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REVIEW

Daniel De Backer
Gustavo Ospina-Tascon
Diamantino Salgado
Raphaël Favory
Jacques Creteur
Jean-Louis Vincent

Monitoring the microcirculation in the critically ill patient: current methods and future approaches

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D. De Backer (✉) · G. Ospina-Tascon · D. Salgado · R. Favory · J. Creteur · J.-L. Vincent
Department of Intensive Care,
Erasme University Hospital,
Université Libre de Bruxelles,
Route de Lennik 808,
1070 Brussels, Belgium
e-mail: ddebacke@ulb.ac.be
Tel.: +32-2-5553380
Fax: +32-2-5554698

Abstract *Purpose:* To discuss the techniques currently available to evaluate the microcirculation in critically ill patients. In addition, the most clinically relevant microcirculatory alterations will be discussed. *Methods:* Review of the literature on methods used to evaluate the microcirculation in humans and on microcirculatory alterations in critically ill patients. *Results:* In experimental conditions, shock states have been shown to be associated with a decrease in perfused capillary density and an increase in the heterogeneity of microcirculatory perfusion, with non-perfused capillaries in close vicinity to perfused capillaries. Techniques used to evaluate the microcirculation in humans should take into account the heterogeneity of microvascular perfusion. Microvideoscopic techniques, such as orthogonal polarization spectral (OPS) and sidestream dark field (SDF) imaging, directly evaluate microvascular networks covered by a thin epithelium, such as the sublingual microcirculation. Laser Doppler and tissue O_2 measurements satisfactorily detect global decreases in tissue perfusion but not heterogeneity of microvascular perfusion. These techniques, and in particular laser Doppler and near-infrared spectroscopy, may help to evaluate the dynamic response of the microcirculation to a stress test. In patients with severe sepsis and septic shock, the microcirculation is characterized by a decrease in capillary density and in the proportion of perfused capillaries, together with a blunted response to a vascular occlusion test. *Conclusions:* The microcirculation in humans can be evaluated directly by videomicroscopy (OPS/SDF) or indirectly by vascular occlusion tests. Of note, direct videomicroscopic visualization evaluates the actual state of the microcirculation, whereas the vascular occlusion test evaluates microvascular reserve.

Keywords Microcirculation · Cardiac output · Hemodynamic monitoring · Capillaries · Oxygen delivery · Outcome

Introduction

The microcirculation plays a fundamental role in gas and nutrient exchange; it must constantly adapt by controlling vascular tone. In disease states, increased permeability may be necessary to provide the inflammatory response, including leukocyte diapedesis. It is difficult to simultaneously evaluate these different aspects of the microcirculation. In this review, we will focus on the role of the microcirculation in oxygenation, dealing with the evaluation of blood flow and its implication for cellular oxygenation.

In experimental conditions, intravital microscopy is considered as a gold standard, allowing measurement of blood flow in individual vessels and could be coupled with measurements of oxygenation, endothelial activation (including generation of reactive oxygen species), and permeability measurements. Unfortunately, this technique is not applicable as such in humans, as it can only be applied on organs that can be submitted to transillumination, with light coming from the opposite side to the microscope objective, such as cremaster muscle, liver edge, intestine, and dorsal skinfold. It also uses specific dyes that are often not registered for human use.

In humans, and especially in critically ill patients, the evaluation of the microcirculation has long been difficult. Recent years have witnessed the development of new techniques that can either directly visualize or indirectly evaluate microvascular perfusion. In order to appreciate the information provided by the various techniques, it is important to understand the architecture of the microcirculation and its behavior in health and disease.

Characteristics of the normal and the diseased microcirculation

The microcirculation comprises vessels smaller than 100 microns, i.e., arterioles, capillaries, and venules. Arterioles divide into small branches, and the terminology of A1, A2-An is used to define each vessel before bifurcation (1st bifurcation for A1, 2nd for A2,…). Arterioles are mostly responsible for vascular tone, with a considerable decrease in blood pressure from proximal to terminal arterioles. Local modulation of arteriolar tone in first-order arterioles is responsible for adapting microvascular perfusion to local O_2 demand [1]. Capillaries originate from the terminal arterioles, are covered by a thin endothelial surface, and are mostly responsible for O_2 and nutrient exchange, as well as elimination of cellular waste products. Capillary networks vary in density and architecture. Capillary architecture differs somewhat among organs, with arborescence being the most common form, but the gut, liver, and kidney have different architecture. In general, arterioles divide into smaller and smaller vessels until the capillaries, and these never merge. The length and orientation of the capillaries may vary from one organ to another. Capillaries flow into small venules which merge into larger ones, and contact between venules and arterioles/capillaries is limited. In some organs, the specific architecture may favor countercurrent exchange mechanisms [2]. Leukocyte adhesion, rolling, and migration, as well as permeability changes take place mostly in venules, although again there may be some variability among organs [3]. Although arterioles are responsible for fine tuning microcirculatory perfusion, events occurring at capillary and even venular sites may affect capillary perfusion as cross-talk occurs within endothelial cells [1, 4].

Typical microcirculatory alterations in disease states

Numerous experimental studies have reported that microvascular blood flow is altered in sepsis. Shortly after endotoxin administration, functional capillary density (FCD) is decreased, and this effect is directly dose-dependent [5]. This decrease in FCD is associated with an increase in the diffusion distance for O_2 [6]. As the shutdown of capillaries is heterogeneous, some areas become deprived of capillaries while others are not, so that perfused capillaries are in close vicinity to non-perfused capillaries [7, 8].

Low-flow conditions such as hemorrhage or cardiogenic shock are associated with a progressive decrease in arteriolar diameter [9], associated with a substantial decrease in FCD [10] as a result of shutting down some capillaries while others remain perfused with reduced flow. The severity of the decrease in FCD is directly related to a poor outcome [10]. When global flow returns, the microcirculation becomes more heterogeneous as a result of the inflammatory response associated with reperfusion [10].

What are the consequences of the heterogeneity of microvascular perfusion?

In normal circumstances, heterogeneity is minimal [11], and matching of perfusion to metabolism improves in hypoxic or low-flow conditions [7, 12]. In sepsis, heterogeneity cannot be improved in response to changes in O_2 demand or to decreases in O_2 delivery [7], and tissue perfusion and oxygenation are, therefore, compromised [13]. Similar findings can be observed in reperfusion injury [11, 14].

Heterogeneity of the microvascular perfusion is associated with heterogeneity in O_2 diffusion distance, with a shift to higher median values [6]. As a result, an O_2 extraction defect is observed, with an increased mixed venous O_2 saturation (SvO_2) [7, 8], even though O_2 extraction in a single perfused capillary may be increased [15]. Importantly, tissues tolerate better a homogeneous decrease in blood flow better than a heterogeneous one [16]. As shown in a theoretical example in Fig. 1, a 50% decrease in flow in a homogeneously perfused tissue is accompanied by preserved tissue O_2 consumption, as a result of increased O_2 extraction. A 50% reduction in capillary density, resulting in heterogeneous perfusion, is associated with a reduction in tissue O_2 consumption (and hence tissue hypoxia) as a result of increased diffusion distance. In these conditions, venous PO_2/SO_2 will

