What is microcirculatory shock?

Vanina S. Kanoore Edul[a,b], *Can Ince*[b], *and Arnaldo Dubin*[b,c]

Purpose of review
Microcirculatory shock is a condition defined by the presence of tissue hypoperfusion despite the normalization of systemic and regional blood flow. In this article, we discuss the characteristics of the microcirculation in septic shock, the main form of microcirculatory shock, along with its interaction with systemic hemodynamics, and the response to different therapies.

Recent findings
In septic shock, microcirculatory abnormalities are common, and more severe in nonsurvivors. In addition, the microcirculation shows a behavior that is frequently dissociated from that of systemic hemodynamics. Therefore, microcirculatory alterations may persist despite correction of systemic hemodynamic variables. Sublingual and intestinal microcirculation might also display divergent behaviors. Moreover, microvascular alterations may improve in response to hemodynamic resuscitation, but the response might depend on the underlying microcirculatory alterations. Particularly, the response to fluids seems to be related to both its basal state and the magnitude of the increase in cardiac output.

Summary
The optimal treatment of microcirculatory shock might require monitoring and therapeutic goals targeted on the microcirculation, more than in systemic variables. The clinical benefits of this approach should be demonstrated in clinical trials.

Keywords
microcirculation, resuscitation, septic shock, tissue perfusion

INTRODUCTION

Shock is the failure of the cardiovascular system to provide oxygen transport (DO_2) necessary to meet oxygen demand. Consequently, anaerobic metabolism ensues. This clinical state of acute circulatory failure can result from four basic mechanisms: reduced intravascular volume, failure of the cardiac pump, obstruction in the circulation, and distributive disorders of the peripheral circulation [1]. In the first three processes, the main hemodynamic feature is low cardiac output (CO), which triggers tissue hypoperfusion and microcirculatory abnormalities. In contrast, distributive shock usually exhibits a normal or high CO, and microcirculatory alterations play a primary role in the development of tissue hypoperfusion [2]. Although septic shock is the most frequent and emblematic example, every type of shock may eventually evolve to distributive shock, as consequence of the inflammatory response elicited by persistent tissue hypoxia. Microcirculatory shock is the condition in which the microcirculation fails to support tissue oxygenation in face of normal systemic hemodynamics.

In this article, we will discuss the characteristics of microcirculation in septic shock, along with its interactions with systemic hemodynamics and response to the different resuscitation therapies. Some of these concepts might be applied to other types of distributive shock, such as traumatic shock [3▪], postcardiac arrest [4], and cardiopulmonary bypass [5].

DETERMINANTS OF MICROVASCULAR OXYGEN TRANSPORT

The main function of the microcirculation is tissue oxygenation. The microvascular oxygen transport (μDO_2) is determined by convective and diffusional

[a]Academic Medical Center, Department of Translational Physiology, University of Amsterdam, Amsterdam, Netherlands, [b]Facultad de Ciencias Médicas, Universidad Nacional de La Plata, Cátedra de Farmacología Aplicada, La Plata and [c]Sanatorio Otamendi y Miroli, Servicio de Terapia Intensiva, Buenos Aires, Argentina

Correspondence to Arnaldo Dubin, MD, PhD, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, Cátedra de Farmacología Aplicada, calle 42 N° 577 (1900) La Plata, Argentina. Tel: +5491150102431; e-mail: arnaldodubin@gmail.com

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KEY POINTS

- Microcirculatory shock is the failure of microcirculation to support tissue perfusion and oxygenation, despite a normal systemic hemodynamics.
- A severely disrupted microcirculation might coexist with a restored systemic hemodynamics.
- The adequacy of tissue sublingual perfusion does not guarantee a proper intestinal microcirculation.
- The basal state of the microcirculation might be useful to predict the response to fluids, vasopressors, and inotropes. The lower the microcirculatory blood flow, the better the response.
- The magnitude of the increase in CO might also predict microcirculatory recruitment by fluid expansion.

mechanisms [6]. The convective or bulk DO_2 depends on the microcirculatory blood flow and the oxygen content. Microvascular blood flow is controlled upstream of the capillary beds by the tone of the arteriolar resistance vessels. Differently to systemic perfusion, the driving pressure for microvascular flow is the difference between the precapillary inflow and the venular outflow pressures [7]. The arteriolar tone is also a major determinant of the capillary hematocrit, which can be significantly decreased under vasoconstriction [8]. Arteriolar vasoconstriction can thus reduce tissue DO_2 by affecting two of its components, flow and hematocrit. In addition, the increase in venous pressure might also diminish capillary perfusion pressure and flow [9].

