Microcirculatory disorders during septic shock

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Purpose of review
Despite the progress made over the past 20 years in the treatment of septic shock, mortality remains high. Microcirculatory disorders raise considerable interest aiming to improve the understanding of the physiopathology of septic shock and its management.

Recent findings
Numerous experimental and clinical studies have gradually focused on the analysis of microcirculatory blood flow and identified alterations in small vessels. These microcirculatory abnormalities appear early, are heterogeneous, and are directly linked to organ failure, as well as the patient's prognosis. These anomalies vary from one patient to the other, and their evolution during resuscitation cannot be predicted by the isolated analysis of global hemodynamic parameters such as blood pressure or heart rate.

Summary
Microcirculatory disorders appear at a central place of the physiopathology and are highly associated with the patient prognosis; it therefore seems important to develop and integrate parameters reflecting tissue perfusion in the management of septic shock.

Keywords
fluid resuscitation, microcirculation, septic shock, tissue hypoperfusion

INTRODUCTION

In septic shock, optimizing blood pressure and cardiac output has proven to be insufficient to systematically offset organ failure. This has given rise to many questions regarding the pathophysiology of the condition, leading investigations downstream to the sites of tissue perfusion. Hence, experimental and clinical studies have gradually focused on the analysis of blood flow in small vessels, revealing a complex set of microcirculatory abnormalities that arise early and are directly related to organ failure and patient prognosis. The questions now concern how to evaluate the microcirculation at the bedside, and how to integrate this information into a therapeutic decision as to whether fluids should be administered or doses of vasopressors adjusted.

VASCULAR PHYSIOLOGY

The vascular system is more than just a simplified assembly of blood tubes connected in series. It has an arborescent structure of successively smaller arteries, starting with large elastic arteries that dampen pulsatility, more muscular arteries that distribute the blood to organs, and arterioles and capillaries that regulate the supply of oxygen and nutrients to the tissues according to their needs [1,2]. The flow in the microcirculation is tightly regulated at the level of the arterioles. The endothelium of these vessels is exquisitely sensitive to physical forces (shear stress, pressure); chemical factors (cytokines, oxidative stress); and signals delivered by the circulating cells (leukocytes and erythrocytes) [3]. Vasoactive factors released by the endothelium control arteriolar tone and thus the microcirculatory blood flow. Arteriolar endothelial cells can be further distinguished between organs both in terms of structure and function, such that the response to a given stimulus will vary from one territory to another [4]. It is therefore understandable that the two parameters that physicians are desperate to optimize in the ICU – systemic

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KEY POINTS

- Microvascular abnormalities appear early in septic shock, and their persistence is closely associated with prognosis.
- Impaired microcirculatory perfusion may persist despite correction of systemic oxygen delivery variables like MAP or cardiac output.
- Clinicians should assess tissue perfusion at the bedside using mottling score, capillary refill time, and urine output.
- In the future, there is a need for a reproducible tool, easy to use, that could help clinicians to detect and monitor tissue hypoperfusion, ideally that could be implemented in a goal-directed management of the patient targeting tissue perfusion.

blood pressure and cardiac output – have little impact on microvascular flow.

PATHOPHYSIOLOGY DURING SEPTIC SHOCK

During severe sepsis, bacterial agents and the inflammatory response they induce cause numerous endothelial alterations, leading to modifications in vasomotor tone, activation of the coagulation cascade, and increased platelet–leukocyte interactions [3]. As a result, tissue perfusion is decreased and the ensuing organ damage can compromise the prognosis of patients. Numerous experimental and clinical studies have reported that small-vessel anomalies are detectable at the onset of sepsis [5,6]. In addition, the severity [7,8] and persistence [9] of these microvascular abnormalities are closely correlated with patient prognosis. Such direct visualization of defects in the microcirculation has highlighted the pathophysiological complexity of the disorder, both in terms of the heterogeneity of organ perfusion and the discrepancy between the overall hemodynamics and local blood flow [10]. Regarding the perfusion heterogeneity, it is well known that different organs are perfused differently in shock; adequate blood flow is maintained in so-called 'noble' organs such as the heart and brain, at the expense of other territories including the skin and the gastrointestinal tract. However, work in animals and intravital microscopy in humans has shown that perfusion is heterogeneous within each organ, with areas that are well perfused and others that are ischemic [11]. Moreover, such territorial disparities are highly variable from one patient to another. In septic shock patients, near-infrared spectroscopy revealed that skeletal muscle oxygen saturation (StO_2) recovery slope values ranged from 0.2 to 2.5%. Similarly, the proportion of perfused small vessels, imaged by side-stream dark field (SDF), ranged from 70 to 90% in septic patients [12]. Unfortunately, global parameters such as heart rate and mean arterial pressure (MAP) cannot identify or quantify microcirculatory abnormalities. They are therefore not appropriate to assess the severity of the patients and to guide their treatment. This is why the last conference of European experts excluded arterial pressure from the definition of shock [13▪].

