

Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock

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Multiple experimental and human trials have shown that microcirculatory alterations are frequent in sepsis. In this review, we discuss the various mechanisms that are potentially involved in their development and the implications of these alterations. Endothelial dysfunction, impaired inter-cell communication, altered glycocalyx, adhesion and rolling of white blood cells and platelets, and altered red blood cell deformability are the main mechanisms involved in the development of these alterations. Microcirculatory alterations increase the diffusion distance for oxygen and, due to the heterogeneity of microcirculatory perfusion in sepsis, may promote development of areas of tissue hypoxia in close vicinity to well-oxygenated zones. The severity of microvascular alterations is associated with organ dysfunction and mortality. At this stage, therapies to specifically target the microcirculation are still being investigated.

Introduction

Septic shock is characterized by profound hemodynamic alterations associated with organ dysfunction. These hemodynamic alterations include some degree of hypovolemia and a decrease in vascular tone and myocardial depression. Even when systemic hemodynamic variables seem to have been corrected and are within therapeutic goals, signs of impaired tissue perfusion may persist. Recently, alterations in microcirculatory blood flow have been identified in severe sepsis¹ and the severity of these alterations is associated with a poor outcome.^{2,3} The impact of therapeutic interventions on microcirculatory function is beginning to be reported.^{4–6} In this manuscript, we discuss the pathophysiology of the alterations in microvascular perfusion in sepsis, and their implications for organ function and for therapy.

Microcirculatory Alterations in Sepsis: Where is the Evidence?

Multiple experimental studies have found that sepsis induces marked alterations in the microcirculation. Compared with normal conditions in which there is a dense network of capillaries,

most of which are perfused, sepsis is associated with a decrease in capillary density in association with an increase in heterogeneity of perfusion because of the presence of intermittently or not perfused capillaries in close proximity to well perfused capillaries.^{7–10} Importantly, this is a dynamic process, as capillaries in which there is no flow at a given time may be perfused a few minutes later. These alterations have been reported after administration of endotoxin or live bacteria and during bacterial peritonitis,^{8,9,11} and have been observed in rodents^{12,13} as well as in large animals.^{9,11} In addition, all studied organs have been affected, including the skin,¹⁴ muscle,^{12,13} eye,¹⁵ tongue,⁹ gut,^{9,10} liver,⁷ heart,¹⁶ and even the brain.¹¹ Hence, these changes seem to be ubiquitous and to have common pathophysiologic mechanisms.

In humans, demonstration of these alterations has been longer in coming, mostly because of technical limitations that prevented exposure of the human microcirculation. The development of new imaging techniques has enabled direct visualization of the human microcirculation with small handheld microscopes.^{17,18} We demonstrated that microcirculatory perfusion is altered in patients with severe sepsis and septic shock.¹ An example of altered human microcirculation in sepsis is shown in **Figure 1**. These alterations in microvascular perfusion are very similar to those occurring in experimental conditions, and are characterized by a decrease in vascular density together with an increased number of capillaries with stopped or intermittent flow. Since this initial study, more than 30 studies have shown similar results.

What are the Consequences of These Alterations?

The decreased capillary density results in an increased diffusion distance for oxygen.¹⁶ More importantly, microvascular blood flow is heterogeneous, with perfused capillaries in close vicinity to non-perfused capillaries, leading to alterations in oxygen extraction and hypoxic zones even when total blood flow to the organ is preserved.¹⁹ Heterogeneity of microvascular perfusion is a crucial aspect. Heterogeneous perfusion leads to more severe alterations in tissue oxygenation than does homogeneously decreased perfusion.^{20,21} Heterogeneity of perfusion is associated with heterogeneity in oxygenation²² but also with altered oxygen extraction capabilities.^{10,20,21,23,24} During episodes of hypoperfusion, the heterogeneity of microvascular perfusion further increases in sepsis instead of being minimized as in normal conditions.²⁴

