A holistic approach for perfusion assessment in septic shock: Basic foundations and clinical applications
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Microcirculation in sepsis: new perspectives

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Abstract

Microcirculatory dysfunction has been recently recognized as a key pathophysiologic process in the evolution of sepsis. In the present review, we discuss fundamental aspects of microcirculatory abnormalities during septic shock, including pathogenic mechanisms, technological assessment, clinical correlates and potential therapies.

The most important function of the microcirculation is the regulation and distribution of flow within the different organs. In septic shock, microcirculatory dysfunction may arise as a result of several factors such as endothelial dysfunction, leukocyte-endothelium interactions, coagulation and inflammatory disorders, hemorheologic abnormalities, and functional shunting. Severity and persistence of these microcirculatory abnormalities are associated with bad prognosis and are not necessarily predicted by systemic variables.

The introduction of bedside techniques that allow evaluation of the microcirculation into clinical practice has opened up a new field of functional hemodynamic monitoring. Recent data suggest that microcirculatory abnormalities can be staged in severity. Some microcirculatory indices are more accurately related to morbidity and mortality, and thus a definition of clinically relevant microcirculatory abnormalities is feasible.

On the other hand, although several systemic variables do not predict microcirculatory status, high norepinephrine (NE) requirements and hyperlactatemia are associated with a much higher prevalence of relevant microcirculatory derangements. Therefore, severe septic shock patients could represent a more precise target for interventions, particularly in microcirculation-oriented clinical trials.

Clinical research has identified various therapeutic approaches that are successful in modifying the microcirculation. Future research must determine whether some of these approaches are successful in improving outcome of critically ill patients by recruiting the microcirculation.
Introduction
Microcirculatory dysfunction has been recently recognized as a key pathophysiologic process in the evolution of sepsis. In the present review, we discuss fundamental aspects of microcirculatory abnormalities during septic shock, including pathogenic mechanisms, technological assessment, clinical correlates and potential therapies.

I. Characteristics of normal microcirculation
By microcirculation we refer to the network of small blood vessels (<100 µm diameter), which comprises arterioles, capillaries, and venules (microcirculatory units) [1]. It includes 10 billion capillaries and is lined with endothelial cells, which on total make up more than 0.5 km² of endothelial surface. In addition to endothelial cells, it includes smooth muscle cells (mostly in arterioles), red blood cells (RBC), leukocytes, and platelets. Microcirculation plays several key roles such as ensuring oxygen delivery to tissues, exchange of nutrients and waste products, and modulating inflammation and coagulation. Most of these functions are controlled by endothelial cells, which release several biologic signals to regulate local blood flow, cell adhesion, permeability, and coagulation activation [2].

Microvascular oxygen delivery cannot be directly predicted from systemic or even regional oxygen delivery. First, microvascular hematocrit is lower than systemic hematocrit due to the Fahraeus effect (dynamic reduction of hematocrit due to axial migration of erythrocytes near the center of the vessel). Second, the distribution of hematocrit is nonlinear at vascular branch points. Third, microvascular partial oxygen pressure (pO₂) is also lower than systemic pO₂ and is heterogeneously distributed. Hence, oxygen delivery is heterogeneously distributed throughout the microcirculatory network [3].

The structure and function of microcirculation is highly heterogeneous in different organs, and it is closely related to the functional role played by a particular organ as a whole. The number of capillaries per unit mass of organ or tissue (capillary density) may be related to the organ metabolic requirements (muscles, heart, brain) or to other functional requirements (skin, gut, kidney) [4].

Microcirculation normally ensures adequate oxygen delivery to meet the oxygen demands of every cell within an organ. A strict regulatory mechanism is in place to achieve this, with multiple signaling pathways interacting at different levels. In this way, oxygen transport to tissues with high oxygen needs is augmented and oxygen transport to tissues with low metabolic activity is restricted [5]. This regulatory mechanism allows microcirculatory flow to occur independent of changes in systemic blood pressure, a mechanism called autoregulation [4]. In general, driving pressure, arteriolar tone, hemorrheology, and capillary patency, are the main determinants of microcirculatory blood flow. Although regional blood flow is determined by large vessels (medium-sized arterioles), which are mainly controlled by the sympathetic nervous system, local distribution of blood flow to tissues is regulated by microcirculation. When terminal arterioles are vasodilated, perfusion of capillaries increases; when terminal arterioles are vasoconstricted, the number of recruited capillaries decreases. These microvessels are primarily under local control,
which is possible because endothelial cells sense metabolic and physical signals, and respond to them by modulating arteriolar smooth muscle cell tone [2]. Nitric oxide (NO) is one of the critical signals produced by endothelial cells to exert this regulation.

