Microcirculatory dysfunction in sepsis: pathophysiology, clinical monitoring, and potential therapies

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Miranda M, Balarini M, Caixeta D, Bouskela E. Microcirculatory dysfunction in sepsis: pathophysiology, clinical monitoring, and potential therapies. Am J Physiol Heart Circ Physiol 311: H24–H35, 2016. First published April 22, 2016; doi:10.1152/ajpheart.00034.2016.—Abnormal microvascular perfusion, including decreased functional capillary density and increased blood flow heterogeneity, is observed in early stages of the systemic inflammatory response to infection and appears to have prognostic significance in human sepsis. It is known that improvements in systemic hemodynamics are weakly correlated with the correction of microcirculatory parameters, despite an appropriate treatment of macrohemodynamic abnormalities. Furthermore, conventional hemodynamic monitoring systems available in clinical practice fail to detect microcirculatory parameter changes and responses to treatments, as they do not evaluate intrinsic events that occur in the microcirculation. Fortunately, some bedside diagnostic methods and therapeutic options are specifically directed to the assessment and treatment of microcirculatory changes. In the present review we discuss fundamental aspects of septic microcirculatory abnormalities, including pathophysiology, clinical monitoring, and potential therapies.

microcirculation; sepsis; microcirculatory monitoring; microvascular resuscitation

IN EARLY STAGES OF SEPSIS, proinflammatory cytokines are released in an attempt to eliminate the offending agent, generating an intense response that impairs the microcirculation (24, 69). Nearly every cellular component of the microcirculation, including endothelial cells, smooth muscle cells, platelets, leukocytes, red blood cells, and adjacent parenchymal cells, is affected (59). The resulting microcirculatory dysfunction is characterized by an increased number of capillaries with stopped flow and maldistribution of microvascular blood flow (15, 40, 68). These microcirculatory changes have been observed in different models of sepsis, organs, and species (5, 31, 42, 68, 78, 95, 101, 111) and appear to have prognostic significance in human sepsis, as the severity of initial microcirculatory derangements in the early resuscitation phase of therapy and their persistence over time have been associated with lower survival rates (5, 7, 93, 105).

This review of fundamental aspects of septic microcirculatory abnormalities includes pathophysiological mechanisms, available techniques for clinical monitoring, and potential therapies to rescue the microcirculation.

The Microcirculation

The microcirculation consists of <100-μm-diameter vessels (arterioles, capillaries, venules, and microlymphatics). It is the major site of blood oxygen release to tissues and works as an integrated system that ensures tissue oxygen delivery adequate to meet cell oxygen demand. Main cell types in the microvasculature are endothelial cells (which line the inside of blood vessels), smooth muscle cells, platelets, leukocytes, red blood cells, and adjacent parenchymal cells, is affected (59). Endothelial cells play a central role in control of microcirculatory function, regulating microvascular thrombosis and fibrinolysis, leukocyte adhesion and migration, vasomotor tone, trafficking of cells and nutrients, and capillary permeability and recruitment (1).

Pathophysiology of Microcirculatory Changes in Sepsis

Local distribution of blood flow to tissues is regulated by the microcirculation. This is possible because, under physiological conditions, endothelial cells sense metabolic and physical signs and respond by regulating microvascular flow through local
release of vasodilators, especially nitric oxide (NO), modulating arteriolar smooth muscle cell tone. NO is an activator of the soluble guanylate cyclase enzyme, responsible for production of cGMP, the mediator of smooth muscle cell relaxation. Therefore, NO is considered a key component in the maintenance and autoregulation of the homeostasis and patency of the microcirculation (52, 104).

During sepsis, the NO system is severely affected: inducible NO synthase (NOS) becomes heterogeneously expressed in different organic vascular beds, resulting in pathological shunt of microvascular blood flow (via arteriovenous shunts), inappropriately deviating blood flow from suffering units. Thus, inducible NOS-deficient areas, which are less vasodilated, become hypoperfused (57, 104). Furthermore, increased reactive oxygen species production during sepsis interferes with NO formation by endothelial NOS and with formed NO, further reducing its concentration (22).

