Assessment of the Microcirculation

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M. R. Pinsky et al. (eds.), *Hemodynamic Monitoring*, Lessons from the ICU,
https://doi.org/10.1007/978-3-319-69269-2_14

Learning Objectives

- To understand what is microcirculation and what are the determinants of microvascular perfusion
- To address the interest and limitations of techniques used to evaluate the microcirculation
- To illustrate the typical microcirculatory alterations encountered in critically ill patients
- To understand the critical role of microcirculatory alterations in the development of organ dysfunction

14.1 Introduction

While tissue perfusion is one of our main targets for hemodynamic resuscitation, classical hemodynamic monitoring only provides indirect evidence of tissue perfusion. Many patients with circulatory failure present alterations in tissue perfusion despite optimization of systemic hemodynamics. While impaired distribution of blood flow has to be considered, microcirculatory alterations have also been implicated. Microcirculatory alterations have been demonstrated in various experimental models. However, the identification of microcirculatory alterations in critically ill patients has long been difficult due to the lack of adequate technology. Recent advances in technology have nevertheless allowed the evaluation of microcirculation in patients. Microvascular dysfunction has first been reported in patients with sepsis and septic shock [1] but was later reported in many other conditions encountered in critically ill patients. In this chapter, we will discuss the specificities of the microcirculation, the evidence for microvascular alterations, and the tools that can be used to assess the microcirculation.

14.2 Anatomical Structure of the Microcirculation

The microcirculation is composed of vessels smaller than 100 microns and is composed of arterioles, capillaries, and venules. The most usual architecture is the branched tree aspect, with arterioles dividing at several branch points into smaller ones, up to capillaries, which collect in venules, themselves collecting in larger venules. The role of arterioles is basically to distribute blood flow to the different parts of the organ, adapting the flow to local metabolism. The larger arterioles are called resistive arterioles, as they experience a large drop in pressure between entry and exit of these vessels. Distal arterioles and capillaries are the places where oxygen exchange with the tissues takes place. As oxygen diffuses from red blood cell flowing in capillaries, the diffusion distance becomes the limiting factor. Hence, at the microcirculatory level, the density of perfused vessels is more relevant for tissue oxygenation than the velocity at which red blood cells are flowing in perfused capillaries.

Organs like the kidney and gut have different microvascular architectures, associated with precapillary shunting or countercurrent exchange, which make these organs more vulnerable to hypoxia than other organs.

The control of microvascular perfusion is influenced by local factors, with backward communication through different channels, allowing adaptation of perfusion to local metabolism.

Another important factor for oxygen delivery at the microcirculatory level is capillary hematocrit. As the volumic effect of the plasma layer at the surface of vascular endothe-

lium is proportionally greater at capillary level than in large vessels, the capillary hematocrit is much lower than the systemic one. In addition, hematocrit is lower in side branch vessels than in straight vessels, due to the kinetic inertia of red blood cells. Accordingly, capillary hematocrit is difficult to predict from measurements of systemic hematocrit.

All these factors make it difficult to predict microvascular perfusion and tissue oxygen delivery from measurements of systemic hemodynamics. Also, therapeutic interventions aiming at increasing systemic oxygen delivery may fail to increase delivery of oxygen at the microcirculatory level.

14.3 Microvascular Alterations in Disease

14.3.1 Sepsis

In a landmark paper published in 2002, De Backer et al. [1] demonstrated that the sublingual microcirculation of patients with sepsis and septic shock was markedly altered compared to that of healthy volunteers and ICU controls. Septic patients experienced a decrease in density of perfused vessels, due to a combined increase in stopped flow as well as in intermittently perfused vessels, with perfused vessels in close vicinity to perfused vessels (Fig. 14.1). These alterations were only observed in vessels smaller than 20 microns, representing mostly capillaries. A key factor of these microcirculatory alterations is heterogeneity inside the observed field but also between several fields closed by a few microns. Importantly, these abnormalities were not fixed, as topical administration of acetylcholine fully normalized the sublingual microcirculation of these septic patients. These results have been reproduced in more than 40 papers from different teams around the world.

What is the relevance of these alterations? In experimental models, zones of impaired microvascular perfusion are co-localized with areas of hypoxia and even cell deaths [2]. In humans, this is more complicated to demonstrate, but improvements in microvascular perfusion are associated with improvement in lactate levels. Several studies have shown that sublingual microcirculatory alterations are associated with outcome [1, 3, 4]. Among the microcirculatory variables associated with outcome, perfused capillary density and proportion of perfused capillaries were positively associated with survival, while heterogeneity index was inversely related with survival [1, 3–5]. On the contrary, the velocity of red blood cells in perfused vessels did not differ between survivors and non-survivors [6], illustrating that diffusion and not convection is crucial for tissue oxygenation. Thus microvascular alterations are associated in the pathophysiology of organ dysfunction and death.

