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The microcirculation and its measurement in sepsis

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Abstract

The microcirculation describes the smallest elements of the cardiovascular conducting system and is pivotal in the maintenance of homeostasis. Microcirculatory dysfunction is present early in the pathophysiology of sepsis, with the extent of microcirculatory derangement relating to disease severity and prognosis in ICU patients. However, at present microcirculatory function is not routinely monitored at the bedside. This article describes the pathophysiology of microcirculatory derangements in sepsis, methods of its measurement and evidence to support their clinical use.

Keywords

Microcirculation, sepsis, spectroscopy, near-infrared, infrared rays, microscopy, video

The microcirculation

The microcirculation comprises the smallest elements of the circulatory system, a dense network of arterioles, capillaries and venules whose diameter is less than 150 µm.[1] It is present in all organs and is integral to the global functions of the cardiovascular system, which are the supply of nutrients and oxygen for aerobic metabolism, and removal of cellular waste products. The microcirculation also plays a pivotal role in the maintenance of homeostasis throughout the body including the autoregulation of blood flow to all organ systems, and temperature regulation by control of cutaneous blood flow.

Under physiological conditions, microcirculatory flow is controlled by both systemic and local mechanisms. Systemic mechanisms that coordinate circulatory function include the autonomic nervous system, the renin-angiotensin system and the vasopressin pathway (neuro-humoral mechanisms). These act by controlling both basal tone of the cardiovascular system and circulating plasma volume, responding in changes in both to maintain homeostasis. Local mechanisms regulating microcirculatory flow describe those molecules acting directly on local vascular smooth muscle. Vasoactive molecules released directly from the endothelium include eicosanoids (prostaglandins and thromboxane), nitric oxide (NO) and endothelin, released in response to shear stress acting on vessel walls. Release of NO can be stimulated by other vasoactive peptides including ADP, bradykinin, substance P and histamine. Vasodilator metabolites, (adenosine, hydrogen ions, potassium ions, CO_2 and oxygen tensions) are also important in the local control of microcirculatory flow.

Sepsis and the microcirculation

Sepsis affects all elements of the microcirculation. It is associated with a decrease in capillary density and increased heterogeneity of perfusion caused by inappropriate vasodilatation and vasoconstriction, leading to decreased oxygen delivery, tissue hypoxia and organ dysfunction.[2] Mechanisms of microcirculatory dysfunction in sepsis include arteriolar hyporesponsiveness and capillary dysfunction, leading to extravasation of fluid protein and neutrophils.

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Mechanisms of microcirculatory dysfunction in sepsis

Nitric oxide dependent

Nitric oxide (NO) is thought to play a key role in the development of arteriolar hypo-responsiveness to vasoactive agents. Nitric oxide is generated from L-arginine via the enzyme nitric oxide synthase (NOS), of which there are three isoenzymes; nNOS (NOS1), iNOS (NOS2) and eNOS (NOS3). Vasomotor tone is maintained via continuous constitutive eNOS activity. NO binds to and activates guanylate cyclase in smooth muscle cells, catalysing the dephosphorylation of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP).

cGMP induces smooth muscle relaxation via a number of mechanisms:[3]

- Inhibition of Ca^{2+} entry in to the cell and decrease in intracellular Ca^{2+} concentration via Ca^{2+} ATPase.
- Activation of cell membrane K^{+} channels leading to hyperpolarisation and vascular smooth muscle relaxation.
- Upregulation of cGMP-dependent protein kinases.

In sepsis, the inducible isoenzyme (iNOS) is activated by various cytokines and endotoxin via a calcium-independent process, generating large amounts of NO.[4] This leads to arteriolar vasodilatation and micro/macrocirculatory dysfunction.

Capillary surface area

Capillary surface area and diffusion distances are major determinants of oxygen flux into cells. Under physiological conditions, in response to increasing oxygen demand, blood flow in capillaries becomes homogenous and plentiful, providing a significant safety margin against tissue hypoxia. In sepsis, however, capillary density is decreased and heterogeneous because of occlusion from non-deformable erythrocytes, neutrophil adhesion and a procoagulant state,[4] leading to tissue hypoxia.

