Pathophysiology of Septic Shock

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KEYWORDS

• Septic shock • Sepsis • Vasodilation • Permeability • Cardiac dysfunction
• Contractility • Nitric oxide • Cytokines

KEY POINTS

- Fundamental features of septic shock reviewed herein are vasodilation, increased permeability, hypovolemia, and ventricular dysfunction.
- Appreciation of the pathophysiology provides a basis for developing novel therapies.
- Increased permeability relates to several pathways (Slit/Robo4, vascular endothelial growth factor, angiopoietin 1 and 2/Tie2 pathway, sphingosine-1-phosphate, and heparin-binding protein), some of which are targets for therapies.

INTRODUCTION

Fundamental features of septic shock reviewed herein are vasodilation, increased permeability, hypovolemia, and ventricular dysfunction. Appreciation of the pathophysiology provides a basis for developing novel therapies.

PERIPHERAL VASODILATION

An integral feature of septic shock is hypotension.[1] Although cardiac dysfunction and hypovolemia contribute to the hypotension, loss of vascular smooth muscle reactivity causing peripheral vasodilation is the major mechanism.[1] Peripheral vasodilation occurs after the failure of normal mechanisms to vasoconstrict vascular smooth muscle. Peripheral levels of catecholamines are dramatically increased in patients with septic shock, with values correlating with sepsis severity, yet there is peripheral vasodilation indicating decreased responsiveness to natural vasoconstrictors.[2,3] There is also

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evidence of activation of the renin–angiotensin system, as well as a deficiency of vasopressin.[4] Once these regulatory mechanisms are overwhelmed, peripheral vasodilation and hypotension develop rapidly.

Vasodilation in sepsis is mediated mainly by two mechanisms: increased nitric oxide (NO) and prostacyclin synthesis. A calcium-independent NO synthase is induced by endotoxin interaction with vascular endothelial cells, leading to increased levels of NO.[5] Prostacyclin is released by endothelial cells in response to both endotoxin and inflammatory cytokines.[6,7] However, the relative role of prostaglandins in the pathophysiology of human sepsis is diminished by the lack of effect on clinical outcomes seen with ibuprofen (a prostaglandin synthesis inhibitor) in a large multicenter randomized controlled trial.[8]

Adrenomedullin is a pleiotropic vasodilating hormone and a cardiac depressant, levels of which are increased in septic shock[9] and associated with increased mortality.[9,10] Adrenomedullin blockade is a putative strategy to improve hemodynamics and outcomes of septic shock. An antiadrenomedullin antibody decreased mortality,[11] increased responsiveness to norepinephrine,[12] and improved renal function in murine cecal ligation and perforation sepsis models.[11,12]

Other mechanisms of vasodilation in sepsis have been identified recently that may be targets for future therapies. Activation of the transient receptor potential vanilloid type 4 (TRPV4) channel has been demonstrated to induce vascular leak and may be involved in the inflammatory cascade, leading to peripheral vasodilation.[13] Pharmacologic inhibition of TRPV4 signaling improved outcomes in both murine endotoxin and cecal ligation and perforation sepsis models.[14]

Norepinephrine, Epinephrine, and Phenylephrine

The cornerstone of current management of patients with vasodilatory septic shock involves the infusion of catecholamines. Norepinephrine as well as epinephrine act on both α-1 and α-2 adrenergic receptors causing vasoconstriction, as well as β-1 and β-2 receptors, increasing cardiac output. Norepinephrine is the suggested first-line agent for hypotension in septic shock, a strong recommendation based on moderate evidence.[15] Norepinephrine, and indeed virtually all vasopressors,[16] can cause excessive vasoconstriction and decrease vital organ perfusion leading to peripheral, myocardial, cerebral, and gut ischemia. Furthermore, norepinephrine has potentially adverse immune effects[17] that limit its safety in septic shock.

Although some trials show that epinephrine is comparable with norepinephrine[18] or norepinephrine plus dobutamine,[19] epinephrine use as a first-line agent is discouraged owing to concerns regarding splanchnic vasoconstriction, tachyarrhythmias, and generation of lactate that may interfere with lactate-guided resuscitation management.[15]

Phenylephrine is a pure α-agonist catecholamine vasopressor that is commonly used as a short-term vasopressor by anesthesiologists in an operative setting. There are concerns regarding splanchnic vasoconstriction leading to gut ischemia with long-term use of phenylephrine and it is not recommended for routine prolonged resuscitation of hypotension in sepsis.[15] A national US shortage of norepinephrine recently led to a natural experiment to compare outcomes of septic shock before, during, and after the shortage.[20] Phenylephrine was the most commonly used vasopressor in this shortage period, during which time a higher mortality was seen compared with the periods with an adequate norepinephrine supply.[20] This information also suggests the primacy of norepinephrine over phenylephrine as vasopressor of first choice in septic shock.