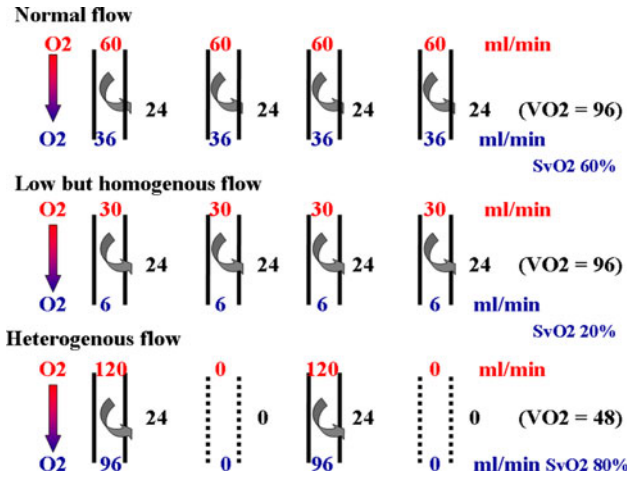

Fig. 1 Impact of heterogenous perfusion on tissue metabolism and venous oxygen saturation. Normal situation (*top panel*): O_2 is delivered at 240 ml/min in four perfused capillaries. The tissues extract oxygen to meet cellular oxygen consumption. Low flow but homogeneous perfusion (*middle panel*): half the oxygen is delivered to the tissue but all the capillaries are perfused. The amount of oxygen is sufficient to meet oxygen requirement of the cells. Hence, VO_2 is preserved even though venous oxygen saturation is severely decreased. Heterogeneous flow (*bottom panel*): even though total oxygen delivery is preserved (240 ml/min) only 50% of the capillaries are perfused. Cells close to the perfused capillaries consume the normal amount of oxygen. Cell too far away from perfused capillaries do not receive enough oxygen to meet their oxygen requirements and become hypoxic. As a consequence, hypoxic zones can be encountered in the presence of an elevated venous oxygen saturation. Note: this schematic presentation is simplified. In normal conditions, recruitment of microcirculation is not maximal and a mild degree of heterogeneity can be observed. In response to systemic low flow, such as illustrated in *middle panel*, the microcirculation tends to adapt by recruiting previously unfilled capillaries and decreasing perfusion heterogeneity [13, 118]. When endothelial dysfunction occurs and heterogeneity develops, such as in *bottom panel*, these adaptive mechanisms are lost. In addition to these, tissues try to limit the impact of decreases in perfusion by decreasing metabolism, which leads to a decrease in O_2 consumption (concept of oxygen conformance [119])

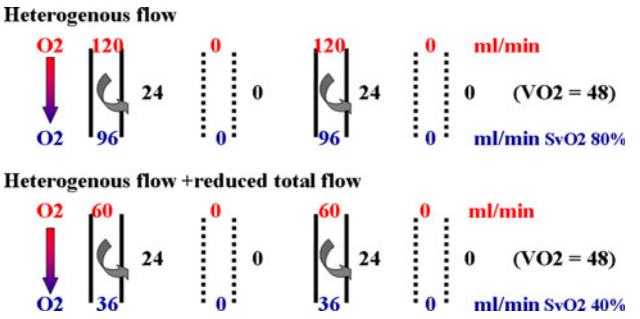

Fig. 2 Venous O_2 saturation can be low in conditions associated with microvascular shunting. When perfusion is heterogeneous, a low venous oxygen saturation can also be encountered. If total flow to the tissue is decreased (*bottom panel*), venous oxygen saturation decreases but this fails to reflect an improvement in perfusion heterogeneity

increase; this explains the typically high SvO_2 in sepsis. Nevertheless, SvO_2 can still decrease in sepsis [17]: as illustrated in Fig. 2, if blood flow decreases by 50% without further altering heterogeneity, SvO_2 will decrease as a result of the increase in extraction in perfused capillaries.

The heterogeneity of tissue perfusion may not be revealed by all methods used to evaluate the microcirculation: these techniques should have a sufficient spatial resolution to detect heterogeneity in blood flow or in PO_2.

Techniques used to evaluate the microcirculation

The evaluation of the microcirculation can include assessment of its transport and exchange functions, permeability, and regulation of inflammation and coagulation. In this manuscript we will focus on the transport and exchange functions. The latter can be assessed by using markers of microvascular perfusion and indirectly by indices of tissue oxygenation (Table 1).

By definition, any device looking at the microcirculation can only evaluate the microcirculation in the microvascular bed in which it is implemented. The ability of that specific window to represent other beds depends on the mechanisms implicated in microvascular disease (generalized, diffuse but somewhat heterogeneous or localized), on organ microvascular architecture, and on local factors (local vasoconstriction/pressure). Some areas may be more relevant than others, as illustrated by a relationship with microcirculatory alterations in that area with outcome. Nevertheless one should, at best, consider that the area being investigated is a window that reflects the minimal alterations that are likely to be observed in other areas, provided that local factors do not exacerbate the lesion in the investigated area.

Evaluation of microvascular perfusion

Clinical evaluation and biomarkers

An impaired microcirculation may be suspected in the presence of mottled skin, acrocyanosis, slow recoloration time, or increased central to toe temperature gradient [18, 19]. These signs of impaired cutaneous perfusion lack specificity (and even sensitivity) for disclosing more central microcirculatory alterations, including the sublingual microcirculation [19]. Skin vasoconstriction is a physiological response to low cardiac output, in an attempt to redistribute blood flow to more central compartments. Accordingly, it is fair to say that these clinical signs indicate the severity of cardiovascular impairment [18] and are, therefore, associated with a poor outcome

Table 1 Techniques used to evaluate the microcirculation at the bedside

	Variable measured	Main limitations
Techniques measuring microvascular perfusion		
Laser Doppler	Flow (relative), hemoglobin content/ microvascular reactivity test	Global flow to relatively large sampling volume (mixture of arterioles, capillaries, and venules)
Nailfold videomicroscopy	Vascular density, heterogeneity, flow	Restricted to fingers/sensitivity to temperature and vasoconstriction
OPS and SDF	Vascular density, perfusion heterogeneity, flow	Mostly restricted to semiquantitative scoring/limited sites to investigate/ movement and pressure artifacts
Techniques measuring tissue oxygenation		
SvO_2	Adequacy of perfusion to flow	Global measurement
O_2 electrodes	Tissue PO_2	Global measurement in sampled volume (mixture of arterioles, capillaries, and venules)
NIRS	Tissue O_2 saturation	Global measurement in sampled volume (mixture of arterioles, capillaries, and venules)
Reflectance spectroscopy	O_2 saturation/microvascular reactivity test	Global measurement in sampled volume (mixture of arterioles, capillaries, and venules) unless SO_2 histograms are provided
Gastric tonometry	Tissue CO_2 (reflects inadequate perfusion and/or anaerobic metabolism)	Interference (feeding/reflux)/difficult discrimination between low flow and anaerobic metabolism
Sublingual capnometry	Tissue CO_2 (reflects inadequate perfusion and/or anaerobic metabolism)	Availability limited/difficult discrimination between low flow and anaerobic metabolism
Microdialysis and equilibrium dialysis	Lactate/pyruvate	Time lag/limited sites to investigate

OPS orthogonal polarization spectral imaging technique; *SDF* sidestream dark field imaging technique; *SvO_2* mixed-venous oxygen saturation; *NIRS* near-infrared spectroscopy; *EMPHO* Erlangen MicroPHOtometer

[20], but they do not provide relevant information on the central microcirculation [19].

Biological markers can also be used. Blood lactate levels may be considered, but they lack sensitivity and specificity. Nevertheless, several trials have shown that therapeutic interventions inducing improvement in microvascular perfusion are associated with an inverse and proportional decrease in lactate levels [21, 22].

In experimental conditions, increased plasma hyaluronan levels were associated with impaired microcirculation in sepsis and therapies that improved the microcirculation also caused a decrease in hyaluronan levels [23]. Whether these levels can be used to detect microvascular alterations in critically ill patients remains to be determined.

Laser Doppler flowmetry

Laser Doppler techniques are frequently used to measure microvascular blood flow. They can be applied on various tissues and probes can even be inserted in the upper digestive tract through a nasogastric tube [24]. As laser Doppler techniques provide measurements of blood flow in relative units (mV), one can only assess relative changes from baseline. The main limitation of this technique is that it measures flow in a variable volume of tissue and it is unable to detect it in individual vessels. The sampling volume of current laser Doppler devices is between 0.5 and 1 mm^3, so that the flow that is measured represents the average flow in at least 50 vessels, including arterioles, capillaries, and venules of variable size, direction, and perfusion. Given the heterogeneous aspect of microvascular alterations, these will be missed by these devices that measure only total blood flow to a piece of tissue.

Scanning laser Doppler and reflected-mode confocal laser scanning microscopy are two attractive developments as they can both visualize the field of interest, allowing semiquantitative evaluation of heterogeneity of perfusion [25, 26]. As with traditional laser Doppler techniques, the resolution of the beam is crucial, the confocal aspect allowing narrowing of the laser beam. With a confocal technique, measurements of vascular density, diameters, and blood flow can be obtained [26, 27]. As a result of the size of the device, it can currently only be applied in humans to study skin perfusion.

