Review
Clinical manifestations of disordered microcirculatory perfusion in severe sepsis

Stephen Trzeciak[1] and Emanuel P Rivers[2]

[1]Section of Critical Care Medicine and the Department of Emergency Medicine, UMDNJ-Robert Wood Johnson Medical School at Camden, Cooper University Hospital, Camden, New Jersey, USA
[2]Departments of Emergency Medicine and Surgery, Henry Ford Hospital, Detroit, Michigan, USA

Corresponding author: Stephen Trzeciak, TRZECIAK-STEPHEN@cooperhealth.edu

Abstract

Microcirculatory dysfunction plays a pivotal role in the development of the clinical manifestations of severe sepsis. Prior to the advent of new imaging technologies, clinicians had been limited in their ability to assess the microcirculation at the bedside. Clinical evidence of microcirculatory perfusion has historically been limited to physical examination findings or surrogates that could be derived from global parameters of oxygen transport. This review explores: (1) the clinical manifestations of severe sepsis that can be linked to microcirculatory dysfunction; (2) the relationship between conventional hemodynamic parameters and microcirculatory blood flow indices; (3) the incorporation of microcirculatory function into the definition of 'shock' in the sepsis syndrome; (4) the role of the microcirculation in oxygen transport; and (5) the potential impact of novel sepsis therapies on microcirculatory flow. Although the study of the microcirculation has long been the domain of basic science, newly developed imaging technologies, such as orthogonal polarization spectral imaging, have now given us the ability to directly visualize and analyze microcirculatory blood flow at the bedside, and see the microcirculatory response to therapeutic interventions. Disordered microcirculatory flow can now be associated with systemic inflammation, acute organ dysfunction, and increased mortality. Using new technologies to directly image microcirculatory blood flow will help define the role of microcirculatory dysfunction in oxygen transport and circulatory support in severe sepsis.

Introduction

Microcirculatory blood flow is markedly impaired in sepsis [1-3], and microcirculatory dysfunction plays a pivotal role in the development of the clinical manifestations of severe sepsis and septic shock. In the past, direct visualization of microcirculatory networks was only possible in experimental models of sepsis using intravital videomicroscopy, which is not possible in human subjects. Newly developed imaging technologies, such as orthogonal polarization spectral (OPS)

imaging, have brought the ability to directly visualize the microcirculation to the bedside. Microcirculatory imaging, however, is still investigational in human sepsis and has not yet been incorporated into routine clinical practice. The purpose of this review, therefore, is to bridge the experimental and clinical aspects of microcirculatory science, and discuss the concepts that can be incorporated into bedside assessments of patients with severe sepsis and septic shock.

"What lies beneath?" The clinical manifestations of microcirculatory dysfunction in severe sepsis

Although the hemodynamic profile and clinical management of septic shock are typically characterized solely in terms of global hemodynamic (i.e. macrovascular) parameters, it is the microcirculation that is responsible for delivering blood flow from the cardiovascular system to the tissues. After conventional cardiovascular support measures achieve restoration of an acceptable arterial blood pressure in a septic shock patient, a clinician may be falsely reassured that the patient is clinically 'stable'. However, there are a myriad of possible pathogenic mechanisms occurring in the microcirculation that are difficult to detect with conventional clinical means and are, in effect, hidden from the clinician. In fact, much of the pathophysiology of severe sepsis can be explained by 'what lies beneath' in the microcirculation [4]. In severe sepsis this can include: (1) global tissue hypoxia [5]; (2) pan-endothelial cell injury [6]; (3) activation of the coagulation cascade [7]; and (4) "microcirculatory and mitochondrial distress syndrome" (MMDS) [8]. These factors, either individually or in some combination, likely represent primary determinants of acute organ dysfunction in severe sepsis.

