REVIEW

The response of the host microcirculation to bacterial sepsis: does the pathogen matter?

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Abstract Sepsis results from the interaction between a host and an invading pathogen. The microcirculatory dysfunction is now considered central in the development of the often deadly multiple organ dysfunction syndrome in septic shock patients. The microcirculatory flow shutdown and flow shunting leading to oxygen demand and supply mismatch at the cellular level and the local activation of inflammatory pathways resulting from the leukocyte–endothelium interactions are both features of the sepsis-induced microcirculatory dysfunction. Although the host response through the inflammatory and immunologic response appears to be critical, there are also evidences that Gram-positive and Gram-negative bacteria can exert different effects at the microcirculatory level. In this review we discuss available data on the potential bacterial-specific microcirculatory alterations observed during sepsis.

Keywords Sepsis · Endothelium · Pathogen · Pathophysiology

Introduction

Septic shock occurs with an increasing incidence over years with a mortality rate remaining unacceptably high when multiple organ dysfunction develops. Clinical research has brought attention to the association of microcirculatory dysfunction and sepsis. Back in 1922, Freedlander and Lenhart already observed the microcirculation from fingers of septic patients, using a standard microscope, and described "capillary stasis without evidence of cardiac decompensation" [1]. Subsequently, these authors and others used the term "endothelium intoxication" which was associated with "capillary stasis and increased permeability due to some products of traumatized or poorly metabolized tissue." Since that time, the pathophysiology of the microcirculatory dysfunction in septic shock has gained major insights. The sepsis is seen as a homogeneous entity resulting from a host inflammatory response to an invading pathogen [2], with an international definition, rarely referring to the nature of the infecting organism. However, the appreciation that the causative microorganisms in sepsis can have varying clinical consequences suggests that substantial differences in the pathophysiology of sepsis may be part of the syndrome. The epidemiology of sepsis is changing with an increasing proportion of cases due to Gram-positive bacteria which appear to yield a worse outcome compared to patients infected with Gram-negative microorganisms [3, 4]. The purpose of this brief review is to discuss potential implications of the nature of the microorganism in the microcirculatory dysfunction observed in sepsis focusing on the differences observed between Gram-negative and Gram-positive bacteria.

Microcirculatory disorders in sepsis: implications for disease

The systemic and pulmonary microcirculations are targets of injury in the course of septic shock. There is overwhelming evidence that microcirculatory disorders occur in the course of septic shock with a decrease of density of

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perfused capillaries with sluggish or stop-flow perfusion patterns [5, 6]. The functional consequence is that some local regions of tissue will be undersupplied with oxygen while others are being oversupplied due to microcirculatory blood flow shunting [7]. Oxygen diffusion distances will increase, and convective oxygen delivery to the cells will be impaired causing initially a mismatch between cell oxygen demand and supply. Tissue hypoxia can then trigger inflammatory pathways which potentially further cause tissue damage. These microcirculatory alterations have been associated with worse outcome and seem to be, at least partially, independent of the macrohemodynamic variables [8, 9]. Red blood cells (RBCs) and platelets aggregation, endothelial cell swelling, arteriole vasoconstriction, endothelium injury, and increased microvascular permeability with interstitial edema are all factors proposed to be responsible for capillary flow shutdown [10]. Coagulation activation is another hallmark of sepsis with the inflammatory response activating tissue factor on endothelial cells and monocytes, intravascular thrombin generation, depletion of anticoagulant factors, and alterations of the fibrinolytic system [11]. Analysis of the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis trial revealed that almost all patients with severe sepsis had stigma of coagulation activation. Markers of coagulation activation such as prothrombin time, level of D-dimer, or protein C were found to be profoundly abnormal [12]. This appeared to be slightly more pronounced in patients with Gram-negative sepsis and bacteremia although the greatest reduction in the mortality rate in patients treated with human drotrecogin alfa (activated), an antithrombotic-targeted therapy, was observed in *Streptococcus pneumoniae*-related sepsis [12].

Besides promoting leukocytes recruitment on the site of infection for bacterial clearance, endothelium activation will subsequently trigger local inflammation and contribute to tissue injury, including vascular injury [13]. Despite large amount of NO being produced by inducible nitric oxide synthase during sepsis, generation of superoxide by adhesive leukocytes can decrease endothelium-derived NO bioavailability and compromise microcirculatory blood flow by inducing vasoconstriction or lost of vasodilation [14].

