Mitigating Microvascular Leak during Fluid Resuscitation of Hemorrhagic Shock

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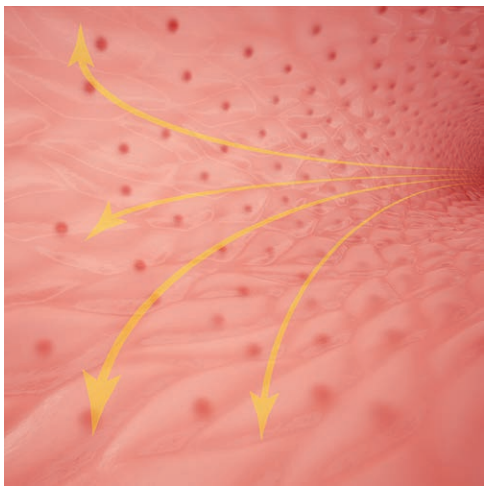
ALTHOUGH it is obvious that some fluid resuscitation of hypovolemic shock is required to increase intravascular volume and deliver oxygen to vital organs, it is also becoming clear that excessive fluid resuscitation has adverse consequences.[1] In the urgent clinical setting, determining the optimum volume of fluid resuscitation is nontrivial. Timing and clinical context are also important. Therefore, any adjunctive strategies that increase safety and decrease apparent need for large-volume fluid resuscitation would be extremely helpful. In this issue of ANESTHESIOLOGY, Trieu *et al.*[2] take some promising first steps in an animal model of hemorrhagic hypovolemic shock.



"[T]he endothelium is a promising target for intervention in clinical shock..."

The plumber's goal of fluid resuscitation is to prime the pump to increase pump output—increase intravascular volume to increase ventricular diastolic filling so that cardiac output is increased *via* the Frank-Starling relationship. This is the "macrovascular" component of fluid resuscitation. However, the capillary microcirculation, where the vast majority of oxygen and metabolite exchange occurs, is also involved, particularly in hemorrhagic and septic shock. Normal homogeneous microvascular flow becomes heterogeneous with stopped flow in some capillaries and excessively high shunt flow in others, so that gas and metabolite exchange is impaired.[3] Adhesion of activated leukocytes to activated microvascular endothelium contributes to stopped flow and impaired microcirculatory function. The duration and extent of hypovolemia both factor into this "no reflow" phenomenon observed in hemorrhagic shock.[4] When severe, the degree of microvascular dysfunction observed in sterile hemorrhagic/hypovolemic shock likely can be as severe as microvascular dysfunction observed in septic shock. Accordingly, resuscitated severe hemorrhagic shock patients often display distributive shock features. Early rapid fluid resuscitation improves microvascular flow, improves oxygen transport to the tissues, and improves organ function.[5] Thus, fluid resuscitation sufficient to improve microvascular function is essential.

Too much fluid delivered to a relatively leaky microcirculation results in tissue edema, increased diffusion distances for gases and metabolites, and increased tissue hydrostatic pressure, which compresses the microcirculation, compounding the microcirculatory problem. In septic shock patients, where microvascular dysfunction is particularly prominent, fluid resuscitation that increases central venous pressure more than 12 mmHg (typically exceeding ~5 l of crystalloid resuscitation) is associated with significantly increased 28-day mortality.[1] Although very early aggressive resuscitation is likely beneficial, fluid resuscitation is often continued for too long so that it is not uncommon for more than 10 l of crystalloid and colloid to be administered in the first 24 h. In most patients, the emerging evidence suggests this is detrimental.

Tie2 expressed on vascular endothelium is a receptor for angiopoietin-1 and -2 and plays a central role in maintaining normal microvascular function and permeability, in particular.[6] Angiopoietin-1 ligation of Tie2 on endothelial cells signals downstream resulting in reduced expression of inflammatory cell adhesion molecules and reduced permeability of intercellular junctions. Thus, angiopoietin-1 signaling *via* Tie2 reduces endothelial activation and helps maintain microvascular function. This is particularly important when conditions such as hemorrhagic or septic shock inflame microvascular endothelium.[7] Interestingly, angiopoietin-2 acts as an endogenous competitive inhibitor of angiopoietin-1 and, therefore, has the opposite effect. Angiopoietin-2 is increased in trauma patients and is associated with adverse outcomes.[8]

Trieu *et al.* contribute to our understanding by finding that vasculotide, an angiopoietin-1 mimetic, protects against microvascular injury during resuscitation of experimental hemorrhagic shock.[2] Hemorrhagic shock resulted in a decrease in continuously perfused capillaries and, hence, an increase in the number of nonperfused capillaries. These nonperfused capillaries were not reopened by fluid resuscitation with crystalloid and blood. However, if vasculotide had been added prior to the induction of hemorrhagic shock or, importantly, soon after initiation of fluid resuscitation,

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Corresponding article on page 361.

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previously nonperfused capillaries were recruited by fluid resuscitation. Measures of microvascular function also were improved by vasculotide. Microvascular leak was decreased by vasculotide pretreatment so that the volume of fluid resuscitation required to restore mean arterial pressure was less with vasculotide pretreatment. Additional biochemical measures shed light on contributing mechanisms. Resuscitation of hemorrhagic shock expectedly increased microvascular inflammation as indicated by several upregulated inflammatory mediators relevant to the microvasculature. Vasculotide reduced circulating angiopoietin-2 levels; angiopoietin-2 being known to increase vascular inflammation and permeability.

These exciting results, together with recent related studies,[9,10] suggest that the endothelium is a promising target for intervention in clinical shock states. The endothelium and microvasculature play a very prominent role in subsequent organ dysfunction. Mitigating endothelial activation, induced by inflammatory stimuli that are a part of hypovolemic shock states, represents a rationale hypothesis aimed at preventing or diminishing the organ dysfunction and death that result from severe microvascular dysfunction.

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Competing Interests

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