and promote the lung cell apoptosis.

Although this is a highly interesting and stimulating study, before extrapolating these data to the clinical settings several limitations should be addressed. It used an *ex vivo*, not perfused lung model, of acute lung injury, which presents a very uniform distribution of lung lesions and high recruitability with PEEP. Furthermore, the absence of the chest wall, which favors the lung collapse at end expiration, magnifies the damage caused by tidal opening and closing.

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Breathing normobaric oxygen protects against splanchnic ischemic injury: How does it work?*

A report by Sukhotnik et al (1) revisits the issue of blood hyperoxygenation as a means of protecting end-organ damage caused by ischemia/reperfusion (I/R) injury. They subjected rats to 30 min of mesenteric ischemia by clamping the superior mesenteric artery and portal vein. Starting 10 min before reperfusion, the animals were randomized to breathe room air (I/R group) or normobaric 100% oxygen (I/R-O_2 group) for 6 hours. The animals were followed up for 24 hours of reperfusion, and then killed. No difference in mortality was observed between the I/R-O_2 and I/R groups. However, convincing histologic evidence of intestinal mucosal preservation was presented. Significantly decreased Park's injury score and increased villous height were observed in animals receiving oxygen therapy. Increased weight and DNA content of ileal and jejunal mucosal specimens from I/R-O_2 animals were consistent with cell preservation. There was a 10% to 20% increase in hemoglobin levels in the I/R group compared with sham animals that were allowed to breathe normal air, but I/R-O_2 animals did not show this increase. Blood pH was significantly decreased in I/R-O_2 animals compared with both groups of sham animals. The "thermochemiluminescence oxidizability" of plasma from sham-operated animals exposed to either air or 100% oxygen and I/R-O_2 animals was significantly higher after the 6-hour oxygen treatment

*See also p. 1054.

Key Words: mesenteric ischemia; reperfusion injury; oxygen inhalation therapy; hyperbaric oxygen; mucosa; intestine; lung

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compared with animals in the I/R group. This assay is performed *in vitro* by measuring photon emission after heat-induced oxidation of carbonyls present in plasma (2). A lower thermochemiluminescence value suggests that the blood was exposed to oxidants *in vivo*. Decreased thermochemiluminescence oxidizability of plasma from I/R animals compared with I/R-O_2 animals is consistent with the idea that fewer reactive oxygen species (ROS) were generated by tissue and/or circulating blood cells in the I/R-O_2 group. This finding was unexpected as hyperoxia would be expected to increase ROS production in sham animals receiving normobaric oxygen compared with sham animals that did not receive normobaric oxygen, and this was not observed (3, 4).

Although the studies reported by Sukhotnik are promising, a failure to see any difference in survival between the I/R and I/R-O_2 groups is problematic. Furthermore, a few critical issues are not addressed by these studies including the question of mechanism. Hemoglobin O_2 binding is essentially saturated at normal alveolar Po_2. Under these conditions, the equivalent of 20.1 mL of oxygen is bound to hemoglobin in 100 mL of blood, whereas only 0.3 mL of oxygen is dissolved in the same volume of plasma (5). Increasing the PO_2 to 100% would be expected to increase-the dissolved oxygen component from 0.3 to 1.5 mL per 100 mL in alveoli. This represents a only a 6% increase in total blood oxygen content when hemoglobin is taken into account. Consistent with this, Sukhotnik et al (1), reported that arterial Po_2 increased just over four-fold in the I/R-O_2 compared with the I/R group.

However, this information is only of minimal value if parameters of oxygen delivery and extraction are not measured. Hughes et al (6) measured the effects of breathing-graded normobaric oxygen concentrations (21% to 100%) on portal blood to flow and oxygen saturation in normal anesthetized rats. After 10 min breathing 100% oxygen, portal blood flow increased 30% compared with rats exposed to normoxia. Portal venous hemoglobin saturation ($PSaO_2$) increased 70% (54% vs. 93% $PSaO_2$) and calculated total blood oxygen content increased 73% in animals breathing 100% compared with 21% oxygen. Increased splanchnic perfusion was suggested by the authors as a consequence of decreased mesenteric vascular resistance because heart rate and mean arterial pressure remained constant regardless of FIO_2. These rather remarkable findings suggest that breathing normobaric oxygen does in fact increase the delivery oxygen to the mesentery by a combined effect of increased total blood oxygen content entering the splanchnic circulation and increased blood flow. The applicability of these findings to animals subjected to 30 min of mesenteric ischemia is not straightforward. The effects of ischemia on splanchnic perfusion are expected to be profound. Therefore, similar studies of portal $PSaO_2$ and blood flow in this or similar models of mesenteric ischemia seem to be indicated.

Another important question arises when one considers that portal $PSaO_2$ in normal rats is approximately 54%. If one was to predict an effect of ischemia on this parameter, it might be that tissue acidosis compounded by increased CO_2 from metabolic processes would increase the Bohr's effect resulting in decreased affinity of oxygen for hemoglobin and increased local Po_2. Hughes et al (6) reported that portal Po_2 was 37 mm Hg and 105 mm Hg in rats breathing 21% and 100% oxygen for 10 min, respectively. Assuming that removal of the atraumatic clamps restores patency to the occluded vessels, reperfusion should deliver sufficient amounts of oxygen to meet the needs of tissue mitochondria that respire maximally at Po_2 as little as 1.5 mm Hg. However, even this simple assumption is probably not correct as we have shown that visceral blood flow after 60 min of superior mesenteric artery occlusion and 60 min of reperfusion only returned to approximately 70% of baseline levels (7). Thus, it would be interesting to know if normobaric oxygen therapy increases splanchnic blood flow in the setting of I/R injury.

