Septic shock: a microcirculation disease

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Purpose of review
The aim of this study was to discuss the implication of microvascular dysfunction in septic shock.

Recent findings
Resuscitation of sepsis has focused on systemic haemodynamics and, more recently, on peripheral perfusion indices. However, central microvascular perfusion is altered in sepsis and these alterations often persist despite normalization of various macro haemodynamic resuscitative goals. Endothelial dysfunction is a key element in sepsis pathophysiology. It is responsible for the sepsis-induced hypotension. In addition, endothelial dysfunction is also implicated involved in the activation of inflammation and coagulation processes leading to amplification of the septic response and development of organ dysfunction. It also promotes an increase in permeability, mostly at venular side, and impairs microvascular perfusion and hence tissue oxygenation.
Microvascular alterations are characterized by heterogeneity in blood flow distribution, with adequately perfused areas in close vicinity to not perfused areas, thus characterizing the distributive nature of septic shock. Such microvascular alterations have profound implications, as these are associated with organ dysfunction and unfavourable outcomes. Also, the response to therapy is highly variable and cannot be predicted by systemic hemodynamic assessment and hence cannot be detected by classical haemodynamic tools.

Summary
Microcirculation is a key element in the pathophysiology of sepsis. Even if microcirculation-targeted therapy is not yet ready for the prime time, understanding the processes implicated in microvascular dysfunction is important to prevent chasing systemic hemodynamic variables when this does not contribute to improve tissue perfusion.

Keywords
endothelium, microcirculation, tissue perfusion, veno-arterial pCO_2 gradients, videomicroscopy

INTRODUCTION

Circulatory failure or shock is defined as a life-threatening, generalized maldistribution of blood flow resulting in failure to deliver and/or utilize adequate amounts of oxygen, leading to tissue dysoxia [1]. Septic shock is a form of distributive shock [2] and is one of the most frequent types of circulatory failure [3]. The haemodynamic alterations in septic shock are characterized by a profound decrease in vascular tone, a hypovolemic component resulting from pooling of blood in capacitance veins due to decrease in venous tone (relative or central hypovolemia) as well as fluid losses related to vascular leak (absolute hypervolemia), a variable degree of myocardial dysfunction, a dysregulation of regional blood flow distribution and microvascular alterations. Although the classical resuscitation strategies are based on vasopressors, fluids and sometimes inotropic agents in order to preserve perfusion pressure and cardiac output [4], tissue perfusion abnormalities often persist after achieving resuscitation targets, contributing to the development of organ dysfunction [3]. Although experimental studies have highlighted the potential role of microvascular perfusion alterations in septic shock, evaluation of microvascular perfusion has long been infeasible in clinical practice. Advances in imaging techniques have allowed the direct visualization of microvascular alterations in patients with septic shock. In this review, we will describe the evidence for endothelial dysfunction in sepsis,

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KEY POINTS

- Endothelial dysfunction is a key player in the pathophysiology of sepsis and contributes to alterations in microvascular perfusion.
- Alterations in microvascular perfusion are frequent in septic patients and are associated with a poor outcome.
- Microcirculation alterations cannot be detected by clinical signs and classical haemodynamic devices.
- Microcirculatory assessment requires direct visualization by handheld microscopes or indirect assessment by surrogate measurements such as veno-arterial pCO_2 differences.
- The effect of usual resuscitation interventions has a variable effect on the microcirculation that may depend on timing of intervention and microcirculation state.

its role in the development of alterations in microvascular perfusion, their consequences and potential lines for therapeutic interventions.

ENDOTHELIAL DYSFUNCTION IN SEPSIS

The endothelium is present everywhere in the vascular system, from large arteries to veins, even though its structure varies according to the various organs. This single cell layer has multiple actions: regulation of vascular tone, inflammation and coagulation, and control of permeability. At the microvascular level, the endothelial layer is a key factor controlling local perfusion by activating local dilation or constriction. In addition, endothelial cells are also implicated in the transmission of information from peripheral to more proximal vessels allowing fine matching perfusion to metabolic needs [5].