Reactive oxygen species

Production of ATP via the electron transport chain (oxidative phosphorylation) leads to the physiological generation of reactive oxygen species (ROS), including superoxide. Reactive oxygen species act as strong oxidising agents, reacting readily with other molecules leading to oxidative damage. Their activity is normally tightly regulated by the antioxidant protective mechanisms; however, sepsis causes an imbalance between generation and inactivation leading to accumulation of ROS, a process known as oxidative stress.[5] Superoxide reacts with NO to form peroxynitrite, which is thought to be responsible for many of the microcirculatory abnormalities associated with sepsis,[6] including endothelial dysfunction and capillary/venular fluid and protein leak.

The importance of microcirculatory assessment in sepsis

Several studies have demonstrated that: (a) improvements in the microcirculatory function in sepsis after early resuscitation are associated with a decreased incidence of organ dysfunction[7] and (b) persistent microcirculatory dysfunction after resuscitation is associated with worse outcomes.[8,9] However, the microcirculation is difficult to monitor in practice and so current resuscitation goals rely on the monitoring and restoration of macro-haemodynamic values (such as systemic arterial pressure, cardiac output, heart rate), along with restoration of organ perfusion (inferred from normalisation of serum lactate and $ScVO_2$).[10] Moreover, restoration of macro-haemodynamic variables such as arterial pressure, especially with vasoactive agents such as noradrenaline, does not guarantee improvements in microcirculatory flow; in fact, noradrenaline can inhibit microcirculatory function irrespective of the presence of hypotension.[11]

Assessment of the microcirculation

Currently, there are no well-established means of detecting and monitoring microcirculatory dysfunction in clinical practice; available methods can be divided into indirect, direct and dynamic techniques (Table 1).

Indirect measures

Indirect measures can be broadly defined as those which assess tissue oxygenation as a surrogate for microcirculatory function and include SvO_2,

Table 1. Methods of microcirculatory assessment.

Indirect methods
Measuring elements of tissue oxygenation
Transcutaneous tissue PO_2
SvO_2
Tissue CO_2 (gastric tonometry, transcutaneous CO_2)
Lactate physiology
Near-infrared spectroscopy (NIRS)
Direct methods
Measuring microcirculatory perfusion
Laser Doppler
Videomicroscopic techniques
Orthogonal polarisation spectral (OPS) imaging
Sidestream dark-field (SDF) imaging
Incident dark-field (IDF) imaging – CytoCam
Dynamic methods
Vascular occlusion tests (VOT)

transcutaneous PO_2, tissue CO_2 (gastric tonometry and transcutaneous CO_2 – not discussed further here), near-infrared spectroscopy and measures of cellular anaerobic metabolism such as serum lactate.

Lactate physiology as a measure of microcirculatory function

Under aerobic conditions, pyruvate is converted to acetyl coenzyme A (acetyl CoA) via the enzyme pyruvate dehydrogenase. Acetyl CoA enters Krebs cycle leading to the formation of multiple cofactors. Cofactors undergo oxidative phosphorylation, with a net generation of 36 molecules of ATP. Under *anaerobic* conditions, pyruvate is converted to lactic acid via the enzyme lactate dehydrogenase, regenerating NAD+ and allowing ongoing glycolysis and ATP generation. In aqueous solution and at physiological pH, lactic acid is almost completely dissociated in to lactate and hydrogen ions.[12]

Several studies have demonstrated the relationship between tissue hypoxia and lactate production,[13] with a sharp rise in lactate concentration when oxygen consumption becomes limited by oxygen delivery.[14] Delivery of oxygen to tissues takes place via the microcirculation and, therefore, microcirculatory dysfunction can be inferred from the hyperlactataemia that occurs with tissue hypoxia. Measurement of serum lactate is integral in the diagnosis and management of patients with sepsis, but its use as a specific measure of tissue hypoxia has problems. Serum lactate concentrations depend on the balance between production and clearance. Stimulation of aerobic glycolysis for any reason increases lactate without microcirculatory dysfunction, a process which can occur in the early phases of sepsis due to increased endogenous or exogenous catecholamine concentrations. Long-term beta-blocker therapy has been shown to decrease blood lactate levels in patients presenting with severe sepsis.[15] Decreased hepatic metabolism and decreased renal clearance will also lead to increased lactate concentrations irrespective of microcirculatory dysfunction.