In addition to NO dysregulation, the function of many cell types in the microcirculation is impaired in sepsis syndrome (Fig. 1). Endothelial cells lose their regulatory function as a consequence of changes in signal transduction pathways, loss of electrophysiological communication, and loss of control over arteriolar smooth muscle cells (59, 70, 71, 109). Besides losing their regulation by endothelial cells, arteriolar smooth muscle cells lose their adrenergic sensitivity and tonus, contributing to perfusion abnormalities in the microcirculation (88, 107). This impaired vascular responsiveness to stimuli appears to be a result of excessive NO production by inducible NOS (115).

In physiological conditions, red blood cells deliver oxygen and sense local oxygen gradients, contributing to the autoregulation of microvascular blood flow and oxygen delivery (14). Hemoglobin has an active role in this process, as increased local oxygen gradients induce conformational changes in the hemoglobin molecule and, thereby, facilitate the release of nitrosothiol (a NO derivative) and vasoactive ATP, signaling the microvasculature to vasodilate (61, 97). During sepsis, red blood cells lose their ability to release vasodilators in the presence of hypoxia, impairing an important physiological regulatory mechanism of microcirculatory blood flow (15, 97). Moreover, red blood cells become less deformable and more easily aggregate with endothelial cells during sepsis, compromising blood flow (13, 25, 38).

**Fig. 1. Pathophysiology of microcirculatory changes in sepsis.** Several mechanisms, such as nitric oxide (NO) dysregulation and functional impairment of many cell types found in the microcirculation, have been involved in the development of microvascular abnormalities. eNOS, endothelial NO synthase; iNOS, inducible NO synthase.
The percentage of activated neutrophils with reduced deformability and increased aggregability due to increased expression of adhesion molecules on both endothelial and immune cells also increases during sepsis (66, 78, 107). These leukocytes generate reactive oxygen species and other inflammatory mediators that directly disrupt microcirculatory structures, such as the endothelial glycocalyx (a complex macromolecular network involved in several endothelial functions). Oxidative stress results in changes in endothelial glycocalyx structure and physiology (23, 51, 100). Continuous glycocalyx degradation and shedding expose endothelial cells to oxidative damage, leading to loss of integrity of adherens junctions and increased paracellular permeability with subsequent impairment of endothelial barrier function (75). Increased endothelial permeability results in fluid leakage from the intravascular space and tissue edema (23, 51, 100). Finally, accumulation of water in tissues leads to tissue hypoxia due to increased diffusion distances between functional capillaries and tissue cells in combination with poor oxygen solubility and transport in tissue water (60). Endothelial glycocalyx degradation during sepsis coincides with microcirculatory dysfunction and has been associated with several sepsis-associated clinical conditions, including acute lung injury and cardiovascular dysfunction (75, 84, 94). More importantly, blood levels of glycocalyx components are significantly higher in nonsurvivors than survivors of septic shock, suggesting that glycocalyx shedding may have prognostic significance in human sepsis (84). Glycocalyx disruption also contributes to enhanced expression of adhesion molecules with increased leukocyte trafficking and transport to a shift toward a procoagulant state (33, 62). The resulting proadhesive and prothrombotic effect further promotes the adhesion of red blood cells, leukocytes, and platelets to the vascular endothelium, causing vascular microthrombosis, capillary plugging, and greater compromise of capillary flow (21, 22, 26, 47, 52, 95). Additional activation of coagulation pathways results in capillary obstruction by platelet/fibrin clots secondary to disseminated intravascular coagulation, contributing to microcirculatory derangements (6, 52, 95).