Laser Doppler devices allow a vasoreactivity test, based on the fact that after transient ischemia obtained by arterial occlusion with a cuff placed around the arm the speed of flow recovery will mostly be determined by the capacity of the microvasculature to recruit arterioles and capillaries. The ascending slope after transient occlusion

is a marker of endothelial reactivity and blood rheology, and can thus be used as a surrogate for the functional integrity of the microvasculature [28]. Although it may not reflect the actual state of the microcirculation, this test provides quantitative information on microvascular reserve within a couple of minutes.

Microvideoscopic techniques

Intravital microvideoscopy is used as a "classical" technique in experimental conditions, but in humans fixed tissue preparations and dyes cannot be used. Microvideoscopy techniques apply light on superficial organs and need technical devices to discard light reflected by the superficial layers of the tissues. Their application in humans requires that either the organ is thin enough to be illuminated from behind (e.g., fingers) or that organs can be made translucent by reflected light.

Nailfold videocapillaroscopy

Nailfold microvideoscopy was the first method used at the bedside [29]. The junction between cuticle and nail is coated with transparent oil and placed on the stage of an ordinary microscope. In addition to morphological abnormalities, mostly encountered in chronic diseases of the microcirculation, capillary density and microvascular blood flow can be measured [30]. This technique is particularly suitable for investigating the microvascular effects of chronic diseases, such as diabetes, vasculitis, and arteritis. Unfortunately, the nailfold area is very sensitive to changes in temperature: one can control ambient but not body temperature. Peripheral vasoconstriction can also occur during chills and acute circulatory failure with or without vasopressor agents. Hence, this area is of limited use in critically ill patients.

Orthogonal polarization spectral and sidestream darkfield imaging techniques

Orthogonal polarization spectral (OPS) and sidestream darkfield (SDF) are two videomicroscopic imaging techniques that can be applied at the bedside. Both are based on the same general principles developed more than 20 years ago [31, 32], but were only recently implemented in handheld devices. If one applies a light source on a tissue, the light is reflected by the deeper layers of the tissue providing transillumination of the superficial layers of the tissue [32]. With both techniques, the selected wavelength (530 nm) is absorbed by the hemoglobin contained in the red blood cells, independently of its oxygenation state, so that these can be seen as black/gray bodies. In OPS (Fig. 3), the applied light is polarized

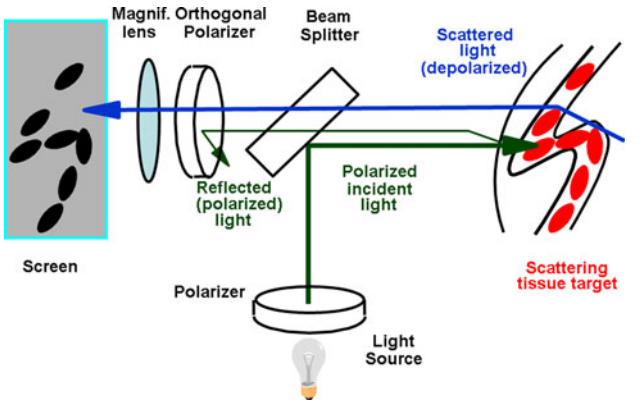

Fig. 3 Orthogonal polarization spectral (OPS) imaging technique. Polarized light is directed to the tissue. Light reflected by the superficial layers is still polarized and discarded by the orthogonal filter. Light reflected from the depth of the tissues has encountered many scattering events and has lost its polarized characteristics so is not discarded by the orthogonal filter; this light is absorbed by hemoglobin contained in red blood cells so that these will be seen as gray/black bodies on the screen

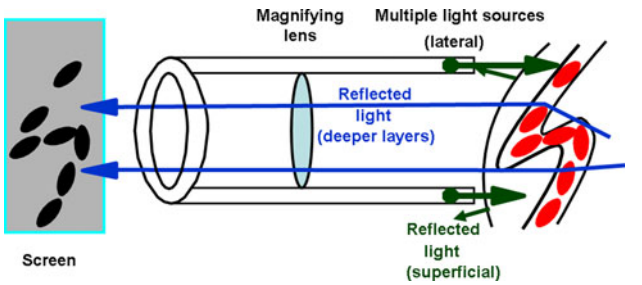

Fig. 4 Sidestream dark field (SDF) imaging technique. Green light is provided by the lateral sides of the device. Light reflected by superficial layers fails to reach the center of the device where the optics are located. Light reflected from the depth of the tissues reaches the center of the device; this light is absorbed by hemoglobin contained in red blood cells so that these will be seen as gray/black bodies on the screen

and the reflected light is depolarized, due to multiple hits on cells in the deep layers of the tissue [33]. The light reflected by the surface of the tissue is still polarized and can easily be discarded by a polarizer filter [33]. The SDF technique (Fig. 4) uses pulsed green light which is provided to the tissue by multiple peripheral emitting diodes while the optics are located centrally [34]. As a result of the isolation of the light source from the inner lenses, the light reflected by the superficial layers is perpendicular to the light source and does not reach the optics. Both devices provide good quality images of microvascular vessels filled with red blood cells. As a result of the peripheral location of multiple stroboscopic diodes and synchronization of light emission and camera frame rate, SDF provides more detailed visualization of capillaries, with sharper and less granular images than OPS [34]. Using the ×5 objective, the on-screen magnification is

×340 for OPS and ×380 for SDF. Importantly, the vascular wall cannot be visualized so that vessels can only be detected if they contain red blood cells. In addition, red blood cells that are not contained in vessels can impair visualization of microvessels. OPS and SDF have been validated against intravital videomicroscopy [35–37] or nailfold capillaroscopy [38]. They can be used at wide ranges of hematocrit [35].

These techniques can be used only on organs covered by a thin epithelial layer. In animals or in patients during surgery, they have been used to evaluate the microcirculation of several organs including the brain [39], lungs [40], tongue [41–44], liver [45, 46], and gut [41–44, 47, 48]. In intact humans, this technique can be applied to the skin [38, 49–51], conjunctiva [52], gingiva [53], sublingual area [54–57], ileostomies or colostomies [58], and rectal mucosa [59]. In the sublingual area, which is the area that has been investigated most, capillaries and venules of variable size (resolution is 2–3 μm) can be visualized; arterioles are usually not visualized because they are located in deeper layers. Red blood cells are identified as black bodies and tissue perfusion can be characterized in individual vessels.

What can be measured with these techniques and what is important? Different variables can be measured, including vascular density, heterogeneity of perfusion, and microvascular blood flow. As mentioned above, estimation of heterogeneity of perfusion (measuring the proportion of perfused vessels, mean flow index, or heterogeneity index) together with an estimate of capillary density are the variables which are the most relevant for tissue perfusion [60]. These are usually measured using a semiquantitative analysis, which can easily be performed by experienced investigators, with excellent reliability (intra- and interobserver variabilities within 5–10% [54, 61, 62] and excellent agreement between investigators [63]). Semiquantitative analysis can even be obtained as a point of care measurement [64], but this kind of analysis has been validated only for a single score and cannot be used to assess capillary density; it should, therefore, only be used for rapid evaluation of the microcirculation. Of note, measurement of blood flow cannot be obtained with these semiquantitative scores. These techniques can be used to quantify flow in various organs. In animals, measurements of gut microvascular perfusion can be made in a similar way to measurements of the sublingual microcirculation, and it has been shown that the evolution over time during sepsis is similar in both sites [43]. However, semiquantitative measurements of gut microcirculation may be more difficult to obtain and less reproducible than measurement of sublingual microcirculation [44], probably because of the specific gut architecture.

New software for computer-assisted microcirculation assessment is currently being developed. With this software, it is usually feasible to measure vessel density and blood flow in microvessels. Unfortunately, manual intervention is still needed for vessel identification as well as for blood flow measurement [65].

Is it relevant to measure blood flow in microvessels? Measuring blood flow in selected microvessels is probably irrelevant, as an increase in flow in a single vessel may reflect improved tissue perfusion as well as an increase in shunt flow. Measuring blood flow in all visible vessels and comparing histograms of blood flow distribution is probably more relevant, but this is not yet feasible as it would take hours to obtain such measurements.