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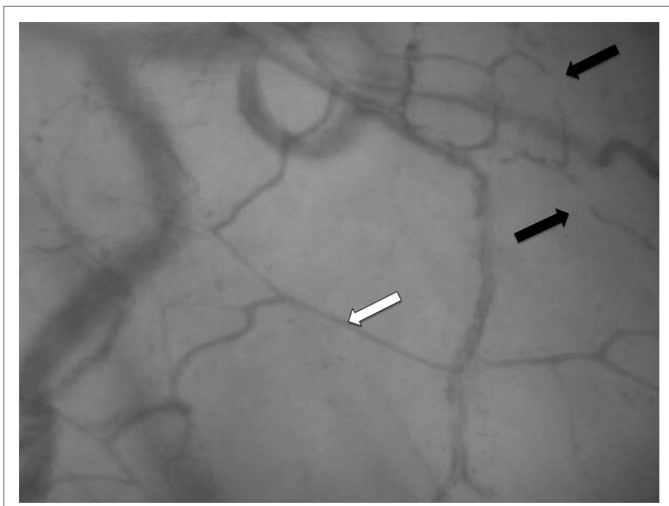


Figure 1. Sublingual microcirculation in sepsis. Photograph of the sublingual microcirculation in a patient with septic shock using a sidestream dark field (SDF) imaging device. The white arrow shows a perfused capillary, the black arrows identify a stopped flow capillary.

These alterations play an important role in the development of organ dysfunction and are not just an indication of the severity of sepsis. Microvascular alterations can lead to cellular injury²⁵ and reversal of these alterations is associated with improvement in lactate⁵ and NADH²⁶ levels, suggesting that microvascular alterations directly impair tissue oxygenation. In addition, several trials have demonstrated an association between the severity of microvascular dysfunction and the development of organ dysfunction²⁷⁻²⁹ and mortality.^{1,2,19,28,30-33}

In a large series of 252 patients with septic shock, microvascular perfusion was an independent factor associated with survival.³ Of note this is not an on-and-off but rather a progressive phenomenon. Dividing the population into quartiles of proportions of perfused capillaries, mortality rates markedly increased with alterations in the microcirculation (Fig. 2).³ Looking at which variables differed between survivors and non-survivors, the proportion of perfused capillaries was the strongest predictor of outcome. Vascular density, and especially vascular density of perfused capillaries, have been associated with outcome,^{1,3,19} as well as the heterogeneity index,^{3,19} but not the velocity in perfused capillaries.¹⁹ More importantly, evolution over time of these alterations also differs in patients with good or poor outcomes,^{2,33} rapidly improving in survivors but remaining disturbed in non-survivors, whether these patients die from acute circulatory failure or from organ failure after resolution of shock.² In children with septic shock, the microcirculation improved from day 1 to day 2 in survivors but remained altered in non-survivors.³³ Interestingly, the severity of microvascular alterations was an independent factor associated with outcome in the early and later phases of sepsis, but the cut-off value separating survivors from non-survivors was lower in the early phase.³

Although one may consider that the microcirculation is just adapting to direct cellular alterations, several factors suggest that microcirculatory alterations are the primary event leading

to cellular dysfunction. First, microcirculatory alterations are colocalized with low PO_2 , production of hypoxia-inducible factor¹⁶ or redox potential²⁶ in experimental conditions. Second, oxygen saturation at the capillary end of well-perfused capillaries is low, not elevated, suggesting that the tissues are using the delivered oxygen.²³ Third, the tissue to arterial PCO_2 gradient, the PCO_2 gap, is increased in sepsis.³⁴⁻³⁸ In addition, there is an inverse relationship between sublingual microvascular perfusion and the PCO_2 gap.³⁵ A similar inverse relationship was found between ileal mucosal perfusion and ileal to arterial PCO_2 gap.³⁸ If flow were just matching metabolism, CO_2 production would be low because the primary alteration is the decrease in metabolism, and PCO_2 gap would be normal, even at low flows. Fourth, perfusion abnormalities precede alterations in organ function.³⁹ Fifth, improvement in the sublingual microcirculation in response to initial resuscitation procedures was associated with an improvement of organ function 24 h later.²⁹ Finally, the decrease in lactate levels is proportional to the improvement of the microcirculation during dobutamine administration.⁵