With respect to diffusional DO_2, according to Fick's law, it is determined by the gradient between capillary and mitochondrial PO_2, the diffusional distances and the area available for gas exchange [6].

Furthermore, the deleterious effects of alterations in diffusional and convective determinants of the μDO_2 can be worsened by the presence of flow heterogeneity (i.e., capillaries with different patterns of flow) [10].

ASSESSMENT OF THE MICROCIRCULATION

For many years, the direct study of the microcirculation was restricted to animal experimentation. The introduction of the orthogonal polarization spectral imaging [11], and its improved version, the sidestream dark-field imaging [12], allowed the noninvasive, bedside visualization of the microcirculation in critically ill patients. Important limiting factors of the techniques are the need of well trained researchers for obtaining good quality videos, and the time-consuming offline analysis. Recently, a third-generation device based on incident dark-field imaging (Cytocam) was developed, with improved optical lenses, a high-resolution computer controlled image sensor, and an application for automatic analysis [13▪].

Evaluation of the video images has been done by means of different scoring methods and variables. Some can be determined by eye, whereas others require a software-assisted analysis. A round table consensus conference suggested that the analysis should include parameters of density (total and perfused vascular densities), perfusion [proportion of perfused vessels (PPVs) and microvascular flow index (MFI)], and heterogeneity [14]. About these variables, some relevant comments are:

(1) MFI, an analogue of flow velocity, consists in a semiquantitative score that distinguishes stopped (0), intermittent (1), slow (2), and continuous (3) flow. It is computed as the mean value of the predominant flow in the four quadrants [15], or the average of each individual vessel [16].
(2) The red blood cell (RBC) velocity can be measured by means of space/time diagrams in single vessels [17].
(3) The perfused capillary density (PCD) is the variable that more comprehensively describes the convective and diffusional determinants of μDO_2, as it involves the total amount or length of the microvessels (diffusion) and the presence of continuous flow (convection). Nevertheless, no single variable reflects the actual μDO_2, given that the real capillary flow and the oxygen content are not considered.

CHARACTERISTICS OF THE MICROCIRCULATION IN SEPTIC SHOCK

The microcirculatory failure in septic shock can result from several mechanisms, which include endothelial dysfunction, glycocalix degradation, capillary leak, loss of vascular reactivity and autoregulation, and microthrombosis [18▪]. Experimental studies showed that, in sepsis, the microcirculation comprises a large number of stopped-flow capillaries, a reduced PCD, and an increased heterogeneity [19,20]. As a consequence, oxygen might shunt from arterioles to venules, rendering the microcirculation hypoxic. This shunting may explain the reduced oxygen extraction (O_2ER) observed in distributive shock [21].

Some years ago, a seminal study demonstrated that the sublingual microcirculation of septic

patients is severely disturbed. The alterations consisted in decreased vascular density, reduced PPV resulting from an increased number of vessels with stopped or intermittent flow, and increased heterogeneity [22]. Subsequent studies confirmed that these abnormalities are more manifest in nonsurvivors [23,24], improve over time only in survivors [25], and are independent predictors of outcome in septic shock [26]. Thus, the state of the microcirculation might be considered an important prognostic indicator in sepsis.

Although some correlation can be present during the early resuscitation phase [23,27], the microcirculation is commonly dissociated from systemic hemodynamics [22,24,25] (Fig. 1). Consequently, microvascular perfusion cannot be predicted by any of the systemic variables. In patients dying of septic shock, however, severe microvascular abnormalities coexist with lactic acidosis, tachycardia, and high requirements of vasopressors [24,28].