Together, all the aforementioned mechanisms lead to a reduction of perfused capillaries (Fig. 2). Decreased functional capillary density (number of spontaneously perfused capillaries per analyzed tissue area) results in an increased distance for oxygen diffusion to surrounding parenchymal cells (40, 42, 68, 104). Thus it is reasonable to suggest that abnormal tissue oxygen transport and tissue hypoxia may ensue when microcirculatory function is impaired, as in sepsis. Supporting this hypothesis, Ellis and colleagues (40) showed profound maldistribution of microvascular blood flow along with changes in oxygen extraction in early stages of experimental sepsis. They suggested that impaired tissue oxygen transport is likely the result of microcirculatory dysfunction (40). In another experimental study, Bateman and colleagues (15) suggested that loss of microvascular autoregulation during sepsis uncouples local oxygen demand and delivery, leaving some tissue regions vulnerable to hypoxia and unable to rapidly respond to oxygen demand. In experimental conditions, septic microvascular abnormalities could be linked to surrogate markers of tissue hypoxia. For instance, microvascular heterogeneity has been associated with hypoxia-inducible factor gene expression (16). Furthermore, reversal of microcirculatory abnormalities has been associated with proportional improvements in lactate and NADH levels (4, 65). Finally, mathematical models of experimental sepsis predict that decreased capillary density and increased flow heterogeneity may play a role in tissue hypoxia, further corroborating the concept that microcirculatory dysfunction impairs tissue oxygenation (48, 49).

Besides microcirculatory dysfunction, other mechanisms at the cellular level, such as cellular metabolic alterations, mitochondrial dysfunction, and dysregulated apoptosis, also take place during sepsis. However, these cellular abnormalities are regarded as late adaptive responses, which may be preceded or triggered by microcirculatory failure (98, 104). Indeed, evidence suggests that microcirculatory derangements are the primary events leading to cellular dysfunction, reinforcing the importance of microcirculatory assessment (10). For instance, Eipel and colleagues (39) showed that microvascular abnormalities are associated with cellular injury during experimental sepsis, leading to apoptosis. In another experimental study, Rosengarten and colleagues (91) demonstrated that microcirculatory dysfunction precedes sepsis-induced disturbances of neuronal cell function. Finally, in vitro studies have shown that NO inhibits mitochondrial respiration, decreasing oxygen consumption during sepsis (20, 43, 73). This finding raises the possibility that sepsis-induced NO overproduction (an important element in the pathophysiology of microcirculatory dysfunction) may contribute to both tissue hypoxia and mitochondrial inhibition (14, 20).

If not corrected, tissue hypoxia, metabolite accumulation, and mitochondrial dysfunction of parenchymal cells trigger a cascade of pathogenic mechanisms that eventually lead to organ failure and death (15, 59). The underlying process that culminates in organ dysfunction in sepsis is not fully understood, but microvascular alterations have been implicated (113). Indeed, Doerschug and colleagues (32) showed that impaired microvascular reactivity is related to tissue hypoxia and organ dysfunction in human sepsis. Sakr and colleagues (93) also showed an association between microcirculatory alterations and organ dysfunction in human subjects. More importantly, capillary perfusion was related to the severity of organ failure when shock resolved (93). Later trials have corroborated these findings, demonstrating an association between the severity of microvascular dysfunction and the development of organ failure (96, 105, 106). All these studies have suggested a connection between microcirculatory alterations and multiple organ failure in sepsis. However, statistical association between outcome and microcirculatory derangements does not imply a mechanistic relation. To date, a cause-and-effect relationship could not be demonstrated (52).

Septic microcirculatory impairment is characterized by heterogeneity of blood flow: some capillaries are hypoperfused, while others exhibit normal or even abnormally high blood flow (15, 37, 40, 110). Some vulnerable microcirculatory units become hypoxic, determining the oxygen extraction deficit associated with sepsis. Because of microcirculatory perfusion heterogeneity, areas of hypoxic tissue may be found in close proximity to areas of well-oxygenated tissue. An impaired ability to regulate local oxygen delivery becomes evident and may further contribute to impaired oxygen extraction (32, 34, 40, 57).