There is still another part of the equation that must be answered to allow us to answer the ultimate question: Does increased tissue perfusion and, more importantly, increased oxygen delivery account for the salutary effects of normobaric oxygen treatment? This missing piece of the puzzle is whether the rate of oxygen extraction by the mucosa is increased or decreased by ischemia. Several groups reported that inducible nitric oxide synthase is induced in rodent models of splanchnic I/R injury, and selective inhibition of this nitric oxide synthase isoform decreases injury (8–10). We have reported that inducible nitric oxide synthase-derived nitric oxide can decrease oxygen consumption by enterocytes secondary to PARP-1 activation and depletion of intracellular NAD^+ levels (11). Therefore, decreased oxygen consumption by the intestinal mucosa after ischemia would be expected to obviate the need for increased oxygen delivery. Thus, tissue oxygen demand must be considered when attempting to address the question of how breathing normobaric oxygen might afford protection to the intestinal mucosa after I/R injury.

If normobaric oxygen treatment is not working simply by increasing local Po_2 in the mesentery, what other explanations are possible? As Sukhotnik et al (1) state in their article, reperfusion is associated with increased production of ROS when animals are allowed to breathe room air. It has long been appreciated that exposure to 100% oxygen increases the generation of ROS in lung (3). Turrens et al (12) reported that lung microsomal and mitochondrial fractions from pigs exposed to pure normobaric oxygen was due to a ten-fold increase in ROS generated in large part by NADPH oxidase and to a lesser extent mitochondrial production. Increased ROS production would be expected to cause profound changes to local parenchyma, resulting in the paracrine release of inflammatory mediators expected to have systemic effects, depending on the severity and duration of oxygen exposure (13). It has become apparent that exposing the lung to normobaric hyperoxia induces dramatic changes in the metabolic activity of resident cells and results in secretion of inflammatory mediators that have systemic affects (3, 4, 14). This was clearly shown in studies, reported by Buras et al (15) where oxygen therapy induced systemic interleukin-10 production that protected mice against lethal polymicrobial sepsis. Hyperbaric oxygen treatment was used in these studies, which failed in interleukin-$10^{-/-}$ mice. The applicability of this model to I/R injury is questionable because Nussler et al (16) reported that interleukin-10 was harmful in a rodent SMA occlusion model, but other systemic anti-inflammatory events are surely active in animals exposed to normobaric and hyperbaric oxygen therapy, and these should be addressed with the appropriate studies.

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Pseudomonas aeruginosa and *Candida albicans*: Do they really need to stick together?*

Pseudomonas aeruginosa and *Candida albicans* are frequently isolated from the respiratory tract in critically ill patients requiring mechanical ventilation. Biofilm formation inside the endotracheal tube plays an important role in the pathogenesis of ventilator-associated pneumonia (VAP) (1). *P. aeruginosa* and *Candida* species are the most common pathogens retrieved from endotracheal tube biofilm in intensive care unit (ICU) patients (2). Although the presence of *Candida* species in respiratory specimen is considered as colonization in the immunocompetent patient (3), *P. aeruginosa* is responsible for severe lower respiratory tract infections (4). According to the results of recent studies, *Candida* species tracheobronchial colonization occurred in 17% to 28% of ICU patients receiving mechanical ventilation >48 hours (5–7). A prospective observational multicenter study found *P. aeruginosa* to be the second most frequently cultured microorganism in patients with VAP (8). *P. aeruginosa* VAP is difficult to treat with high rates of inappropriate initial antibiotic treatment and relapse (9, 10). In addition, *P. aeruginosa* VAP is associated with increased mortality and morbidity (10, 11).

Recently, a pathogenic interaction between *P. aeruginosa* and *C. albicans* was identified. Experimental studies demonstrated physical, chemical, environmental, and phylogenetic similarities between the two pathogens (12–14). *C. albicans* morphology and virulence are significantly affected by the presence of *P. aeruginosa*. A cell–cell signaling molecule capable of inhibiting *C. albicans* filamentation is produced by *P. aeruginosa*. Additionally, *P. aeruginosa* forms a dense biofilm on *C. albicans* filaments and kills the fungus. In contrast, *P. aeruginosa* neither binds nor kills yeast forms of *C. albicans*. Several *P. aeruginosa* virulence factors that are important in disease are involved in killing of *C. albicans* filaments (13). In patients with cystic fibrosis, *P. aeruginosa* and *C. albicans* coexist in the lower respiratory tract. A recent study demonstrated that whereas some clinical *P. aeruginosa* strains affected *C. albicans* morphology, others did not (15). This correlated closely with the amounts of *N*-acyl homoserine lactones produced by the isolates. In addition, signaling was bidirectional, and *C. albicans* inhibited swarming motility of *P. aeruginosa* strains isolated from patients with cystic fibrosis.

The relationship between *Candida* species tracheobronchial colonization and *P. aeruginosa* VAP was investigated in a cohort of 803 ICU patients requiring mechanical ventilation >48 hours (6). *Candida* species tracheobronchial colonization was identified as an independent risk factor for subsequent *P. aeruginosa* pneumonia. However, no cause-to-effect

***See also p. 1062.**

Key Words: *Pseudomonas aeruginosa*; *Candida*; interaction; ventilator-associated pneumonia; prevention; animal study; antifungal treatment

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relationship has been demonstrated in that study. In addition, *Candida* species tracheobronchial colonization and *P. aeruginosa* pneumonia could both be a consequence of prior antibiotic treatment. However, the lack of association with *Staphylococcus aureus* pneumonia, another consequence of antibiotic treatment, indicated that an association between *Candida* species tracheobronchial colonization and *P. aeruginosa* remained plausible. Further, a retrospective case–control study was performed in 102 mechanically ventilated patients with *Candida* species tracheobronchial colonization to determine the impact of antifungal treatment on tracheobronchial colonization or VAP related to *P. aeruginosa* (7). Nineteen patients (18%) developed *P. aeruginosa* VAP or tracheobronchial colonization and were all successfully matched with 38 controls. Antifungal treatment was independently associated with reduced risk for *P. aeruginosa* VAP or tracheobronchial colonization.

