Editorial

Hemodynamic and Metabolic Therapy in Critically Ill Patients

THE poliomyelitis epidemic of 1952 in Denmark was a key impetus for the development of modern critical care medicine. Mortality among patients with respiratory failure was dramatically reduced by applying techniques normally used in operating rooms and by placing these patients in a designated area of the hospital, where their condition could be constantly monitored by members of the medical staff. The benefits derived from normalizing abnormal physiological functions in these patients represented a clinical vindication of the 19th-century theories of Claude Bernard, who proposed that systems respond to pathogens by maintaining cellular homeostasis. Much of modern critical care practice is based on the principle of restoring aberrant respiratory, cardiovascular, and other functions to physiologic levels. Two articles in this issue of the *Journal* extend this principle more broadly. Rivers et al.[1] evaluated the effects of early goal-directed therapy designed to balance tissue oxygen demand and oxygen delivery in patients with severe sepsis, septic shock, or the sepsis syndrome. Van den Berghe et al.[2] studied the effects of strict glycemic control in patients who required intensive care after surgery.

Sepsis and related syndromes are the chief cause of multiple-organ failure and death in patients with critical illnesses. Thirty to 60 percent of patients with these syndromes die.[3] Inflammatory processes triggered by infection and other conditions lead to the activation of neutrophils and endothelial cells and then to increased vascular permeability, decreased erythrocyte and leukocyte deformability, and platelet aggregation. Vascular smooth muscle loses its ability to contract adequately, an alteration that leads to refractory hypotension, insufficient tissue oxygenation,[4] and cellular dysfunction. The inflammatory cascade may also have a direct effect on cellular mitochondrial and metabolic activity, resulting in organ dysfunction.[5]

Rivers and colleagues studied early goal-directed therapy designed to optimize cardiac preload, afterload, and contractility. They randomly assigned patients to this therapy or to standard (control) therapy at the time of presentation, before admission to the intensive care unit.[1] After arterial and central venous cannulation, the standard-therapy group underwent treatment that included critical care consultation and were transferred to the intensive care unit as soon as possible (on average, after 6.3 hours). The group randomly assigned to early goal-directed therapy was treated in the emergency department for at least 6 hours (average, 8.0 hours) before admission. These patients received, in a sequential fashion, fluid resuscitation, vasopressor or dilator agents, red-cell transfusions, and inotropic medications to achieve target levels of central venous pressure (8 to 12 mm Hg), mean arterial pressure (65 to 90 mm Hg), urine output (at least 0.5 ml per kilogram of body weight per hour), and central venous oxygen saturation (at least 70 percent). Patients who did not have a response to these approaches underwent sedation and mechanical ventilation.

In-hospital mortality differed significantly between the two groups: 30.5 percent in the group assigned to early goal-directed therapy and 46.5 percent in the group assigned to standard therapy. Moreover, in almost all (99.2 percent) of the patients in the early-therapy group, as compared with approximately 86 percent of those in the standard-therapy group, the combined hemodynamic goals were achieved during the first six hours after the start of treatment. During the period from 7 to 72 hours, the patients assigned to early goal-directed therapy had significantly higher mean central venous oxygen saturations and arterial pH values and lower lactate levels, base deficit values, and organ-dysfunction scores than those assigned to standard therapy.

Previous studies in patients with sepsis have likewise focused on reestablishing normal or even supranormal hemodynamic values. The encouraging results of those studies led to widespread enthusiasm for the application of "optimization" strategies in patients with a variety of critical illnesses. However, controlled trials[6,7] involving patients with established sepsis demonstrated that interventions aimed at achieving a supranormal cardiac index (and thus supranormal oxygen delivery) or a normal mixed venous oxygen saturation (and thus an improved level of cellular oxygen utilization) not only failed to reduce mortality but also could be detrimental.

Why, then, does the study by Rivers et al. have such apparently contradictory results? The explanation may lie in the extremely short interval between the initial hospital assessment and the enrollment of the patients. Those randomly assigned to early therapy were much less likely to progress to cardiovascular collapse than those in the standard-therapy group. Early goal-directed therapy has likewise been useful in high-risk patients undergoing major surgery.[8,9] In this situation, it is also used before the development of inflammation and associated complications. By contrast, the trials in which early goal-directed therapy was unsuccessful involved patients with established critical illness.[6,7]

Few trials have attempted to manipulate the cellular or metabolic responses to critical illness, such as increased energy expenditure and changes in substrate utilization and negative nitrogen balance. These re-

sponses are attributable in part to the development of resistance to growth hormone and to decreases in the production and activity of insulin-like growth factor I, a change that leads to insulin resistance and muscle wasting, or catabolism.[10] In the study by Van den Berghe and coworkers, critically ill patients were randomly assigned, at the time of admission to the surgical intensive care unit, either to strict normalization of blood glucose (to 80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]) with intensive insulin therapy or to conventional treatment, in which insulin was given only when the blood glucose level exceeded 215 mg per deciliter.

The study was terminated early because mortality in the intensive care unit in the group assigned to intensive insulin therapy was significantly lower than that in the group assigned to conventional therapy (4.6 percent vs. 8.0 percent). The benefit was observed specifically in patients requiring intensive care for more than five days and was achieved principally through a reduction in the incidence of multiple-organ failure with a proven septic focus. Overall in-hospital mortality was lower by a third in the intensive-treatment group than in the conventional-treatment group (7.2 percent vs. 10.9 percent). Morbidity (including, for example, renal dysfunction and the need for red-cell transfusion) was also lower in this group than in the conventional-treatment group.

The value of this impressive study is limited by the authors' acknowledged inability to conduct the study in a blinded fashion. Furthermore, the patient population was limited to those undergoing surgery (most often cardiac surgery) at a single institution. The results therefore cannot be readily extrapolated to patients in nonsurgical intensive care units or to those with other types of critical illness.

The wide range of benefits associated with strict control of glycemia is not easily explained. Van den Berghe and colleagues hypothesize that insulin resistance or hyperglycemia has an adverse effect on outcome. In a previous study, therapy with recombinant growth hormone doubled the mortality rate in critically ill patients.[11] This type of therapy is known to aggravate insulin resistance and hyperglycemia. In addition, the in vitro responsiveness of leukocytes stimulated by inflammatory mediators is inversely correlated with glycemic control.[12] Other studies, involving nondiabetic patients, found that the plasma glucose level on admission is an independent predictor of prognosis after myocardial infarction[13] or of the need for coronary-artery bypass grafting.[14]

What are the clinical implications of these reports? Therapeutic interventions aimed at improving the vascular and metabolic derangements associated with critical illness may be beneficial in appropriate groups of patients. Goal-directed therapy should be initiated as early as possible in patients who present with sepsis or sepsis-like syndromes. Furthermore, simple physiological end points appear to be sufficient to monitor the effects of early supportive interventions. An aggressive approach to glycemic control appears to reduce mortality and morbidity substantially in surgical patients who require prolonged intensive care. However, further study of this approach in other groups of patients is essential to confirm its benefits. Until then, widespread adoption of this treatment would be premature.

Once systemic inflammation is complicated by organ failure, there are few options. Treatment with activated protein C lowers the risk of death[15] but is associated with an increased risk of bleeding and is likely to be expensive. The strategies described by Rivers et al. and Van den Berghe et al. offer the opportunity for even greater benefit, by preventing the progression[1] or even the development[2] of sepsis and its complications.

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