DO_2 = oxygen delivery; EGDT = early goal-directed therapy; MAP = mean arterial pressure; MMDS = microcirculatory and mitochondrial distress syndrome; OPS imaging = orthogonal polarization spectral imaging; pCO_2 = partial pressure of CO_2; PGI_2 = prostacyclin; pHi = gastric intramucosal pH; $PslCO_2$ = sublingual pCO_2; ROSC = return of spontaneous circulation; SvO_2 = mixed venous oxygen saturation; VO_2 = oxygen consumption.

Many of the pathogenic mechanisms of severe sepsis take place in the microcirculatory unit [4], which is comprised of the arteriole, the capillary bed, and the postcapillary venule. The role of microcirculatory dysfunction in the pathogenesis of acute organ system dysfunction has been discussed elsewhere in this supplement [9]. However, there are microcirculatory derangements pertaining to acute cardiovascular system dysfunction that merit special discussion here. It is the microcirculatory unit, and specifically the arterioles, where vasoactive mediators of sepsis exert their vasodilatory effects. This manifests clinically as a low systemic vascular resistance and profound arterial hypotension requiring the administration of vasoconstrictor agents. It is the capillary network where endothelial injury and ongoing capillary leakage occur in severe sepsis, which can manifest clinically as profound hypovolemia and persistently low cardiac filling pressures despite efforts to expand intravascular volume [10]. Therefore, basic elements of the hemodynamic profile, such as hypotension and hypovolemia thought typically to be macrovascular derangements in nature, are actually rooted in the microcirculation.

The relationship of conventional hemodynamic parameters and tissue perfusion in severe sepsis

Shock is typically defined as a failure of the cardiovascular system to maintain effective tissue perfusion, resulting in cellular dysfunction and acute organ system failure. If effective tissue perfusion is persistently impaired and not corrected, the cellular dysfunction and organ failure may become irreversible. Some shock etiologies will impair tissue perfusion because of a markedly low cardiac output. However, septic shock can cause an impairment of effective tissue perfusion because of: (1) a maldistribution of blood flow (despite a normal or elevated cardiac output) secondary to microcirculatory dysfunction; or (2) impaired use of substrate due to defects in cellular oxygen utilization. In shock profiles other than sepsis where the microcirculation is not affected to such an extent, correction of global hemodynamic parameters would likely ensure adequate oxygenation of tissues. This is not true in severe sepsis, where regional hypoperfusion abnormalities can persist even after global optimization of conventional hemodynamic and oxygen-derived parameters.

Historically, the conventional clinical signs of hypoperfusion that can be easily assessed at the bedside have included hypotension, tachycardia, oliguria, encephalopathy, cool extremities, slow cutaneous capillary refill, and metabolic (lactic) acidosis. Although the presence of arterial hypotension is clearly an ominous sign indicating a high severity of illness, arterial blood pressure alone is an insensitive indicator of tissue hypoperfusion in sepsis. It has been well documented in experimental and clinical studies alike that tissue hypoperfusion abnormalities, either with or without an impairment in cardiac output, can occur long before the manifestation of hypotension. Therefore, blood pressure parameters alone are insufficient to identify the need for aggressive resuscitation [5,11,12].

In the absence of profound hypotension, there appears to be a complex relationship between macrocirculatory hemodynamic parameters and microcirculatory blood flow. In a study by LeDoux and colleagues [13], 10 patients with septic shock received increasing doses of norepinephrine to drive up the mean arterial pressure (MAP) from 65 to 85 mmHg, and no changes were reported in indices of regional perfusion (as measured by skin capillary blood flow, red blood cell velocity, urine output, and gastric mucosal partial pressure of CO_2 [pCO_2]). The authors concluded that the use of vasopressors to elevate the arterial blood pressure to above 65 mmHg in septic shock did not affect regional blood flow [13]. This was recently supported by data from Bourgoin and colleagues [14]. Two recent studies of OPS imaging in septic shock by De Backer and colleagues [1] and Sakr and colleagues [3] reported that microcirculatory perfused vessel density was independent of arterial blood pressure. The data suggest that microcirculatory blood flow in severe sepsis is not simply a function of local perfusion pressures. There appears to be a degree of disconnection between the macrocirculation and the microcirculation, indicating that blood pressure-targeted management strategies in severe sepsis will not necessarily ensure adequate regional perfusion.