Nonspecific microcirculatory phenomena in bacterial sepsis

Most of our current understanding of the molecular pathogenesis of sepsis-induced microvascular dysfunction has been derived from experimental animal models (Fig. 1). Downstream the bacterial signal, local and systemic inflammatory pathways activation are a hallmark of sepsis

[2]. The microvasculature will respond to inflammatory stimuli mainly through activation of the endothelium. On the front line is the expression of adhesion molecules which will enhance endothelial–leukocyte interaction [15]. P-selectin, which is preformed and stored in Weibel–Palade bodies in the endothelial cells, is exposed within minutes on the endothelial cell surface after proinflammatory stimulation while E-selectin, intercellular adhesion molecule-1, or vascular cellular adhesion molecule-1 are upregulated within hours by gene-transcription under regulation of transcription factors such as nuclear factor-κβ (NF-κβ) [16, 17].

Other NF-κβ-regulated genes in endothelial cells include plasminogen activator inhibitor-1, cyclooxygenase-2, and inducible nitric oxide synthase [17], all involved in the microcirculatory blood flow regulation. Liaison of endothelial adhesion molecules to the neutrophil ligand E-selectin ligand-1 (ESL-1), P-selectin glycoprotein ligand-1, and CD44 will subsequently allow leukocyte adhesion and transmigration through the endothelial layer. Nonbacterial inflammatory stimulation such as tumor necrosis factor-α (TNF-α) can disrupt the microvasculature, increase the vascular permeability [18], and promote leukocytes and bacterial recruitment [19]. Hidalgo et al. have recently shown how administration of TNF-α triggers interaction of leukocytes with circulating RBCs and platelets [20]. Interaction of the endothelial adhesion molecules E-selectin with its ligand ESL-1 on leukocytes initiated a second wave of activation after it upregulated the alphaM beta2 integrin on neutrophils, allowing interaction with RBCs and platelets. These interactions will in turn induce the formation of reactive oxygen species (ROS) by neutrophils and lead to impairment of capillary blood flow and vascular damage [21]. Decrease of endothelial cells' antioxidant defense mechanisms in sepsis can then further expose cells to ROS-induced damage [22]. The interactions of RBCs with leukocytes take place mainly in inflamed venules. The high shear stress may prevent leukocyte–endothelium interaction in arterioles. The prevention of increased permeability of venules in platelet-depleted mice underlined the role of platelets in inflammation-induced vascular damage [23]. Angiotensin II is a another mediator which has been found to stimulate NF-κβ expression through induction of oxidative stress in endothelial cells, which in turn promote the expression of adhesion molecules [24]. Interestingly, Laschke et al. reported that stimulation of the endothelium with TNF-α does not necessarily translate into changes of microcirculatory blood flow. They found no difference in microhemodynamics after applying topically TNF-α on skinfold chamber of hamsters infected with *Staphylococcus aureus* [25]. Finally, it has been hypothesized that severe endothelial injury could impair bacterial clearance due to the inability of