II. Microcirculatory alterations in sepsis

Although microcirculatory alterations in sepsis have been recognized from long ago from experimental data, clinical interest in this field has been growing strongly during the last decade after the introduction of bedside videomicroscopic techniques, which have validated that these microcirculatory disturbances can be also observed in septic patients. The presence and persistence of such abnormalities has been found to be associated with prognosis. De Backer [6] reported a significant decrease in vessel density and in the proportion of small perfused vessels in septic patients compared to healthy volunteers, where this impairment of microcirculation was more severe in non-survivors. These results were later confirmed by Trzeciak [7]. Interestingly, Trzeciak also found that alterations in microcirculation were related to the severity of organ failure, as assessed by the Sequential Organ Failure Assessment (SOFA) score. Sakr [8] has characterized the time course of microcirculatory alterations in patients with septic shock and its relation to outcomes. Although similar at baseline, microcirculation improved rapidly in survivors as compared to non-survivors, even though global hemodynamic variables did not differ. More importantly, capillary perfusion when shock resolved was related to the severity of organ failure. However, the reported statistical association between outcome and microcirculatory abnormalities does not imply a mechanistic relation. Such potential relationship could only be demonstrated by a large multicentric trial targeting these abnormalities and showing an outcome improvement.

Microcirculatory alterations during sepsis may be explained by multiple mechanisms, involving all the components of microcirculation [1, 9, 10]: redistribution of blood flow from compliant vascular beds (skin and the splanchnic area) to more crucial body areas (brain, heart), with secondary microvascular derecruitment; endothelial activation and injury; loss of the glycocalyx, which covers the endothelium and forms an important barrier and transduction system; increased microvascular permeability with capillary leakage, edema formation, and hypovolemia; decreased RBC deformability, with secondary capillary plugging; increased leukocyte adhesion to the endothelial surface; production of reactive oxygen species (ROS) that directly disrupt microcirculatory structures, cellular interactions, and haemostasis; capillary obstruction by platelet/fibrin clots secondary to disseminated intravascular coagulation; and impaired arteriolar smooth muscle cell tone and reactivity, secondary to dysregulation of NO production. The role of endothelial dysfunction, and the consequent increase in platelet and leukocyte adhesion, has been recently emphasized as a potential mechanism contributing to microcirculatory flow abnormalities [11]. Increased expression of adhesion molecules on both, endothelial and immune cells, has been consistently demonstrated during sepsis.

The combination of these mechanisms contributes to a reduction in perfused capillaries (decreased functional capillary density), the development of heterogeneous abnormalities in
microcirculatory blood flow, and the loss of intrinsic vasoregulation in most vascular beds. The decreased capillary density implies that the diffusion distance for oxygen is increased [4]. The increased heterogeneity of microcirculation, in which some vascular beds exhibit a preserved functional capillary density, whereas others have a sluggish blood flow and still others have no flow at all, generates areas of hypoxia and impairs oxygen extraction in both mathematical and animal models of septic shock [9]. These alterations generate an impaired ability to regulate local oxygen delivery, which translates to rapid onset of tissue hypoxia [12].

III. Bedside visualization of microcirculation

One of the most important advances in the study of sepsis in recent years has been the development of microscopic imaging techniques incorporated in hand held devices designed to filter out surface reflections caused by illumination light. These techniques for filtering out surface reflections have been termed orthogonal polarization spectral (OPS) imaging and sidestream dark field (SDF) imaging and are based on intravital microscopy principles developed more than 20 years ago but only recently implemented in handheld device. The principles and technical aspects of these devices have been recently extensively reviewed [13-22].