What could be the potential mechanisms responsible for these alterations? Experimental models of sepsis highlighted that several mechanisms are implicated, including endothelial dysfunction, impaired backward communication, impaired sensitivity to vasoconstrictive and vasodilating substances, glycocalyx alterations, and adhesion of circulating cells [7].

Are these alterations related to alterations in systemic hemodynamics? The relation between microvascular perfusion and arterial pressure or cardiac output is, at best, loose [8, 9]. Microvascular alterations are similar in low- and high-cardiac-output septic patients [10]. Hence these cannot be detected by looking at systemic hemodynamics. Can systemic hemodynamics be neglected? Obviously not, microvascular perfusion cannot be sustained if a minimal cardiac output or blood pressure is not obtained, but this value is quite

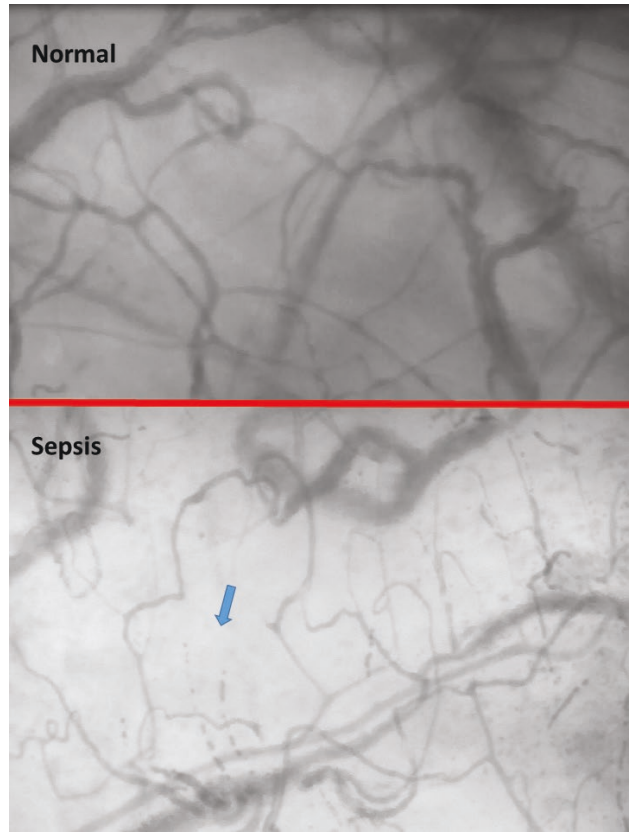

Fig. 14.1 Examples of microvideoscopic evaluation of sublingual microcirculation. SDF images recorded in a control patient (normal) and in a patient with septic shock (sepsis). The blue arrow denotes a not-perfused area

variable among individuals so that it is quite difficult to identify a clear cutoff value. For this reason, increasing perfusion pressure and cardiac output are both associated with a variable and unpredictable response [8, 11].

14.3.2 Microvascular Dysfunction in Other Conditions

Microvascular alterations relatively similar (even though often less severe) to those reported in septic shock have also been observed in other conditions. In patients with cardiogenic shock, microvascular density and perfusion of capillaries are decreased, together with an increase in perfusion heterogeneity [12, 13]. These alterations are associated with outcome [12, 13].

In patients resuscitated from trauma, the severity and duration of microvascular perfusion are associated with organ dysfunction [14]. Similarly, high-risk surgical patients presenting postoperative complications had more severe and more prolonged perioperative microvascular dysfunction than their counterpart with uncomplicated course [15].

Microvascular dysfunction has also been observed in eclampsia [16] or after cardiac arrest [17].

14.4 How to Assess the Microcirculation

As reported above, microvascular alterations cannot be detected by classical hemodynamic monitoring. At best, these can be suggested in a patient with cardiac output and arterial pressure values within targets and a high venous oxygen saturation (SvO_2) presenting clinical signs of hypoperfusion or with increased lactate levels. Biomarkers such as lactate may indicate tissue hypoxia, but the origin of it cannot be located in the microcirculation. In addition, lactate decrease may take time once perfusion is restored.