Several limitations should be acknowledged. Secretions and movement artifacts may impair image quality. In addition, movement artifacts can spuriously interrupt flow in some microvessels. Special care should be taken to prevent this. To limit movement artifacts and to decrease the risk of pressure artifacts, use of stabilization devices has been proposed [43, 66]. These are especially convenient in experimental conditions but their application in humans is still anecdotal. Sterile cover caps need to be used, but these do not impair image quality. Finally, the investigation of the sublingual area is only feasible in sedated or cooperative patients. It is also impossible to evaluate the sublingual microcirculation in hypoxemic patients who are being treated with non-invasive mechanical ventilation.

Evaluation of tissue oxygenation (SvO_2/NIRS/PO_2 electrodes/reflectance spectroscopy)

Measurements of O_2 tension or saturation in a piece of tissue reflect the balance between O_2 transport and O_2 consumption in that tissue. These measurements are, therefore, influenced by flow but also by hemoglobin content, arterial PO_2, and O_2 consumption.

Venous oxygen saturation

Venous O_2 saturation is often considered as a gauge for the circulation [17, 67], but this measurement can be misleading. As illustrated in Figs. 1 and 2, venous O_2 saturation is a poor indicator of microvascular dysfunction: venous O_2 saturation can be high or low for the same degree of microvascular shunting. Several studies have shown that measuring SvO_2 does not provide much information about microvascular alterations [54, 68, 69].

PO_2 electrodes

PO_2 can be measured in tissues with Clark-type electrodes, which are made of multiple platinum wires that measure PO_2 in the surrounding tissue. These electrodes accurately measure tissue PO_2 when PO_2 is homogenously decreased

but they are not suitable in conditions of PO_2 heterogeneity, as they are sensitive to the highest PO_2 in the sampling volume. The most modern tissue PO_2 electrodes measure PO_2 on a tissue surface of 8 mm^2 over a depth of a few microns [70]. This represents a sampling volume of at least 0.5 mm^3. Such a volume includes at least 100 microvessels, including arterioles, capillaries, and venules, as well as interstitium and other cells, which all contribute to the PO_2 value.

Some investigators have used PO_2 electrodes [62, 70–73], but they are not useful to assess microvascular perfusion. They can be used to assess adequacy of perfusion and/or oxygenation in a piece of tissue, especially in low-flow conditions [72].

Reflectance spectroscopy

Reflectance spectroscopy measures tissue SO_2. Light generated with a rapidly rotating filter disk at 64 different wavelengths of 2-nm increments in the range 502–628 nm is directed through a microlight guide to the tissues. The use of different wavelengths allows SO_2 measurement due to light absorption by oxy- and deoxyhemoglobin. The resolution of the probe is very sharp (1 nm) allowing SO_2 measurements in a very small area. Nevertheless, the depth of the tissue sampled is quite large [74], so that the sampling volume is not so small. A histogram of tissue SO_2 is generated, which provides information on the heterogeneity in tissue oxygenation. Reporting only the mean value of tissue SO_2 is misleading [75, 76], and no conclusions can be drawn on the presence or absence of hypoxic areas. Initially, this technique, known under the name of Erlangen MicroPHOtometer (EMPHO), was mostly used in experimental conditions and heterogeneity of tissue oxygenation was reported in several conditions [74, 77]. Some investigators have been able to embed this technique on an endoscope, enabling measurement of human gastric SO_2 [78]. Recent developments have allowed miniaturization of the technique, making it suitable for measurement of skin and sublingual SO_2 [76], but unfortunately these new devices only provide mean SO_2.

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) is a technique that utilizes near-infrared light to measure chromophores (oxy- and deoxyhemoglobin, myoglobin, and cytochrome aa3) in tissues [79]. The fractions of oxy- and deoxyhemoglobin are used to calculate tissue O_2 saturation (StO_2). In addition, total light absorption is used to compute total tissue hemoglobin (HbT) and the absolute tissue hemoglobin index (THI), two indicators of blood volume in the region of microvasculature sensed by the probe [80]. According to Beer's law, the NIRS signal is limited to vessels that have a diameter less than 1 mm (arterioles, capillaries, and venules), but, as 75% of the blood in a skeletal muscle is venous, NIRS StO_2 measurements mostly represent local venous hemoglobin O_2 saturation. This represents the aggregate of O_2 saturations in the sampling volume and this technique is not suitable in conditions of heterogeneous blood flow. Indeed, even though StO_2 is slightly lower in septic patients compared to healthy volunteers, there is a huge overlap between the groups [81, 82]. StO_2 also differs from $ScvO_2$ saturation in sepsis [68].

The analysis of changes in StO_2 during a brief episode of forearm ischemia enables quantification of microvascular dysfunction [83–85]. This technique, which can easily be repeated [83], is particularly promising as it provides quantitative information on microvascular function within a few minutes. One should bear in mind that NIRS does not measure microcirculatory blood flow, making interpretation of the absolute StO_2 value in terms of tissue oxygenation difficult. As StO_2 represents the balance between O_2 delivery and O_2 consumption, any change in StO_2 can reflect a change in flow in the same direction and/or a change in metabolism in the opposite direction. More importantly, proportional changes in flow and metabolism may be associated with unchanged StO_2. In addition, the vasoreactivity test evaluates a different aspect of microvascular function than flow: it evaluates microvascular reserve more than actual microvascular perfusion.

NIRS-derived measurements are influenced by adipose tissue thickness as well as the presence of edema; hence, in the majority of studies, the thenar eminence has been used because the thickness of skin and adipose tissue covering this muscle is less influenced by any increase in fluid content or body mass index. The influence of temperature and vasoactive substances on NIRS-derived variables obtained in the thenar eminence need to be evaluated. Likewise, the relationship between peripheral and more central microvascular beds need to be further studied in critically ill patients.

Finally, NIRS devices vary in terms of wavelength and number of wavelengths, optode spacing, and algorithms [86]. Accordingly, the data reported with the different devices may vary somewhat and this absence of standardization may limit comparisons of results from different trials.

PCO_2-derived measurements

Tissue CO_2 represents the balance between CO_2 production and flow to the tissue. It is influenced by arterial CO_2, so that the tissue to arterial gradient, or PCO_2 gap, is usually calculated. The PCO_2 gap reflects more the adequacy of flow than the presence of tissue hypoxia, unless

very high PCO_2 gap values are reached [87, 88]. Tissue PCO_2 can be measured by electrodes inserted in tissues, probes in contact with the tissue, or tonometry. Even though the sampling volume is large, the measured value reflects the most abnormal (highest) value in the sampled volume. Hence, this measurement can detect zones of impaired perfusion and/or tissue hypoxia even when total perfusion is preserved but heterogeneous.

Gastric tonometry raised a lot of interest. A gastric PCO_2 gap above 20 mmHg discriminated survivors from non-survivors [87]. More importantly, these variables had a stronger prognostic value when systemic variables were already corrected [89]. But what does PCO_2 gap really measure? Does it reflect splanchnic, serosal, or mucosal blood flow? Even though it was initially proposed as a surrogate of splanchnic perfusion, several studies suggest that it mostly reflects gut mucosal microcirculation. In experimental conditions, there was a close relationship between mucosal PCO_2 and mucosal perfusion [41, 42, 48]. In patients with sepsis, there was no correlation between the gastric PCO_2 gap and total splanchnic perfusion [90], although changes in mucosal PCO_2 correlated with changes in mucosal perfusion [91]. The technique has now been abandoned, mostly because of technical problems. In particular, duodeno-gastric reflux and feeding can interfere with PCO_2 measurements. Sublingual and buccal PCO_2 monitoring have been developed [92, 93]. Sublingual PCO_2 is often increased in sepsis, especially in non-survivors [94–96]. Using this technique, we demonstrated that sublingual PCO_2 tracks microvascular blood flow, as the sublingual PCO_2 gap is inversely related to the proportion of perfused capillaries [97]. This technique, although attractive, is unfortunately not easily available at the present time (available for research purposes only).

Microdialysis and equilibrium dialysis

Microdialysis allows measurements of different molecules in the extracellular space. Soluble substances equilibrate through a semipermeable membrane of hollow fiber perfused at a constant rate with saline, and are recovered in the dialysate. In the equilibrium dialysis technique, a probe covered by a semipermeable membrane is used without infusing fluids, solutes slowly equilibrate through the membrane, and the content of the probe is sampled intermittently for analysis (and replaced by saline). Lactate and pyruvate can be measured; measurements of the lactate/pyruvate ratio are particularly appealing, as this variable is less sensitive to dialysate perfusion rate and problems of incomplete recovery (absence of full equilibration).