In sepsis, dysregulation of endothelial cells is associated with an impaired sensitivity to vasodilating and vasoconstrictive substances. Endothelial dysfunction related to sepsis contributes to the alterations in the distribution of regional perfusion. Sepsis is also associated with a loss of endothelium structure, contributing to the increased vascular permeability. Endothelial cells activation in sepsis results in a procoagulant and proinflammatory state, and secretion of adhesion molecules. Altogether, this favour microthrombi formation and adhesion of circulating cells to the endothelium.

In addition, the glycocalyx, which is the layer of glycosaminoglycans, proteoglycans and glycoproteins at the surface of endothelial cells, is degraded in sepsis so that this layer is thinner in sepsis [6▪▪,7▪]. The degradation of glycocalyx contributes to (micro)vascular dysfunction, favours adhesion of circulating cells, microthrombosis and increased permeability. The severity of glycocalyx breakdown is associated with a poor clinical outcome [8▪].

CHARACTERIZATION OF MICROVASCULAR PERFUSION IN SEPSIS

Various experimental studies have demonstrated the occurrence of alterations in microvascular perfusion. These were characterized by a decrease in the density of perfused vessels (functional capillary density) and heterogeneity of perfusion between areas close by a few microns. Similar alterations have been reported in various species, from rodents to large animals, and in all organs that have been investigated.

In humans, De Backer *et al.* [9] first demonstrated that the sublingual microcirculation is altered in patients with sepsis. More than 30 publications replicated these findings throughout the world. All these studies found that the density of perfused vessels is decreased and that heterogeneity is increased, with presence of nonperfused capillaries in close vicinity of perfused vessels. These observations are very similar to those observed in experimental conditions.

Most of these trials investigated the sublingual area. More recently, some investigators explored the conjunctival area, demonstrating similar alterations as in the sublingual area [10▪▪]. Admittedly, direct evaluation of inner organs, such as kidney, liver, heart and brain, remains unfeasible at this stage in humans.

CONSEQUENCES OF MICROVASCULAR ALTERATIONS

The most immediate consequence of the decrease in perfused capillary density is the increase in intercapillary distance, resulting in an increased oxygen diffusion distance, potentially leading to hypoxic pouches. In rat cardiomyocytes, diffusion distance for oxygen increased by 50% after endotoxin administration, and this was associated with an increase in expression of hypoxic factor gene [11]. In an experimental model of peritonitis, microvascular blood flow heterogeneity was closely related to the mesenteric oxygen extraction ratio, suggesting the key role of microvascular blood flow distribution on oxygen uptake during development and resuscitation from septic shock [12]. In addition, redox potential is increased in zones with poor microvascular perfusion, suggesting occurrence of tissue hypoxia [13]. In humans, demonstration of local zones of tissue hypoxia is more complicated. Only indirect evidence suggest that microvascular alterations contribute to local zones of tissue hypoxia. First, the

improvement in microvascular perfusion is associated with a decrease in lactate levels [14] and in tissue to arterial pCO_2 gradients [15]. Second, improvement in microvascular perfusion is associated with improved organ function [16,17,18▪]. Changes in microvascular perfusion during early resuscitation procedures were associated with inverse changes in organ function score the next day [16]. In patients receiving fluid administration, organ function improved in patients who improved their microvascular perfusion but not in the others [17].

Many trials showed that the severity of microvascular alterations is associated with outcome in patients with septic shock [9,19–22,23▪,24▪▪,25▪▪]. Although most trials evaluated differences in microvascular perfusion between survivors and non survivors on admission, the evolution of microvascular perfusion over time also differs between them: microvascular alterations improved over time in survivors but remain stable in nonsurvivors [22].

WHAT IS THE LINK BETWEEN SYSTEMIC AND MICROVASCULAR PERFUSION?

It is quite obvious that microvascular perfusion cannot be sustained without some minimal systemic flow and organ perfusion pressure. Physiologically, microvascular blood flow depends on the perfusion of each organ, which in turn depends on cardiac output, perfusion pressure (which depends not only on upstream arterial pressure but also on venous pressure and interstitial pressure) and regional blood flow distribution. In addition, at the organ level, microvascular perfusion depends on local regulation based on biofeedback systems allowing fine matching of perfusion to metabolic needs. In sepsis, several factors affect these complex mechanisms regulating tissue perfusion.