Another controversial issue is the existence of hyperdynamic flow. An augmented RBC velocity might disturb tissue O_2ER. According to mathematical models, the reduction in RBC capillary transit time might not allow the complete unload of O_2, and so contribute to tissue hypoxia [29]. Although some video images could be suggestive of hyperdynamic flow, its presence has been presumed, but never clearly demonstrated. A study in septic rats reported an increased proportion of fast-flow to normal-flow capillaries, but this was due to a decrease in normal-flow capillaries whereas the number of fast-flow capillaries remained unchanged [20]. The definition of fast flow was also arbitrary. In other studies, the pattern of RBC velocities was shifted to low flow [30–32].

To rule out the existence of hyperdynamic microvascular flow, we performed the first quantitative evaluation of sublingual microcirculation by using a software-assisted analysis, in healthy volunteers and patients with septic shock [24]. Our results showed that the septic microcirculation is characterized by decreased PCD, which is completely explained by the reduction in the PPV, given that the total density is not affected; increased heterogeneity; and slow RBC velocity (Figs 2 and 3). In addition, although PCD and heterogeneity were more compromised in nonsurvivors than in survivors, RBC velocity was similar in both. These findings suggest that the variables representative of diffusional μDO_2, such as PCD and heterogeneity, are more related to outcome than a pure convective parameter such as RBC velocity.

In contrast to septic shock, hyperdynamic capillaries were described during cardiopulmonary bypass, a condition that can produce distributive shock [33▪].

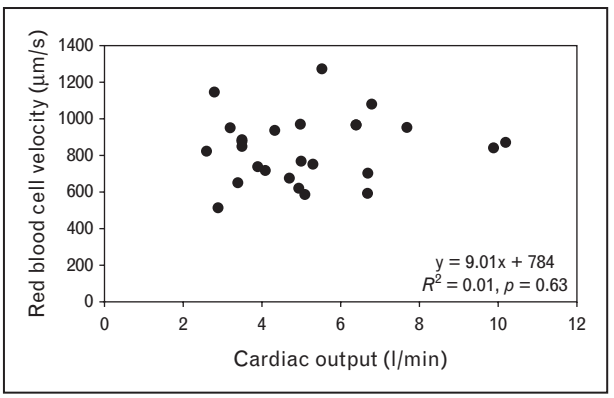

FIGURE 1. Lack of correlation between cardiac output (CO) and red blood cell (RBC) velocity in patients with septic shock. Reproduced from [24].

HETEROGENEITY IN DIFFERENT MICROVASCULAR BEDS

Even though the presence of microcirculatory heterogeneity has repeatedly been demonstrated within a particular capillary bed, a particular concern is if sublingual microcirculation reflects other territories, such as the intestinal villi. If not, gut ischemia might be present even when the sublingual mucosa is well perfused. Villi hypoperfusion may lead to alteration in the barrier function, with subsequent translocation of bacteria and their products to the systemic circulation, one conceivable mechanism of multiple organ failure [34]. Experimental research has shown a different behavior of sublingual and gut microcirculation. In sheep endotoxemic shock, fluid resuscitation normalized sublingual microcirculation, but the villi remained hypoperfused [35]. In another septic model, fluid resuscitation improved both areas, but the intestinal PCD did not reach basal values [36▪]. Conversely, in a cholangitis model, comparable sublingual and intestinal alterations were reported [30]. An explanation for these contradictory findings is that in the latter study, the alteration in microvascular perfusion was extreme (PPV ~0.3). Consequently, such a severe condition might have affected the different microcirculatory territories more uniformly. A clinical study in patients with abdominal sepsis found a lack of correlation between the sublingual and intestinal stoma MFIs, during the first postoperative day [37]. We recently showed in patients with abdominal sepsis a dissociation between sublingual and intestinal microcirculation in both the basal condition and the response to volume