Admittedly, microcirculatory alterations are not the sole mechanism contributing to organ dysfunction in sepsis. Cellular metabolic alterations and in particular mitochondrial dysfunction may also contribute. Discussion of these factors is beyond the scope of this review. Importantly, there is an interplay between hypoxia and inflammation and mitochondrial dysfunction.⁴⁰ Limiting perfusion abnormalities is associated with reduced expression of inflammatory molecules, caspases, and mitochondrial abnormalities.^{41,42}

What Mechanisms Could Be Involved in the Development of These Alterations?

Endothelial dysfunction is one of the key mechanisms underlying these alterations. We have seen earlier that endothelial reactivity to vasoconstrictive and vasodilating substances is decreased in sepsis, and both constriction and dilation are important for the regulation of microvascular blood flow. This aspect of endothelial involvement is illustrated by the alteration in post-ischemic hyperemic response, which is blunted in patients with sepsis.^{27,32,43-47} Furthermore, alterations in the descending (oxygen consumption) or ascending slope are associated with development of organ failure.^{27,32} In addition, and perhaps more importantly, communication between endothelial cells may be altered. In normal conditions, matching of tissue perfusion with metabolism is obtained by backward communication through perivascular nerves but also by transmission of information between endothelial cells. Indeed, the stimulation of endothelial cells in a given area results in a change in membrane potential which is transmitted to contiguous cells, resulting in transmission of the information to upstream arterioles up to a distance of 1000 μm .⁴⁸ During endotoxic conditions, the communication rate between microvessels 500 microns apart is markedly impaired, but this phenomenon is transient and fully reversible after recovery from endotoxin exposure.⁴⁹ The interaction between the endothelial surface and circulating cells is also impaired in sepsis. In particular, the glycocalyx is altered in sepsis. The glycocalyx is a thin

layer of glucosaminoglycans that covers the endothelial surface and in which various substances, such as superoxide dismutase and antithrombin, are embedded. The glycocalyx facilitates the flow of red blood cells and limits adhesion of white blood cells and platelets to the endothelium. The size of the glycocalyx is markedly decreased in sepsis⁵⁰⁻⁵² and byproducts of its degradation are found in the blood.^{50,53} In addition, the glycocalyx is made more permeable to labeled substances.⁵¹ Alteration in the glycocalyx layer promotes leukocyte rolling and adhesion to the endothelium.^{51,54} Administration of hyaluronidase, which partially destroys the glycocalyx layer, mimics sepsis-induced alterations in microcirculatory perfusion.⁵⁵

Activation of coagulation may also play a key role in the pathogenesis of microcirculatory alterations^{8,56} even though microthrombi formation is rarely documented in experimental sepsis.⁷ In mice challenged with endotoxin, fibrin deposition occurred in a significant proportion of capillaries; the addition of antithrombin decreased the number of non-perfused capillaries, whereas this number was increased after addition of FeCl₃, a factor locally activating coagulation.⁸

Finally, circulating cells also play a key role in these alterations. Leukocyte and platelet rolling and adhesion to the endothelial surface is increased in sepsis,^{7,8} which may impair the circulation of other cells. Red blood cells also may play a role, with alterations in red blood cell deformability,⁵⁷ impaired release of nitric oxide (NO), and/or adhesion of red blood cells to the endothelium.⁵⁸ Altogether, these data suggest that multiple mechanisms are involved in the development of microvascular dysfunction, and that it is unlikely that an intervention focused on a single pathway would be effective. As an example, chemotherapy-induced neutropenia and thrombopenia does not prevent microcirculatory alterations from occurring,⁵⁹ which nicely illustrates that this mechanism in isolation is not enough to generate microvascular alterations.