Several trials have shown that microcirculatory alterations may be detected even when systemic haemodynamics are within resuscitation targets [9,14,26,27]. There is no link between microvascular perfusion and oxygen delivery or mean arterial pressure [20]. Similarly, the velocity of red blood cells in sublingual microcirculation is not related to cardiac output or mean arterial pressure [26]. The severity of alterations in microvascular blood flow is similar in hyperdynamic and normodynamic septic shock [26]. During therapeutic interventions manipulating perfusion pressure and/or cardiac output, changes in microvascular perfusion were independent of changes in arterial pressure [28,29] or cardiac output [14].

Different combinations or preserved/impaired macro and microcirculations can be observed (Fig. 1). In some cases, macro and micro are both altered (global circulatory failure) or preserved (normal condition or patient adequately resuscitated). The microcirculation can be impaired and microcirculation normal. This situation has been nicely illustrated in experimental shock, where microcirculation initially tries to compensate for the decrease in systemic perfusion [30]. Finally, the microcirculation can be altered even when systemic circulation is apparently corrected: this is the most frequent situation, amply described above, where dissociation between micro and macrocirculation explain the impaired tissue perfusion [9,14,26].

HOW TO DETECT MICROVASCULAR ALTERATIONS IN PATIENTS WITH SEPTIC SHOCK?

Can clinical signs and biological signs detect microvascular perfusion? As mentioned above, the link between systemic haemodynamics and

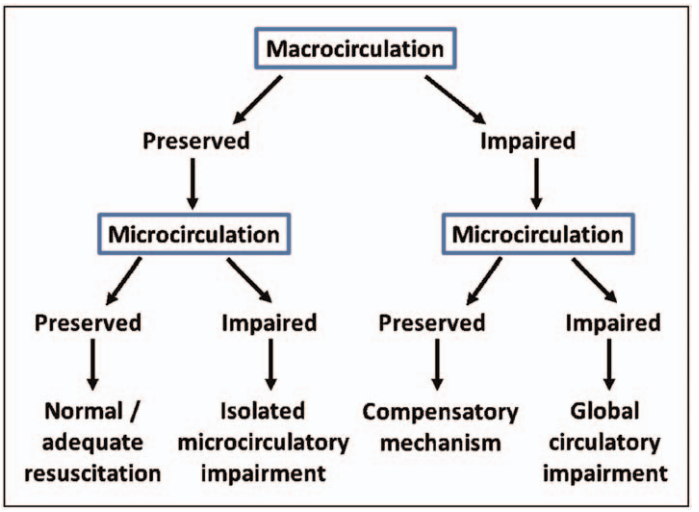

FIGURE 1. Interpretation of the different combinations of microcirculation and microcirculation states.

microcirculatory perfusion is at best loose. Clinical signs of skin hypoperfusion such as capillary refill time and mottling score are very useful to detect impairment in peripheral tissue perfusion and can even be used to guide resuscitation [31▪▪]. Skin mottling severity correlates with local impairment in tissue perfusion [32], skin oxygenation and haemoglobin content [33▪] and biological markers of endothelial dysfunction [33▪]. However, local factors (such as use of vasoconstrictor agents, environmental temperature and so on) may alter peripheral microcirculation more than central microcirculation. In addition, cardiovascular comorbidities and some skin vasculitis can also affect mottling score and capillary refill time. In patients with septic shock, skin perfusion evaluated by central to toe temperature difference failed to reflect a more central area such as the sublingual area [34].

Lactate may theoretically be a good candidate to detect microvascular alterations. In experimental sepsis, zones of impaired microvascular perfusion are colocalized with hypoxic areas [11,35]. Impairment of villi perfusion was associated with increased portal vein lactate levels and lactate to pyruvate ratio [12,36]. In septic patients, the link between hyperlactatemia and microvascular perfusion was less obvious, perhaps due to interaction with other factors such as lactate clearance and nonhypoxic generation of lactate. Nevertheless, changes in microvascular perfusion are associated with inverse changes in lactate levels [37].

