

Guilherme Loures Penna<sup>1,3</sup>,  
Diamantino Ribeiro Salgado<sup>2</sup>,  
André Miguel Japiassú<sup>1</sup>, Marcelo  
Kalichsztein<sup>1</sup>, Gustavo Freitas  
Nobre<sup>1</sup>, Nivaldo Villela<sup>2</sup>, Eliete  
Bouskela<sup>3</sup>

## Microcirculatory assessment: a new weapon in the treatment of sepsis?

*Avaliação da microcirculação: uma nova arma no manejo da sepse?*

1. Intensive Care Unit, Casa de Saúde São José – Rio de Janeiro (RJ), Brazil.
2. Hospital Universitário Clementino Fraga Filho – Rio de Janeiro (RJ), Brazil.
3. Vascular Biology Clinical and Experimental Research Laboratory (BioVasc), Biomedical Center, Universidade do Estado do Rio de Janeiro – UERJ – Rio de Janeiro (RJ), Brazil.

### ABSTRACT

The progression into multi-organ failure continues to be a common feature of sepsis and is directly related to microcirculatory dysfunction. Based on a PubMed database search using the key words microcirculation and sepsis, twenty-six articles were selected for this review. The relevant references from these articles were also selected and included in this analysis. Orthogonal polarization spectral imaging allows for the bedside assessment of the microcirculation of critically ill patients. Such imaging

has established a correlation between microvascular dysfunction and patient outcomes, which allows practitioners to directly assess the effects of therapeutic interventions. However, the causal relationships between microcirculatory dysfunction, adverse outcomes, and the effects of therapies aimed at these microcirculatory changes in sepsis, are not clear.

**Keywords:** Microcirculation/physiology; Sepsis/physiopathology; Organ dysfunction; Mortality; Hemodynamics; Shock, septic/therapy

### INTRODUCTION

In spite of the significant advances in the study of the pathophysiology and treatment of sepsis, mortality remains high.<sup>(1)</sup> The progression into multi-organ failure is a common feature of sepsis, even after hemodynamic stability is achieved. Multi-organ failure is apparently related to the redistribution of blood flow to the organs, as has been shown in studies on microcirculation and morphologic or functional cell changes, such as mitochondrial dysfunction.

During the 1990s, microcirculation studies that used invasive techniques in experimental sepsis models described microcirculatory changes that showed a marked reduction in capillary density.<sup>(2-4)</sup> During this period of research, human studies were dependent upon the large microscopes that were used for periungual microcirculation assessments. These assessments showed a reduced rate of capillary flow in normotensive patients with fever.<sup>(5)</sup>

Orthogonal polarization spectral imaging (OPS) has the capacity to assess microcirculation in the sublingual mucosa and in other tissues covered by thin epithelial layers (such as the conjunctiva, the rectal mucosa, the vagina and the newborn axilla). The use of OPS as a real-time non-invasive tool for observation has been validated in several trials.<sup>(6,7)</sup> The technology used in OPS is based on Beer's law, which states that the constant found by dividing

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#### Corresponding author:

Guilherme Loures Penna  
Rua Dona Mariana, 143 - Sala B 31 -  
Botafogo  
Zip Code: 22280-020 - Rio de Janeiro  
(RJ), Brazil.  
Phone /Fax: +55 21 2226-1035  
Email: guipenna@terra.com.br

the object's optic density by the wave length is directly proportional to the concentration of the constituents causing the absorbance. In the case of microcirculation, the constituent is primarily hemoglobin. OPS imaging has the capacity to evaluate microcirculation up to 3 millimeters under the examined surface if the light intensity is sufficient, the light sources are orthogonally situated, and an appropriate objective is used. The OPS device is easy to use and is portable. More recently, the sidestream dark field (SDF) technique was also developed, based on the same principles.<sup>(8)</sup>