Fig. 1 Proposed Mechanisms of the role of microcirculatory alterations in sepsis-related multiple organ failure. Recognition of bacterial products by pattern-recognition receptor (PRR) on immune and endothelial cells initiate host responses at the microcirculatory level leading to endothelial cells damage, leukocytes activation and adhesion, and production of reactive oxygen species (ROS). Microcirculatory flow shutdown will follow due to microthrombi, interstitial edema, and alteration of vascular tone
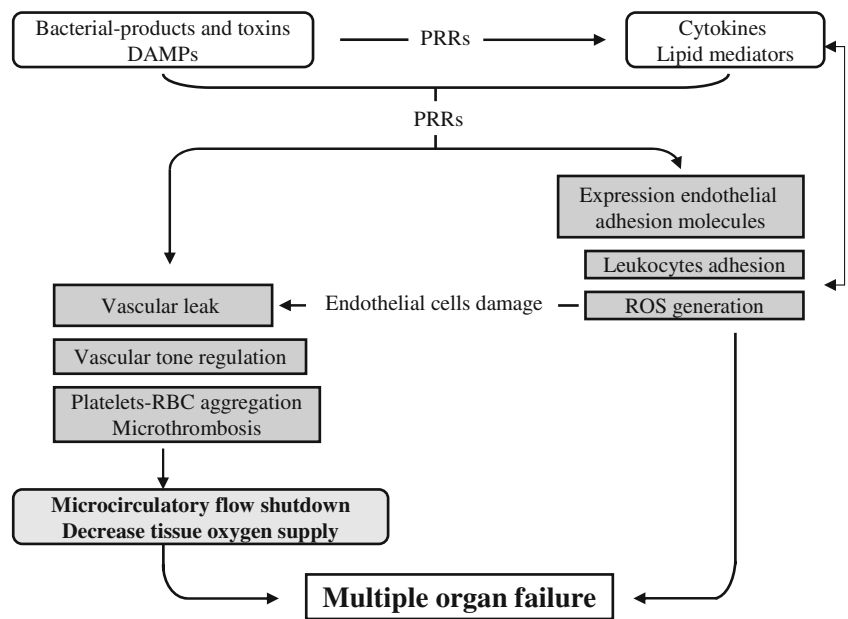
endothelial cells to undergo the active cytoskeletal rearrangements necessary to allow leukocyte transmigration [26]. We also have to bear in mind that the response of the endothelium to inflammatory stimuli may differ among different sites of the microvasculature and between organs. To conclude, microcirculatory perfusion abnormalities are often associated with sepsis and are thought to result from hemodynamic determinants, inflammation, and host-immune response interactions. This ultimately leads to endothelial adhesion molecule expression with tissue recruitment of inflammatory cells and microcirculation perfusion alterations.

The pathogen-specific microvascular alterations in bacterial sepsis: Gram-negative versus Gram-positive bacteria

The outcome of a bacterial infection depends upon the molecular interactions between the invading microorganism and the human host. Although the mediators of inflammation appear to be central in the development of organ dysfunction, it is now appreciated that pathogens and pathogen-derived products from Gram-negative and Gram-positive bacteria called pathogen-associated molecular patterns (PAMPs) can activate different specific inflammatory pathways leading to microvascular injury (Table 1). Endotoxin is a lipopolysaccharide (LPS) from which most of the toxicity resides in the lipid A in the innermost core region. Even extremely debated, the presence of endotoxemia is thought to be a major component of the pathophysiology of Gram-negative bacterial sepsis and seems to correlate with severity of the disease [27]. Recently, the use

of polymyxin B-immobilized hemoperfusion, to remove circulating endotoxin by adsorption, has been reported to improve hemodynamic variables during the course of abdominal sepsis [28]. Such a concept of circulating LPS as a risk factor fits, of course, well with Gram-negative infection but can also fit with Gram-positive infection. In this particular situation as in many other severe acute inflammations, LPS alone or Gram-negative bacteria may cross the tissue–vascular barrier, especially in the gut. Although LPS induces microcirculatory alterations, other bacterial factors can be involved in the leukocyte–endothelium interaction in the course of Gram-negative bacterial sepsis. This is illustrated by the study of Moreland et al. who found that intact *Escherichia coli* bacteria elicited much more PMN migration than purified *E. coli* LPS at corresponding LPS concentrations [19].

Endotoxemia is not a feature of Gram-positive bacterial sepsis. Indeed, the plasma membrane of gram-positive bacteria is surrounded by a thick layer of peptidoglycan, which embeds molecules of lipoteichoic acid (LTA). Yipp et al., using intravital microscopy to visualize muscle microvasculature in mice, have provided evidence that pathogen-derived products can exert different microvascular effects [29]. While local administration of LPS from *E. coli* induced leukocyte rolling, adhesion, and migration in postcapillary venules with increased expression of endothelial adhesion molecules, administration of LTA from *S. aureus*, had a minor effect on leukocyte–endothelial interaction or expression of these adhesion molecules. On the other hand, systemic injection of live *S. aureus* induced responses similar to LPS, probably partially mediated by peptidoglycan [30]. In the same line, Klintman et al. examined the liver microvascular effects of staphylococcal

Table 1 Summary of the bacterial and inflammatory mediators involved in the pathogenesis of the microcirculatory dysfunction of sepsis