Although microcirculatory dysfunction may occur to varying degrees in most clinical conditions that result in shock, autoregulatory mechanisms of microvascular function are most
severely impaired during sepsis, indicating that microcirculatory dysfunction is a pathophysiological sign of sepsis syndrome (83, 104).

**Clinical Monitoring**

Hemodynamic coherence between macro- and microcirculation exists when therapeutic interventions aimed at correction of systemic hemodynamic variables are effective in correcting regional and microcirculatory parameters (60). Loss of such coherence is most frequently found during sepsis, when microcirculatory recruitment is rarely observed, despite an appropriate treatment of macrohemodynamic abnormalities (60, 93, 106). The disparity between macro- and microhemodynamic abnormalities is explained by the presence of functional shunts in the microcirculation that “hide” the microcirculatory dysfunction from systemic circulation. Sepsis is associated with dysregulation of the opening of these shunts, pushing the microcirculatory partial pressure of oxygen (PO₂) to a level below venous PO₂, constituting the “PO₂ gap” and determining tissue distress, despite adequate systemic hemodynamic parameters (57). This distributive defect associated with sepsis is characterized by stagnation of capillary blood flow, reducing functional capillary density, in the presence of practically normal flow in larger blood vessels of the microcirculation (59). Microvascular blood flow is more depressed in smaller vessels and affects fewer larger vessels, which partly explains why systemic hemodynamic variables do not reflect the hemodynamic properties of the microcirculation in a reliable manner. Hypoxic tissues with severe oxygen extraction deficit may be found even when total blood flow to the respective organ is preserved (58).

Besides blood flow heterogeneity, other microcirculatory alterations underlying the loss of hemodynamic coherence, such as hemodilutional microvascular anemia, stasis of microcirculatory blood flow, and increased capillary leak, have also been identified (60). These alterations cannot be detected by conventional hemodynamic monitoring systems available in clinical practice. By simply monitoring the macrocirculation,
these systems fail to detect changes in microcirculatory parameters and responses to treatments, as they do not evaluate intrinsic events that occur in the microcirculation (58, 60).

Use of a reliable diagnostic tool capable of assessing the microcirculation is urged in the diagnosis and treatment of sepsis. The ideal monitoring method for critically ill patients should allow assessment at bedside and be able to assess local transport of oxygen and changes in vascular permeability, inflammatory response, and coagulation. Finally, the method should allow direct noninvasive visualization of microvascular changes, such as decreases in functional capillary density, vascular diameters, and flow rates (11). Unfortunately, no single method is capable of monitoring all these functions related to the microcirculation. Moreover, whatever the monitoring method, only the microvascular bed on which the method is being used is actually being assessed at that time. This is particularly important in sepsis, a systemic syndrome characterized by great heterogeneity of the microcirculation.

Currently available methods in clinical use for microvascular perfusion monitoring can be divided into biomarkers, videomicroscopy techniques, tissue oxygenation evaluation techniques, and partial pressure of carbon dioxide (PCO2)-based evaluation techniques.

Biomarkers

Blood lactate measurement is widely used in the evaluation of critically ill patients. When present, hyperlactatemia may indicate tissue hypoperfusion with increased lactate production by anaerobic metabolism, but other mechanisms not related to cellular hypoxia and anaerobic metabolism may explain the elevation of lactate concentration in critically ill patients. In the absence of hyperlactatemia, inadequate tissue perfusion is not excluded, because blood lactate measurement is a diagnostic test with low sensitivity and specificity. Despite its limitations, lactate is a good surrogate marker of tissue hypoperfusion in shock states. A blood lactate level ≥4 mmol/l increases the probability of finding clinically relevant microcirculatory abnormalities, which may help explain the high mortality risk associated with hyperlactatemia. Accordingly, a decrease of ≥10% in serial measurements of blood lactate level is among the goals to be achieved in the treatment of severe sepsis/septic shock: existing evidence shows a correlation between a decline in lactate level and an improvement in microvascular perfusion (2, 52, 63, 85).