Recognition of shock in sepsis syndrome

Arterial blood pressure is likely to be an insensitive indicator of the need for aggressive cardiovascular support, in a similar way that blood pressure-guided resuscitation may be suboptimal for ensuring regional tissue perfusion. Therefore, one of the most critical clinical objectives in severe sepsis management is the early recognition of the patient with impaired tissue perfusion. In a subgroup analysis [15] of the randomized, controlled, early goal-directed therapy (EGDT) trial by Rivers and colleagues [5], individuals with severe sepsis who initially presented with a MAP >100 mmHg and a serum lactate level >4 mM ($n = 23$) had a significantly increased mortality rate (60.9%) compared with patients who had originally presented with hypotension (MAP <70 mmHg) ($n = 68$, 42% mortality), despite the fact that the two groups were treated with the same 'standard care' therapeutic algorithm. Currently, consensus recommendations for sepsis management [16] advocate the addition of serum lactate measurements to blood pressure parameters to help identify normotensive patients who are in 'cryptic shock' [17] and in need of aggressive resuscitation. Despite the fact that lactate is nonspecific for anaerobic metabolism (i.e. other mechanisms related to metabolic derangements can cause lactate elevation), impaired microcirculatory flow is one of the many possible mechanisms for hyperlactatemia in severe sepsis [18]. Regardless of etiology, lactate elevation in severe sepsis and persistence of elevated lactate over time can identify a patient with a high risk of death [11,19-21]. Elevated lactate can help to rapidly identify patients with tissue hypoperfusion, and, if levels are markedly elevated, can serve as a qualitative trigger for initiating an EGDT protocol [5].

Incorporating additional indicators of tissue perfusion into our bedside assessments may help to improve the identification of the hypoperfused patient. An optimal strategy for recognizing shock in sepsis would include sensitive means of detecting regional and microcirculatory perfusion abnormalities. A perfusion-based scoring system for shock recognition has been proposed by Spronk and colleagues [22] (Table 1). Although exact calculation of a perfusion-based score is not likely to be necessary at the bedside, this type of conceptual framework can be useful to the clinician in bedside assessments by extending the recognition of shock severity to markers of small vessel perfusion (in addition to global hemodynamic and oxygen-derived parameters).

Oxygen transport and the role of the microcirculation

The microcirculation plays a critical role in oxygen transport to tissues. Although the provision of goal-directed circulatory support is typically focused on achieving target values for global hemodynamic and oxygen-derived parameters (hereafter referred to as 'upstream' endpoints of resuscitation), as well as tracking the response of variables directly related to tissue perfusion such as acid–base parameters and gastric intramucosal pH (pHi)/sublingual pCO_2 (PslCO_2) (hereafter referred to as 'downstream' markers of effective resuscitation), an intact microcirculatory network is a critical intermediary between the cardiovascular system and effective tissue oxygenation, effectively serving as the bridge between the upstream and downstream parameters (Fig. 1). The Krogh model of microcirculatory oxygen diffusion [23] is a conceptual framework that underscores the importance of the microcirculation in oxygen transport. Oxygen is transported to tissues by diffusion from capillary (and arteriolar [24]) blood. The diffusion distance for oxygen increases as the density of perfused capillaries decreases (Fig. 2). If the diffusion distance for oxygen exceeds a critical point in tissues, then anaerobic metabolism will likely occur. In severe sepsis, this may occur regionally either with or without marked derangements of global hemodynamic or oxygen-derived parameters.