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) utilises the attenuation of non-visible wavelengths of light by oxygenated and de-oxygenated haemoglobin. The near-infrared (NIR) spectrum lies between the wavelengths of 700–1000 nm (Figure 1), with the clinically utilised wavelengths between 700 and 850 nm. Unlike plethysmographic pulse oximetry, NIRS uses the attenuation of both infrared and NIR light by oxygenated and deoxygenated haemoglobin. The attenuation of light by a chromophore is proportional to its absorption coefficient and the path-length of the light, as determined by the Beer–Lambert laws[16] (Figure 2). If all other components of the law are known, then the concentration of the chromophores in question can be determined. NIR provides a non-invasive means of continually assessing tissue oxygen saturation (StO_2) and, therefore, indirectly microcirculatory function.

Bazerbashi et al.[17] demonstrated that a spot/static (single time-point) StO_2 value of <70% at presentation to the Emergency Department was associated with a 2.87 times increase in ICU admission compared to those with StO_2 of >70%. Data from our own group demonstrated that in patients presenting to the Emergency Department, spot StO_2 values did not improve following resuscitation with iv fluids in

$$A = log_{10}\frac{I_0}{I} = \varepsilon 1C$$

Figure 2. Beer–Lambert Law.
A: absorbance; I: intensity of light; ε: molar absorptivity; l: length of solution the light passes through; c: concentration of solution.

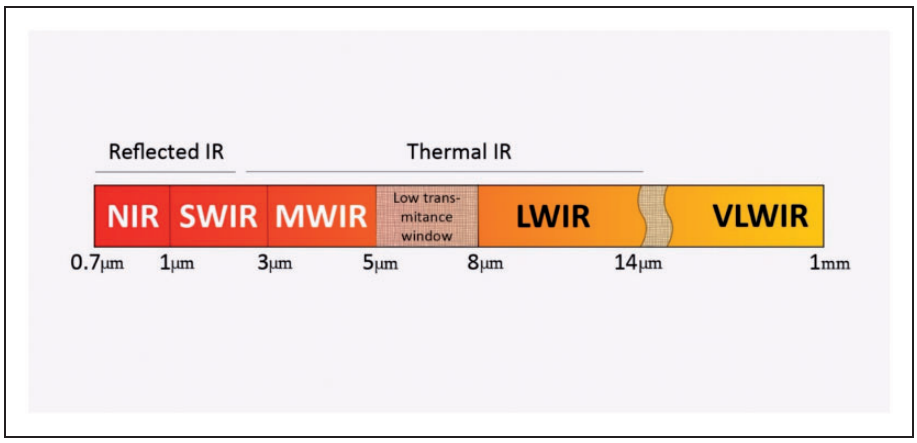

Figure 1. Infrared electromagnetic spectrum.
N: near; SW: short wave; MW: mid wave; LW: long wave; VLW: very long wave.

non-survivors, and mortality was also increased two-fold in patients with an absolute StO_2 value <75% after resuscitation.[18] Conversely, a number of studies have demonstrated an overlap in static StO_2 measurements between those patients with sepsis (of varying severity) and healthy volunteers.[19,20] Doerschug et al.[21] compared StO_2 in 24 patients with severe sepsis and 15 healthy volunteers, demonstrating similar baseline StO_2 values of 82% and 84% respectively.

Direct measures

Most direct measures of the microcirculation encompass techniques involving highly sensitive video microscopes. Video microscopic techniques provide in vivo visualisation of the microcirculation, allowing direct measurement of capillary density, perfusion and flow dynamics. Abnormalities of the microcirculation detected by video microscopy have been associated with an increased in hospital mortality in unselected ICU patients.[22] However, until recently these techniques, which included orthogonal polarisation spectral (OPS) and sidestream dark-field (SDF) imaging, have been clinically inaccessible owing to their large size, operator-dependent output and requirement for time-consuming offline analysis to generate data.

A third-generation handheld microscope has recently been developed (CytoCam-IDF, Braedius Medical, NL), utilising incident dark-field (IDF) illumination and real-time automated digital image analysis (Figure 3). Dark-field microscopy allows visualisation of the microcirculation by means of epi-illumination, without the requirement for illumination from below the tissue (as would be required in standard bright field microscopy). This new device employs a revolutionised hardware platform incorporating a high-resolution sensor displaying an image area of $1.55 \times 1.16\,mm^2$, almost twice the size of earlier devices, alongside a vastly improved resolution and a stepping motor for automatic focusing to within 2 µm of the target.[23] IDF-based microscopy has been shown to correlate well with the established techniques;[24] however, there are no data as to its usefulness as a diagnostic instrument, nor regarding what values of microcirculatory function are considered 'normal.'