In this issue of *Critical Care Medicine*, Roux et al (16) report the results of a randomized controlled animal study aiming to determine the effect of *C. albicans* tracheobronchial colonization on pneumonia related to *P. aeruginosa*. Tracheobronchial colonization was obtained by intratracheal instillation with *C. albicans* (2×10^6 colony forming unit [CFU]). Pneumonia was defined as the conjunction of macroscopic pulmonary inflammation and a lung pseudomonal count $> 10^4$ CFU per lung. The bronchial instillation of *P. aeruginosa* (10^4 CFU) was performed in animals with or without *C. albicans* tracheobronchial colonization. Significantly higher rates of *P. aeruginosa* pneumonia were found in animals with *C. albicans* tracheobronchial colonization compared with those without. In addition, higher levels of tumor necrosis factor-α, interferon-γ, and interleukin-6 were measured in the lungs of animals instilled with *P. aeruginosa* with prior *C. albicans* colonization compared with those without *C. albicans* colonization. Further, *in vitro* experiments found the production of reactive oxygen species by alveolar macrophages to be altered in the presence of *C. albicans*. The authors suggested that this might explain the increased incidence of *P. aeruginosa* pneumonia in animals with prior *C. albicans* tracheobronchial colonization. The investigators ought to be complemented for conducting such an interesting study with potential implications in the prevention of VAP related to *P. aeruginosa*. These novel data raise a number of important questions.

The mechanism suggested for the interaction between *P. aeruginosa* and *C. albicans* in the respiratory tract is plausible. However, as acknowledged by the authors, the role of alveolar macrophages in innate immunity against *P. aeruginosa* pneumonia is controversial. Therefore, further studies should clarify the mechanism of interaction between these microorganisms in the respiratory tract.

Are there other possible interactions between bacteria and yeasts? *Aspergillus fumigatus* also frequently coexists with *P. aeruginosa* in the respiratory tract of cystic fibrosis patients. In addition, *A. fumigatus* is frequently found in respiratory specimen in critically ill patients. However, whether an interaction exists between this pathogen and *P. aeruginosa* is unknown. Another recent study outlined a link between *Staphylococcus epidermidis* and *C. albicans* (17). In an animal neonatal model, coinfection with these two pathogens significantly increased mortality compared with infection with a single species. Antifungal treatment with fluconazole significantly reduced morbidity and mortality in this animal model.

Further animal studies should determine the impact of antifungal treatment on *P. aeruginosa* and *Candida* species interaction in the respiratory tract. In addition, a randomized controlled study is warranted in mechanically ICU patients with *Candida* species tracheobronchial colonization to determine the effect of antifungal treatment on the incidence of VAP related to *P. aeruginosa*. Meanwhile, *C. albicans* tracheobronchial colonization in immunocompetent ICU patients undergoing mechanical ventilation should not be routinely treated. Inappropriate use of antifungals is associated with higher rates of fungal resistance and mortality in ICU patients (18, 19).

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Transfusion improves cerebral oxygenation . . . but not always*

Anemia is associated with increased in-hospital mortality (1) and poor outcome in traumatic brain injury (TBI) (2, 3). Yet, there is little evidence to support packed red blood cell (PRBC) transfusion practice standards to correct anemia in TBI; risks of PRBC transfusion–such as acute lung injury, longer intensive care unit and hospital stay, and mortality–may be one reason (4–6). The transfusion requirements in critical care (TRICC) trial investigators observed that in critically ill patients, a restrictive transfusion strategy (trigger hemoglobin [Hb] 7.0 g/dL) is at least as effective as and possibly superior to a liberal strategy (trigger Hb 10.0 g/dL) (7). Others have suggested that patients with TBI may not benefit from a different (higher) transfusion threshold than other critically ill patients (2), and some have cautioned against the liberal use of blood transfusion in TBI (3).

Mechanisms of anemia-mediated cerebral injury are multifactorial and include tissue hypoxia, inflammation, generation of reactive oxygen species, and/or excitotoxicity (8). Anemia may also initiate cerebroprotective mechanisms such as hypoxia-inducible factor-1α, erythropoietin, and vascular endothelial growth factor (8). Although increase in cerebral blood flow during acute anemia can improve oxygen delivery, high hematocrit after PRBC transfusion may potentially decrease cerebral blood flow and increase the risk of cerebral ischemia (9). However, anemia due to hemodilution may impair cerebral autoregulation (10). The overall effects of anemia on the brain might, therefore, depend on the relative balance between these competing protective and harmful factors of anemia and PRBC transfusion. The recent availability of advanced technologies, such as brain tissue oxygen tension ($PbtO_2$) monitors, gives us an opportunity to better understand some of the cerebral effects of systemic therapies, such as PRBC transfusion, in TBI (11).

In this issue of *Critical Care Medicine*, Zygun et al (12) report the results of a well-performed prospective randomized study showing a 0.10 kPa increase in $PbtO_2$ per g/dL increase in Hb 180 minutes after two units of PRBC transfusion in 30 adults with severe TBI. This $PbtO_2$ increase was more pronounced in patients with lactate–pyruvate ratio (LPR) >25 (12). However, transfusion did not lead to any appreciable overall increase in cerebral metabolism, suggesting that while PRBC transfusion resulted in more available oxygen, utilization did not change, perhaps due to mitochondrial dysfunction in severe TBI. Findings in this study confirm the previous work by Leal-Noval et al (11) who similarly reported an increase in $PbtO_2$ with PRBC transfusion. Interestingly, although patients were randomized to receive PRBC transfusion at Hb of 8, 9, and 10 g/dL, the investigators reported an increase in $PbtO_2$ regardless of baseline Hb.