Although the sampling volume of this device is large, measurements are influenced by the most abnormal values so that it should be able to detect the consequence of tissue heterogeneity. Using this technique, several studies have shown that the lactate/pyruvate ratio may be increased in septic shock [98–100].

Importantly, measurements of the lactate/pyruvate ratio may be useful to detect the occurrence of tissue hypoxia but cannot identify whether it is because of insufficient flow or other causes of tissue hypoxia. In addition, it cannot detect alterations in microvascular perfusion before they are associated with cellular hypoxia.

Microcirculatory alterations in critically ill patients

In the following sections, we will illustrate some of the main disease states with involvement of the microcirculation. The list is far from exhaustive and microcirculatory alterations have been found in many other circumstances.

Severe sepsis and septic shock

Using the OPS technique, we [54] evaluated the sublingual microcirculation in 50 patients with severe sepsis and in a cohort of healthy volunteers and non-infected intensive care unit (ICU) controls. We observed a significant decrease in vessels density and, more importantly, a decreased proportion of perfused small vessels (<20 μm), mostly capillaries, from 90% in controls to 48% in septic patients. This decrease in the proportion of well-perfused small vessels was due to a combined increase in non-perfused and intermittently perfused vessels. In addition, the heterogeneity between areas distant by a few microns was also increased. These results are in line with experimental findings and were later confirmed by other groups of investigators [57, 101]. These alterations can be observed very early in the course of sepsis, even within a few hours of hospital admission [57, 101]. Similar alterations, of lower magnitude, can be induced by low-dose endotoxin administration in healthy volunteers [102].

Interestingly, microcirculatory alterations were more severe in non-survivors than in survivors [54, 101, 103]. More importantly these microcirculatory changes rapidly resolved in response to therapy in survivors but persisted in patients dying in acute circulatory failure or later from organ failure after recovery from shock [103]. Changes in microvascular perfusion during the first day of ICU admission are more strongly associated with outcome than changes in cardiac output, arterial pressure, or SvO_2 [103]. Trzeciak et al. [104] showed that early improvement in microvascular perfusion in response to goal-directed therapy was associated with an improvement in organ function. Even though these data strongly suggest that microcirculatory alterations are implicated in the development of organ failure, interventional studies guiding therapy at the microcirculation should be conducted to evaluate whether improving microcirculatory

alterations may be associated with an improvement in organ dysfunction.

Using a vascular occlusion test combined with NIRS measurements, several studies have shown that patients with severe sepsis frequently have profound alterations in microvascular reactivity [81, 84, 85, 105, 106] and that these alterations are associated with a high risk of organ dysfunction [105] and death [81].

Cardiogenic shock

We observed that, compared to patients with coronary artery or valvular disease who were scheduled for cardiac surgery, patients admitted to the ICU for acute decompensation of severe heart failure or cardiogenic shock had microvascular alterations, consisting of a decrease in vessel density and in the proportion of perfused capillaries [55]. These findings were later confirmed by other groups of investigators [107–110]. More severe alterations were observed in patients with higher lactate levels [110] and poor outcome [55]. These alterations could be improved by nitroglycerin [107, 108] or mechanical support such as aortic counterpulsation [109, 111] or ventricular assist devices [112].

High-risk surgery

High-risk surgery is a new area in which microcirculatory alterations have been observed. In patients submitted to high-risk non-cardiac surgery, Jhanji et al. [62] observed that the density and proportion of perfused capillaries was lower in the 14 patients who subsequently developed postoperative complications than in the 11 patients with an uneventful postoperative course. Subcutaneous tissue PO_2 and laser Doppler cutaneous blood flow did not differ between the groups, further highlighting the lack of sensitivity of these methods to detect heterogeneous perfusion. Interestingly, there was no significant difference in global O_2 delivery between the groups; it would be interesting to evaluate the impact of hemodynamic optimization on these microvascular alterations, as this approach has been shown to improve outcome in high-risk surgical patients [113]. Although the link between global hemodynamics and microvascular perfusion is quite loose, interventions aimed at improving global hemodynamics also have microvascular effects [21, 22, 114], which may be mediated by effects independent of changes in global hemodynamics. Further studies should address this issue.

Microcirculatory alterations may also occur in patients undergoing cardiac surgery. Bauer et al. [115] first reported that microcirculatory perfusion was transiently altered in humans after cardiopulmonary bypass. Similar findings were reported more recently by other groups [116, 117]. More importantly, these alterations can also be observed in patients who undergo surgery without cardiopulmonary bypass [117]; of note, the sublingual microcirculation was still slightly abnormal up to 24 h after surgery in these patients [117]. As in non-cardiac surgery, the severity of perioperative microvascular alterations correlated with peak lactate levels and severity of organ dysfunction after surgery [117].

Conclusions

Microcirculatory alterations are frequently observed in critically ill patients, and especially in patients with severe sepsis. These alterations are characterized by a decrease in capillary density and an increase in heterogeneity of perfusion with non-perfused in close vicinity to well-perfused capillaries. As a heterogeneous decrease in perfusion is less well tolerated than a homogenously decreased perfusion, the diagnostic tool used to assess the microcirculation should be able to detect heterogeneity of perfusion. This is best achieved with handheld microvideoscopic techniques, such as OPS and SDF. The use of vascular occlusion tests with laser Doppler or NIRS investigates microvascular reactivity, another important, but different, aspect of microvascular function. Combining techniques may be of interest in the future.

Guiding resuscitation with the use of these tools may allow more complete resuscitation and improve outcomes.

References

1. Beach JM, McGahren ED, Duling BR (1998) Capillaries and arterioles are electrically coupled in hamster cheek pouch. Am J Physiol 275:H1489–H1496
2. Haglund U, Rasmussen I (1993) Oxygenation of the gut mucosa. Br J Surg 80:955–956
3. Aird WC (2007) Phenotypic heterogeneity of the endothelium: II. Representative vascular beds. Circ Res 100:174–190
4. Collins DM, McCullough WT, Ellsworth ML (1998) Conducted vascular responses: communication across the capillary bed. Microvasc Res 56:43–53
5. Hangai-Hoger N, Nacharaju P, Manjula BN, Cabrales P, Tsai AG, Acharya SA, Intaglietta M (2006) Microvascular effects following treatment with polyethylene glycol-albumin in lipopolysaccharide-induced endotoxemia. Crit Care Med 34:108–117