Direct biomarkers of endothelial damage could be of great interest during sepsis. For instance, adhesion molecules (intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin, and P-selectin) can be assayed in the serum of septic patients and reflect endothelial cell activation (or endothelium disruption) and increased leukocyte-endothelial interactions. Although not commonly used in clinical practice, an increase in the level of these molecules in the serum was correlated with severe microcirculatory changes in pediatric patients with meningococcemia, pending validation (86).

Direct Microcirculatory Assessment: Videomicroscopy Techniques

Historically, for intravital microscopy, anatomical dissections were required in animal models. The development of new techniques and portable instruments for minimally invasive microscopy allowed direct visualization of the microcirculation in tissues using video capillaroscopy, orthogonal polarization spectral imaging (OPS), sidestream dark-field (SDF), or incident dark-field (IDF) illumination, making it possible to assess the microcirculation in humans. The main limitation of all these methods is related to the difficulty of their continued use, limiting the information to that acquired at the time of the examination.

Nail-fold video capillaroscopy, the first method used at bedside, uses a microscope to evaluate capillaries located between the cuticle and the nail (114). It allows the detection of morphological, capillary density, and microvascular flow abnormalities at rest and after vascular occlusion tests (arterial and venous). This method has not become popular for the monitoring of septic patients: because the nail-fold vascular bed is very sensitive to peripheral vasoconstriction, vasopressor agents, and changes in temperature, its use in this population is very restricted.

OPS and SDF techniques are based on a common principle: the use of polarized light with a 530-nm wavelength, absorbed by the hemoglobin of red blood cells regardless of its state of oxygenation, generating gray-scale images. Thus only blood vessels filled with red blood cells are displayed. In OPS, depolarized light provides the contrast when it is reflected by deeper layers of the evaluated tissue, generating a clear background. In SDF, image contrast is shown by a pulsating green light. Unfortunately, for technical reasons, neither method allows direct visualization of blood vessel walls. The captured image is optically magnified five times and digitally increased 340 times in OPS or 380 times in SDF. Functional capillary density, predominant type of blood flow, and degree of flow heterogeneity are generally analyzed (9). Microcirculatory blood flow parameters are calculated as surrogates of the convective capacity of the microcirculation, while functional capillary density represents the diffusive capacity (52). Among these variables, functional capillary density is the most validated parameter for assessment of microcirculatory function. Unfortunately, specific cutoff values that correlate with relevant clinical outcomes, such as disease severity or mortality, have not been identified (52). Main limitations for the use of these technologies include the need of special equipment and operator training (to avoid pressure and motion artifacts) and the possibility of bleeding of the site under analysis. The OPS technique is more prone to artifacts and is no longer routinely used (19).

Orthogonal polarization techniques reach a depth of 5 mm, allowing microcirculatory assessment only in tissues covered by a thin epithelial layer, of which the most studied and used is the sublingual mucosa (Fig. 3). This region is preferred because of its embryological origin, which is the same as that of the gastrointestinal tract. Consequently, microcirculatory changes in the sublingual mucosa could reflect splanchnic microcirculatory abnormalities (5). However, a correlation between sublingual and intestinal microcirculatory parameters is still in debate (52).