MICROCIRCULATION AND RESUSCITATION

Vasopressors

In a model of endotoxinemic shock in sheep, Dubin *et al.* [14] reported that the administration of vasopressors quickly restored MAP, but did not improve the intestinal microcirculatory perfusion, highlighting the discrepancy between overall hemodynamics and the microcirculation. In humans, the effects of vasopressors are variable and even more difficult to predict. Several authors have shown that adjusting norepinephrine doses gradually, to achieve a MAP of 75 and then 85 mmHg, was beneficial in some patients, but frankly deleterious in others [12,15]. Likewise, the administration of norepinephrine improved small-vessel perfusion in some but not all patients [15,16]. These studies demonstrated that although a minimal threshold MAP is required to perfuse tissues, it is not sufficient to normalize the microcirculatory perfusion. More importantly, the persistence of microvascular anomalies after resuscitation was found to be predictive of death [8,9]. It therefore appears that the optimal MAP differs from one patient to another. This explains, at least in part, why strategies targeting a single MAP objective for all patients in septic shock have failed.

Inotropes

During septic shock, the different clinical studies that used the beta1 sympathomimetic dobutamine to optimize cardiac output failed to show improved tissue oxygenation. Some reported no benefit [17] and others even revealed excess mortality [18]. In a very recent multicenter study, a hemodynamic optimization strategy, on the basis of the evaluation of central venous oxygen saturation ($ScvO_2$) and flow, provided no benefit compared with the standard care strategy, on the basis of clinical perfusion parameters. Dobutamine was used six times more frequently in the 'optimized' group than in the control group (15.4 versus 2.6%; $P < 0.001$), confirming

the lack of benefit of increasing cardiac output [19▪]. By contrast, decreasing the cardiac output by continuous infusion of esmolol – a beta1 blocker – showed no negative impact on tissue oxygenation in a swine model of endotoxemia [20] and even improved survival in patients with septic shock [21]. These paradoxical findings reinforce the notion that during septic shock, hemodynamic optimization strategies fail because there is no relationship between cardiac output and the perfusion of small vessels. Indeed, using sublingual microscopy, De Backer *et al.* [22] found no statistical relationship between cardiac index and microcirculatory perfusion. In fact, cardiac index was never identified as a prognostic factor in septic shock; in many trials, cardiac index could not distinguish between survivors and nonsurvivors on day 14 [8,23,24▪] or day 28 [7]. Even during cardiogenic shock, cardiac index did not appear as a prognostic factor, in contrast to tissue hypoperfusion parameters (such as oliguria, altered consciousness, or cold extremities) [25].

Optimization of blood volume

The optimization of blood volume is a daily concern in the ICU, despite the fact that there is no strong evidence of benefit from intravenous fluids. Only the study by Rivers *et al.* [26] in 2001, using an 'intensive' blood volume expansion algorithm based on the monitoring of central venous pressure and $ScvO_2$, showed a benefit in terms of survival. Since then, several multicenter studies have failed to confirm this result. The PROtocol based Care for Early Septic Shock (PROCESS) study, published in 2014, shows that 'basic' support, based primarily on clinical parameters of tissue perfusion (mottling, diuresis, conscience, and lactate levels) without requiring invasive continuous hemodynamic monitoring ($ScvO_2$, central venous pressure, invasive arterial blood pressure), gives the same results in terms of organ failure and mortality as the 'optimized' management of Pro *et al.* [27]. The variable benefits of fluid loading on microcirculatory perfusion may partly explain these negative results. Using sublingual SDF imaging, Pottecher *et al.* [28] showed that volume expansion in 'preload-dependent' patients was accompanied by an increase in cardiac output and a parallel increase in microcirculatory perfusion. However, this effect quickly leveled off at the beginning of the filling test. Ospina-Tascon *et al.* [29] confirmed that vascular filling induced a significant increase in the density of small