Despite the important observation that PRBC transfusion increased cerebral oxygenation independent of cerebral perfusion pressure and Pa_{O_2}, some aspects of this study merit discussion. First, although the primary outcome measure was change in $PbtO_2$, the threshold for transfusion was Hb and only 3 of 30 patients had low $PbtO_2$ before transfusion. This is important because the advantage of increasing $PbtO_2$ in patients with normal cerebral oxygenation values is unclear. Second, $PbtO_2$ response to transfusion was variable; in 43% patients, $PbtO_2$ did not change or decrease. More detailed clinical characterization of responders to transfusion may have helped identify the subpopulation of patients with severe TBI who may actually benefit from PRBC transfusion. Third, some patients had LPR >25 despite normal $PbtO_2$, suggesting that increasing oxygen supply was not the rate-limiting step in oxygen metabolism to start with and in these patients, PRBC transfusion would not be expected to lower LPR. Despite the fact that patients with LPR >25 had the greatest increase in $PbtO_2$, a study examining change in LPR in patients with low vs. high $PbtO_2$ is required to understand the relationship between oxygen supply and use. Previous work suggests that patients with severe TBI and with the most baseline cerebral oxygenation derangements benefit the most from PRBC transfusion (11). Finally, the limitations of $PbtO_2$ technology may impact our ability to ascertain the true cerebral effects of PRBC transfusion because the increase in $PbtO_2$ is not necessarily reflective of changes in the "at-risk" brain tissue and may only reflect regional effects (13).

The work by Zygun et al provides some interesting data regarding the potential benefit of PRBC transfusion to correct anemia and improve systemic oxygen content and cerebral oxygenation in severe TBI. However, as the investigators have shown, baseline anemia (Hb <10 g/dL) was not associated with cerebral hypoxia in most patients. Therefore, the overall benefits of increasing $PbtO_2$ remain unclear and the transfusion trigger remains undefined. Fundamental questions regarding the reasons for variability in $PbtO_2$ response to PRBC transfusion, risk-benefit ratio of PRBC transfusion, the effect of higher $PbtO_2$ on cerebral metab-

*See also p. 1074.

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olism, and clinical outcomes will need to be answered before a specific transfusion trigger can be adopted or before the current trend of restrictive transfusion strategies reverses, in favor of a more liberal transfusion strategy in TBI. Finally, the variable results in most studies of severe TBI repeatedly remind us of the heterogeneous nature of TBI and also of the challenges involved to characterize the underlying pathophysiology.

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The digital patient: Predicting physiologic dynamics with mathematical models*

Critical care seeks to improve outcome by manipulating physiology. In principle, knowledge of an initial state (e.g., heart rate and blood pressure) and availability of a complete description of physiologic dynamics (e.g., equations governing the entire circulatory system) are sufficient to predict the effects of available interventions. Clinicians would then be able to choose a course that maximizes benefit while minimizing harm.

Unfortunately, we clinicians are never issued complete descriptions of physiologic dynamics. Furthermore, different dynamics can produce indistinguishable states. Consider a patient with mild oliguria and normal heart rate and blood pressure. Is the patient merely hypovolemic? Is there congestive heart failure? Is there renal parenchymal disease? The state variables alone are insufficient to discriminate among these possibilities, and, therefore, we cannot know whether the next best treatment is to administer fluid, to provide inotropic support, or to simply observe.

Such clinical dilemmas are recognized by mathematicians and engineers as *inverse problems*. Strategies for their solution are well described (1). Two complementary tactics are of special interest to intensivists. One approach recently considered by Zenker et al (2) is to ensure that uncertainties from all sources are quantitatively reflected in the mathematical solution, which then takes the form of a probability distribution. Although such distributions accurately reflect physiologic dynamics, observation strategies (e.g., how often and how precisely measurements are taken), and Bayesian inference techniques, their clinical utility is often limited. Clinicians confront this at the bedside when all available data are insufficient to point to a best "next step." Clinically and also mathematically, more information is needed to resolve ambiguity about the underlying dynamics.

"More information" emerges from the second approach to the inverse problem, namely perturbing the system and recording the response. A familiar clinical example is a fluid challenge. Unfortunately, there is a Catch-22 here. Even small perturbations not only change the state of the system but can also cause harm to the patient. This leads to a clinically and mathematically important question: What minimal perturbation is sufficient to solve an inverse problem with enough precision to make meaningful predictions about treatment effects?

***See also pp. 1079 and 1169.**

Key Words: mathematical modelling; physiological dynamics; forecasting

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In this issue of *Critical Care Medicine*, Wakeland et al (3) demonstrate in their study of children with traumatic brain injury so severe that they can ill-afford unplanned physiologic excursions the use of ordinary care maneuvers that minimally perturb intracranial pressure dynamics to solve an inverse problem. They report that mild alterations in head-of-bed elevation and in minute ventilation provided sufficient data to fit a six-compartment mathematical model accounting for volumes of blood and cerebral spinal fluid. Their mathematical model dynamically expresses flows that rebalance intracranial volumes within the constraint of the Monro-Kellie doctrine (4).