Recently, a third-generation hand-held videomicroscope, based on the principle of IDF illumination, was introduced for clinical use. This imaging device was developed in an attempt to overcome technical limitations of its predecessors (OPS and SDF), such as use of analog video cameras, heavy weight of
Oxygen consumption can be indirectly assessed by near-infrared spectroscopy (NIRS). The NIRS technique uses electromagnetic waves in the near-infrared spectral region to measure the chromophores oxy- and deoxyhemoglobin, myoglobin, and oxidized cytochrome aa3. Oxy- and deoxyhemoglobin measurements are used to calculate the tissue oxygen saturation (SO2) while oxidized cytochrome aa3 measurement allows the assessment of mitochondrial PO2. As the wavelength used (~650–900 nm) penetrates the skin, subcutaneous tissue, skeletal muscle, and bone tissue, NIRS is able to penetrate the body up to a few centimeters, allowing organ-specific tissue SO2 monitoring. Brain and muscles are the most commonly monitored organs. Tissue SO2 can be evaluated at rest and after venous and arterial occlusion tests. Tissue SO2 at rest mainly reflects local venous compartment SO2, while postocclusion tests allow the calculation of muscle oxygen consumption, peripheral/regional blood flow, and deoxygenation and reoxygenation velocities. The dynamic analysis of tissue SO2 changes produced by transient ischemic maneuvering (vascular occlusion test) allowed the assessment of microcirculatory/endothelial dysfunction and has added clinical value to this technology (29). Main limitations of the method include the presence of thick adipose tissue and/or swelling at the site of sensor application, low temperatures, and the use of vasoactive drugs (72).

Real-time monitoring of SO2 in venous blood obtained by a central venous catheter (central venous SO2) or a pulmonary artery catheter (mixed venous SO2) is often used in the management of severe sepsis and septic shock. Venous SO2 is assumed to reflect the balance between oxygen transport and global oxygen consumption, provided arterial blood SO2 is normal (102). However, it does not show a direct correlation with microvascular dysfunction and fails to predict microcirculatory abnormalities in septic patients, because venous SO2 monitoring is unable to assess local perfusion deficits (5). Consequently, it may present normal or increased values, even in situations where regional microcirculation is greatly impaired by shunt, heterogeneous flow, and intense tissue hypoxia (76). Difficulties and risks related to the insertion of catheters should also be taken into account when choosing this monitoring method. Despite these drawbacks, central venous SO2 is still widely used in clinical practice to guide resuscitation of septic patients.

Transcutaneous PO2 measurement is a commonly used method for the indirect estimation of oxygen transport. Initially created to be correlated with arterial PO2, avoiding serial collection of arterial blood samples for blood gas analysis, this method uses a Stow-Severinghaus-type sensor coupled to the skin. As in septic patients, especially those in circulatory shock, there is no correlation between blood oxygenation and skin oxygenation; transcutaneous PO2 can be interpreted as a surrogate marker of skin perfusion (or oxygen transport): the transcutaneous PO2 index (transcutaneous PO2/arterial PO2) estimates the adequacy of cardiac output and peripheral blood flow. Besides raw data, trend analysis is used for the diagnosis of shock and therapy optimization. The main limitations of the method include the presence of skin lesions that prevent electrode installation, swelling or thick adipose tissue, and the use of vasoactive drugs.

Assessment of Tissue Oxygenation

One of the main goals of sepsis treatment is to adjust oxygen transport and tissue delivery to its pathological condition of consumption. Unfortunately, direct monitoring of many components involved in the oxygen supply-consumption balance is not possible in clinical practice. However, some indirect measurement methods are available for routine use.
Microcirculatory Assessment Based on $\text{PCO}_2$

Tissue $\text{PCO}_2$ represents the balance between local blood flow and carbon dioxide production. Tissue hypercarbia ensues when carbon dioxide clearance is reduced as a result of decreased vascular flow and/or when carbon dioxide generation is increased. Transcutaneous $\text{PCO}_2$ is measured by the same monitor and sensor used to measure transcutaneous $\text{PO}_2$ and correlates inversely with cardiac index during low-flow shock. The rise in transcutaneous $\text{PCO}_2$ has been proposed to be an early and better index of tissue hypoxia than traditional markers (27). Raw data and trends should be evaluated. Besides arterial hypercapnia, the main limitations of the method are similar to those discussed for transcutaneous $\text{PO}_2$ monitoring (90).

Gastric tonometry is an organ-specific minimally invasive technique that measures $\text{PCO}_2$ in the gastric mucosa, assessing the adequacy of the balance between oxygen supply and consumption in this mucosa. As anatomical characteristics of the intestinal mucosa make it particularly vulnerable to hypoxia, gastric tonometry has attracted special interest. Unfortunately, no correlation between gastric $\text{PCO}_2$ and overall splanchnic perfusion has been found in septic patients (28). The main limitation of the technique, which restricts its use, is the interference caused by enteral nutrition or duodenogastric reflux.