Although global parameters of oxygen transport are typically thought to be insensitive indicators of change in regional blood flow, there are some bedside observations that can be made from derangements of global oxygen-derived parameters that are central to the concept of microcirculatory oxygen transport. For example, profoundly low mixed venous oxygen saturation (SvO_2), a global parameter that represents the oxygen saturation of pooled blood from all the postcapillary venules in the body, may identify when anaerobic metabolism is likely to be occurring in the tissues (i.e. global tissue hypoxia) [5]. Regardless of the oxygen saturation on the arteriolar side of capillaries, a markedly low SvO_2 identifies that the venular ends of capillaries likely contain deoxygenated blood. Conceptually speaking, the cylindrical area of tissue in the Krogh model (Fig. 3) that is supplied by this deoxygenated

Table 1

**Integrative clinical approach for defining a state of shock**

Item evaluated	Points

Hemodynamic variables
    Heart rate > 100 bpm or
    MAP < 50 mmHg and (CVP < 2 or CVP > 15 mmHg) or
    CI < 2.2 l/min per m²
	2

Peripheral circulation
    Mottled skin or
    T_c–T_p difference > 5°C or
    Pfi < 0.3 or
    Impaired peripheral capillary refill
	2

Microvascular variables
    Increased tonometric CO_2 gap or
    Increased sublingual CO_2 gap or
    Impaired sublingual microvascular perfusion (OPS imaging)
	1

Systemic markers of tissue oxygenation
    Lactate > 4 mmol/l or
    SvO_2 < 60%
	1

Organ dysfunction Diuresis < 0.5 ml/kg per hour[a]	1
Decreased mental state[a]	1

A state of shock is present if the score exceeds 2 points. CI, cardiac index; CVP, central venous pressure; MAP, mean arterial pressure; OPS, orthogonal polarization spectral imaging; Pfi, peripheral perfusion index; SvO_2, mixed venous oxygen saturation; T_c, core temperature; T_p, peripheral toe temperature. [a]Due to present disease. Reprinted with permission [22].

capillary blood (the so-called "lethal corner") is at risk for anaerobic metabolism. This has clinical importance, as global tissue hypoxia has been associated with endothelial cell activation and injury, triggering of systemic inflammation, activation of the coagulation cascade, and multiorgan dysfunction [6,25,26]. This cascade of events caused by global tissue hypoxia bears a striking resemblance to key pathogenic elements in the microcirculation that are directly attributable to sepsis. Avoidance of global tissue hypoxia, therefore, is an important goal of cardiovascular support in clinical practice, as failure to correct this physiologic derangement may compound the pathophysiologic effects of severe sepsis in the microcirculation.

Finding a normal or high SvO_2 value (i.e. venous hyperoxia) at the bedside does not preclude that tissue dysoxia is occurring, because derangements of cellular oxygen utilization (i.e. cytopathic hypoxia [27]) may be playing a significant role (especially in established or late-phase sepsis). Although cytopathic hypoxia is a well recognized mechanism that can cause venous hyperoxia, an alternative hypothesis to explain this finding is that microcirculatory shunting may also be contributing, such that some degree of venous hyperoxia measured at the bedside may actually be caused to some extent by microcirculatory dysfunction. In this model, blood is shunted to open areas of the microcirculation when weak microcirculatory units are effectively shut down