In septic patients who have severe microvascular alterations, we demonstrated that topical administration of a large dose of acetylcholine, an endothelium-dependent vasodilating agent, restored the microcirculation to a state similar to that of healthy volunteers and non-septic ICU patients.¹ This observation has profound implications. First, sepsis-associated microcirculatory alterations are functional and can be totally reversed. Complete obstruction of microvessels by clots is thus unlikely. Second, the endothelium, although dysfunctional, is still able to respond to a supraphysiological stimulation. These observations suggest that therapeutic interventions could be used to try to reverse these alterations.

The mechanisms involved in microvascular alterations differ from those involved in the development of systemic hemodynamic alterations. Accordingly, it is expected that microcirculatory derangements may be present even when systemic hemodynamics are within acceptable limits.

It should be noted that many of the mechanisms involved in microcirculatory dysfunction are probably mandatory for the control of infection. Activation of inflammation and coagulation are important for compartmentalization of infection; rolling and adhesion of white blood cells and increased permeability are

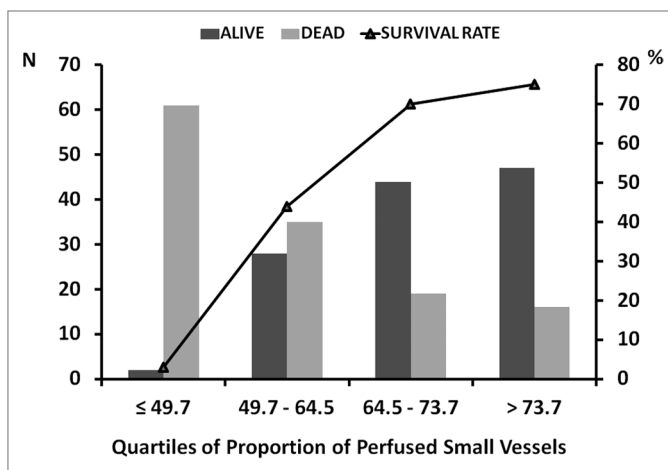


Figure 2. Relationship between sublingual microcirculation and ICU mortality in patients with severe sepsis. In this series of 252 patients with severe sepsis, the sublingual microcirculation was assessed either with an orthogonal polarization spectral (OPS) or a sidestream dark field (SDF) imaging device. The patients were grouped into quartiles of proportion of perfused capillaries. From reference 3 with permission.

needed to allow these cells to enter the tissue and kill bacteria; intravascular neutrophil extracellular traps (NETs) bind circulating bacteria and are useful for bacterial clearance even though they may impair circulation of blood cells.⁶⁰ Hence, totally inhibiting the factors responsible for the activations of these processes does not seem to be a rational approach, rather it should be modulated, to maintain a limited, beneficial level.

Therapeutic Interventions Targeted at the Microcirculation

Given the heterogeneous nature of the microvascular alterations, it is more important to recruit the microcirculation than to increase total flow to the organ. Ideally, the intervention should affect one or several of the mechanisms involved in the development of these microvascular alterations. Nevertheless, most interventions that are currently used for their impact on systemic hemodynamics may also influence the microcirculation to some degree.

Fluids and vasoactive agents are key components of hemodynamic resuscitation, given with the aim of improving tissue perfusion. However, improved cellular oxygen supply implies an improvement in microvascular perfusion. Two recent trials have demonstrated that fluids can improve microvascular perfusion, increasing the proportion of perfused capillaries and decreasing perfusion heterogeneity.^{4,61} Importantly, in both trials the microcirculatory effects were relatively independent of the systemic effects. The microcirculatory effects of fluids seem to be mostly present in the early phase of sepsis (within 24 h of diagnosis) whereas later (after 48 h) fluid administration failed to improve the microcirculation even when cardiac output increased.⁴ Whether different types of fluid are associated with different microvascular responses is still debated. In some experimental conditions, colloids may increase microcirculatory perfusion