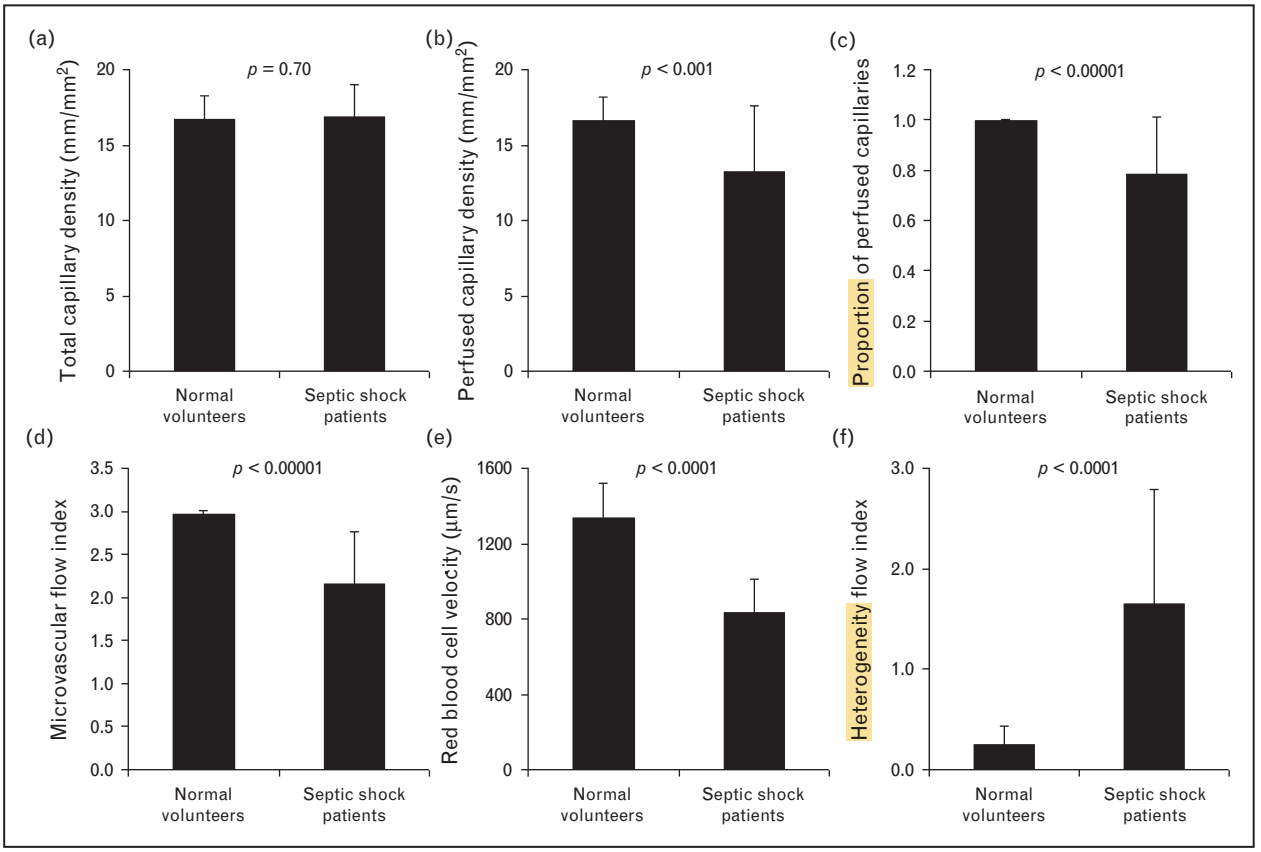

FIGURE 2. Microcirculatory variables in healthy volunteers and patients with septic shock. Panel a: total capillary density. Panel b: perfused capillary density. Panel c: proportion of perfused capillaries. Panel d: capillary microvascular flow index. Panel e: capillary red blood cell velocity. Panel f: capillary heterogeneity flow index. Reproduced from [24].

expansion [38▪] (Fig. 4). Although fluids were able to improve the sublingual perfusion, the gut remained hypoperfused. Moreover, the intestinal microcirculation variables were more severely compromised in nonsurvivors compared with survivors, but neither of the sublingual parameters was. Nonetheless, these results do not challenge the established value of sublingual microcirculation as a prognostic index in septic patients [22–26], but simply reflect that, in these surgical patients, the local ischemia in the villi is probably more relevant than the state of perfusion in other vascular beds. Accordingly, isolated villi ischemia might influence the outcome in the absence of microvascular disorders in other territories because of the putative role of that vascular bed in the development of multiorgan failure [34].

MICROCIRCULATORY RESPONSE TO RESUSCITATION

In the following paragraphs, we will briefly summarize relevant information about the microcirculatory response to some of the modalities more frequently used in the resuscitation of septic shock: fluids, vasopressors, and inotropes.