Clinical signs may appear attractive. Skin mottling, capillary refill time, and skin temperature are excellent indices of skin microvascular perfusion [18]. These are easily measured and often inexpensive. In addition, skin perfusion alterations have been associated with outcome [19, 20]. Unfortunately, these clinical signs are only approaching skin microvascular perfusion and are very influenced by local conditions (ambient temperature) or patient condition (peripheral arterial disease, Raynaud phenomenon, etc.) or vasopressor use. In addition, the skin microvasculature may not reflect more central microvascular areas, especially as skin vasoconstriction is an important physiological response helping to preserve perfusion to more vital organs. Hence, skin microvascular perfusion assessment is very helpful as a triage tool but lacks specificity. Chasing normalization of skin microvascular perfusion thus carries the risk of overtreating some patients or even diverting blood flow from vital organ to skin perfusion (as it may occur with some vasodilatory agents).

14.4.1 Direct Visualization of the Microcirculation

Two different handheld microscopes are currently used to visualize the microcirculation in critically ill patients (sidestream dark-field (SDF) and incident dark-field (IDF) imaging) [21]. Basically, these illuminate the field using light reflection from deeper layers, and vessels are visualized because light is absorbed at the selected wavelength by the hemoglobin contained in the red blood cells. These microscopes are mostly applied on the sublingual area (Fig. 14.1), as skin is covered by a thick epithelium rendering difficult visualization of the microcirculation. The sublingual microcirculation has the advantage of being relatively central and at core temperature, being less influenced by ambient temperature and peripheral vasoconstriction. Unfortunately, it is difficult to apply these devices on the sublingual area in non-intubated patients. In addition great care should be taken to discard secretions and to limit pressure artifacts. Recommendations on image acquisition and analysis have recently been published [21]. Microcirculatory images are mostly analyzed by offline manual analysis using a grid to count the vessels. Eyeballing is feasible and reliable for evaluation of simple variables. Software-assisted analysis is becoming available.

14.4.2 Indirect Assessment of Microvascular Perfusion

14.4.2.1 Vasoreactivity Tests

Due to the heterogeneity of microvascular perfusion in disease, microcirculation cannot be evaluated directly by laser Doppler or oxygen sensors. Indeed, these measure perfusion or oxygenation in a relatively large volume (at least 1 mm^3) which

contains many vessels including arterioles, capillaries, and venules. Accordingly, the measured value represents the average of flow/PO_2 in the various vessels and fails to take into account the non-perfused vessels. However, microcirculation can be indirectly evaluated by the estimation of vasoreactivity after a transient occlusion. Analysis of changes in blood flow/O_2 saturation during a brief episode of forearm ischemia enables quantification of microvascular reserve. Several indices can be measured, but the ascending slope, or recovery slope, is the easiest to measure and is the most reproducible.

Iontophoresis [22] and thermal challenge [23], both coupled with laser Doppler, can both be used to evaluate skin response to various vasodilatory drugs or to standardized heating, respectively. Compared to transient occlusion, these have the advantage to explore more central skin areas and not to be sensitive to peripheral vasoconstriction which occurs in response to disease as well as to vasopressor administration.

14.4.2.2 PCO_2 Gradients

Tissue PCO_2 increases in low flow conditions. In order to get rid of the influence of arterial PCO_2, the tissue to arterial PCO_2 gradient, or PCO_2 gap, is computed. Measurements of tissue PCO_2 have been used to reflect microvascular perfusion in sublingual or even gastric area. Unfortunately, these techniques are no more available.

Venoarterial gradients in PCO_2 can be used to indirectly evaluate microvascular perfusion [24]. Venous PCO_2 is measured on venous blood gas obtained in central venous or pulmonary artery catheter, simultaneous to an arterial blood gas. As PCO_2 can diffuse longer distances than PO_2, accumulation of PCO_2 in non-perfused areas is slowly diffusing to drainage veins (Fig. 14.2) so that the venoarterial PCO_2 gradient also increases in case of microcirculatory alterations, even though less significantly than in tissue itself. Venoarterial PCO_2 gradients have to be interpreted in conjunction with venous O_2 saturation: the increased venoarterial PCO_2 gradient mostly represents an altered cardiac output when venous O_2 saturation is low, while it mostly represents microvascular alterations when venous O_2 saturation is normal or elevated [25].

14.5 Limitations

One of the most important limitations is that we are looking at the microcirculation in one organ expecting that it may represent the microcirculation of other organs. While the process leading to endothelial dysfunction is affecting the microcirculation in the various organs (it has nicely been demonstrated in experimental setting that in sepsis the microcirculation is similarly affected in all organs, including the brain, liver, and kidney), some anatomical specificities or local factors can make some organs even more sensitive than others. Accordingly, it is usually considered that the microcirculatory alterations detected in the sublingual area likely reflect the minimal alterations that can be observed in other organs, while other organs may present more severe alterations or respond differently to therapeutic interventions due to local factors.