The analysis of microcirculation can provide relevant information. The total capillary density corresponds to all field visible capillary vessels, which is proportional to the number of capillary vessels crossing three horizontal and three vertical screen lines. The capillary vessels are categorized as perfused in the following manner: the vessels show continued flow, no flow, any flow that can be identified, or intermittent

flow if no flow is seen for at least 50% of the time. The density and percentage of perfused vessels can be calculated with the use of particular mathematical formulas. Capillary vessels, which are less than 20 micrometers in diameter, can also be differentiated from venules. Microvascular flow heterogeneity, which is present in sepsis, is assessed by the comparison of the four quadrants.<sup>(9)</sup> In an experimental trial, Verdant et al. showed that septic microcirculatory changes were similar in both the intestinal and sublingual mucosa, perhaps because of their shared embryonic origin.<sup>(10)</sup> Due to its accessibility, the sublingual mucosa was selected for microcirculatory studies in septic patients.

### Evidence of septic microcirculatory changes

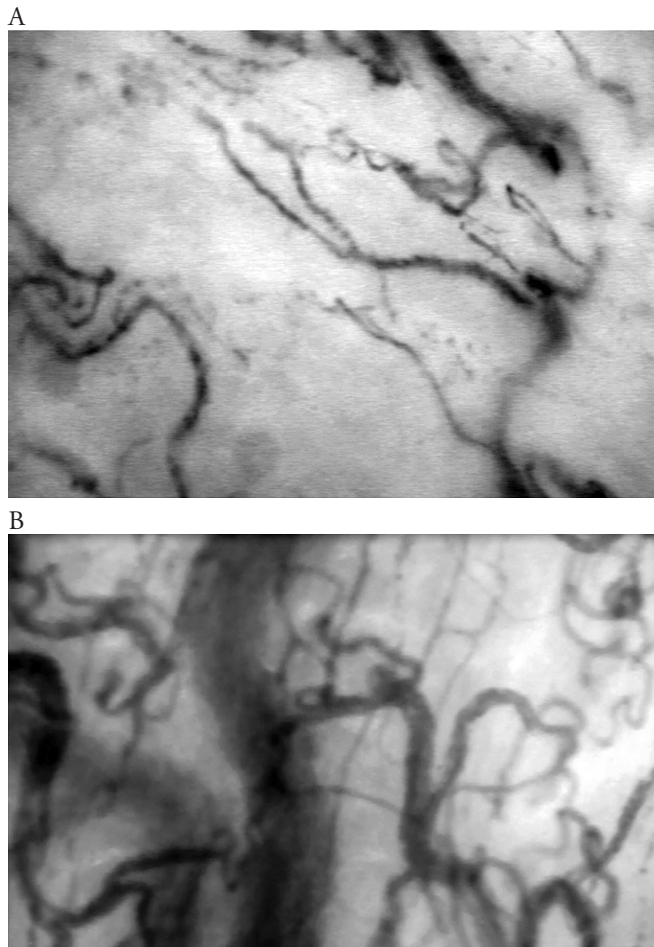
Several trials in which OPS was used to evaluate microcirculation in sepsis were recently published (Table 1). De Backer et al. showed evidence of reduced functional capillary density, reduced proportion of