more than crystalloids,⁶² but this difference has not been confirmed in septic patients.⁴ The mechanisms by which fluids may improve the microcirculation are not well understood, but may be related to a decrease in viscosity, a decrease in white blood cell adhesion and rolling, or, indirectly, to a decrease in endogenous vasoconstrictive substances. Whether the effects of fluids, when observed, will persist or be transient, and also whether this effect can be “saturated”, i.e., only the initial effects would be beneficial and further administration of fluids would have minimal effect, requires further study. This “saturable” effect is suggested by the observations of Pottecher et al.⁶¹ who reported that the first bolus of fluids improved microvascular perfusion but the second had no effect even though cardiac output increased further.

The effects of red blood cell transfusions are variable and may depend on the severity of underlying microcirculatory alterations. In patients with sepsis, transfusions failed to improve the microcirculation in the entire population; however, transfusions did improve microvascular perfusion in patients with the most severely altered microcirculation at baseline and even worsened the microcirculation in patients with microcirculation closer to normal values.⁶³

Beta-adrenergic agents have been shown to improve microvascular perfusion, increasing not only convective but also diffusive transport.^{5,64} These effects were dissociated from the systemic effects of these agents.⁵ Similar effects were observed with milrinone⁶⁵ but the effects of levosimendan may be even more pronounced.^{6,65}

Vasopressor agents also have variable effects. Correction of severe hypotension does not impair and may even improve microvascular perfusion,^{66,67} probably through the restoration of organ perfusion by restoring a minimal perfusion pressure. However, increasing blood pressure further (mean arterial pressure from 65 to 75 and 85 mmHg) may not improve microvascular perfusion. Of note, these data were obtained in small cohorts of patients and there was large inter-individual variability.⁶⁸⁻⁷⁰ Interestingly, the increase in arterial pressure impaired the sublingual microcirculation in patients with close to normal microcirculation at baseline, whereas it was beneficial in the most severe cases.⁶⁹

Vasodilating substances may have a role in manipulation of the microcirculation because local constriction–dilation is involved in the regulation of flow and capillary recruitment and decreased vascular density and stopped-flow capillaries may be the result of excessive vasoconstriction. We demonstrated that topical administration of a large dose of acetylcholine (10^{-2} M directly on the sublingual area) reversed microvascular alterations in patients with severe sepsis.¹ In a small series of patients, Spronk et al.⁷¹ reported in a research letter that nitroglycerin administration rapidly improved the microcirculation. These results have been challenged. In an experimental trial in endotoxic sheep, nitroglycerin administration at a fixed rate of 0.2 $\mu\text{g}/\text{kg}\cdot\text{min}$ did not improve gut mucosal microcirculation or gut mucosal PCO_2 .⁷² A randomized trial that included 70 patients with septic shock showed no effect of nitroglycerin on the microcirculation.⁷³ Does this second trial close the issue? Probably not, because important differences exist between the studies. In particular, Spronk et al.⁷¹ assessed the microcirculation 2 min after

administration of a bolus dose of 0.5 mg nitroglycerin whereas Boerma et al.⁷³ evaluated the microcirculation 30 min after initiation of a continuous infusion of 4 mg/h (0.07 mg/min). Dosing may be crucial, as illustrated in cardiogenic shock.⁷⁴ In the first trial,⁷¹ the bolus dose of nitroglycerin was associated with marked hypotension and fluid boluses were administered rapidly. Importantly, the microcirculation was minimally altered at baseline in the trial by Boerma et al.,⁷³ because the proportion of perfused capillaries was already normal (98%), leaving no room for further improvement. Other vasodilating agents have been used, especially in experimental models. Salgado et al.⁷⁵ recently evaluated the effects of angiotensin converting enzyme inhibition in an ovine model of septic shock. The sublingual microcirculation was slightly less severely altered in treated animals compared with controls but these effects were not accompanied by an improvement in organ function. Administration of other vasodilatory agents, such as magnesium sulfate, also failed to improve the microcirculation.⁷⁶ Accordingly, at this stage, the use of vasodilating agents cannot be recommended. One of the reasons for this relative failure is the lack of selectivity of these agents, which dilate both perfused and non-perfused vessels, thus leading to luxury perfusion of some areas and diverting flow from areas that require it most.