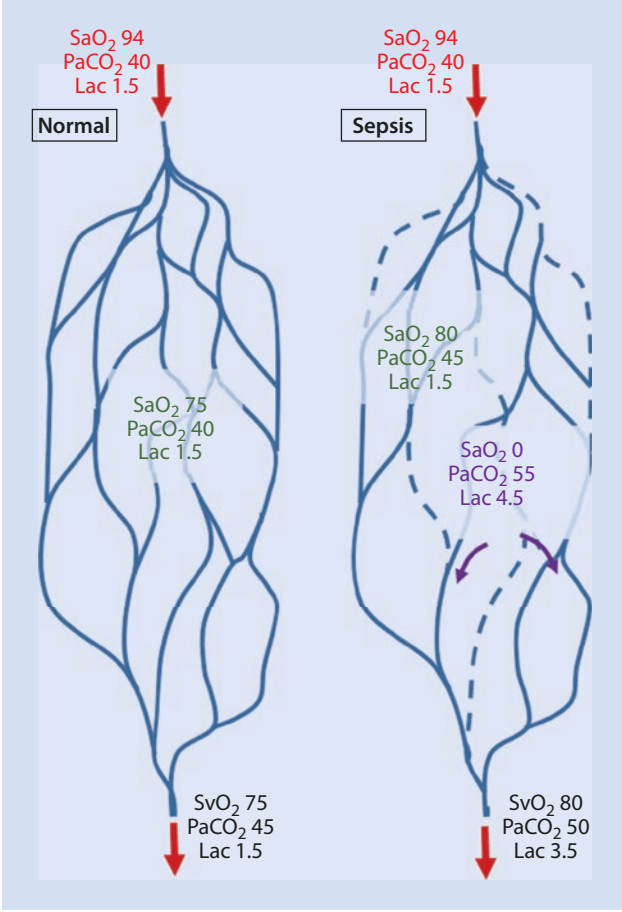

Fig. 14.2 Relationship between venoarterial PCO_2 gradients and microvascular alterations. In normal conditions, most areas are adequately perfused and thus oxygenated. Metabolic requirements are met and there is no flow stagnation. CO_2 production is rapidly washed out, and venoarterial PCO_2 gradient is minimal. In septic conditions, the microcirculation is heterogeneous, with areas that are poorly perfused in close vicinity to well-perfused areas. In the not-perfused areas, there is CO_2 increase due to flow stagnation and indirect anaerobic CO_2 generation due to buffering of H^+ generated by ATP hydrolysis. Interestingly, CO_2 diffuses longer distances than O_2 so that it can reach drainage venules. In the well-perfused areas, flow becomes excess, so that venous SO_2 of this area is in excess, contributing to the high SvO_2. Hence, the venular side of the diseased microcirculation is characterized by a high SvO_2, PCO_2, and lactate

Practical Implications

1. The microcirculation is a critical determinant of organ perfusion. Once a satisfactory cardiac output and arterial pressure are generated, microcirculatory alterations become the primary determinant of tissue perfusion.
2. Microcirculatory alterations have been demonstrated mostly in sepsis but also in severe heart failure, trauma, and high-risk surgery. These alterations are characterized by a decrease in density of perfused vessels and heterogeneity of areas close by a few microns.
3. Microcirculatory alterations cannot be detected by classical hemodynamic tools. The link between arterial pressure/cardiac output and microvascular perfusion is at best relatively loose.
4. Clinical evaluation of the microcirculation is often not contributing as dissociation from peripheral to more central circulation is often observed.

5. The microcirculation should either be directly measured (handheld microscopes applied on the sublingual area) or indirectly evaluated by measuring venoarterial PCO_2 gradients.
6. Given the characteristics of the microcirculation alterations, these often fail to classical hemodynamic interventions (fluids/inotropic agent/vasopressor agents). While experimental studies have reported promising results with some interventions, the beneficial effects of these need to be confirmed in the clinical area.
7. While evaluation of the microcirculation remains in the research area, comprehension of microcirculatory alterations is nevertheless very important for the understanding of persistent perfusion alterations despite correction of alterations in systemic hemodynamics.

Conclusions

The microcirculation is a key determinant of tissue perfusion, and microcirculatory alterations often persist after correction of systemic alterations. Even though investigation of the microcirculation still belongs to the research area, it is important to understand these may exist and contribute to organ dysfunction.

Take-Home Message

Microcirculatory alterations are present in many critically ill patients, and especially in sepsis, and contribute to organ dysfunction and poor outcome.
Even if it is not always feasible to directly visualize these alterations nor to manipulate these, it is important to understand that these may exist in order either to ensure better control of sepsis source or to prevent attempts to increase tissue perfusion by pushing further the systemic hemodynamics while the microcirculation fails to respond to these interventions.

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