IV. Clinical relevance of microcirculatory abnormalities, and relationship with systemic hemodynamics and perfusion parameters

Several recent small studies have been focused on potential therapies to improve microcirculatory flow [23-27]. However, there are still fundamental aspects that need to be resolved before launching a major controlled clinical trial. First, the prevalence of microcirculatory disorders in critically ill patients is unknown. This subject is being addressed by the microSOAP study (Microcirculatory Shock Occurrence in Acutely ill Patients registered at ClinicalTrials.gov (NCT01179243)), which will include at least 400 patients and is currently in the phase of image analyses. Second, although several indices to evaluate sublingual microcirculation have been proposed, specific cut-off values that correlate to severity have not been identified, and thus the clinical relevance of individual microcirculatory abnormalities is unknown [18]. In addition, the dynamic relationship between systemic hemodynamics, global perfusion parameters and microcirculatory abnormalities is still obscure and far from being well established [7, 28, 29]. Therefore, it is not clear if, and to what extent, macrohemodynamic or perfusion parameters can predict the finding of severe microcirculatory derangements.

To address these subjects, Hernandez et al. conducted a multinational retrospective cross-sectional study 1. One hundred and sixty-five septic shock patients recruited in

7 different clinical studies were included. All were managed with perfusion-driven protocols, and were subjected to at least one microcirculatory assessment, concomitantly to evaluation of systemic hemodynamic and perfusion parameters, during the first 24 h of resuscitation. ROC curve analysis demonstrated that among microcirculatory parameters, PPV and PVD exhibited a significant predictive value for mortality, with cut-offs of 86% for PPV, and 12 n/mm for PVD, while MFI exhibited only a trend toward significance. Sensitivity analyses confirmed that these cut-off values could be defined as *clinically relevant microcirculatory abnormalities*, since both were associated with highly significant differences in mortality, organ dysfunctions, and severity of shock. Although these findings should be tested and confirmed in a prospective study, they could be relevant. In fact, they are consistent with previous studies involving smaller sample sizes and different methodology, describing that a PPV >80% could be significantly related to survival in septic patients [8, 29, 30]. With regard to PVD, there are no clear normal reference values. Nevertheless, some studies have described basal pre-resuscitation PVD values of 12-13 n/mm that can improve with therapy [25, 27]. Thus, the cut-off value of 12 n/mm for PVD is also consistent with literature. The lack of predictive value for MFI in this study is intriguing since this parameter has been related to outcome in previous studies [7, 31]. Since MFI is inherently subjective, it is possible that intercenter differences in analysis may have compromised its prognostic value.

Additionally, logistic regression analysis demonstrated that among systemic variables, only NE doses (OR 39 [4-341]) and lactate levels (OR 1.3 [1.1-1.6]) were significantly associated with the probability of finding a PPV<86%. NE requirements ≥ 0.3 mcg/kg/min and hyperlactatemia ≥ 4 mmol/l, more than doubled the probability of presenting *clinically relevant microcirculatory abnormalities*. These results tend to confirm that hyperlactatemia during septic shock effectively reflects a wide array of derangements among the determinants of tissue perfusion, including an abnormal microcirculatory flow. This could explain at least in part, the high mortality risk associated with hyperlactatemia. In contrast, a relatively better preserved microcirculation in patients with septic-related hypotension but without hyperlactatemia, could explain the better prognosis associated with this condition [32].

Nevertheless, the preceding studies do not clarify if hyperlactatemia in the setting of microcirculatory dysfunction may reflect hypoxia or simply a stagnant lactate accumulation.

On the other hand, mean arterial pressure (MAP), cardiac index (CI), or central / mixed venous O₂ saturation (SvO₂) values, commonly used to assess response to septic resuscitation, failed to predict microcirculatory abnormalities. In the case of SvO₂, it could be surprising since an impaired O₂ extraction capacity has been attributed to potential microcirculatory abnormalities during septic shock [33, 34]. Even more, a normal SvO₂ in the presence of hyperlactatemia has been advocated as an indication for the use of vasodilators to improve microcirculatory flow [35], and SvO₂ is a commonly recommended resuscitation goal [36]. Thus, in contrast to common beliefs [37], microcirculatory status may not be predicted by any SvO₂ value.

In summary, recent data suggest that microcirculatory abnormalities can be staged in severity. Some microcirculatory indices are more accurately related to morbidity and
mortality, and thus, a definition of clinically relevant microcirculatory abnormalities is feasible. On the other hand, although several systemic variables do not predict microcirculatory status, high NE requirements and hyperlactatemia are associated with a much higher prevalence of relevant microcirculatory derangements. Therefore, severe septic shock patients could represent a more precise target for interventions, particularly in microcirculation-oriented clinical trials.