**Table 1 – The main set of published articles on microcirculation and sepsis**

Author	Year	Journal	Method	Title
Lam et al. <sup>(2)</sup>	1994	J Clin Invest.	Experimental	Microvascular perfusion is impaired in a rat model of normotensive sepsis.
Piper et al. <sup>(3)</sup>	1996	Am J Respir Crit Care Med.	Experimental	Microcirculatory changes in rat skeletal muscle in sepsis.
Farquhar et al. <sup>(4)</sup>	1996	J Surg Res.	Experimental	Decreased capillary density in vivo in bowel mucosa of rats with normotensive sepsis.
De Backer et al. <sup>(11)</sup>	2002	Am J Respir Crit Care Med.*	Clinical	Microvascular blood flow is altered in patients with sepsis.
Sakr et al. <sup>(12)</sup>	2004	Crit Care Med.*	Clinical	Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock.
De Backer et al. <sup>(24)</sup>	2006	Crit Care Med.*	Clinical	Effects of drotrecogin alfa activated on microcirculatory alterations in patients with severe sepsis.
Sakr et al. <sup>(20)</sup>	2007	Crit Care Med.*	Clinical	Microvascular response to red blood cell transfusion in patients with severe sepsis.
Trzeciak et al. <sup>(13)</sup>	2008	Intensive Care Med.*	Clinical	Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis.
Verdant et al. <sup>(10)</sup>	2009	Crit Care Med.*	Experimental	Evaluation of sublingual and gut mucosal microcirculation in sepsis: a quantitative analysis.
Dubin et al. <sup>(19)</sup>	2009	Crit Care Med.*	Clinical	Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study.
Bücheler et al. <sup>(23)</sup>	2009	Crit Care Med.*	Clinical	Effects of hydrocortisone on microcirculatory alterations in patients with septic shock.
Pottecher et al. <sup>(21)</sup>	2010	Intensive Care Med.*	Clinical	Both passive leg raising and intravascular volume expansion improve sublingual microcirculatory perfusion in severe sepsis and septic shock patients.
Boerma et al. <sup>(26)</sup>	2010	Crit Care Med.*	Clinical	Effects of nitroglycerin on sublingual microcirculatory blood flow in patients with severe sepsis/septic shock after a strict resuscitation protocol: a double-blind randomized placebo controlled trial.
Su et al. <sup>(30)</sup>	2010	Shock.*	Experimental	Effects of a novel anticoagulant compound (TV7130) in an ovine model of septic shock.
Salgado et al. <sup>(29)</sup>	2011	Shock.*	Experimental	Sublingual microcirculatory effects of enalaprilat in an ovine model of septic shock.

\*Studies using orthogonal polarization spectral imaging (OPS)/sidestream dark field (SDF).

perfused capillary and flow heterogeneity with no flow capillary vessels in severe sepsis patients as compared to healthy subjects (Figure 1).<sup>(11)</sup>



**Figure 1 – Orthogonal polarization spectral imaging (OPS) of a patient admitted to the intensive Care Unit of Casa de Saúde São José: A) during septic shock; B) during recovery after shock just before extubation.**

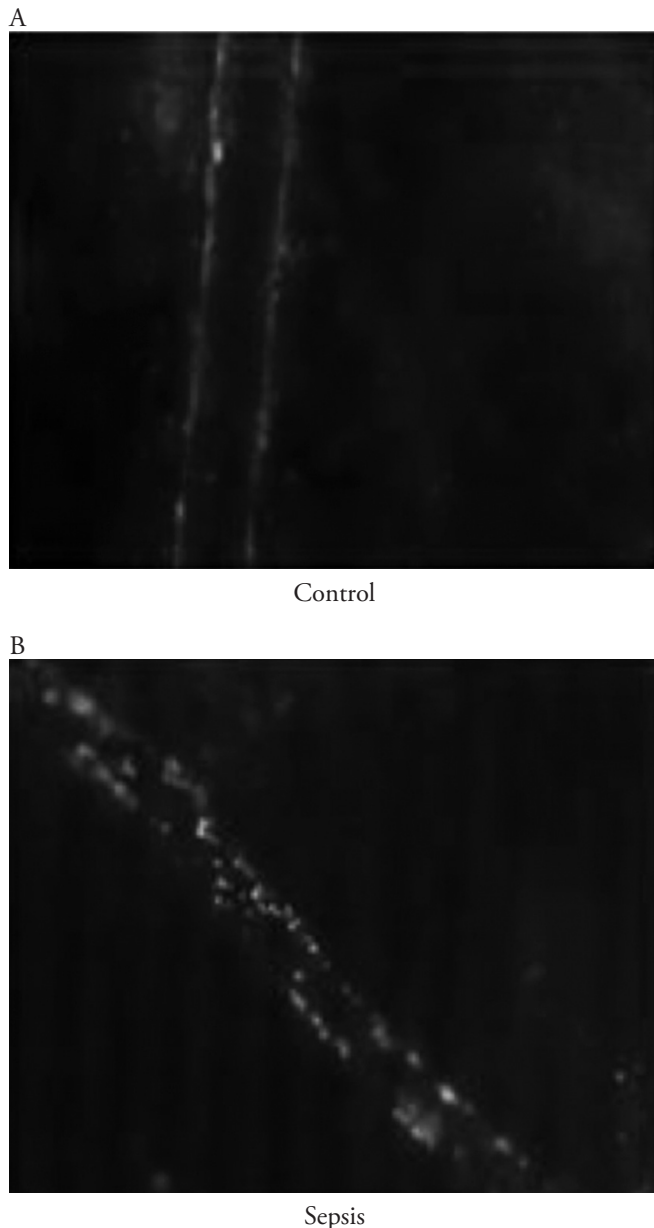
In another study, persistent microcirculatory changes in septic patients were shown to be associated with poorer outcomes.<sup>(12)</sup> OPS was used to assess the microcirculatory status of patients each day from the first day of septic shock until the shock was resolved or the patient had died. During the first rounds of microcirculatory assessment, surviving patients had shown a capillary density that was similar to the non-surviving patients. However, patients who maintained a reduced capillary density, even if the initial septic shock was reversed, did not survive. Even with improved hemodynamic stability, a microcirculatory assessment was able to discriminate between patients