Figure 1
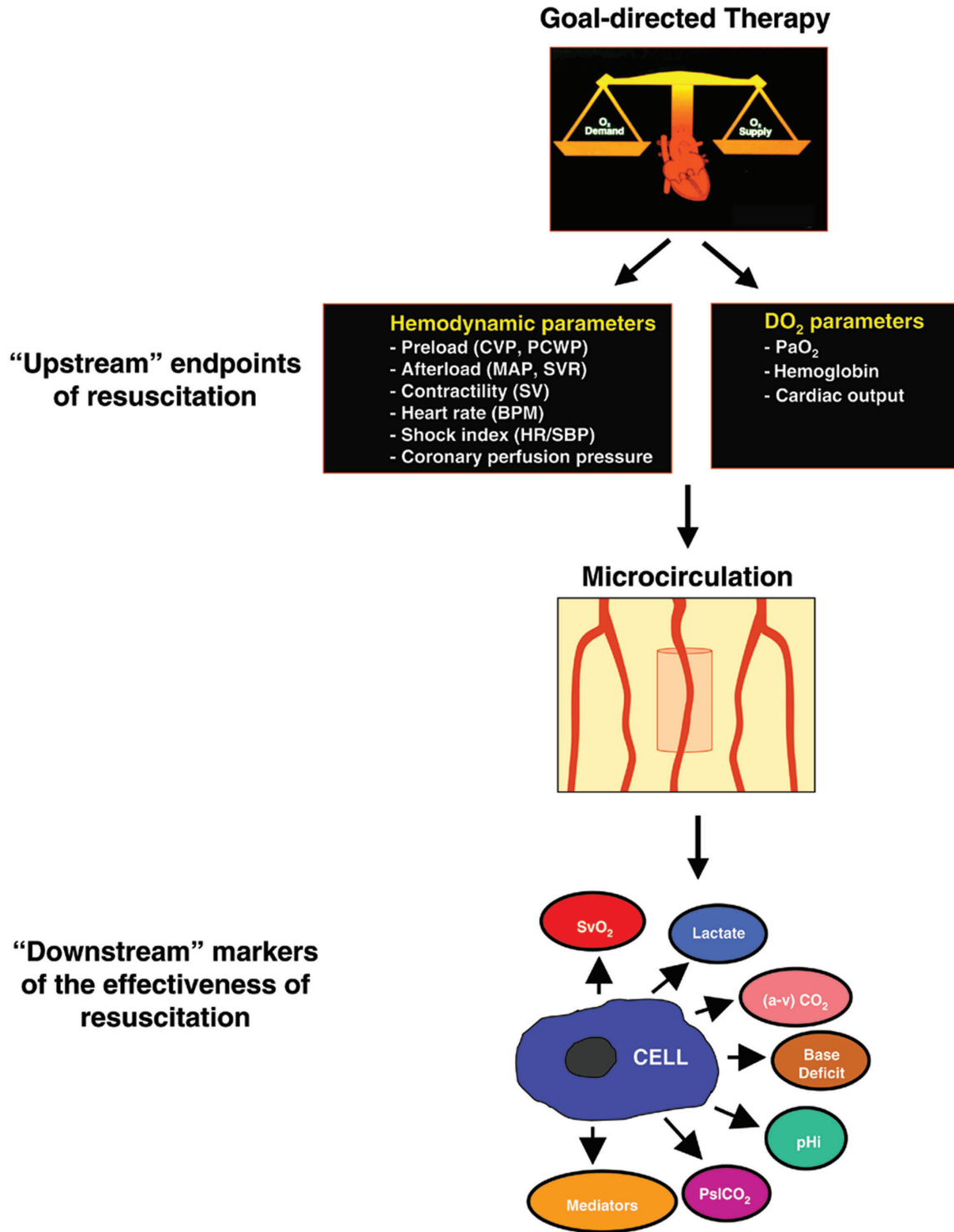
The role of the microcirculation in goal-directed circulatory support. The upstream endpoints of resuscitation are hemodynamic and oxygen-derived variables that can be modulated by circulatory support interventions. The downstream variables are markers of tissue perfusion and effectiveness of resuscitation. The microcirculation is the critical intermediary that delivers blood flow from the cardiovascular system to the tissues. BPM, beats per minute; CVP, central venous pressure; DO_2, oxygen delivery; HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; pHi, gastric intramucosal pH; $PslCO_2$, sublingual pCO_2; SBP, systolic blood pressure; SV, stroke volume; SvO_2, mixed venous oxygen saturation; SVR, systemic vascular resistance.