V. Therapeutic strategies

Fluid resuscitation

Fluid resuscitation is a fundamental therapy aimed at restoring circulating volume, and consequently increasing cardiac output and arterial blood pressure in septic shock patients. Fluid loading may improve microcirculatory blood flow through several mechanisms. Among them, volume resuscitation could increase perfusion pressure and/or CI, induce rheologic changes with decreased microvascular blood viscosity, trigger local vasodilation, or modulate interactions between the endothelium and circulating cells [26, 38]. Pottecher et al. showed that sublingual microcirculatory perfusion in septic shock patients was significantly improved following fluid loading [26]. Interestingly, both passive leg raising maneuver and effective volume expansion simultaneously increased microcirculatory functional capillary density (FCD) and flow (MFI and PPV), and reduced microvascular heterogeneity. Since MFI is known to be sensitive to flow variations, while changes in FCD or PPV are more likely related to microcirculatory recruitment, these results reflect a global impact of fluid resuscitation over several determinants of microcirculatory perfusion.

Another interesting aspect of the previous study [26] is that in contrast to other reports [38], changes in microcirculatory flow exhibited some correlation with improvement in global hemodynamics, particularly with CI. These results in preload-responsive patients confirm the findings of Trzeciak et al. showing correlations between macrocirculatory and microcirculatory variables in patients studied within 6 h of early goal-directed therapy [7]. Thus, it appears that during early resuscitation, microcirculatory flow can be improved with aggressive fluid resuscitation in parallel with changes in systemic hemodynamics. In fact, the very low values of MFI found by Trzeciak et al. early on after emergency room admission in pre-resuscitated patients have not been reproduced in the ICU arena. In the same line, Boerma et al. reported that MFI increased from 1.42 to 2.25, after only 2 hours of resuscitation in the placebo arm of their nitroglycerin trial [23]. These data taken together suggest that MFI values are very low in non-resuscitated patients but may improve rapidly after initial fluid expansion, resembling what happens with $SvO_2$. In summary, fluid loading is an essential first step in the resuscitation of the microcirculation.

Concerning the type of fluids, Dubin et al. demonstrated that a hydroxyethyl starch solution (HES) had superior microcirculatory recruitment power compared to a saline solution in early goal-directed therapy in septic patients [24]. The beneficial effects of HES on sublingual microcirculation seen in this study might be related to potential effects on several mechanisms involved in septic-related microcirculatory dysfunction, as has been
suggested by several experimental studies. Infusion of HES could modulate the inflammatory response, including reductions in extravascular fluid losses, endothelial cell activation [39], neutrophil adhesion and transendothelial migration [40]. A HES solution could also reduce platelet aggregation [41], but the effect of different HES solutions on blood viscosity is variable and probably depends on molecular weight [42]. Finally, other explanations for the favorable effects of HES could be a better intravascular volume expansion and less edema formation [43].

**Red blood cell transfusions**

There are conflicting data concerning the effect of RBC transfusions over microcirculatory parameters in septic patients, although at least patients with more severe microvascular dysfunction at baseline may benefit [44-49]. This fact highlights the relevance of monitoring sublingual microcirculation in critically ill septic patients to target therapies on an individual basis.

**Arterial pressure and vasopressors**

When MAP decreases below an autoregulatory threshold of 60 to 65 mm Hg, organ perfusion becomes pressure dependent and, consequently, the use of vasopressors to increase MAP could improve tissue perfusion in septic shock patients. Georger et al. evaluated the effects of increasing MAP on NIRS-derived thenar oxygenation parameters in 28 severely hypotensive septic shock patients [50]. Administration of NE in doses up to 0.7 mcg/kg/min was associated with significant increases on MAP from 54 ± 8 to 77 ± 9 mmHg, on CI from 3.14 ± 1.03 to 3.61 ± 1.28 L/min/m², on thenar tissue oxygen saturation (StO₂) from 75 ± 9 to 78 ± 9%, and on StO₂ recovery slope from 1.0 ± 0.6 to 1.5 ± 0.7%/s.