who would survive and those who would progress into multi-organ failure. The relevance of microcirculatory oxygenation is that, even when global oxygen supply is preserved, microcirculatory impairment may lead to tissue hypoxia. In another trial, Trzeciak et al. have shown that the rate of capillary flow is closely correlated to the patient's outcome.<sup>(13)</sup> In this trial, a microcirculatory assessment was completed during the first 3 hours of early goal directed therapy (EGDT)<sup>(14)</sup> and repeated 3 to 6 hours later. The Sequential Organ Failure Assessment (SOFA) score was calculated at the start of EGDT and after 24 hours. Out of 33 patients, 48% had at least a 2 point drop in their SOFA score. The Age, Acute Physiology and Chronic Health Disease Classification System (APACHE II) score, along with overall hemodynamics, were not significantly different between the groups. Among patients who had a decrease in their SOFA score, 88% had a mean microcirculatory flow improvement of 23%. Those with no SOFA score improvement had a mean decrease in microcirculatory flow of 5%. An improvement in microcirculation would apparently reduce the likelihood of organ failure.

The hemodynamic parameters used for EGDT, such as central venous pressure, central venous saturation, blood pressure and urinary output should always be optimized during the management of sepsis, especially in the early stages of treatment, as hemodynamic stability reduces mortality. However these parameters are not directly related to the prognostic relevancy of microcirculatory changes.<sup>(15)</sup>

#### **Possible pathophysiologic explanations**

Septic microcirculatory changes can broadly be understood as the impaired balance between vasoconstrictor and vasodilator production and release, which leads to a reduction in microvascular flow. There is also an increase in the production of free oxygen radicals. These radicals react with nitric oxide (NO) and reduce its intracellular levels. Adequate levels of NO are needed to activate the enzyme guanylate cyclase, which is responsible for the production of cyclic GMP (a mediator of smooth muscle cell relaxation).<sup>(16)</sup> In addition, the endothelium normally acts as an anti-adhesive barrier for blood components. However, septic endotoxins create pro-adhesive and pro-thrombotic effects on red and white blood cells and platelets that then alter the capillary flow.<sup>(17)</sup> Free oxygen radicals also increase the adhesive effects of white blood cells, platelets and red blood cells along the endothelium (Figure 2).<sup>(18)</sup>



**Figure 2 – Intravital microscopy images from experimental animals studies from the Vascular Biology Clinical and Experimental Research Laboratory of Universidade do Estado do Rio de Janeiro. The images show the adhesion of white blood cells to the vessel wall during septic shock. A) Control; B) During sepsis.**

#### Effect of different therapeutic interventions

The therapeutic interventions initiated during sepsis affect the microcirculation. Although it is known that the microcirculation will be impaired during severe hypotension, it is difficult to establish the ideal mean blood pressure (MBP) that will optimize microcirculatory flow. Dubin et al. evaluated the microcirculation of 20 septic shock patients with a mean blood pressure (MBP) of 65

mmHg. After an increase in the noradrenalin infusion, which increased the MBP to 75-85 mmHg, they reassessed the microcirculatory status of the patients and found that microvascular perfusion was not significantly changed across the entire set of patients, in spite of any inter-subject variation. However, there was an increase in capillary density for those patients with baseline microcirculatory changes. Capillary density worsened for those patients with normal microcirculatory baselines.<sup>(19)</sup> Similarly, in a series that included 35 severely septic patients, Sakr et al. showed that the transfusion of 1 to 2 units of packed red blood cells did not improve microcirculatory flow. There was, however, a considerable degree of inter-subject variability. Patients with worse baseline microcirculatory perfusion presented with a remarkable improvement in capillary perfusion.<sup>(20)</sup> To optimize microcirculation, it must be monitored.