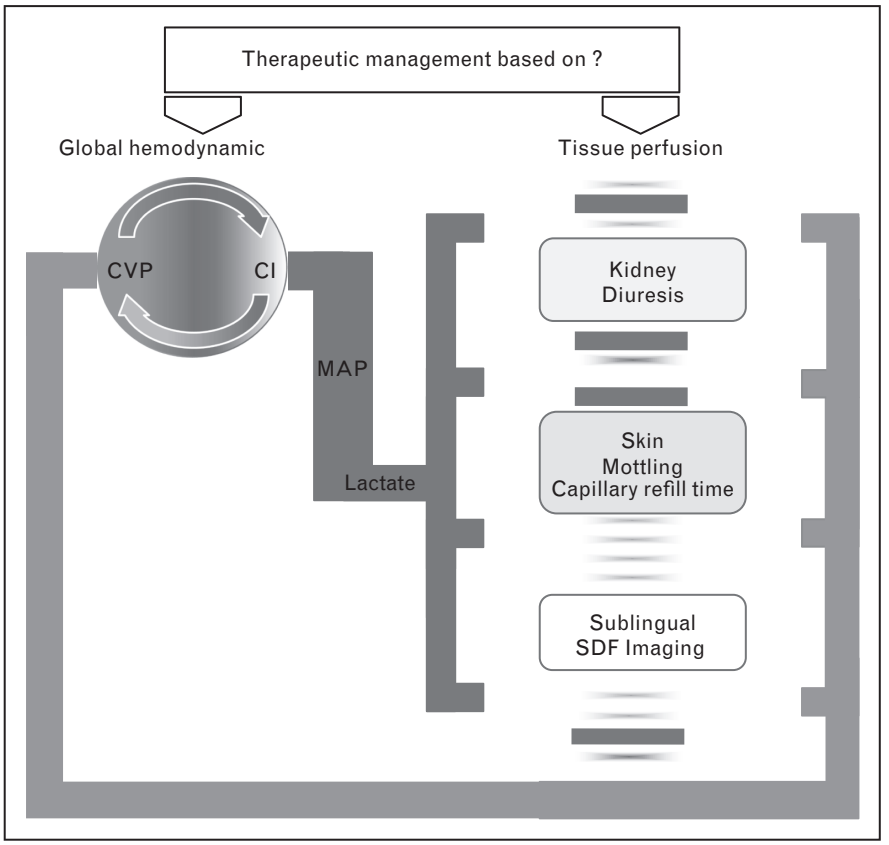

FIGURE 1. Management of septic shock should be based on both global hemodynamic parameters and tools that reflect tissue perfusion.

perfused vessels, but they did not find any relationship between changes in cardiac output and changes in microvascular perfusion. Furthermore, the beneficial effects of filling on small-vessel perfusion were observed only in cases where sepsis was caught early (diagnosis time <48 h) [29]. When it comes to red blood cell transfusion, the results of multicenter studies that evaluated mortality among nonselected resuscitation patients are mixed [30,31]. However, one study reported that in patients with severe sepsis, transfusion of red blood cells improved microcirculatory perfusion in patients with the most serious anomalies [32]. Finally, Pranskunas *et al.* [33] studied the hemodynamic effects of fluid resuscitation in patients receiving catecholamine whose clinical parameters of low perfusion called for volume expansion. They showed that even among 'preload independent' patients, volume expansion could improve sublingual microcirculatory perfusion [33]. The mechanisms that explain this improvement are unknown, but could be related to a decrease in blood viscosity, reduced platelet/leukocyte adhesion, or a dilution of vasoconstrictor factors. Hence, some plasma volume expanders may have specific properties, beyond their ability to expand volume, which could be beneficial at the microcirculatory level. For example, albumin has antioxidant functions that might limit the destruction of the glycocalyx and dampen leukocyte adhesion [34–36].

CONCLUSION

It is now accepted that global hemodynamic parameters are not sufficient to assess tissue perfusion of patients. The main challenge we face today is to develop an easily usable tool to evaluate microcirculatory perfusion at the bedside – a tool that would be sensitive enough to detect tissue hypoperfusion and to follow its evolution over the different therapeutic interventions. Several observational studies have highlighted the prognostic value of clinical parameters of tissue perfusion such as mottling score [8,23], capillary refill time [24▪,37], or urine output over the span of shock (Fig. 1). However, no study so far has shown that management based on these parameters can improve the prognosis of patients.

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Conflicts of interest

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- ▪ of special interest
- ▪▪ of outstanding interest

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