However, vasopressors, although effective in increasing blood pressure, may do so at the expense of microcirculatory flow suggesting that in some circumstances excessive vasoconstriction could be deleterious to the microcirculation [51]. Jhanji et al. recently demonstrated that increasing MAP from 60 to 90 mm Hg with NE resulted in an increase in global DO₂, but caused no change in cutaneous microvascular flow and tissue pO₂, or in sublingual microcirculation [52]. Dubin et al. titrated NE to increase MAP from 65 to 75 and then to 85 mm Hg to evaluate effects on sublingual microcirculation in septic patients [53]. Their main finding was that increasing MAP failed to improve sublingual microcirculation or any other variable related to tissue oxygenation or perfusion such as arterial lactate, anion gap, pCO₂ gradients, and oxygen-derived parameters. Interestingly, there was considerable variation in the individual responses that were strongly dependent on the basal condition of microcirculation. In fact, PVD improved in patients with an altered sublingual perfusion at baseline and decreased in patients with a preserved baseline microvascular perfusion.

There are conflicting reports about the microcirculatory effects of other vasopressors such as phenylephrine or vasopressin analogues, but at least some studies have demonstrated detrimental effects, and thus should be used with caution in patients with suspected microcirculatory dysfunction [51].
In summary, there is no doubt that increasing MAP with NE in refractory hypotension improves microcirculatory flow, but the preceding data suggest that optimal MAP for microcirculatory perfusion is quite variable and should be selected on an individual basis.

**Vasodilators**

The rationale for the use of vasodilators in sepsis is based on experimental findings of pockets of ischemic areas lying close to well-perfused zones [54]. Vasodilators may increase the driving pressure of blood flow at the entrance of the microcirculation and perfuse hypoxic zones [5]. Nitroglycerin undergoes intracellular metabolism in order to produce NO-mediated vasodilatation. Despite the fact that excessive NO production is believed to play an important role in sepsis-induced hypotension, it has also been suggested as a therapeutic strategy to overcome heterogeneity in microcirculatory blood flow [55]. The general idea that increasing MAP results in a higher net microcirculatory perfusion pressure is not in line with physiological theory of the microcirculation as a low-pressure vascular compartment [51, 56].

In a small series of septic patients who fulfilled static systemic hemodynamic resuscitation endpoints, Spronk et al. found an improvement in sublingual perfusion despite a significant decrease in MAP, after a bolus of 0.5 mg followed by an infusion of 2 mg/h nitroglycerin (NTG) [57]. Of note, improvement of microcirculatory blood flow after the NTG bolus was instantaneous, indicating some NO-mediated endothelial ability for vasodilatation. However, it is important to consider that this study protocol included a large fluid challenge, and thus it is rather difficult to isolate the effects of concomitant fluids vs. NTG. Nevertheless, Spronk's observations together with the recent report of sublingual microcirculatory recruitment after topical acetylcholine in already resuscitated septic patients [29], challenge the general idea of endothelial hyporesponsiveness in sepsis-induced hypotension. More recently Boerma et al, in a double-blind placebo-controlled study, demonstrated that sublingual microcirculatory perfusion improved significantly over time, but no effect of NTG in comparison to placebo could be shown [23]. Although other NO-donors or vasodilators have been tested in experimental or clinical settings, the role of vasodilators in sepsis as a therapeutic strategy to recruit “microcirculatory weak units” is yet to be elucidated [51].

**Inodilators**

Dobutamine has both inotropic and vasodilatory effects. In an open label setting addition of dobutamine in septic patients was associated with improved OPS-measured sublingual microcirculatory perfusion over time, irrespective of changes in systemic hemodynamic variables [29]. However, this was an uncontrolled study and it is rather difficult to isolate net dobutamine effects from previous fluid loading or ongoing background resuscitation. In contrast, other controlled experimental and clinical studies in sepsis challenge the common view that dobutamine can improve regional or microcirculatory flow [25, 58, 59].

Levosimendan, a calcium-sensitizer drug with inotropic and vasodilator effects has been proven useful in cardiogenic shock. Some recent experimental and small clinical trials have
shown favorable effects on regional and microcirculatory flow as compared to dobutamine, in septic shock [25, 58, 59]. The place of these inodilators in a microcirculation-oriented resuscitation strategy has yet to be defined in view of the discordant results cited above.

Other therapies

Other potential therapies such as recombinant activated protein C (APC) [60-66], steroids (67,68], and high volume hemofiltration [27,69,70] have been tested with variables degrees of success and low levels of evidence.

In conclusion, the present review has covered the current state of knowledge concerning the effects on the microcirculation of disease and therapy in critically ill patients.

References

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