$\text{PCO}_2$ can also be measured in the sublingual mucosa in a noninvasive manner using a microelectrode sensor. An inverse correlation between mucosal $\text{PCO}_2$ values and functional capillary density in the sublingual mucosa has been shown in septic patients (27). As tissue carbon dioxide is greatly influenced by arterial $\text{PCO}_2$, a better way to assess mucosal $\text{PCO}_2$ is to calculate the gradient between mucosal and arterial $\text{PCO}_2$ (the tissue-arterial $\text{PCO}_2$ gradient, or $\text{PCO}_2$ gap) (76). This gradient is increased in sepsis.

Potential Therapies

Persistent microcirculatory abnormalities are more commonly found among nonsurviving than surviving septic patients (93, 106). Thus, drugs that assist in the reversal of microcirculatory changes could be decisive in sepsis treatment.

It has been demonstrated that the dysfunctional endothelium is still able to respond to stimulation and that sepsis-associated microcirculatory derangements are functional and is liable to be completely reversed with adequate treatment (10). As multiple mechanisms are involved in the pathogenesis of microvascular dysfunction, a single-pathway intervention is unlikely to be effective in recruitment of the microcirculation. In fact, drugs or treatments with pleiotropic effects have greater therapeutic potential than compounds directed against a single target. The best approach seems to be a multimodal therapy targeting different mechanisms involved in microcirculatory distress (19).

Currently available treatments to correct microcirculatory abnormalities in septic patients aim at favorably modulating the systemic response to infection and/or increasing the driving pressure of blood flow at the microcirculation (Fig. 4). Further research should focus on whether these therapeutic approaches improve the outcome of septic patients.

Fluid Resuscitation

Fluid resuscitation is an essential therapy for sepsis-induced hypoperfusion and may improve microcirculatory blood flow through several mechanisms (Fig. 4). Beneficial microvascular effects were seen in the early, but not late, phase of sepsis, supporting current recommendations of timely aggressive fluid loading in sepsis treatment (64, 85). Interestingly, microcirculatory effects of fluids are independent of global hemodynamic effects.

Hydroxyethyl starch 130/0.4 allowed better resuscitation of the microcirculation than crystalloid solutions (35, 64). However, several randomized clinical trials have provided evidence that starches impair kidney function and hemostasis and may increase mortality in critically ill septic patients. Human serum albumin solutions have also proved to be effective in microcirculatory resuscitation and may have beneficial effects on endothelial dysfunction by decreasing the inflammatory response and oxidative stress (19, 67, 77).

Red Blood Cell Transfusion

Red blood cell transfusion is another commonly used therapy to restore oxygen-carrying capacity in critically ill patients. The microvascular response to transfusions is quite variable because of considerable interindividual variation. Conflicting data regarding the effects of red blood cell transfusion on microcirculatory parameters suggest that microvascular perfusion and reactivity improve in patients with abnormal microcirculatory parameters at baseline but deteriorate in patients with normal baseline parameters (30, 92). Apparently, patients with severe microvascular dysfunction at baseline may benefit from transfusion therapy, highlighting the importance of microvascular monitoring in septic patients in targeting therapies on an individual basis (52).

Other variables may influence the net effect of blood transfusion over tissue oxygenation and microcirculation. For instance, the storage process is related to reduction of red blood cell deformability and 2,3-diphosphoglycerate levels, while the capacity of stored red blood cells to capture NO is enhanced. These alterations may affect the efficacy of transfusions, leading to the worsening of tissue oxygen delivery and further microcirculatory dysfunction (52).