Once fitted, the Wakeland model not only reproduced the intracranial pressure responses, but also provided modestly successful predictions of the intracranial pressure response to further therapeutic manipulations (meaning that the inverse problem had been solved). Within-session predictions were more successful than between-session predictions in individual patients. This is expected because not only the physiologic state but also underlying dynamics of the patient are hopefully improved by treatments between sessions.

Several Points Bear Emphasis

First, fitting mathematical models to account for individual physiologic dynamics is an essential next step toward personalized medicine in the intensive care unit. Our current evidence-based approach to care may guarantee "greatest good for greatest number," but evidence-based medicine equally guarantees suboptimal care in a minority of instances. Patients in that minority are entitled to better informed individual decision making.

Second, dynamical mathematical modeling is broadly applicable in clinical physiology, including dispersed systems such as the immune system (5). Furthermore, dynamical mathematical models can and will eventually be used to link across multiple spatial scales and physical processes, although this will likely require new mathematical tools (6).

Third, the use of dynamical models encourages clinicians to make the subtle but important distinction between outcomes and processes. The dynamical models used by Wakeland et al are parameterized, meaning that explicit weights are given to a set of processes. To the extent that any particular therapy uniquely affects a process, clinicians can then construct combinations of therapies that will lead to predictable results. (Clinicians commonly manipulate hemodynamics in this way, separately titrating agents that independently modulate inotropy, arteriolar tone, venous capacitance, etc.) The parameter space is typically much smaller than the state space, meaning that dynamical modeling guides clinicians toward establishing an optimal physiologic trajectory with fewer treatments and fewer adjustments of those treatments. This, in turn, should minimize adverse interactions among the treatments.

Skeptics of the modeling approach to decision making in critical care argue that humans are too individual, physiology is too complicated and Murphy (of Murphy's law) appears too often to expect benefit from dynamic modeling. These arguments do not stand up to scrutiny. Although physiology is complicated, the discipline of modeling forces descriptive, testable hypotheses about processes, treatments, and their consequences. Humans are surely individual, but pairs of humans typically have more in common than a Piper Cub and a Boeing 777, yet the aircraft shares common dynamical models in flight simulator software. As for the unexpected responses to treatments that punctuate critical care, it may be less Murphy's caprice and more an incomplete model that should be held to account. If meteorological models can reliably predict weather 10 days hence, surely we can discover how to reliably predict the behavior of our patients' physiologies over 10 hours.

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Understanding the shared responsibility in assessing the benefits and risks of research for the vulnerable critical care patient*

Translational research for critical care patients is essential to improve safety and efficacy of clinical practice. It is inevitable that research to improve clinical practice will involve highly dependent and high-risk patients. From time to time, this work will require participants to encounter a level of risk with no direct benefit to the individual participant, with the intention that future patients may benefit from the application of new knowledge. Without such research, clinical questions for the critically ill will remain unanswered.

Shepherding clinical questions along the research pathway to provide answers and innovations poses practical challenges. Where empirical research requires interventions with no direct benefit, only potential harm (albeit low), it is often difficult to balance risk and ensure the well-being of participants and to meet the clinical research objectives. The interventions for data acquisition protocols and computer data modeling presented by Wakeland et al provoke reflection on these issues.

Research involving vulnerable populations, such as children and individuals in highly dependent medical situations with potentially impaired capacity, including intensive care patients, highlight numerous significant challenges (1–4). The rights and welfare of participants must be scrupulously protected and the transparency of practice in the conduct, monitoring, and reporting of clinical research needs to be ensured. Few clinicians, researchers, patients, or those engaged in research ethics review would hold an opposite view.

Due diligence in the conduct of translational research goes beyond formulating robust methodologies. Risk management strategies, reflective of the ethical and regulatory frameworks, are required to conduct and monitor ethical research practice. Safety and respect for individual autonomy are paramount.

There is potential for variability in the application of novel treatments in different critical care settings, in different institutions, and by different clinicians. The definition of safe bounds for acceptable manipulation of intercranial pressure for dynamic data acquisition would be one example of this variation. In this issue of *Critical Care Medicine*, a study to refine modeling and prediction of intercranial pressure responses in children with head injuries is presented by Wakeland et al (5). The article describes modeling of intercranial pressure (ICP) changes in pediatric patients with severe head injuries, using pathophysiologic data collected from nine subjects during 24 sessions. Random interventions were used to provoke changes in ICP among the subjects. Incremental variations in head of bed elevation (to modify venous drainage and cerebral perfusion pressure) and minute ventilation (to modify the vascular tone via $Paco_2$) were used. The protocol was stopped if the ICP was >25 mm Hg for 5 minutes, cerebral perfusion pressure <40 mm Hg, systemic hypotension <2 SD below normal for age, or Spo_2 $<90\%$.

The interventions were *a priori* judged to be relatively mild compared with other therapeutic interventions and would most often produce a mild pathophysiologic response. The challenges were administered over 2–3 hours or as long as clinically stable as determined by the attending intensive care unit physician. The project was approved by two institutional research ethics committees or boards, and written permission for the children's participation was obtained from parents or guardians. The computer modeling conducted in this research suggests that a real-time tool to predict ICP changes, and thus guide therapeutic decisions in the future regarding children with head injuries, is a possibility.

During the review process, one of the peer reviewers (DAC) was confronted by the realization that he would have declined participation of his patients in this study. The reviewer's background in computer modeling, adult trauma and neurocritical care, and ongoing involvement in clinical ethical deliberations led to particular views of the risks and physiologic perturbations presented by this study. The protocol, *prima facie,* is safe, but at times, intercranial hypertension is provoked in the participants during data collection.