Fluids

Volume expansion is the first approach to the resuscitation of septic shock. The optimal type and amount of fluid are controversial. The effects of fluids on the microcirculation depend on several factors [39▪▪]. Fluids may increase convective microvascular blood flow as a consequence of their effects on CO and perfusion pressure. Excessive fluid administration, however, may jeopardize diffusional μDO_2 because of tissue edema, which results in reduced PCD, decreased area for gas exchange, and longer diffusional distances. In addition, the increase in viscosity might be critical to maintain capillary flow and hematocrit [40].

With respect to the type of fluid, several experimental studies showed beneficial effects of starches on the microcirculation [41,42]; and a randomized controlled pilot study suggested their superiority for the resuscitation of the microcirculation, compared with isotonic saline solution, during the early goal

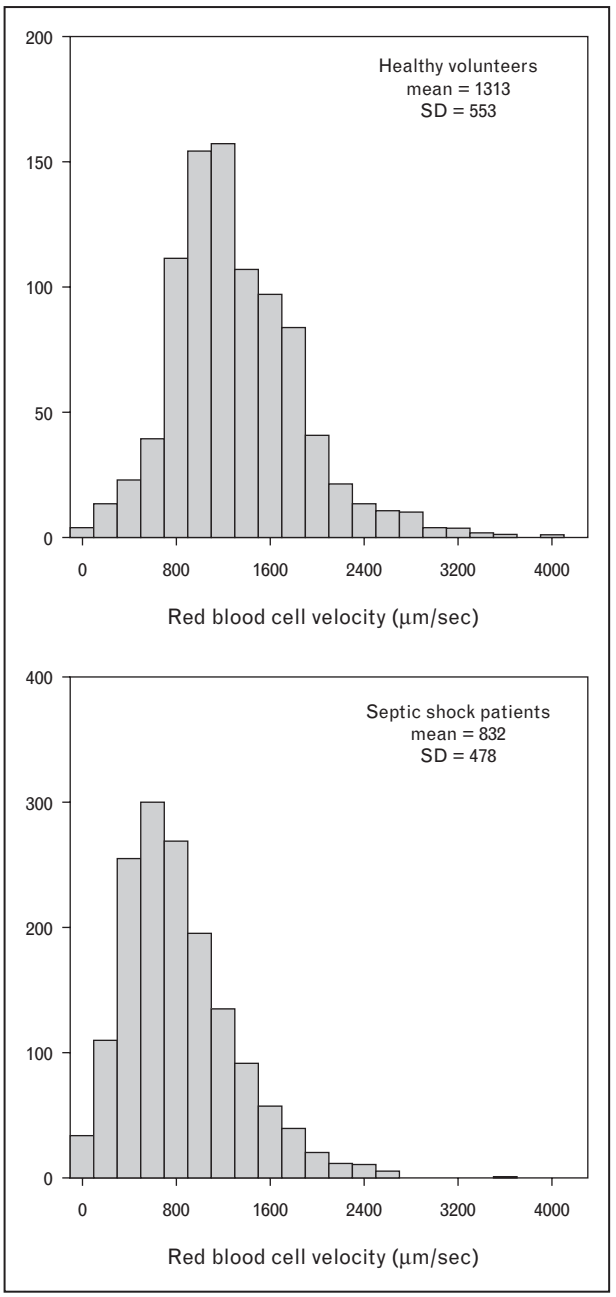

FIGURE 3. Histograms of capillary red blood cell (RBC) velocities in healthy volunteers (upper panel) and patients with septic shock (lower panel). Velocities in septic patients are shifted to the low-flow range. Only 4% of the capillaries analyzed showed RBC velocities higher than the 75th percentile of the values for the normal volunteers. Reproduced from [24].

directed therapy [43]. Unfortunately, safety issues preclude the use of starches in critically ill patients [44].

Recently, some studies have tried to identify patients likely to recruit the microcirculation after fluid expansion. With respect to the timing of the administration of fluids, sublingual microcirculation has been shown to improve in the early (<24 h) but not in the late (>48 h) phase of sepsis [45]. Another study showed that, after volume expansion, patients with early septic shock and fluid responsiveness increased the sublingual microcirculation. These changes correlated with CO variations [46].