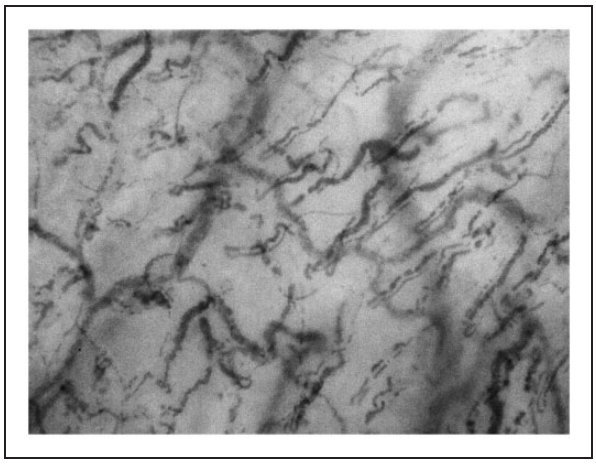

Figure 3. IDF image of the sublingual microcirculation.

Analysis of the sublingual microcirculation

A round table discussion in 2006 by experts in the field sought to clarify the features that should be included in microcirculatory analysis, concluding that assessment of the microcirculation should include measures of vascular density, assessment of capillary perfusion and a heterogeneity index[25] (in vessels of <20 µm diameter) (Table 2). In sepsis, perfused vessel density (PVD), proportion of perfused vessels (PPV), microvascular flow index (MFI), are all decreased and heterogeneity index (HI) increased, irrespective of the macro-haemodynamic condition.[26] Total capillary density appears to be unaffected by sepsis. These findings were corroborated by the International Study on Microcirculatory Shock Occurrence in Acutely Ill Patients (microSOAP).[27]

The microSOAP study is the largest trial to date investigating the significance of microcirculatory alterations in a heterogeneous ICU population (not just those with sepsis). This study found that of the 501 patients included for analysis, 86 (17%) had an abnormal MFI (defined a priori as <2.6). Of those with an abnormal MFI, the HI was increased with decreased PPV and PVD. Total vessel density was not affected. Abnormal MFI in conjunction with tachycardia was associated with an increased mortality (OR 3.24).

Dynamic methods of assessment

Along with continuous 'static' measurements of tissue oxygenation, 'dynamic' measures (although still indirect), can be obtained after brief periods of arterial occlusion by means of a blood pressure cuff inflated above systolic pressure (a vascular occlusion test (VOT)). Plotting StO_2 against time allows the derivation of desaturation, re-saturation and hyperaemic slopes, correlating to oxygen consumption (VO_2) and microvascular reactivity[28] allowing us to interrogate the function of microcirculation in more detail (Figure 4).

Specific alterations in dynamic measurements occur in patients with sepsis, the most sensitive of which appears to be the resaturation slope after a period of stagnant hypoxia. Skarda et al.[30] compared StO_2 recovery slopes in age-matched healthy volunteers to patients with severe sepsis. StO_2 recovery slope (%/second) was found to be 3.3 [0.7] in the volunteer group as compared to 2.3 [1.0] in the severe sepsis group ($p = 0.05$). A meta-analysis by Neto et al. demonstrated a decrease in the StO_2 recovery

Table 2. Microcirculatory variables.

Microcirculation variable	Information provided	Measurement
Microvascular flow index (MFI)	Perfusion quality	Image divided in to quadrants. A number is assigned to each quadrant according to predominant flow type (0 = no flow, 1 = intermittent, 2 = sluggish, 3 = continuous). The MFI results from the mean of the four values.
Total vessel density (TVD)	Vessel density	The total length of the vessels divided by the total surface area of the analysed area.
Perfused vessel density (PVD)	Functional vessel density	Total length of perfused vessels (MFI score 2/3) divided by the analysed area.
Proportional of perfused vessels (PPV)	Perfusion quality	100 * number of perfused vessels divided by the total number of vessels.
Heterogeneity index (HI)	Measure of the heterogeneity of flow between vessels.	Highest MFI – lowest MFI divided by mean MFI across all sites analysed.