The article by Wakeland et al highlights the need to acknowledge the shared responsibility borne by all those involved in clinical research to ensure the safety and ethical conduct of clinical research. The examination of therapies or physiologic studies in clinical research, particularly involving critically ill patients, is a responsibility that must be shared. It does not rest solely with the institutional Human Research Ethics Committees (Human Research Ethics Committees in Australia, Institutional Review Boards in the United States) or Safety Review Boards, the researchers who propose and describe the study, the clinical researchers who personally carry out the study interventions and data collection, or with the clinicians who are responsible for the care of their patients. It does not also rest entirely with the patients or guardians who agree on the patient's behalf to participation. Finally, it does not rest solely with peer reviewers, the editorial team, and publishers.

In Australia, the *National Statement* (2007) (6) and the *Code of Practice for the Responsible Conduct of Research* (2007) (7) acknowledge the shared responsibilities of the key players in undertaking research involving human participants. The risks to patients are justified by the benefits to the individual participants and to future patients. The risk should be minimized wherever possible, and the ongoing safety of the interventions should be examined.

***See also pp. 1079 and 1167.**

Key Words: ethics; research; critical care

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We note that some particular responsibilities are borne by specific links in the research chain. Researchers must identify, gauge, minimize, and manage any risks involved in their project, and present this for review and when seeking informed consent. Institutions must decide the appropriate level of ethical review for the types of work conducted in their jurisdictions. Human Research Ethics Committees must consider the research proposal, and make judgments on whether risks are justified and balanced against potential benefits (albeit indirect for the benefit of future patients). Recent debate and policy reform acknowledge the value of ethically approved research that may involve greater than a minimal risk and without the prospect of direct benefit to the participant (4). Consideration of the need for added diligence by all parties where substitute consent is involved is warranted. Participants or their substitute decision makers (parents/guardians) must evaluate whether perceptions of risks and benefits justify involvement. There is potential for tension between the obligations to address clinical questions, to give scope to participants' freedom to accept risk, and to see that research is conducted in a way that is beneficial and minimizes harm.

Natale et al (1) present an examination of their own research experience following the conduct of a multisite phase II safety and feasibility study of traumatic brain injury in children. They review similar studies to identify a number of challenges and possible responses from the perspective of families, investigators, funding agencies, and the wider society. They acknowledge that there is limited literature on the quantitative or phenomenological "estimates" of research risk or the effective communication of risk. The study explains that translational research in the intensive care unit setting, including traumatic brain injury research, will often involve "greater than minimal risk" and that where minors are already seriously or even fatally injured, two contradictory questions arise: 1) "does such extreme risk constitute this child's 'normally occurring' situation and is it acceptable to expose them to a research risk that is equivalently grave?" 2) "Given such extreme risk, is it acceptable to further increase the risk of potential morbidity and mortality?" This dilemma has a dynamic that will be uniquely resolved for each proposed project. To this end, we support Natale et al in recommending that further dialogue is vitally important to further develop balanced standards.

Ultimately, the study by Wakeland et al can contribute to our understanding of traumatic brain injury in children, and we may be a little closer to more effective managements for this condition. Advancing treatment outcomes and effective clinical monitoring practices, including predictive modeling techniques, for pediatric patients with traumatic brain injury via translational clinical research on medically highly dependent patients is vital. However, such clinical advancements necessitate recognition and reevaluation of the scientific and ethical challenges that need to be addressed. Reflective and informed research practice is the shared responsibility of all parties engaged in clinical research: scientists, clinicians and human research ethics committees, guardians/parents, publishers and reviewers, and the wider society as potential beneficiaries of translational research.

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Ultrasound is coming to a pediatric intensive care unit near you*

Ultrasound (US) guidance for vascular access procedures has been a possibility for about two decades. Many of the early users were physicians placing a large number of urgent central venous lines (CVLs). Consequently, these physicians faced many access procedures made more difficult by patient instability or site limitations. It does not take that many minutes at the bedside of an unstable patient with few CVL options due to trauma, burns, or small size to make sane physicians open to assistance with the inevitable access challenges.

Because US technology has improved and become more accessible, clinicians in the operating room, the emergency room, and the intensive care unit have asked whether US guidance should be routine for CVL placement. Many studies, variably persuasive, have been done. Meta-analyses have been performed, review articles written, and governmental and specialty groups have made pronouncements (1–6). It is relatively clear that the body of evidence supports US guidance in adults undergoing internal jugular venous cannulation. Other sites in adults and CVL placement in children and infants have been less well studied.

In this issue of *Critical Care Medicine*, the report by Froehlich et al (7), adds a

*See also p. 1090.

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prospective pediatric intensive care unit study to the pediatric operating room and emergency room literature that supports the use of US guidance. Their demonstration of decreased attempts/cannulation and decreased incidental arterial punctures lead the authors to conclude that "US guidance should be encouraged for all operators for all CVL placements in patients in the pediatric intensive care unit" with particular emphasis on inexperienced operators or high-risk patients. Based on the totality of accumulated studies and >10 years of experience using US in the pediatric intensive care unit, this editorial author considers that statement an aggressive but increasingly defendable recommendation. The authors of this study have added to our understanding of US use in the pediatric intensive care unit. They have also pointed out some study limitations and careful readers will consider some additional issues.

Their study is prospective but sequential. The landmark group was completed before US training and enrollment of the US-guided placement group. Details of the training are not provided. Although the statistical methods are sophisticated, some analytical problems persist.

The two groups are largely comparable, although not totally. Almost 30% of the landmark group was considered emergent compared with 18% of the US group, a factor of potential influence.

The unexpected suggestion of increased attempts/cannulation in the higher median weight group provokes a bit of skepticism because the authors report having inspected the plotted data before committing to analysis. The statistical process is then contaminated by that foreknowledge. No body mass index data are provided.

