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Microcirculation: Physiology, Pathophysiology, and Clinical Application

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Abstract
This paper briefly reviews the physiological components of the microcirculation, focusing on its function in homeostasis and its central function in the realization of oxygen transport to tissue cells. Its pivotal role in the understanding of circulatory compromise in states of shock and renal compromise is discussed. Our introduction of hand-held vital microscopes (HVM) to clinical medicine has revealed the importance of the microcirculation as a central target organ in states of critical illness and inadequate response to therapy. Technical and methodological developments have been made in hardware and in software including our recent introduction and validation of automatic analysis software called MicroTools, which now allows point-of-care use of HVM imaging at the bedside for instant availability of functional microcirculatory parameters needed for microcirculatory targeted resuscitation procedures to be a reality.

Introduction

Resuscitation from states of shock is conventionally achieved by the restoration of systemic hemodynamic variables using fluid and vasoactive compounds with the aim of promoting tissue perfusion and oxygen transport to tissue. However, whether this aim is actually achieved is uncertain. This condition leads to inappropriate use of drugs, which in turn can cause an increase in organ injury and adverse outcome. The physiological basis of this clinical dilemma has been exposed by our clinical introduction of hand-held vital microscopes (HVM) for bedside monitoring of the microcirculation. To this end, a deeper insight into the functional anatomy and (patho) physiology of microcirculatory alterations associated with disease and therapy is needed.

The Microcirculation

The microcirculation is the terminal vascular network of the systemic circulation consisting of microvessels with diameters <20 μm. These microvessels consist of arterioles, post-capillary venules, capillaries, and their (sub) cellular constituents (Fig. 1). The microcirculation is the final destination of the cardiovascular system and is ulti-

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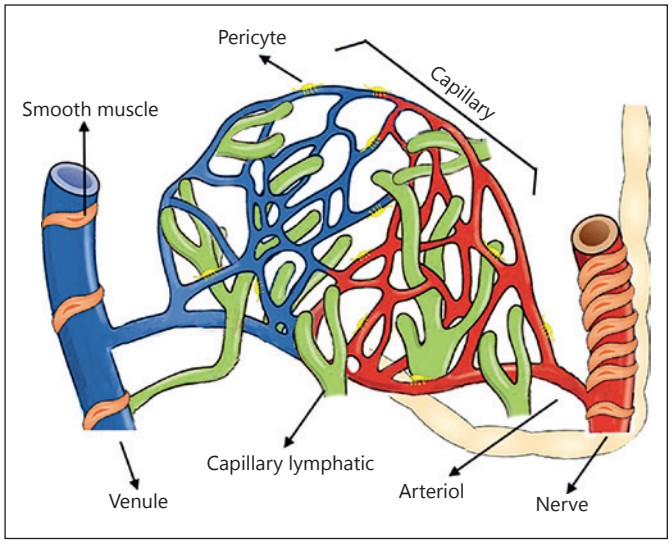

Fig. 1. Microvascular anatomy. The microcirculation is the part of the vascular system and consists of the small vessels so-called arterioles, capillaries, and venules. The lymphatic capillaries carry the extravascular fluid into the venous system. The arterioles are surrounded by vascular smooth muscle cells responsible for the regulation of arteriole tone.

mately responsible for oxygen transfer from the red blood cells (RBC) in the capillaries to the parenchymal cells where oxygen is delivered to meet the energy requirements of the tissue cells in support of their functional activity. Other functions of the microcirculation include the regulation of solute exchange between the intravascular and tissular space and is responsible for the transport of all blood-borne hormones and nutrients to the tissue cells including mediating the functional activity of the immune system and hemostasis. It is arguably the most important compartment of the cardiovascular system, since it is in direct contact with the parenchymal cells, which rely on its proper function to maintain their viability to support organ function.

Oxygen transport by RBC flow in the microcirculation to the tissues is accomplished by 2 primary mechanisms. These are convection of the oxygen-carrying RBCs and diffusion of the oxygen from the RBCs to the respiring mitochondria of the tissue cells. The former component of oxygen transport to the tissues is described by RBC flux or flow, and the diffusional component of oxygen transport can be quantified by the functional capillary density (FCD) of the microcirculation [1].