6. Bateman RM, Tokunaga C, Kareco T, Dorscheid DR, Walley KR (2007) Myocardial hypoxia-inducible HIF-1α, VEGF and GLUT1 gene expression is associated with microvascular and ICAM-1 heterogeneity during endotoxemia. Am J Physiol Heart Circ Physiol 293:H448–H456
7. Farquhar I, Martin CM, Lam C, Potter R, Ellis CG, Sibbald WJ (1996) Decreased capillary density in vivo in bowel mucosa of rats with normotensive sepsis. J Surg Res 61:190–196
8. Goldman D, Bateman RM, Ellis CG (2006) Effect of decreased O_2 supply on skeletal muscle oxygenation and O_2 consumption during sepsis: role of heterogeneous capillary spacing and blood flow. Am J Physiol Heart Circ Physiol 290:H2277–H2285
9. Borgstrom P, Bruttig SP, Lindbom L, Intaglietta M, Arfors KE (1990) Microvascular responses in rabbit skeletal muscle after fixed volume hemorrhage. Am J Physiol 259:H190–H196
10. Kerger H, Waschke KF, Ackern KV, Tsai AG, Intaglietta M (1999) Systemic and microcirculatory effects of autologous whole blood resuscitation in severe hemorrhagic shock. Am J Physiol 276:H2035–H2043
11. Zuurbier CJ, van Iterson M, Ince C (1999) Functional heterogeneity of oxygen supply-consumption ratio in the heart. Cardiovasc Res 44:488–497
12. Stein JC, Ellis CG, Ellsworth ML (1993) Relationship between capillary and systemic venous PO2 during nonhypoxic and hypoxic ventilation. Am J Physiol 265:H537–H542
13. Humer MF, Phang PT, Friesen BP, Allards MF, Goddard CM, Walley KR (1996) Heterogeneity of gut capillary transit times and impaired gut oxygen extraction in endotoxemic pigs. J Appl Physiol 81:895–904
14. Ince C, Vink H, Wieringa PA, Giezeman M, Spaan JA (1990) Heterogeneous NADH fluorescence during post-anoxic reactive hyperemia in saline perfused rat heart. Adv Exp Med Biol 277:477–482
15. Ellis CG, Bateman RM, Sharpe MD, Sibbald WJ, Gill R (2002) Effect of a maldistribution of microvascular blood flow on capillary O_2 extraction in sepsis. Am J Physiol 282:H156–H164
16. Goldman D, Bateman RM, Ellis CG (2004) Effect of sepsis on skeletal muscle oxygen consumption and tissue oxygenation: interpreting capillary oxygen transport data using a mathematical model. Am J Physiol Heart Circ Physiol 287:H2535–H2544
17. Rivers E, Nguyen B, Havstadt S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
18. Joly HR, Weil MH (1969) Temperature of the great toe as an indication of the severity of shock. Circulation 39:131–138
19. Boerma EC, Kuiper MA, Kingma WP, Egbers PH, Gerritsen RT, Ince C (2008) Disparity between skin perfusion and sublingual microcirculatory alterations in severe sepsis and septic shock: a prospective observational study. Intensive Care Med 34:1294–1298
20. Lima A, Jansen TC, van Bommel J, Ince C, Bakker J (2009) The prognostic value of the subjective assessment of peripheral perfusion in critically ill patients. Crit Care Med 37:934–938
21. De Backer D, Creteur J, Dubois MJ, Sakr Y, koch M, Verdant C, Vincent JL (2006) The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. Crit Care Med 34:403–408
22. Ospina-Tascon G, Neves AP, Occhipinti G, Donadello K, Buchele G, Simion D, Chierego M, Oliveira Silva T, Fonseca A, Vincent JL, De Backer D (2010) Effects of fluids on microvascular perfusion in patients with severe sepsis. Intensive Care Med 36:949–955
23. Marechal X, Favory R, Joulin O, Montaigne D, Hassoun S, Decoster B, Zerimech F, Neviere R (2008) Endothelial glycocalyx damage during endotoxemia coincides with microcirculatory dysfunction and vascular oxidative stress. Shock 29:572–576
24. Duranteau J, Sitbon P, Teboul JL, Vicaut E, Anguel N, Richard C, Samii K (1999) Effects of epinephrine, norepinephrine, or the combination of norepinephrine and dobutamine on gastric mucosa in septic shock. Crit Care Med 27:893–900
25. Boyle NH, Roberts PC, Ng B, Berkenstadt H, McLuckie A, Beale RJ, Mason RC (1999) Scanning laser Doppler is a useful technique to assess foot cutaneous perfusion during femoral artery cannulation. Crit Care 3:95–100
26. Altintas MA, Altintas AA, Guggenheim M, Aust MC, Niederbichler AD, Knobloch K, Vogt PM (2010) Insight in microcirculation and histomorphology during burn shock treatment using in vivo confocal-laser-scanning microscopy. J Crit Care 25:1–7
27. Altintas MA, Altintas AA, Guggenheim M, Steiert AE, Aust MC, Niederbichler AD, Herold C, Vogt PM (2009) Insight in human skin microcirculation using in vivo reflectance-mode confocal laser scanning microscopy. J Digit Imaging. doi:10.1007/s10278-009-9219-3
28. Lamblin V, Favory R, Boulo M, Mathieu D (2006) Microcirculatory alterations induced by sedation in intensive care patients. Effects of midazolam alone and in association with sufentanil. Crit Care 10:R176
29. Fagrell B, Fronek A, Intaglietta M (1977) A microscope-television system for studying flow velocity in human skin capillaries. Am J Physiol 233:H318–H321
30. Awan ZA, Wester T, Kvernebo K (2010) Human microvascular imaging: a review of skin and tongue videomicroscopy techniques and analysing variables. Clin Physiol Funct Imaging 30:79–88
31. Sherman H, Klausner S, Cook WA (1971) Incident dark-field illumination: a new method for microcirculatory study. Angiology 22:295–303
32. Slaaf DW, Tangelder GJ, Reneman RS, Jager K, Bollinger A (1987) A versatile incident illuminator for intravital microscopy. Int J Microcirc Clin Exp 6:391–397
33. Groner W, Winkelman JW, Harris AG, Ince C, Bouma GJ, Messmer K, Nadeau RG (1999) Orthogonal polarization spectral imaging: a new method for study of the microcirculation. Nat Med 5:1209–1212
34. Goedhart P, Khalilzada M, Bezemer R, Merza J, Ince C (2007) Sidestream dark field (SDF) imaging: a novel stroboscopic LED ring-based imaging modality for clinical assessment of the microcirculation. Optics Express 15:15101–15114
35. Harris AG, Sinitsina I, Messmer K (2001) Validation of OPS imaging for microvascular measurements during isovolumic hemodilution and low hematocrits. Am J Physiol Heart Circ Physiol 282:H1502–H1509
36. Laemmel E, Tadayoni R, Sinitsina I, Boczkowski J, and Vicaut E (2000) Using orthogonal polarization spectral imaging for the experimental study of microcirculation: comparison with intravital microscopy. In: Messmer K (ed) Orthogonal polarization spectral imaging—Progress in applied microcirculation, vol 26, pp 50–60. Basel, Karger

