Peripheral Vascular Responses in Septic Shock

Direct or Reflex Effects?

While clinical sepsis is known to induce profound effects on many organ systems, it is perhaps best known for the cardiovascular dysfunction it induces. In both the pulmonary and systemic circulations, sepsis has been shown to produce increases in vascular permeability. The resulting vascular leak promotes edemagenesis, which can interfere with gas exchange between alveolar gas and pulmonary capillary blood in the lung, and between capillary blood and parenchymal cells in the systemic circulation.

Another aspect of vascular dysfunction relates to changes in intrinsic vascular reactivity. In the mid 1950s, Zweifach and colleagues found that endotoxin administration led to early augmentation, and later ablation, of microvascular responses to topically applied catecholamines. Subsequent in vivo studies in experimental animals have found a progressive attenuation in vascular responsiveness to catecholamines, angiotensin II, and other vasoconstricting agents in models of sepsis.\(^2\) Clinically, an impaired ability of arteries and veins to constrict normally can lead to the rapid development of septic shock, unless therapy is initiated. In the venous capacitance vessels, a loss of normal constrictor tone can lead to the pooling of blood in the venous circulation. This undermines venous return and cardiac output, which must be restored by fluid resuscitation. In the arterioles, a loss in contractile function leads to a fall in systemic vascular resistance, which can progress to the terminal stage where systemic blood pressure cannot be maintained despite the infusion of potent vasoconstricting agents. Even before this terminal state, a microvascular dysfunction may contribute to hypoxic tissue injury by undermining the physiologic regulation of oxygen delivery both within and among organ systems.

When arterioles are unable to respond to physiologic adjustments in vasomotor tone, excessive blood flow to some capillary units may occur, depriving other units with high metabolic activity in the so-called "vascular steal" phenomenon. This can cause some tissue units to become hypoxic, even though overall blood flow to the tissue is high. It may also explain the observed pathological oxygen supply dependence of oxygen uptake in some patients, since increases in oxygen delivery may restore oxygen consumption in vascular units that had been hypoperfused and anoxic.\(^4\)

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Recent investigations have led to an improved understanding of the cellular mechanisms underlying the alterations in vascular responsiveness in sepsis. Vascular tissue obtained from experimental animals administered endotoxin \textit{in vivo} fails to contract normally \textit{in vitro} in response to phenylephrine.\(^5\) A similar contractile defect can be induced in normal vascular rings by incubating them \textit{in vitro} with endotoxin for several hours. This contractile impairment can be prevented by prior treatment with cycloheximide, which inhibits protein synthesis.\(^6\) The systemic hypotension caused by infusion of TNF-\(\alpha\) can be rapidly reversed by infusing N-monomethyl-L-arginine, a competitive blocker of nitric oxide synthetase.\(^7\) Finally, the inhibition of nitric oxide synthesis \textit{in vitro} appears to reverse the contractile impairment in vascular rings obtained from endotoxin-treated animals. Moreover, this effect was found in intact as well as endothelium-denuded vascular rings.\(^8\) Collectively, these findings suggest that sepsis may, perhaps through cytokine release, induce the synthesis of nitric oxide within vascular myocytes. This may contribute to the impaired contractile ability by activating guanylate cyclase in the myocyte, thereby activating the cyclic-GMP mediated relaxation pathway. In addition to the contractile dysfunction, other studies suggest that endothelial-mediated relaxation may be impaired. Vascular rings obtained from animals given endotoxin relaxed normally in response to nitrovasodilators that act directly on the myocytes. However, relaxation to acetylcholine, which is mediated by release of endothelial derived relaxing factor (EDRF), was impaired.\(^9\) This suggested that endothelial changes may also contribute to the vascular response to sepsis.

In this issue, Astiz and colleagues (see page 1072) describe a clinical study of the effects of sepsis on systemic vascular function. Using a noninvasive plethysmographic technique, they compared forearm blood flow, vascular resistance, and venous capacitance in septic, shock, and control groups. The sepsis group without coexistent shock showed evidence of decreased forearm venous capacitance, but normal blood flow and vascular resistance. A second group with sepsis and hypotension showed even further decreases in venous compliance, although blood flow and resistance were not changed significantly. In both septic groups, the forearm blood flow response to transient occlusion (reactive hyperemia) was attenuated, compared to the controls. Since the magnitude of the changes appeared to be related to the severity of the septic shock, the authors suggest that the
observed changes may be early indicators of septic shock.

The data they report must, by definition, reflect an integration of the direct effects of sepsis or septic shock on vascular tissue, and the reflex responses to the hypotension that may arise. In this regard, the failure of forearm resistance to increase in response to hypotension in the septic shock group is unexpected, and may reflect an impaired ability of arteries to contract in septic shock. However, it is difficult to separate the direct effects of sepsis on the venous compliance vessels from the reflex effects of the hypotension. Since the septic shock group was studied prior to fluid resuscitation, their hypotension would be expected to elicit increases in sympathetic nervous system tone, which should decrease venous compliance even in the absence of sepsis. Indeed, Figure 1 of their paper demonstrates a relatively low slope in the volume-pressure relationship for the septic shock group, which reflects either a low venous compliance or a decrease in the unstressed volume of the system. This, along with an attenuated reactive hyperemia response, is a normal physiologic response to hypotension. It is similar to what others have found in left ventricular failure and hypotension without sepsis,10 as the authors point out. They conclude that the changes seen are proportional to the severity of the sepsis. While this is true in one sense, it is important to keep in mind that the proportionality may arise solely from the reflex effects of hypotension, as opposed to the effects of sepsis on the vessels. One way to settle this in the future would be to compare vascular responses in septic and nonseptic hypotensive groups prior to, and after fluid resuscitation. In this setting, the direct effects of sepsis might be separated from the reflex effects of hypotension.

Paul T. Schumacker, Ph.D.
Chicago

REFERENCES

Who Should Receive Corticosteroids as Adjunctive Treatment for Pneumocystis carinii Pneumonia?

Pneumocystis carinii pneumonia remains the most common cause of serious morbidity and mortality in patients with the acquired immunodeficiency syndrome (AIDS). For patients who present with room air PaO₂ <70 mm Hg or Pa(A-a)O₂ >35 mm Hg, the risk of a fatal outcome is in the range of 20 to 40 percent with conventional therapies.1-6 Experimental therapies such as efornithine or trimetrexate have not substantially improved outcome for patients with severe episodes. Thus, results of three controlled studies indicating that early adjunctive therapy with corticosteroids improves outcome and reduces mortality should be embraced with considerable enthusiasm.6-7

The first study was a double-blind trial that involved 38 patients with baseline oxygen saturations of 85 to 90 percent at rest or a 5 percent decline in saturation with exercise.6 Of those patients randomized to receive 60 mg of prednisone daily for three weeks, only 6 percent had a 10 percent or greater decline in oxygen saturation, compared with 42 percent in the group who received placebo. There was no difference in survival between the groups. However, in the second study, which evaluated 40 mg of prednisone twice daily for five days followed by tapering doses over the three-week course of anti-Pneumocystis therapy, there were major clinical benefits.6 Of 220 patients with proven and 31 with presumed Pneumocystis pneumonia, oxygenation failure (defined by PaO₂/FIO₂ <75), need for mechanical ventilation, and death were each reduced approximately 50 percent in the patients randomized to receive corticosteroids compared with the treatment group not receiving corticosteroids. The demonstrable benefit was limited to patients with moderately severe episodes, as there were no statistical...