The response to volume expansion seems strongly dependent on the status of microcirculation. In patients with an MFI less than 2.6, significant increases in microvascular blood flow and attenuation of clinical signs of impaired organ perfusion occurred [47]. On the contrary, no changes were seen with MFI at least 2.6. We recently demonstrated that the effects of a fluid challenge on sublingual microcirculation were dependent on both the basal microvascular perfusion and the magnitude of the increase in CO [38▪] (Fig. 4). Therefore, we can expect higher improvement in microcirculation when CO is substantially increased in patients with severe microvascular derangements. In this way, the assessment of microcirculatory flow abnormalities, prior to fluid therapy, has been proposed to increase the pretest likelihood of a successful intervention [39▪▪].

Vasopressors

The goal of vasopressors is to reach a mean arterial pressure (MAP) above the lower autoregulatory threshold that allows tissue perfusion, while avoiding excessive vasoconstriction. A study in patients with septic shock evaluated the effects of stepwise increases in MAP from 60 to 90 mmHg by means of norepinephrine. The systemic DO_2 and the cutaneous perfusion increased without changes in the preexistent sublingual microcirculatory alterations. The conclusion was that significant improvement in global hemodynamics and tissue DO_2 could be achieved without worsening the microcirculation [48]. Nevertheless, a more careful analysis shows that when MAP increased from 70 to 90 mmHg, the MFI, the PPV, and the PCD were reduced about 10%. Accordingly, we showed in septic shock patients that the increase in MAP from 65 to 85 mmHg was associated with a linear trend to a reduced PCD [49]. Our main finding, however, was that the effects were highly variable but strongly dependent on the basal state of the microcirculation. When the PCD was normal at a MAP of 65 mmHg, further increases in MAP worsened the PCD, probably as a consequence of excessive vasoconstriction. On the contrary, the increase in MAP, in patients with a compromised PCD at baseline, improved the microcirculation. The clinical implication is that the optimal MAP might be set according to the state of the microcirculation.