Veno-arterial differences in pCO_2 ($PvaCO_2$) can be used to detect microvascular alterations and to track microvascular perfusion derangements. Stagnation of flow and tissue hypoxia are both associated with an increase in tissue $pCO2$. As CO_2 diffuses easily in tissues, venous pCO_2 increases even when perfusion is altered, so that $PvaCO_2$ can be used to detect hypoperfused areas [38]. In patients with septic shock, Ospina-Tascón *et al.* [39] observed that $PvaCO_2$ was inversely related with perfused vascular density vessels and directly related with heterogeneity index. In these patients who were meeting global haemodynamic goals, changes in $PvaCO_2$ also correlated with changes in microvascular perfusion but not with changes in cardiac output.

Direct evaluation of the microcirculation by handheld microscopes is the technique of reference, even though still restricted to research arena. Orthogonally polarized spectral (OPS), sidestream dark-field (SDF) and incident dark-field (IDF) imaging techniques are the various techniques that were/are used to evaluate the microcirculation at bedside [6▪▪,9,20,40▪]. Various indices can be obtained to evaluate the microcirculation and these are described in depth in a recent consensus organized by the European Society of Intensive Care Medicine [41▪▪]. Limitations of the use of videomicroscopic techniques unfortunately limit their broad use in clinical practice [42▪▪].

WHAT IS THE IMPACT ON THE MICROCIRCULATION OF INTERVENTIONS USED FOR HEMODYNAMIC RESUSCITATION IN SEPTIC SHOCK?

Fluids are cardinal in the hemodynamic resuscitation of septic shock. Hypovolemia and preload dependence are associated with microcirculatory alterations [43▪▪]. Fluids may improve microvascular perfusion, but the effect is quite variable and may depend on the timing at which these are administered: fluids improve microvascular perfusion within 12–24 h of sepsis recognition, while these have limited or even detrimental impact on the microcirculatory perfusion at later stages [37]. The improvement in microvascular perfusion is not dependent on the amount of fluid administered [44▪,45]. Accordingly, it seems that administration of limited amount of fluids at initial stage improves the microcirculation, while further fluid administration seems ineffective even when cardiac output increases. Interestingly, organ function improves when fluids improve the microcirculation [17]. Importantly, all organs may not respond similarly [46]. In patients with abdominal sepsis, the sublingual microcirculation improved with fluid administration, while the gut microcirculation failed to improve [47]. Several factors may contribute to these differences, including a local inflammatory process and a raised intraabdominal pressure. Considering the de-escalation stage [3], fluid management may also impact the microcirculation. Although fluid withdrawal may result in an improved microvascular perfusion by decreasing interstitial oedema [48▪], excessive fluid removal speed may be associated with deterioration of microvascular perfusion [49]. Hence, the impact of fluid management on the microcirculation varies according to the phase of resuscitation (Fig. 2).

The type of fluid may also matter. In experimental settings, colloids and especially albumin may better preserve the glycocalyx [50▪] and improve more the microcirculation than crystalloids [51]. In patients, these differences are less obvious. The response of the microcirculation was similar with crystalloids and albumin solutions, both at early and late stages of sepsis [37]. Hypertonic sodium lactate showed very promising results in experimental sepsis, but clinical data are still lacking.

Red blood cell transfusions may theoretically be very promising but the results of the various studies