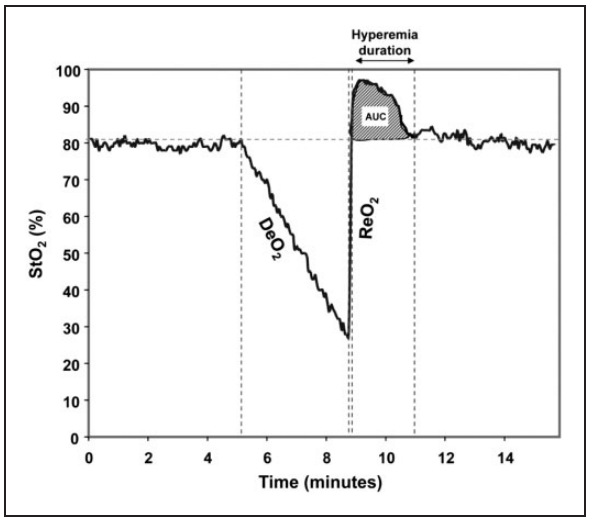

Figure 4. Desaturation and resaturation slopes after a VOT.[29]

slopes between healthy controls (245 patients), severe sepsis (160 patients) and septic shock (455 patients), these being 5.19 [2.86], 3.27 [0.71] and 2.45 [0.41] %/second, respectively ($p = 0.008$). Not only is this feature characteristic of sepsis, it correlates with outcome: the slope of the recovery phase was significantly reduced in non-survivors.[31–33]

Despite these studies providing evidence as to the usefulness of NIRS in measuring disease severity in sepsis, dynamic NIRS measurements have not yet been investigated as a potentially useful *diagnostic* tool in the early phases of sepsis. NIRS allows investigation of the microcirculation via non-invasive means, allowing potential use in patients who would otherwise be unsuitable for invasive monitoring in intensive care.

Clinical examination

Examination of the skin is done in clinical practice to evaluate the function of the microcirculation. Cool peripheries, delayed capillary refill time and skin mottling are used as indicators of reduced peripheral perfusion/circulatory failure. Mottling is an irregular patchy discolouration of the skin caused by heterogeneous blood flow and has been assessed as a potential prognostic feature in sepsis.

Two small studies by Ait-Oufella et al.[34,35] investigated skin mottling over the anterior surface of the knee in patients with a clinical diagnosis of sepsis. Mottling was a frequent clinical finding in patients with septic shock (46% and 70% in these studies), and was associated with increased mortality. Coudroy et al.[36] performed a prospective observational study of this clinical finding in intensive care patients: those with septic shock and mottling had an almost four-fold increase in ICU mortality. However, the assessment of mottling in these studies was entirely subjective and not investigated before admission to ICU. Mottling cannot always be seen in patients with darker skin pigmentation.

Skin temperature

Microcirculatory function is important in the maintenance and regulation of body temperature, with skin blood flow varying from 1 to 150 mL.100g^{-1}.min^{-1}, via local and systemic neurohumoral mechanisms.[37] Microcirculatory dysfunction with loss of autoregulation can lead to core body temperature derangements during sepsis. Therefore, measurement of skin temperature may be a useful means of non-invasively assessing microcirculatory function, with infrared thermal imaging a potential method of quantifying this.

The potential role of infrared thermal imaging

Infrared thermal imaging describes the acquisition of passively emitted infrared radiation and its pictorial representation as an infrared image. Images are colour-coded to represent the relative intensity of radiated energy and therefore temperature according

to the Stefan–Boltzmann laws. Thermal imaging provides a highly accurate (<0.02°C between pixels), two dimensional and non-contact means of demonstrating temperature distribution. Thermal imaging has been used in various areas of medicine including the diagnosis of breast cancer and a variety of rheumatological conditions, but there is little published evidence of its use in septic illness despite an obvious potential to monitor the cutaneous microcirculation. The sensitivity in thermal imaging cameras may allow quantification of cutaneous temperature gradients (and therefore the underlying microcirculation) before this becomes apparent clinically. This includes the ability to detect 'thermal mottling' before it is apparent to the clinician's naked eye.

Summary

Microcirculatory derangement is common in patients with sepsis and cannot necessarily be predicted from macro-haemodynamic values. Improvement in macro-haemodynamic values in the critically ill does not imply improvement in microcirculatory flow and patients whose microcirculation fails to improve following resuscitation are at increased risk of mortality. Detection of microcirculatory dysfunction may aid diagnosis and risk stratification in patients with sepsis; restoration of the function of the microcirculation may be a useful therapeutic target for resuscitation but further data are needed.

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