Another recent trial focused on the influence of rheological factors on microcirculation. A group of patients underwent passive leg raising maneuvers and a later infusion of a crystalloid solution. The patients showed similar increases in cardiac output, functional capillary density, microcirculatory flow rate and the number of perfused capillary vessels for both interventions. There appeared to be no rheological influence, at least with the limited volume of infusion.<sup>(21)</sup> In a recent study, Ospina-Tascon et al. compared a volume infusion of either crystalloids or colloids in two groups of patients: a group with severe sepsis for less than 24 hours and a group with severe sepsis for more than 48 hours. A significant increase in small vessel density and perfusion was shown only in the former group, which demonstrates the relevance of early optimization of microcirculation. The observed microcirculatory effects were not related to the overall hemodynamic parameters or the type of volume expansion solution.<sup>(22)</sup>

Other non-vasopressor drugs affect microcirculation in the setting of severe sepsis. Hydrocortisone and activated protein C can improve capillary perfusion, although the modes of action are not clear.<sup>(23,24)</sup> Hypothetically, nitroglycerin, a NO donor vasodilator could improve microcirculatory flow heterogeneity and provide capillary recruitment, as has been described in the literature.<sup>(25)</sup> However, a randomized double-blind trial infusing either nitroglycerin or a placebo failed to show these benefits in septic patients after volume resuscitation and hemodynamic stabilization.<sup>(26)</sup> Microcirculatory parameters were considerably improved during the initial clinical stabilization, but the effects did not last later in the clinical course of treatment.<sup>(27)</sup> The sedative agent propofol reduced capillary density by 9.1%,<sup>(28)</sup> but the drug's effect on septic patients needs to be clarified. Experimental



studies have explored the possible therapeutic effects of drugs such as enalapril<sup>(29)</sup> or the anticoagulant TV7130<sup>(30)</sup> on microcirculatory flow improvement. These studies show the possible range of experimental and clinical trials over the next few years.

### CLOSING REMARKS

Microcirculatory dysfunction is directly related to poorer patient outcomes. The impairment of microcirculation in sepsis is heterogeneous with some capillary areas showing very slow flow or even no flow, while in neighboring areas, capillary perfusion is preserved. An organ, then, may be ischemic even when the global oxygen supply for this organ is preserved. It is not known if any causal relationship exists, or if microcirculatory changes can be more than a marker. Future studies are expected to test the hypothesis that improvements in microcirculation may serve as effective intervention in the treatment of sepsis.

### RESUMO

A evolução para disfunção de múltiplos órgãos ainda é comum na sepse e está relacionada diretamente com a disfunção microcirculatória. Através de pesquisa nas bases de dados PubMed, empregando-se os unitermos microcirculação e sepse, vinte e seis artigos foram selecionados para esta revisão, bem como citações consideradas relevantes extraídas de artigos de revisão. Com o advento da técnica de imagem obtida através de polarização ortogonal, que permite a observação à beira do leito da microcirculação em pacientes críticos, é possível estabelecer uma relação entre disfunção microvascular e prognóstico, além de observar diretamente o efeito de diferentes intervenções terapêuticas. No entanto, a relação causal entre disfunção microcirculatória e prognóstico adverso na sepse, bem como os efeitos de terapias dirigidas para correção destas anormalidades microcirculatórias ainda precisam ser melhor definidos.

**Descritores:** Microcirculação/fisiologia; Sepse/fisiopatologia; Disfunção orgânica; Mortalidade; Hemodinâmica; Choque séptico/terapia

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