	Target	Identified mechanisms	References
Nonspecific mediators			
IL-1β, IL-6, IL-8, IL-12, IL-15, IL-18, TNF-α, MIF, HMGB1[a] Platelet-activating factor, prostaglandins, leukotrienes, thromboxane, tissue factor	Vascular endothelium: modify vascular tone, microvascular thrombi increased vascular permeability	Increase inducible nitric oxide synthase expression; induce endothelial cells apoptosis and necrosis pathways; activate neutrophils; upregulate cellular adhesion molecules; and promote interaction of leukocytes with red blood cells and platelets; ROS generation	[18, 20, 47]
Bacterial mediators			
Gram-negative bacteria	Microvascular thrombi		[48]
LPS (lipid A)	Inflammation stimulation Damage vascular endothelium Increased vascular permeability Impaire RBC deformability	Expression of endothelial adhesion molecules; activate leukocytes and macrophages; increase inducible nitric oxide synthase expression; ROS generation	[16, 18, 22, 29, 33, 49, 50]
Hemolysin A		Inducible nitric oxide synthase expression	
Gram-positive bacteria			
Peptidoglycan, cell wall components, LTA Exotoxins (pneumolysin, α toxin, h-toxin)	Inflammation stimulation; damage vascular endothelium	Expression of endothelial adhesion molecules; endothelial cells apoptosis Activate leukocytes and macrophage inducible nitric oxide synthase expression ROS generation	[26, 30, 36, 38, 43]
M protein	Vascular leakage	Heparin-binding protein secretion by activated neutrophils	[45]
Exotoxins	Microcirculatory flow shutdown	Coaggregation of platelets and neutrophils, activation of platelet adhesion glycoproteins GPIIb/IIIa	[50, 51]
Surface proteins (protein A, fibronectin-binding proteins ClfA, SdrE, proteins A)	Coaggregation of platelets and neutrophils	Bind to Von Willebrand factor recognized by the GpIb receptor	

Drawing a direct relationship between a bacterial product and an effect would be oversimplistic since most of them have multiple targets and cause effects through interlinked mechanisms involving the host inflammatory response

ROS reactive oxygen species, *HMGB1* high-mobility group B1, *TNF-α* tumor necrosis factor alpha, *MIF* migration inhibitory factor, *ClfA* clumping factors A, *SdrE* serine–aspartate repeat protein

[a] Note that Gram-positive and Gram-negative bacteria can exert their effects through the inflammatory response which may markedly differ between microbial pathogens

enterotoxin A and LPS in mice. They found that entero-toxin A-induced liver injury was FasL-mediated but was independent of leukocyte recruitment while LPS provoked a TNF-α-dependent liver injury and enhanced leukocyte adhesion in the postsinusoidal venules [31].

These observations may arise from difference in expression of the Toll-like receptors (TLRs). TLRs have been identified as receptors able to recognize molecular structures of microorganisms termed PAMPs [32]. PAMPs include double-stranded RNA from bacteria products (LPS and LTA, respectively) and flagellin, a component of motile microorganisms. After binding to their ligands, TLRs activate transcription factors (namely intranuclear NF-$\kappa\beta$, activator protein-1, and interferon response factor-3) which result in the transcription of many proinflammatory genes, including inducible nitric oxide synthase, TNF-α, and of interferon-β. TLR2, involved in the recognition of LTA, is not expressed on the endothelium, in contrast with the TLR4, which is involved in the recognition of LPS and found highly expressed on endothelial cells [33]. Activation of TLR2 or TLR4 can then result in different cytokine and chemokine gene transcription. This is coherent with some observations that patients with Gram-negative sepsis can have higher levels of the cytokine TNF-α and interleukin (IL)-6 than Gram-positive patients do [34]. Finally, TLR5 has been identified as the specific receptor for the bacterial structural protein flagellin which is expressed on intestinal microvascular endothelial cells with a role in the intestinal innate immune response [35]. The pattern of this inflammatory response has been proposed to be informative of the nature of the pathogen involved.

The pathogenicity of microorganisms can also depend upon different membrane molecules expressions which determine their ability to interact with the endothelium. For instance, neutrophil migration in response to S. pneumoniae and S. aureus requires endothelial cell expression of CD18, whereas E. coli-induced migration seems independent of CD18 [19]. On the other hand, the pattern recognition molecule CD14 seems to be to LPS and of the Gram-positive bacterial components peptidoglycan and LTA. The ability of Neisseria meningitidis to cross the blood–brain barrier leading has been found to depend upon signals triggered by their type IV pili. Coureuil et al. found that after adhering and dividing onto brain endothelial cells, the bacteria will spread on the surface of the cells and mimic the signal of adherens junction's cell–cell formation which will disorganize the intercellular junctions and allow meningeal invasion [36].