Figure 2
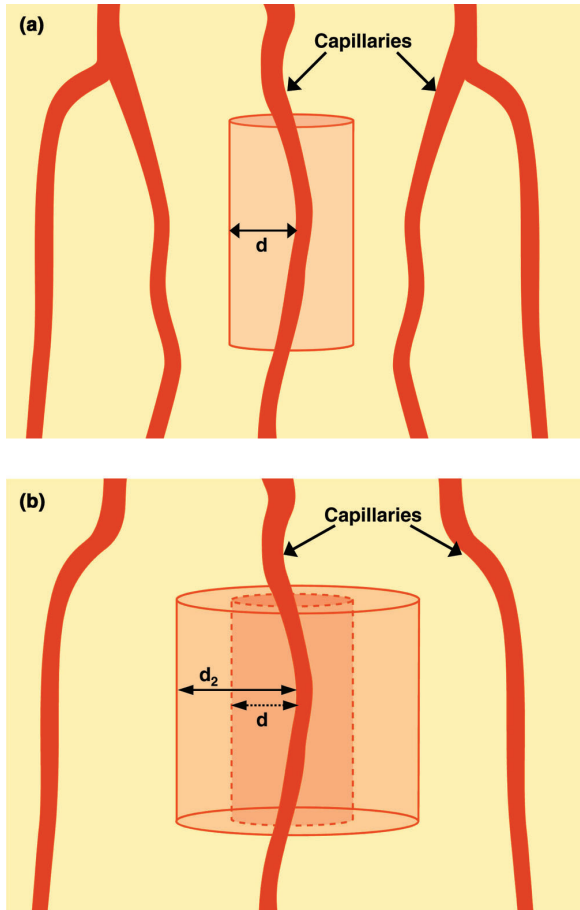
The Krogh conceptual model of oxygen diffusion from the capillaries.
(a) The area of tissue that is supplied by an individual capillary is
represented by a cylinder. The diffusion distance for oxygen in the tissues
is shown (d). **(b)** If perfused capillaries drop out because of the micro-
circulatory alterations of severe sepsis, and the perfused vessel density
decreases, the diffusion distance for oxygen increases (d_2). This illustrates
how perfused vessel density plays a critical role in oxygen transport.

because of severe flow impairment [28]. Shunting could
potentially contribute to decreased systemic oxygen
utilization, venous hyperoxia observed at the bedside, and an
elevation of serum lactate concentration (Fig. 4). Venous
hyperoxia has been observed in patients with cardiac arrest
after return of spontaneous circulation (ROSC) [29], and
appears to be significantly associated with the amount of
epinephrine administered during resuscitative efforts [30].
However, it is not clear to what extent (if any) microcirculatory
dysfunction plays a role in the post-ROSC patient, as
derangements of cellular oxygen utilization have been
hypothesized to be the driving force of this observation. In
severe sepsis, where microcirculatory derangements are a
key component of the pathophysiology, microcirculatory
shunting and cytopathic hypoxia are likely both occurring, and
are probably not mutually exclusive processes. The relative
contribution of each is currently unclear.

Figure 3
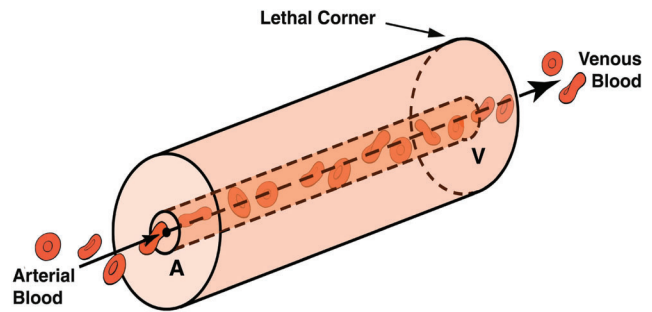
A conceptual model of capillary flow and oxygen diffusion. A cylinder
represents the area of tissue surrounding an individual capillary. A
markedly low value for the (global) mixed venous oxygen saturation
(SvO_2) reflects markedly deoxygenated blood in the pooled post-
capillary venules. Regardless of how well oxygenated the blood may be
on the arteriolar side of the capillary (A), a very low SvO_2 indicates that
tissues near the venous end of the capillary (V) are supplied by
deoxygenated blood ('lethal corner'). This conceptual model explains
how a low SvO_2 is associated with tissue dysoxia.