37. Harris AG, Sinitsina I, Messmer K (2000) The Cytoscan^{TM} Model E-II, a new reflectance microscope for intravital microscopy: comparison with the standard fluorescence method. J Vasc Res 37:469–476
38. Mathura KR, Vollebregt KC, Boer K, De Graaff JC, Ubbink DT, Ince C (2001) Comparison of OPS imaging and conventional capillary microscopy to study the human microcirculation. J Appl Physiol 91:74–78
39. Pennings FA, Ince C, Bouma GJ (2006) Continuous real-time visualization of the human cerebral microcirculation during arteriovenous malformation surgery using orthogonal polarization spectral imaging. Neurosurgery 59:167–171
40. den Uil CA, Bezemer R, Miranda DR, Ince C, Lagrand WK, Hartman M, Bogers AJ, Spronk PE, Simoons ML (2009) Intra-operative assessment of human pulmonary alveoli in vivo using sidestream dark field imaging: a feasibility study. Med Sci Monit 15:137–141
41. Dubin A, Edul VS, Pozo MO, Murias G, Canullan CM, Martins EF, Ferrara G, Canales HS, Laporte M, Estenssoro E, Ince C (2008) Persistent villi hypoperfusion explains intramucosal acidosis in sheep endotoxemia. Crit Care Med 36:535–542
42. Dubin A, Pozo MO, Ferrara G, Murias G, Martins E, Canullan C, Canales HS, Kanoore Edul V, Estenssoro E, Ince C (2009) Systemic and microcirculatory responses to progressive hemorrhage. Intensive Care Med 35:556–564
43. Verdant CL, De Backer D, Bruhn A, Clausi C, Su F, Wang Z, Rodriguez H, Pries AR, Vincent JL (2009) Evaluation of sublingual and gut mucosal microcirculation in sepsis: a quantitative analysis. Crit Care Med 37:2875–2881
44. Bracht H, Krejci V, Hiltebrand L, Brandt S, Sigurdsson G, Ali SZ, Takala J, Jakob SM (2008) Orthogonal polarization spectroscopy to detect mesenteric hypoperfusion. Intensive Care Med 34:1883–1890
45. Langer S, von Dobschuetz E, Harris AG, Krombach F, Messmer K (2000) Validation of the orthogonal polarization spectral imaging technique on solid organs. In: Messmer K (ed) Orthogonal polarization spectral imaging—Progress in applied microcirculation, vol 24, pp 32–46. Basel, Karger
46. Puhl G, Schaser KD, Vollmar B, Menger MD, Settmacher U (2003) Noninvasive in vivo analysis of the human hepatic microcirculation using orthogonal polorization spectral imaging. Transplantation 75:756–761
47. Biberthaler P, Langer S, Luchting B, Khandoga A, Messmer K (2001) In vivo assessment of colon microcirculation: comparison of the new OPS imaging technique with intravital microscopy. Eur J Med Res 6:525–534
48. Tugtekin I, Radermacher P, Theisen M, Matejovic M, Stehr A, Ploner F, Matura K, Ince C, Georgieff M, Trager K (2001) Increased ileal-mucosal-arterial PCO2 gap is associated with impaired villus microcirculation in endotoxic pigs. Intensive Care Med 27:757–766
49. Lupi O, Semenovitch I, Treu C, Bouskela E (2008) Orthogonal polarization technique in the assessment of human skin microcirculation. Int J Dermatol 47:425–431
50. Genzel-Boroviczeny O, Strotgen J, Harris AG, Messmer K, Christ F (2002) Orthogonal polarization spectral imaging (OPS): a novel method to measure the microcirculation in term and preterm infants transcutaneously. Pediatr Res 51:386–391
51. Kroth J, Weidlich K, Hiedl S, Nussbaum C, Christ F, Genzel-Boroviczeny O (2008) Functional vessel density in the first month of life in preterm neonates. Pediatr Res 64:567–571
52. Schaser KD, Settmacher U, Puhl G, Zhang L, Mittlmeier T, Stover JF, Vollmar B, Menger MD, Neuhaus P, Haas NP (2003) Noninvasive analysis of conjunctival microcirculation during carotid artery surgery reveals microvascular evidence of collateral compensation and stenosis-dependent adaptation. J Vasc Surg 37:789–797
53. Lindeboom JA, Mathura KR, Harkisoen S, van den Akker HP, Ince C (2005) Effect of smoking on the gingival capillary density: assessment of gingival capillary density with orthogonal polarization spectral imaging. J Clin Periodontol 32:1208–1212
54. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL (2002) Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med 166:98–104
55. De Backer D, Creteur J, Dubois MJ, Sakr Y, Vincent JL (2004) Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. Am Heart J 147:91–99
56. Spronk PE, Ince C, Gardien MJ, Mathura KR, Oudemans-van Straaten HM, Zandstra DF (2002) Nitroglycerin in septic shock after intravascular volume resuscitation. Lancet 360:1395–1396
57. Trzeciak S, Dellinger RP, Parrillo JE, Guglielmi M, Bajaj J, Abate NL, Arnold RC, Colilla S, Zanotti S, Hollenberg SM (2007) Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. Ann Emerg Med 49:88–98
58. Boerma EC, van der Voort PH, Spronk PE, Ince C (2007) Relationship between sublingual and intestinal microcirculatory perfusion in patients with abdominal sepsis. Crit Care Med 35:1055–1060
59. Dondorp AM, Ince C, Charunwatthana P, Hanson J, van Kuijen A, Faiz MA, Rahman MR, Hasan M, Bin YE, Ghose A, Ruangveerayut R, Limmathurotsakul D, Mathura K, White NJ, Day NP (2008) Direct in vivo assessment of microcirculatory dysfunction in severe falciparum malaria. J Infect Dis 197:79–84
60. De Backer D, Hollenberg S, Boerma C, Goedhart P, Buchele G, Ospina-Tascon G, Dobbe I, Ince C (2007) How to evaluate the microcirculation: report of a round table conference. Crit Care 11:R101
61. Buchele GL, Silva E, Ospina-Tascon G, Vincent JL, De Backer D (2009) Effects of hydrocortisone on microcirculatory alterations in patients with septic shock. Crit Care Med 37:1341–1347
62. Jhanji S, Lee C, Watson D, Hinds C, Pearse RM (2009) Microvascular flow and tissue oxygenation after major abdominal surgery: association with post-operative complications. Intensive Care Med 35:671–677
63. Boerma EC, Mathura KR, van der Voort PH, Spronk PE, Ince C (2005) Quantifying bedside-derived imaging of microcirculatory abnormalities in septic patients: a prospective validation study. Crit Care 9:R601–R606
64. Arnold RC, Parrillo JE, Phillip DR, Chansky ME, Shapiro NI, Lundy DJ, Trzeciak S, Hollenberg SM (2009) Point-of-care assessment of microvascular blood flow in critically ill patients. Intensive Care Med 35:1761–1766
65. Salgado DR, Favory R, Creteur J, Vincent JL, De Backer D (2009) Automate microcirculation analysis still requires a human intervention. Intensive Care Med 35:S27 (abstract)
66. Lindert J, Werner J, Redlin M, Kuppe H, Habazettl H, Pries AR (2002) OPS imaging of human microcirculation: a short technical report. J Vasc Res 39:368–372