Vaspressors

In septic shock, vaspressors are used to counteract the intense vasoplegia and could improve tissue perfusion when mean arterial pressure falls below the autoregulatory threshold (60–65 mmHg), as organ perfusion becomes pressure-dependent below this level of mean arterial pressure (45, 103). However, vaspressors may increase mean arterial pressure at the expense of microcirculatory flow (17, 52). Despite considerable variation in individual responses, the microvascular response to vaspressors appears to be dependent on the basal condition of the microcirculation: capillary perfusion improves in patients with an altered perfusion at baseline but decreases in those with close-to-normal baseline perfusion (36). This suggests that vaspressors should be titrated under microcirculatory monitoring on an individual basis (64).
Inotropes

Dobutamine, milrinone, and levosimendan have been shown to improve microvascular perfusion during sepsis in experimental, small, or uncontrolled studies (4, 79, 81). Although both inotropic and vasodilatory effects are common to these drugs, microvascular effects were independent of changes in systemic hemodynamic variables. Unfortunately, the role of inotropes in microcirculatory recruitment remains undefined because of conflicting results in recent controlled experimental and clinical studies (52, 53).

Vasodilators

The use of vasodilators could compensate for the heterogeneity of septic microcirculatory blood flow, promoting the perfusion of ischemic/hypoxic areas (called “microcirculatory weak units”) (52). Indeed, it has been shown that NO donors, such as nitroglycerin, are capable of improving microcirculatory oxygenation in experimental and human sepsis when used in combination with fluids (99). However, this result has been challenged by recent experimental and clinical studies (18). Negative results may be explained by the use of nonselective agents, which dilate both perfused and nonperfused microvascular units, leading to hyperperfusion of some areas and flow diversion from others. As for inotropes, the role of vasodilators in microcirculatory recruitment remains undefined (10, 52, 64).

Sedatives

Studies addressing the effects of propofol and midazolam on microcirculation agree that they exert negative effects, even in nonseptic states, leading to microcirculatory derangements. Conversely, recent data suggest that dexmedetomidine yields beneficial effects on microcirculatory function during experimental sepsis, attenuating capillary perfusion deficits (78).

Anticoagulants

Activated protein C, antithrombin, unfractionated heparin, and low-molecular-weight heparin have shown beneficial microcirculatory effects during sepsis (12, 54, 56, 80). Interest-
ingly, microcirculatory recruitment appeared to be independent of the anticoagulant effects of these drugs (6, 10, 54, 64, 80). Despite microvascular improvement, none of these agents have consistently improved the outcome of septic patients in numerous clinical trials, but all significantly increased the risk of bleeding (44, 80). Activated protein C was withdrawn from markets worldwide in the wake of a clinical trial showing that, compared with placebo, this agent did not significantly reduce mortality in patients with septic shock (89). Increasing uncertainty regarding efficacy and concerns about bleeding risk challenged the role of anticoagulants in microcirculatory recruitment.

**NOS Modulation**

Nonselective NOS inhibition aggravates microvascular perfusion abnormalities, affecting tissue oxygenation and increasing mortality (74, 104). On the other hand, endothelial NOS modulation by tetrahydrobiopterin leads to increased microvascular perfusion, improved organ function, and greater survival during experimental sepsis due to stimulation of NO production, suggesting that upregulation of NO formation in some microvascular beds may be an adaptive and protective mechanism during sepsis (10, 19, 50, 108).

**Conclusions**

Multiple experimental and clinical trials have shown that microcirculatory dysfunction occurs in sepsis. Several mechanisms have been involved in the development of microvascular abnormalities, such as NO dysregulation and functional impairment of many cell types found in the microcirculation, particularly the endothelial cell. Despite recent advances in the understanding of pathophysiological mechanisms involved in septic microcirculatory dysfunction, the diagnosis of microcirculatory changes and the adoption of therapeutic measures aimed at treatment of these changes are not yet part of routine management of the majority of septic patients because of the lack of easy-to-use and widely available bedside technology, validated microcirculatory end points for resuscitation, or efficient treatment (that actually improves patient outcomes).

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**


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