Figure 4
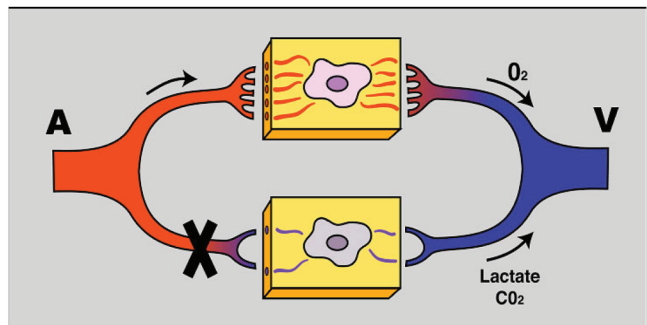
The microcirculatory shunting model of sepsis. Severe flow impairment
(denoted by X) in weak microcirculatory units causes a shunting of
blood to open microcirculatory units. Elevation of serum lactate
concentration (from the microcirculatory units with impaired flow) may
be simultaneously observed along with venous hyperoxia from the
shunted units. Adapted with permission [22].

Novel sepsis therapies and their potential impact on microcirculatory blood flow

Effectively serving as the bridge between the upstream and
downstream endpoints of resuscitation, the microcirculation
could be an attractive target for novel sepsis therapies. This
may be particularly true if downstream markers of the
effectiveness of resuscitation (i.e. lactate, base deficit,
$pHi/PslCO_2$) fail to normalize despite successful achievement
of predefined target values for the upstream endpoints of
resuscitation in goal-directed therapy (Fig. 1). A persistent
derangement of downstream markers may be attributable to
MMDS [8], and may identify the ideal individual for demon-
strating the specific effects of novel agents to recruit the

microcirculation. In theory, novel agents that could specifically augment microcirculatory blood flow would probably be either: (1) agents that improve flow by modulating actions on the endothelial cell surfaces; or (2) vasodilators. The potential effects of activated protein C on microcirculatory flow are discussed elsewhere in this supplement [31]. Vasodilators that have been studied in human septic shock include prostacyclin, dobutamine, and nitric oxide donor agents, and these agents merit special discussion here because of their potential effects on microcirculatory flow.

Clinical studies of vasodilator agents in septic shock

The clinical use of vasodilator agents in shock states has typically been limited to macrocirculatory effects, such as modulation of afterload on the heart in cardiogenic shock. There is limited clinical data on the use of vasodilators in sepsis. In a recent study using OPS imaging, De Backer and colleagues demonstrated that a marked impairment of sublingual microcirculatory blood flow in patients with septic shock was reversible with local administration of acetylcholine [1]. This indicates that the endothelium in septic shock is still responsive to mediators of vascular tone and suggests that vasodilatory response in small vessels can be manipulated with therapeutic agents. In theory, the systemic administration of vasodilator agents in septic shock could recruit microcirculatory units, decrease microcirculatory shunting, and improve regional tissue oxygenation [32]. Because systemic oxygen consumption (VO_2) only occurs in the capillaries and terminal arterioles, a true increase in VO_2 (as opposed to one that is only apparent because of mathematical coupling of the variables) associated with the use of a vasodilator agent in septic shock could indicate that oxygen needs are being met with increasing microcirculatory blood flow, and this finding could support the theory that microcirculatory shunting in severe sepsis plays a significant role in oxygen transport.