67. Pinsky MR, Vincent JL (2005) Let us use the pulmonary artery catheter correctly and only when we need it. Crit Care Med 33:1119–1122
68. Podbregar M, Mozina H (2007) Skeletal muscle oxygen saturation does not estimate mixed venous oxygen saturation in patients with severe left heart failure and additional severe sepsis or septic shock. Crit Care 11:R6
69. Marik PE, Bankov A (2003) Sublingual capnometry versus traditional markers of tissue oxygenation in critically ill patients. Crit Care Med 31:818–822
70. Dyson A, Stidwill R, Taylor V, Singer M (2009) The impact of inspired oxygen concentration on tissue oxygenation during progressive haemorrhage. Intensive Care Med 35:1783–1791
71. VanderMeer TJ, Wang H, Fink MP (1995) Endotoxemia causes ileal mucosal acidosis in the absence of mucosal hypoxia in a normodynamic porcine model of septic shock. Crit Care Med 23:1217–1225
72. Dyson A, Stidwill R, Taylor V, Singer M (2007) Tissue oxygen monitoring in rodent models of shock. Am J Physiol Heart Circ Physiol 293:H526–H533
73. Jhanji S, Stirling S, Patel N, Hinds CJ, Pearse RM (2009) The effect of increasing doses of norepinephrine on tissue oxygenation and microvascular flow in patients with septic shock. Crit Care Med 37:1961–1966
74. Schwarz B, Hofstotter H, Salak N, Pajk W, Knotzer H, Mayr A, Labeck B, Kafka R, Ulmer H, Hasibeder W (2001) Effects of norepinephrine and phenylephrine on intestinal oxygen supply and mucosal tissue oxygen tension. Intensive Care Med 27:593–601
75. Albuszies G, Radermacher P, Vogt J, Wachter U, Weber S, Schoaff M, Georgieff M, Barth E (2005) Effect of increased cardiac output on hepatic and intestinal microcirculatory blood flow, oxygenation, and metabolism in hyperdynamic murine septic shock. Crit Care Med 33:2332–2338
76. Sakr Y, Gath V, Oishi J, Klinzing S, Simon TP, Reinhart K, Marx G (2010) Characterization of buccal microvascular response in patients with septic shock. Eur J Anaesthesiol 27:388–394
77. Vollmar B, Rüttinger D, Menger MD (1997) Monitoring of microvascular hemoglobin oxygenation in liver and skeletal muscle tissue of endotoxin-exposed rats using reflection spectrophotometry. Adv Exp Med Biol 428:397–402
78. Temmesfeld-Wollbrück B, Szalay A, Mayer K, Olschewski H, Seeger W, Grimminger F (1998) Abnormalities of gastric mucosal oxygenation in septic shock. Am J Respir Crit Care Med 157:1586–1592
79. Jobsis FF (1977) Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 198:1264–1267
80. Myers DE, Anderson LD, Seifert RP, Ortner JP, Cooper CE, Beilman GJ, Mowlem JD (2005) Noninvasive method for measuring local hemoglobin oxygen saturation in tissue using wide gap second derivative near-infrared spectroscopy. J Biomed Opt 10:034017
81. Creteur J, Carollo T, Soldati G, Buchele G, De Backer D, Vincent JL (2007) The prognostic value of muscle StO_2 in septic patients. Intensive Care Med 33:1549–1556
82. Mulier KE, Skarda DE, Taylor JH, Myers DE, McGraw MK, Gallea BL, Beilman GJ (2008) Near-infrared spectroscopy in patients with severe sepsis: correlation with invasive hemodynamic measurements. Surg Infect (Larchmt) 9:515–519
83. Gomez H, Torres A, Polanco P, Kim HK, Zenker S, Puyana JC, Pinsky MR (2008) Use of non-invasive NIRS during a vascular occlusion test to assess dynamic tissue O_2 saturation response. Intensive Care Med 34:1600–1607
84. Pareznik R, Knezevic R, Voga G, Podbregar M (2006) Changes in muscle tissue oxygenation during stagnant ischemia in septic patients. Intensive Care Med 32:87–92
85. De Blasi RA, Palmisani S, Alampi D, Mercieri M, Romano R, Collini S, Pinto G (2005) Microvascular dysfunction and skeletal muscle oxygenation assessed by phase-modulation near-infrared spectroscopy in patients with septic shock. Intensive Care Med 31:1661–1668
86. Boushel R, Piantadosi CA (2000) Near-infrared spectroscopy for monitoring muscle oxygenation. Acta Physiol Scand 168:615–622
87. Levy B, Gawalkiewicz P, Vallet B, Briancon S, Nace L, Bollaert PE (2003) Gastric capnometry with air-automated tonometry predicts outcome in critically ill patients. Crit Care Med 31:474–480
88. Schlichtig R, Bowles SA (1994) Distinguishing between aerobic and anaerobic appearance of dissolved CO2 in intestine during low flow. J Appl Physiol 76:2443–2451
89. Poeze M, Solberg BC, Greve JW, Ramsay G (2005) Monitoring global volume-related hemodynamic or regional variables after initial resuscitation: what is a better predictor of outcome in critically ill septic patients? Crit Care Med 33:2494–2500
90. Creteur J, De Backer D, Vincent JL (1999) Does gastric tonometry monitor splanchnic perfusion? Crit Care Med 27:2480–2484
91. Nevière R, Mathieu D, Chagnon JL, Lebleu N, Wattel F (1996) The contrasting effects of dobutamine and dopamine on gastric mucosal perfusion in septic patients. Am J Respir Crit Care Med 154:1684–1688
92. Weil MH, Nakagawa Y, Tang W, Sato Y, Ercoli F, Finegan R, Grayman G, Bisera J (1999) Sublingual capnometry: a new noninvasive measurement for diagnosis and quantitation of severity of circulatory shock. Crit Care Med 27:1225–1229
93. Cammarata GA, Weil MH, Castillo CJ, Fries M, Wang H, Sun S, Tang W (2009) Buccal capnometry for quantitating the severity of hemorrhagic shock. Shock 31:207–211
94. Marik PE (2001) Sublingual capnography: a clinical validation study. Chest 120:923–927
95. Baron BJ, Dutton RP, Zehtabchi S, Spanfelner J, Stavile KL, Khodorkovsky B, Nagdev A, Hahn B, Scalea TM (2007) Sublingual capnometry for rapid determination of the severity of hemorrhagic shock. J Trauma 62:120–124
96. Rackow EC, O'Neil P, Astiz ME, Carpati CM (2001) Sublingual capnometry and indexes of tissue perfusion in patients with circulatory failure. Chest 120:1633–1638
97. Creteur J, De Backer D, Sakr Y, koch M, Vincent JL (2006) Sublingual capnometry tracks microcirculatory changes in septic patients. Intensive Care Med 32:516–523
98. de Boer J, Potthoff H, Mulder PO, Dofferhoff AS, van Thiel RJ, Plijter-Groendijk H, Korf J (1994) Lactate monitoring with subcutaneous microdialysis in patients with shock: a pilot study. Circ Shock 43:57–63
99. Jorgensen VL, Nielsen SL, Espersen K, Perner A (2006) Increased colorectal permeability in patients with severe sepsis and septic shock. Intensive Care Med 32:1790–1796
100. Jorgensen VL, Reiter N, Perner A (2006) Luminal concentrations of L- and D-lactate in the rectum may relate to severity of disease and outcome in septic patients. Crit Care 10:R163

101. Spanos A, Jhanji S, Vivian-Smith A, Harris T, Pearse RM (2010) Early microvascular changes in sepsis and severe sepsis. Shock 33:387–391
102. Draisma A, Bemelmans R, van der Hoeven JG, Spronk P, Pickkers P (2009) Microcirculation and vascular reactivity during endotoxemia and endotoxin tolerance in humans. Shock 31:581–585
103. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL (2004) Persistant microvasculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med 32:1825–1831
104. Trzeciak S, McCoy JV, Phillip DR, Arnold RC, Rizzuto M, Abate NL, Shapiro NI, Parrillo JE, Hollenberg SM (2008) Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. Intensive Care Med 34:2210–2217
105. Doerschug KC, Delsing AS, Schmidt GA, Haynes WG (2007) Impairments in microvascular reactivity are related to organ failure in human sepsis. Am J Physiol Heart Circ Physiol 293:H1065–H1071
106. Skarda DE, Mulier KE, Myers DE, Taylor JH, Beilman GJ (2007) Dynamic near-infrared spectroscopy measurements in patients with severe sepsis. Shock 27:348–353
107. den Uil CA, Caliskan K, Lagrand WK, van der Ent M, Jewbali LS, van Kuijk JP, Spronk PE, Simoons ML (2009) Dose-dependent benefit of nitroglycerin on microcirculation of patients with severe heart failure. Intensive Care Med 35:1893–1899
108. den Uil CA, Lagrand WK, Spronk PE, van der Ent M, Jewbali LS, Brugts JJ, Ince C, Simoons ML (2009) Low-dose nitroglycerin improves microcirculation in hospitalized patients with acute heart failure. Eur J Heart Fail 11:386–390
109. den Uil CA, Lagrand WK, van der Ent M, Jewbali LS, Brugts JJ, Spronk PE, Simoons ML (2009) The effects of intra-aortic balloon pump support on macrocirculation and tissue microcirculation in patients with cardiogenic shock. Cardiology 114:42–46
110. Jung C, Ferrari M, Rodiger C, Fritzenwanger M, Goebel B, Lauten A, Pfeifer R, Figulla HR (2009) Evaluation of the sublingual microcirculation in cardiogenic shock. Clin Hemorheol Microcirc 42:141–148
111. Jung C, Rodiger C, Fritzenwanger M, Schumm J, Lauten A, Figulla HR, Ferrari M (2009) Acute microflow changes after stop and restart of intra-aortic balloon pump in cardiogenic shock. Clin Res Cardiol 98:469–475
112. Jung C, Ferrari M, Gradinger R, Fritzenwanger M, Pfeifer R, Schlosser M, Poerner TC, Brehm BR, Figulla HR (2008) Evaluation of the microcirculation during extracorporeal membrane-oxygenation. Clin Hemorheol Microcirc 40:311–314
113. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds M, Bennett D (2005) Early goal directed therapy following major surgery reduces complications and duration of hospital stay. A randomized, controlled trial. Crit Care 9:R687–R693
114. Pottecher J, Deruddre S, Teboul JL, Georger J, Laplace C, Benhamou D, Vicaut E, Duranteau J (2010) Both passive leg raising and intravascular volume expansion improve sublingual microcirculatory perfusion in severe sepsis and septic shock. Intensive Care Med. doi:10.1007/s00134-010-1966-6
115. Bauer A, Kofler S, Thiel M, Eifert S, Christ F (2007) Monitoring of the sublingual microcirculation in cardiac surgery using orthogonal polarization spectral imaging: preliminary results. Anesthesiology 107:939–945
116. den Uil CA, Lagrand WK, Spronk PE, van Domburg RT, Hofland J, Luthen C, Brugts JJ, van der Ent M, Simoons ML (2008) Impaired sublingual microvascular perfusion during surgery with cardiopulmonary bypass: a pilot study. J Thorac Cardiovasc Surg 136:129–134
117. De Backer D, Dubois MJ, Schmartz D, koch M, Ducart A, Barvais L, Vincent JL (2009) Microcirculatory alterations in cardiac surgery: effects of cardiopulmonary bypass and anesthesia. Ann Thorac Surg 88:1396–1403
118. Parthasarathi K, Lipowsky HH (1999) Capillary recruitment in response to tissue hypoxia and its dependence on red blood cell deformability. Am J Physiol 277:H2145–H2157
119. Schumacker PT, Chandel N, Agusti AGN (1993) Oxygen conformance of cellular respiration in hepatocytes. Am J Physiol 265:L395–L402