The variability in the response to fluids, red blood cell transfusions, inotropic, and vasopressor agents suggests that systematic use of these agents cannot be recommended and that a patient centered approach with evaluation of the impact of each intervention on the microcirculation should be preferred. Vasodilating agents cannot be recommended at this stage.

Modulation of endothelial NO synthase (eNOS) appears attractive. eNOS is actively involved in the control of blood flow at the microcirculatory level, its stimulation leading to an increase in perfusion in the concerned vessels. In sepsis, eNOS may be dysfunctional, which results not only in impaired perfusion and endothelial reactivity but also in overproduction of reactive oxygen species, including peroxynitrite.⁷⁷ Modulation of eNOS, enabling NOS to locally produce NO could thus be beneficial for tissue perfusion but also for cellular function. Tetrahydrobiopterin (BH4) is an important cofactor of endothelial NOS and the ratio of BH4 to dihydrobiopterin determines production of NO rather than superoxide and peroxynitrite production.⁷⁸ In human healthy volunteers challenged by low doses of endotoxin, BH4 administration restored the forearm blood flow response to acetylcholine. This property of BH4 to restore endothelial function has been observed in various models, including acute hyperglycemia⁷⁹ and ischemia–reperfusion injury.⁸⁰ In a rodent model of septic shock, BH4 improved microvascular perfusion,⁸¹ and this effect was not observed in endothelial NOS knockout mice, demonstrating the involvement of eNOS in this effect. In a sheep model of septic shock induced by fecal peritonitis, BH4 administered 4 and 12 h after the onset of sepsis blunted the decrease in proportion of perfused capillaries and in functional capillary density, and limited the increase in heterogeneity in capillary perfusion.⁸² There was also indirect evidence of blunted increased microvascular permeability in this model. More importantly, BH4 administration was associated with an

improvement in organ function and increased survival duration. Accordingly, BH4 seems to be a promising agent to manipulate the microcirculation.

Vitamin C is another agent active on eNOS, in part by increasing BH4 levels.⁸³ Interestingly, administration of vitamin C improved the microcirculation in various experiments in rats with peritonitis.^{81,84,85} It was not only beneficial when administered just after,⁸⁴ but also when administered 6 h⁸¹ and even 24 h⁸⁵ after the insult.

Various anticoagulant agents have been shown to improve the microcirculation, including activated protein C^{50,86-88} antithrombin,⁸⁹ and low molecular weight heparin.^{90,91} The anticoagulant effect seems not to be crucial for the microcirculatory effects of these agents: a modified antithrombin, deprived of its ligation site for the endothelium but with preserved anticoagulant activity, failed to improve the microcirculation in endotoxic animals.⁸⁹ In line with these findings, hirudin, a pure thrombin inhibitor, did not improve the microcirculation of septic animals.⁹² Some experimental data suggest that decreased white blood cell and platelet rolling and adhesion,^{86,87} preservation of glycocalyx size,⁵⁰ and improvement in endothelial reactivity⁹³ are the most likely

mechanisms involved in the improvement in microvascular perfusion induced by these agents.

Conclusions

Multiple experimental and clinical trials have shown that microcirculatory alterations occur in sepsis and that they may play a role in the development of organ dysfunction. Various mechanisms can be involved in the development of these alterations, including endothelial dysfunction and failure of communication between endothelial cells, glycocalyx alterations, and altered interactions between the endothelium and circulating cells. Although observation of microcirculatory alterations has helped us to better understand the pathophysiology of sepsis and multiple organ failure, monitoring of the microcirculation is not yet ready for routine clinical practice because microcirculatory endpoints for resuscitation and the impact of many therapeutic interventions have not yet been defined.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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