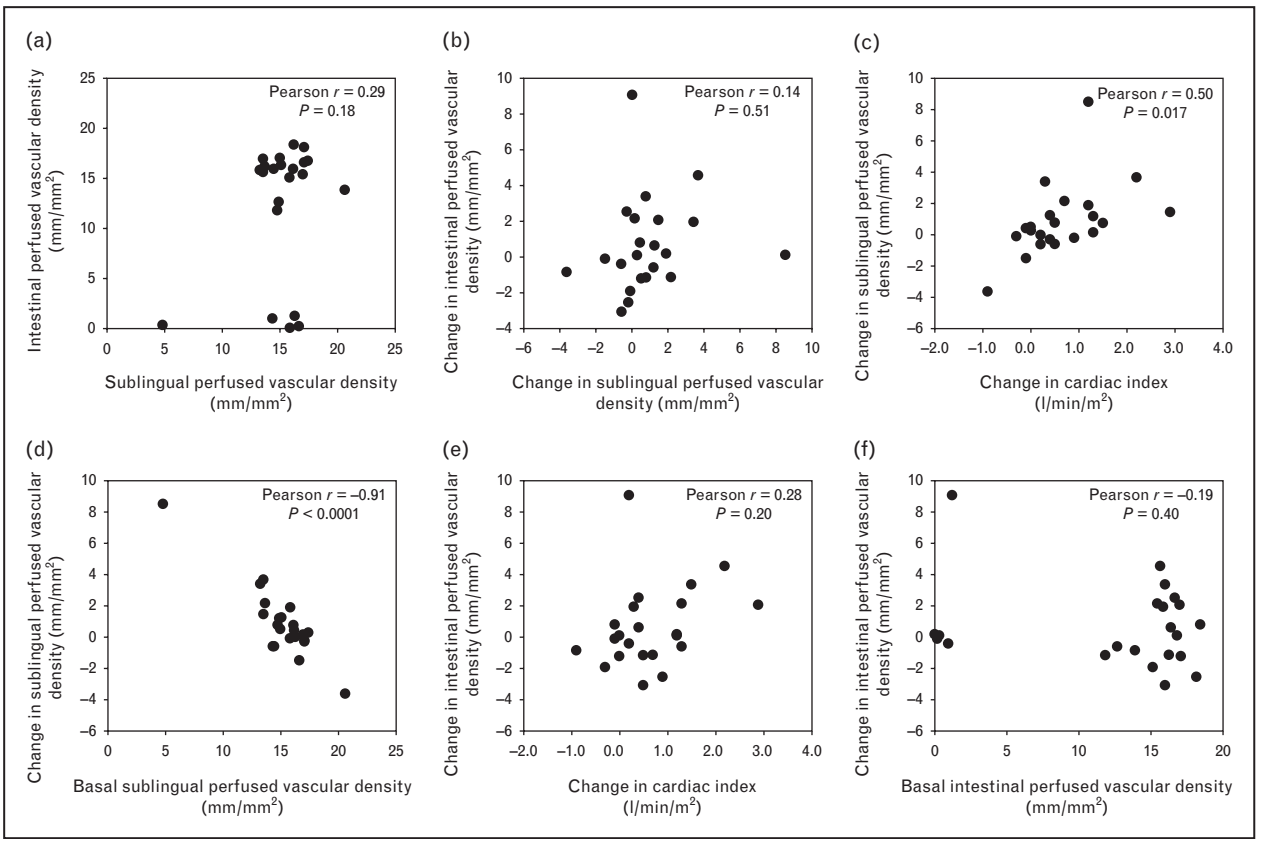

FIGURE 4. Red blood cell (RBC) velocity. Panel a: correlation between basal sublingual and intestinal RBC velocity. Panel b: correlation between the changes in sublingual and intestinal RBC velocity in response to the fluid challenge. Panel c: correlation between the changes in cardiac index and sublingual RBC velocity in response to the fluid challenge. Panel d: correlation between the changes in sublingual RBC velocity in response to the fluid challenge and the basal sublingual RBC velocity. Panel e: correlation between the changes in cardiac index and intestinal RBC velocity in response to the fluid challenge. Panel f: correlation between the changes in intestinal RBC velocity in response to the fluid challenge and the basal intestinal RBC velocity. Reproduced from [38▪].

Inotropes

In an observational study, the infusion of 5 μg/kg/min of dobutamine increased the PPV from 0.58 to 0.75%, regardless of the changes in CO or MAP [50]. We also assessed the effects of increasing doses of dobutamine in patients with septic shock [51]. The microcirculatory alterations did not improve in the whole group. These contradictory responses to dobutamine might be ascribed to the different basal states in the microcirculation in the two studies because patients with more severe alterations (PCD $\leq$12 mm/mm^2) improved their microcirculation, similarly to the previous study [50]. As a matter of fact, in this subgroup of patients, the PPV increased from 0.57 to 0.72. Thus, both studies showed that in the presence of severe derangements in sublingual microcirculation, dobutamine improves microvascular perfusion. Although a small crossover study reported that dobutamine has no beneficial effects on the microcirculation, the PPV increased from 0.75 to 0.79 ($P = 0.09$) [52].

CONCLUSION

Microcirculatory shock is a condition in which tissue hypoxia results from microvascular alterations, despite normal systemic hemodynamics. Moreover, considerable heterogeneity between microcirculatory territories might occur. The effect of some therapies on microcirculation might differ, according to their systemic effects and the basal microvascular condition. Therefore, fluid resuscitation might be more effective in the presence of fluid responsiveness and severe microvascular hypoperfusion. The microvascular effects of vasoconstrictors and inotropes also seem dependent on the state of microcirculation. All this information points to the need of a microcirculatory-targeted resuscitation. Clinical trials are needed to show that this approach can improve the outcome of septic shock.

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Conflicts of interest

C.I. has developed SDF imaging and is listed as inventor on related patents commercialized by Micro Vision Medical (MVM) under a license from the Academic Medical Center (AMC). He has been a consultant for MVM in the past, but has not been involved with this company for more than 5 years now, except that he still holds shares. Braedius Medical, a company owned by a relative of C.I., has developed and designed a hand held microscope called CytoCam-IDF imaging. He has no financial relation with Braedius Medical of any sort, that is, never owned shares, or received consultancy or speaker fees from Braedius Medical. The remaining authors have no conflicts of interests.

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