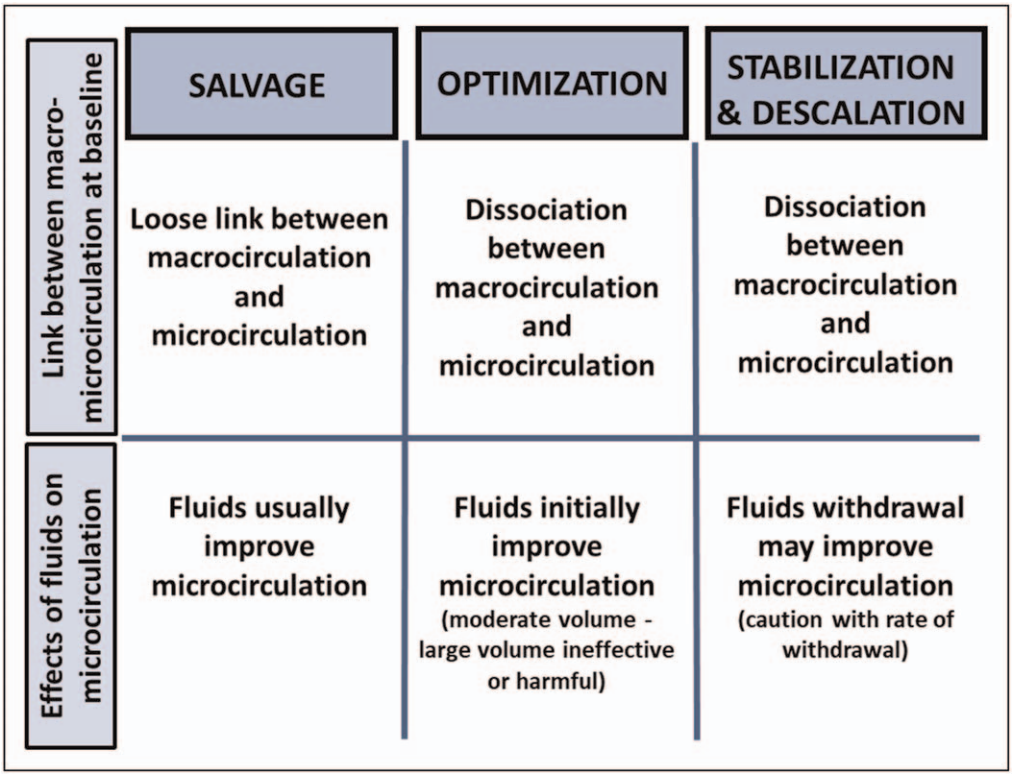

FIGURE 2. Impact of the different phases of shock on microvascular perfusion and on the microvascular response to fluids. The different stages of shock resuscitation, the SOSD concept as defined by Vincent and De Backer [3]: salvage, optimization, stabilization and de-escalation. The link between systemic haemodynamics and microcirculation varies according to the stage. The impact of fluid management on the microcirculation is identical during stabilization and de-escalation so that these two phases were grouped.

were somewhat disappointing. In septic patients, Sakr *et al.* [52] reported a variable effect of red blood cell transfusions on sublingual microcirculation. Microvascular perfusion improved in patients with very severe microcirculatory alterations at baseline, although it deteriorated in patients with minimal pretransfusion alterations. Other groups confirmed these results [53,54]. Among the factors explaining such a variable response, the free haemoglobin content of the bag and/or quality of red blood cells transfused may play a role, as microcirculatory changes were shown to be inversely related to changes in plasma-free haemoglobin [53]. Interestingly, haemoglobin levels at baseline did not influence the response to transfusions [54]. Accordingly, transfusions should be restricted to patients with severe alterations in microvascular perfusion and should not be based only on haemoglobin thresholds.

Inotropic agents were shown to have variable effects on the microcirculation [14,55,56▪,57]. The effects of these agents on the microcirculation are independent of their systemic effects [14,57] so that microcirculation should be directly measured if these are judged indicated. Interestingly, the decrease in lactate levels may be used to indirectly track the effectiveness of dobutamine-induced changes in microvascular perfusion [14].

Vasopressor agents also have variable effects on the microcirculation. The microvascular impact of vasopressors may depend on the blood pressure target and the dose and type of the agent itself. Although correction of severe hypotension is consistently associated with an improvement in microvascular perfusion [58,59], increasing mean arterial pressure above 65 mmHg had variable effects, inversely related to basal alterations in microvascular perfusion [60]. Dose and type of vasopressor agents may also matter. Addition of vasopressin to norepinephrine-improved microvascular perfusion in patients with septic shock receiving high doses of norepinephrine but not in those treated with low doses [61].

CONCLUSION

Endothelial dysfunction is a hallmark of septic shock and contributes to an impaired microvascular perfusion. Microcirculatory alterations are frequently observed in patients with septic shock

and their severity is associated with poor outcome and organ dysfunction.

These alterations are characterized by the presence of well perfused areas close to nonperfused areas, and this pattern typically explain the distributive nature of septic shock.

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Conflicts of interest

D.D.B., G.A.O-T and F.R. have no conflict of interest to declare.

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