Vessels of the microcirculation are almost entirely lined by endothelial cells (EC). These cells contain fenestrations and pores and are held together by various molecules, including cadherins as well as current-carrying gap junctions, which allow upstream electrical communication between EC. These endothelial structures can vary in density and morphology between the different organs and vessels. EC in symbiosis with smooth muscle cells regulate the microvascular blood flow predominantly by regulation of the vasotone of arterioles. There are 3 main mechanisms that cause this regulation: myogenic, metabolic, and neurohumoral control mechanisms. One of the most important subcellular structures of the endothelium mediating its function is the glycocalyx present on the luminal side of the endothelium [2–4]. It is a 0.2–0.5 μm gel-like layer synthesized by EC. It is composed of 3 major components, proteoglycans, glycosaminoglycans, and plasma proteins, and harbors various substances such as antithrombin and superoxide dismutase. The glycocalyx is responsible for several critical physiologic processes including homeostasis, solute transport, hemostasis, and immunological functions. Although it is generally thought that the glycocalyx integrity is the main determinant of the vascular barrier, we showed in a recent study that this is not the case and that the glycocalyx can be shed in conditions of shock without compromising the vascular barrier function [5]. It is generally considered that endothelium dysfunction can be considered one of the main cellular events responsible for hemodynamic collapse seen in states of shock and responsible for the ineffectiveness of routine resuscitation procedures [4]. The microcirculation is of key importance for the functioning of the kidney due to its central role in delivering oxygen to the renal microcirculation [6, 7]. The majority (>80%) of oxygen delivered to the kidney is utilized for production of ATP needed by the Na+/K+ pump whose activity is essential for tubular sodium reabsorption [8]. Injury of the renal microcirculation resulting in acute kidney injury (AKI) can be caused by hypoxia, oxidative/nitro stress, and/or inflammatory mediators, and is thought to be central in the sequelae leading to AKI [9]. Experimental models have shown that targeting inflammation [10] and microcirculatory oxygen delivery [11] can be successful in resolving AKI in such models.

Clinical Measurement of the Microcirculation Using HVM

Previously the measurement of the microcirculation in vivo was limited to experimental studies where intravital microscopes were used to observe the microcircula-

tion in mainly muscle tissues (cremaster and hind limb muscle). In clinical studies, such microscopes were used to asses the function of the nail fold capillary bed in patients with peripheral vascular disease. In the 1990s, however, our group introduced HVM to the clinics, which allowed the first time observation of the microcirculation of the brain during surgery [12]. These first-generation HVM devices were based on orthogonal polarized spectral imaging and made use of cross-polarized green light to image the microcirculation without the need to transilluminate the organ surface from below as was needed before [13]. This methodology allowed clear video observation of the flowing RBCs of the microcirculation. Due to the limited applicability of the bulky apparatus and the need for high-powered light sources of orthogonal polarized spectral imaging, we developed a battery-based device based on sidestream dark field imaging [14]. Later a third-generation device with improved image quality was introduced based on incident dark field imaging [15]. In clinical conditions, these devices were mostly used to observe the sublingual microcirculation. In a large number of studies, sublingual microcirculation proved to be a highly clinically relevant location, where alterations were found to be highly sensitive and specific, much more than alterations in systemic hemodynamic variables, in predicting morbidity and mortality in various clinical patient groups [16–22].

To identify the sublingual microcirculation as a clinically relevant location representative of microcirculatory dysfunction in other organ beds, studies were carried out showing that sublingual microcirculation alterations paralleled microcirculatory alterations in other organs such as the intestines and kidneys [23–25]. Addressing this question in a clinical study, Boerma et al. [26] looked out the correlation between sublingual and intestinal microcirculation in patients having developed sepsis as a result of stoma surgery. Although they found no correlation early on in sepsis, later there was a correlation between the intestinal and sublingual microcirculation in these septic patients showing how regional microcirculatory alterations can develop into a systemic microcirculatory alteration in the course of time [26].

HVM studies were carried out in a range of different clinical applications including on organ surface during surgery [12, 27–29]. Furthermore, methodologies were developed to identify other aspects of the microcirculation such as methodologies to identify leucocyte kinetics [30] and the presence of the glycocalyx [31] and methodologies to identify microcirculatory reserve by topical application on the sublingual area of nitroglycerine [32].

The prevalence of the HVM devices and the growth in the number of studies showing adverse outcome to be linked to the persistence of microcirculatory alterations independent of alterations in systemic hemodynamic variables led the publication of an international consensus paper under the auspices of a task force of the European Society for Intensive Care Medicine on the measurement of sublingual microcirculation in critically ill patients using HVM [33]. One of the most important recommendations of their consensus guidelines was the need for the development of a validated automatic software analysis platform. At the time, the only validated software analysis platform was the semi-automatic AVA software developed by us [34] requiring time-consuming offline analyzing of images to produce functional microcirculatory parameters. Several automatic software platforms have been attempted, but these were either inadequate or not validated with sufficient rigor to allow these to be used in a reliable point-of-care application. Especially the quantitative measurement of capillary flow was found to be a major challenge in the automatic analysis of microcirculatory images. This changed with our recent development of an experimentally and clinically validated automatic software platform, called MicroTools, which allowed an almost 500 × faster automatic analysis of HVM generated microcirculatory than the previous AVA software [35] (website: [36]). This software platform calculates all the relevant parameters identified by the consensus paper as necessary for describing the functional state of the microcirculation, including quantitative velocity measurements of each vessel in the field of view. MicroTools thereby allowed a quantitative measure of the convective (RBC velocity and flow) and diffusive capacity (FCD) of the microcirculation instantaneously at the bedside. This important development has now made integrating the monitoring of the microcirculation using HVM into conventional systemic hemodynamic monitoring at the bedside as a point-of-care modality a reality.