Clinical studies of prostacyclin (PGI_2) in severe sepsis have demonstrated a change in global parameters of oxygen transport, including a rise in VO_2 [33-35]. Bihari and colleagues [35] demonstrated that PGI_2 administration was associated with a marked increase in both oxygen delivery (DO_2) and VO_2, and the authors concluded that PGI_2 could identify a change in VO_2 that represented an occult oxygen debt. In a study by Radermacher and colleagues [36], septic shock patients were treated with intravenous volume expansion and inotropic support to maximize DO_2, and then PGI_2 was administered. Prostacyclin improved gastric pHi and the authors concluded that this represented a recruitment of splanchnic perfusion (despite the fact that global oxygen uptake directly measured from respiratory gases was unchanged). Prostacyclin has been poorly tolerated in clinical studies because of inducing or exacerbating arterial hypotension.

Nitroglycerin and dobutamine administration have been associated with increases in microcirculatory blood flow in

sepsis [2,37,38]. In a recent study of resuscitated septic shock patients, Spronk and colleagues [2] demonstrated a severe impairment in sublingual microcirculatory blood flow that was sharply improved with an infusion of nitroglycerin. De Backer and colleagues administered both PGI_2 and dobutamine in a clinical study of severe sepsis [33], and dobutamine significantly increased both DO_2 and VO_2. Shoemaker and colleagues [39] also demonstrated that giving dobutamine to critically ill surgical patients resulted in an improvement in global parameters of oxygen transport, including a rise in both DO_2 and VO_2. The authors concluded that this rise in VO_2 indicated an improvement in tissue perfusion. Note that the results of these studies of vasodilators and the potential relationship (if any) between the change in VO_2 and presumed microcirculatory recruitment should be interpreted with caution. Because a minority of studies of vasodilators directly measured VO_2 via respiratory gases, observed changes in VO_2 could have more to do with the calculation (mathematical coupling of the oxygen transport variables) than an actual improvement in small-vessel perfusion.

The clinical impact of using nitric oxide donor agents (such as nitroglycerin) or dobutamine to open the microcirculation [32] and improve tissue perfusion is unclear at present. However, it is notable that in the randomized controlled trial of EGDT, the goal-directed protocol included: (1) nitroglycerin for a MAP > 90 mmHg; and/or (2) dobutamine for a central venous oxygen saturation < 70% (after correction of central venous pressure, MAP, and hematocrit) [5]. For individuals in the EGDT group, the impact that these agents had on microcirculatory blood flow is unknown.

New technologies and future directions

New technologies such as OPS imaging have recently brought to the bedside the ability to image the microcirculation, and have allowed the direct visualization of marked microcirculatory flow impairments that characterize severe sepsis [1]. Although it has been debated that microcirculatory dysfunction and the clinical manifestations of severe sepsis may just be epiphenomena, De Backer and colleagues used OPS imaging and logistic regression analysis to identify that an impairment of capillary perfusion was an independent predictor of mortality in a series of severe sepsis patients [40]. Sakr and colleagues [3] reported that nonsurvivors who died with persistent multiorgan failure due to sepsis had markedly impaired small-vessel perfusion over time compared with survivors. The degree of improvement in small-vessel perfusion over the first 24 hours of therapy was a good predictor of mortality, suggesting that the capacity to impact clinical outcome via restoration of microcirculatory perfusion may be time sensitive [3]. This supports the concept that optimal circulatory support in sepsis should be achieved early.

Future studies using these new technologies during severe sepsis resuscitation will help to define: (1) the role of

microcirculatory dysfunction in oxygen transport during conventional goal-directed circulatory support; (2) the prognostic value of microcirculatory dysfunction for subsequent acute organ dysfunction and mortality; and (3) the effects of novel antisepsis therapies on microcirculatory blood flow. Although the optimal agents for achieving microcirculatory recruitment, as well as the optimal place in our current goal-directed therapy algorithms for use of such agents, have yet to be determined, these new bedside imaging modalities will provide a window of the microcirculation to help answer these questions.

Competing interests
EPR is a speaker for Edwards Lifesciences.

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