Gram-positive bacteria can also exert endothelial toxicity through the release of various exotoxins. Pneumolysin is such an example common to all serotypes of S. pneumoniae. The endothelium is a major target of pore-forming bacterial exotoxins. Pneumolysin appeared to be required for the passage of pneumococci through the endothelial barrier by inducing endothelial cell apoptosis [37]. This makes pneumolysin an essential actor in the pathophysiology of bacterial meningitis allowing invasion of the cerebrospinal fluid from the blood compartment. Microvascular effects of pneumolysin have also been associated with pneumococcal-related acute lung injury. Intravascular administration of pneumolysin has been reported to result in an increase of pulmonary vascular resistance and permeability in a dose-dependent manner through platelet-activating factor-mediated release of thromboxane [38, 39]. S. aureus α-toxin and E. coli hemolysin A are other examples of such toxin which can create an inner hydrophilic cavity in cell membrane leading to endothelial cell damage and subsequent vascular hyperpermeability [40]. For instance, S. aureus α-toxin has been shown to increase vascular permeability by producing discontinuation of vascular junctional proteins (i.e., vascular-endothelial-cadherin and occluding) [41]. Interestingly, although both S. aureus α-toxin and E. coli hemolysin A can affect the myocardial circulation with increased coronary vascular resistance and loss in contractile function, the two exotoxins can exert different effects on myocardial perfusion. In a model of rat isolated hearts, Grandel et al. reported subendocardial perfusion impairment with hemolysin while α-toxin rather impaired the epicardial microcirculatory flow [42]. Release of hemolysin A can then stimulate vasodilation through the stimulation of constitutive nitric oxide synthase-dependant NO release [43].

Streptococcal toxic shock syndrome (STSS) arises from invasive Streptococcus pyogenes infections and is associated with a massive vascular leakage. Previous work has shown that secreted S. pyogenes streptolysin-O, a soluble extracellular toxin, plays an important role in the vascular dysfunction of STSS by inducing coaggregation of platelets and neutrophils mediated by platelet P-selectin [44]. Then, M protein contributes to the vascular leakage in STSS in activating neutrophils to secrete heparin-binding protein, a powerful inducer of increased vascular permeability [45]. Clostridium perfringens, a Gram-positive strict anaerobic bacteria, has also been reported to impair muscle microvascular blood flow. This effect is linked to the generation of intravascular platelet–leukocyte aggregates via activation of platelet adhesion glycoproteins GPIIb/IIIa and P-selectin by α-toxin and h-toxin (also named perfringolysin O) [26]. Finally, the staphylococcal superantigen-like protein 5 has been found to inhibit the leukocyte activation induced by chemokines and anaphylatoxins and can therefore prevent leukocyte recruitment on the site of infection. This illustrates the highly complex regulation of cellular response to the invading pathogen [46]. Therefore, there are evidences that pathogens can activate different pathways which will affect the microcirculation. The interaction of some pathogens or

their products with the endothelium will be central in their pathogenicity (e.g., meningeal invasion and *N. meningitidis* and vascular leakage in STSS). On the other hand, although experimental data suggest specific signaling pathways, the microcirculatory alterations witnessed in sepsis appear to be mainly dependant on nonspecific host inflammatory and immune response. The paucity of clinical data on this issue appeals for well-designed clinical trials to better appreciate the respective role of the host response and pathogens in the microcirculatory alterations in sepsis.

Conclusion

Sepsis results from the interaction between a host and an invading pathogen associated with microcirculatory alterations. First, leukocytes and circulating inflammatory cells will be recruited on the site of infection by adhering to the endothelium and be activated for bacterial clearance with potential tissue damage as a consequence. Second, the systemic inflammatory and immune response to the pathogen will damage the endothelium in remote organs, increase the microcirculatory permeability, and induce production of reactive oxygen species which will compromise tissue oxygen supply. Some pathogens and their products can activate different pathways which are essential in their pathogenicity. However, the downstream host response in sepsis appears to be central in the development of microcirculatory dysfunction. Well-designed clinical trials are now required to determine whether targeting the microcirculatory compartment can prevent organ failure in sepsis.

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