The authors have wisely defined their highest attempts/cannulation group as >4. This minimizes the statistical effect of one of the mysteries of this report, that is, what circumstances lead to five patients being stuck more than 25 times, two more than 40 times, and one patient had 60 attempts. The presence of these cases argues for finding a better way. If one excludes the patients depicted in Figure 1, who had more than 20 attempts, the graph of attempts vs. weight still supports the suggestion of increased placement difficulty in the landmark group, however.

The strongest data from this study are presented in Table 2 and demonstrate fewer attempts/cannulation in the US group as well as fewer accidental arterial punctures. The number of attempts per cannulation can reasonably be expected to correlate with the risk of other complications, including structural damage and infection.

This editorialist, who started placing CVLs in adults and children in 1975, wholeheartedly accepts the utility of US in facilitating central line placement in pediatric patients. The caveats, however, are numerous and preclude a blanket requirement that US guidance for all pediatric CVL placements be considered "Standard of Care."

The careful, experienced operator placing a routine femoral venous line in a 20 kg or heavier uncomplicated patient may surely use the landmark technique without violating a standard of care. Many other exceptions are conceivable. Indeed, surveys of practitioners show limited utilization rates despite available instruments and national guidelines and policies for US guidance (8).

My support for pediatric critical care US, however, goes well beyond the access issue and suggests that every pediatric intensive care unit should have capable US equipment. Furthermore, almost every pediatric intensivist and trainee should develop a basic skill set using the US not only for vascular access guidance in placing internal jugular catheters, but also for a variety of rapid clinical diagnostic or therapeutic maneuvers. Quality control will, of course, be a large issue.

Appropriate US training and equipment will allow the pediatric intensivist to

- evaluate vascular access sites that present anatomical or positional difficulties;
- evaluate sites previously used for CVLs or heart cath procedures;
- facilitate placement of arterial lines, PICC lines, and even peripheral IVs in difficult cases;
- use static or real-time guidance for accurate placement of chest tubes for fluid drainage;
- quickly distinguish ascites from abdominal organomegaly and edema and, if indicated, select a relatively unencumbered site for drainage;
- select a desirable site for placement of an acute peritoneal dialysis catheter;
- evaluate the bladder in a difficult-to-palpate, nonvoiding patient;
- identify a large pericardial effusion; and
- facilitate repositioning of an errant subclavian or femoral CVL.

As experience and expertise grow, the intensivist may make limited evaluations of gross cardiac contractility, venous filling, renal anatomy, and hematomas or abscesses.

The list is actually longer and will grow. However, these uses should virtually never replace the careful, detailed definitive US studies currently being performed by trained ultrasonographers and cardiologists. For the intensivist, ultrasonography will largely be directed at relatively simple questions that need timely answers.

What is the way forward? Clearly pediatric intensivists need to continue to report their controlled and uncontrolled experiences, the former aiding in the design of the latter. Fellowship training must respond to the evidence as it accumulates, and consideration must be given to the model established by the emergency medicine specialty, which devotes considerable energy to the technical and practical US education of its practitioners.

In fact, the Society of Critical Care Medicine has begun that effort. A Fundamentals of Critical Care Ultrasound course is planed for July 12–13, 2009. Will it be useful for pediatric intensivists? From an US perspective, patients heavier than 20 kg certainly share a lot of issues with adults.

Courses such as this "Fundamentals" course are a good start. They identify reasonable expectations and provide cautions against dangers. They also provide the technical knowledge needed to get started responsibly, although individual institutions may appropriately consider attendance only one of the steps needed for credentialing.

How will pediatric critical care make the best use of the US tool? If you were interested enough to read this far, you can probably help decide.

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The "how to" of temperature management in the intensive care unit*

In this issue of *Critical Care Medicine*, Poldermann and Herold (1) present a timely review of induced hypothermia and controlled normothermia in the intensive care unit (ICU). Their analysis is based on a comprehensive literature review as well as drawing from their significant first-hand experience in therapeutic hypothermia. The article describes the "how to" of hypothermia, not so much "the why" (indications and controversies), and provides specific pearls as to complication avoidance and management. Therefore, this review is most practical and useful as well as timely and comprehensive.

First, I would like to provide a brief comment on "the why," and how widespread this practice might become. Therapeutic hypothermia is currently indicated for selected comatose survivors of witnessed cardiac arrest (2). Hypothermia is currently being evaluated in trials of traumatic brain injury, spinal cord injury, and stroke. A far wider application of aggressive temperature management has been advocated as the deleterious effects of fever on long-term outcome are recognized (3–5).

Hypothermic treatment is examined in three phases (induction, maintenance, and rewarming), each with specific challenges and concerns for both physician and nursing care in the critical care unit. Means of successful induction of hypothermia are presented in both the text and in the tables; the tables throughout this review are useful tools for ICU practitioners and trainees alike. The final table, labeled "Checklist for induced hypothermia" is a valuable patient safety and learning tool. Similar checklists should be developed for many if not most ICU procedures and practices.

The means of induction are well-described—cold fluid infusion, surface methods, and invasive cooling devices, each with a role, with specific advantages and risks. The goal is rapid induction that is safe and reasonably comfortable. The reason for rapidity, described as an "event to target temperature," is to maximize the efficacy of the treatment (improved neurologic outcome), to compress and minimize the time course of physiologic instability (fluid and electrolyte shifts, hemodynamic changes, blood gas fluctuations, and shivering), and to limit and focus the need for corrective interventions.

The development of invasive devices (catheter-based cooling systems) that permit rapid and relatively exact temperature management are, in part, at the heart of the new popularity and promise of aggressive temperature management. This degree of control was previously lacking except with cardiac bypass machines and extracorporeal heat exchangers, with their attendant need for anticoagulation and other very intensive (and potentially risky) interventions.

Shivering is a major concern for practitioners more familiar with unintentional hypothermia, and who are well aware of the deleterious effects and marked elevation of metabolic rates reported with shivering. The uses of magnesium infusion, meperidine, adequate sedation, and rapid achievement of target temperature are appropriately stressed and thoroughly examined in this review.

The hardest part of safe induction is rapid lowering of core temperature without overshooting the target (33°C–34°C for moderate hypothermia)—life-threatening cardiovascular complications and severe coagulopathies maybe seen if temperature goes below 30°C (severe or extreme hypothermia) and are rare if temperature remains above 32°C. The use of continuous real-time temperature monitoring, as well as invasive catheter systems with preset targets, helps to avoid unintended severe hypothermia and its complications. The review discusses at length the cardiac effects and complications of varying degrees of hypothermia; key points include the need to avoid potentially life-threatening arrhythmias because they are very difficult to treat in the setting of hypothermia.

Maintenance strategies are relatively simple, compared with induction, and key points include adequate sedation, adequate fluid status (in the face of "cold diuresis"), and realizing the normal physiologic parameters of stable hypothermia (e.g., bradycardia). Blood gas interpretation and subsequent ventilator management are discussed at length. Key points include the recognition that Po_2 and Pco_2 are overestimated and pH underestimated in warmed blood gas analysis. Additionally, the effects of hypothermia on drug metabolism are significant (6), and an argument is made for the use of intermittent drug therapy

***See also p. 1101.**

Key Words: hypothermia; temperature management; shivering; neurologic injury; complication avoidance; patient safety

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(i.e., bolus mode), particularly with sedatives, rather than the continuous infusion model that is used in most critical care units today.

Rewarming strategy is summed up simply—very controlled and very slow. This approach allows correction (by the patient's own physiology and the ICU practitioner, if needed) of the electrolyte, blood gas, and fluid states of the patient, and avoids deleterious hyperthermic rebound.

The underlying theme of this review is that hypothermic therapy can and should be safe. The scientific basis for and means of complication avoidance are well described. The technical means to provide hypothermia are increasingly available. However, the most serious complication of hypothermia is infection, the one complication that cannot be negated by careful and accurate induction, maintenance, and rewarming strategies. As therapeutic hypothermia becomes more widely utilized, the effectiveness of this therapy for particular classes of patients will depend on whether this treatment reduces the severity of the primary and secondary neurologic injury without increasing the incidence and severity of infections.

This review clearly aids in making the application of hypothermia safer. Whether it is safe enough in terms of infection risk and whether it is effective when broadly applied for the treatment of a given problem remains to be seen.

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Functional capillary density measurement: A useful new tool to assess the peripheral circulation in infants?*

In this issue of *Critical Care Medicine*, Top et al (1) report the findings of an investigation of microvasculature in severely ill infants with respiratory failure before and after treatment with extracorporeal membrane oxygenation (ECMO) using the technique of functional capillary density (FCD) measurement. The article has several strengths. It is clearly written and describes the measurement technique and patient population well. More importantly, it draws attention to an area of pathophysiology that has received limited attention and is not easily monitored in the clinical settings.

When it comes to assessing circulatory status in infants, clinicians have focused for too long on variables that are easy to measure, such as blood pressure and heart rate. Because of small size and the risk of complications, invasive hemodynamic measurements are seldom available in newborn infants, making clinical assessment of circulatory status difficult. It has been shown that systemic blood pressure is a poor indicator of cardiac output and tissue perfusion, especially in infants (2, 3). Thus, a noninvasive means of assessing the status of the peripheral circulation and estimating adequacy of organ perfusion is an important unmet need. FCD measurement may be a useful tool in this regard, although its clinical usefulness at the bedside is yet to be clearly demonstrated.

FCD uses orthogonal polarization spectral imaging to directly visualize the microcirculation. Total length of capillaries with flowing cells (i.e., functionally open capillaries) per field of view is then determined using specialized software and expressed as FCD (4). The clinical utility of this approach may be facilitated by the recent development of automated image analysis techniques (5). Unlike other techniques, this approach provides direct visual evidence of the state of the microcirculation in the area being examined and thus, presumably, the adequacy of peripheral perfusion. Arguably, this should be more informative than blood pressure measurement, heart rate, or assessment of serum lactate.

The authors report that FCD was quite low initially and improved after completion of treatment with ECMO, when the infants were no longer very sick and were actually receiving treatment with vasodilators, in contrast to the vasopressors that they received before ECMO. This finding, of course, is hardly a surprise. The authors go to some length to try to convince us that the changes in FCD are related to ECMO itself. The case is not convincing, because the comparison was between sick infants on high vasopressor support before ECMO and much less ill infants receiving systemic vasodilators, with ECMO just happening to intervene in between. In other words, it is likely that the improved FCD is the result of the general improvement in cardiorespira-

*See also p. 1121.

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tory status, whether as a result of ECMO or other therapies. There is nothing unique about ECMO that should have a specific effect on the microcirculation. The second control group that was added to bolster the case is not directly comparable and the patients were not exposed to vasodilators to the same extent.

The specific explanation for the documented improvement in FCD is, in fact, immaterial. The valuable contribution of this report is that it documents, for the first time, the feasibility of FCD measurement in sick preterm infants and its ability to apparently accurately assess the state of the microcirculation. Although it is too early to hail this as a breakthrough technology, the approach seems to offer important insights into functional physiology of the sick preterm infants, which has not been readily available in the past. What role FCD will eventually claim alongside other techniques, such as near-infrared spectroscopy (6, 7), which is also aimed at evaluating adequacy of the peripheral circulation and tissue oxygen delivery remains to be seen.

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