Microvasculatory Shock and Renal Compromise

Sepsis is associated with profound changes in microcirculation due to several mechanisms including endothelial dysfunction, glycocalyx degradation, altered blood cell rheology (reduced RBC deformability), and dysbalance between the levels of vasodilating and vasoconstricting substances [37] (Fig. 2). An oxygen extraction deficit

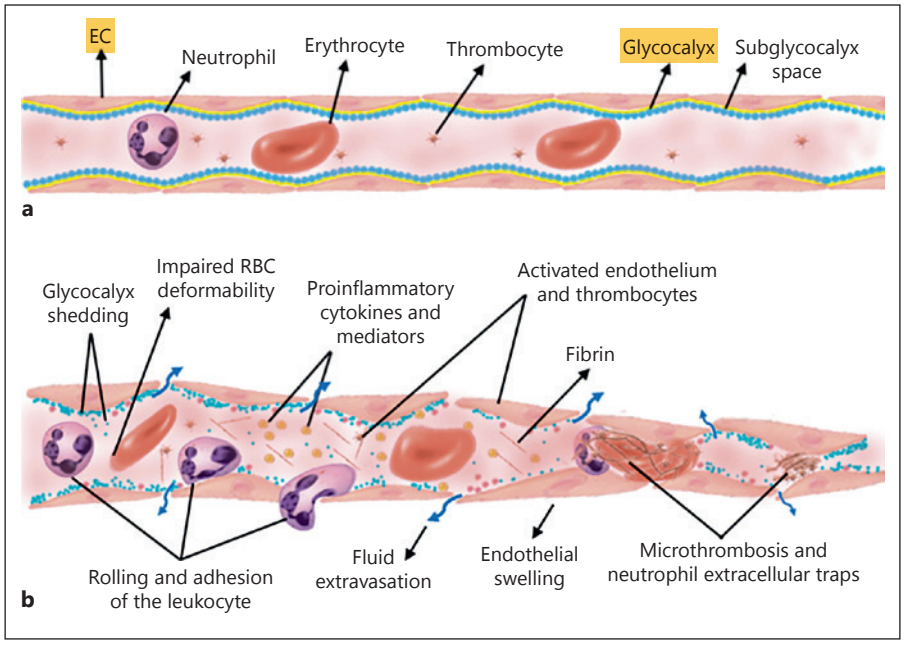

Fig. 2. Microvascular dysfunction and vascular endothelial damage. **a** The structure of a healthy microvessel is shown. EC and glycocalyx cover the lumen of the microvessel. The blood cells (leukocytes, RBC, thrombocytes) flow together with plasma inside the microvessels. **b** Microcirculatory damage can be caused by ischemia, reperfusion, inflammation, and hypoxia, resulting in endothelial and glycocalyx and RBC damage. Activation of leukocytes induces rolling, adhesion, and ultimately extravasation to the tissue, which further accelerates the inflammation. Decreased vascular permeability causes vascular leakage and edema formation. RBC, red blood cell; EC, endothelial cells.

by the tissues is considered a main characteristic hemodynamic defect in sepsis. This defect was found to be unresolved by therapeutic increases in systemic oxygen delivery [38]. This property in sepsis has made it difficult to choose an effective resuscitation target for its hemodynamic resolution. The underlying mechanism of the reduced capacity of the tissues to extract oxygen from the circulation was identified in a series of experimental studies to be caused by microcirculatory dysfunction resulting in functional oxygen shunting of the microcirculation [39]. This condition manifests itself clinically as a reduction in the oxygen extraction capacity of the tissues, a condition that can occur in the presence of normalized systemic hemodynamic variables following resuscitation. The clinical introduction of HVM to the study of critically ill patients verified this mechanism by the observation of persistent RBC plugging of capillaries next to capillaries with normal RBC flow despite apparent adequate resuscitation based on the normalization of systemic hemodynamic variables. Studies using HVM in states of sepsis and shock showed these microcirculatory alterations to be related to adverse outcome and organ failure independent of systemic hemodynamic conditions [17, 18, 40, 41].

During states of cardiovascular compromise, resuscitation-induced improvement in systemic hemodynamic parameters does not necessarily result in a parallel improvement in the microcirculation. Such a condition, which is expected to occur under normal physiology, we termed as there being a "loss of hemodynamic coherence" between the macrocirculation and microcirculation. If persistent it has been shown to be an independent predictor of adverse patient outcome despite macrocirculatory normalization [36].

The loss of hemodynamic coherence has been found to be associated with 4 main types of hemodynamic microcirculatory alterations, all associated with a loss of oxygen extraction capacity of the tissues (Fig. 3). Type 1 alteration is characterized by heterogeneity in capillary density and blood flow and shunts in microvascular blood flow (as seen in sepsis). Type 2 alteration is associated with inadequate transport of oxygen to the microcirculation due to dilutional anemia caused, for example by hemodilution. Type 3 alteration is seen as a stasis of microcirculatory blood flow, for example, by the use of too much vasopressors [42] or tamponade caused by an increase in venous pressure [43]. Type 4 alteration is typically seen in states of edema where FCD is low.

The observations of states of microcirculatory shock using HVM despite normalized systemic hemodynamics achieved by resuscitation have led to many studies being carried out to investigate the efficacy of various therapeutic interventions to resuscitate the microcirculation. The response of the microcirculation to vasoactive compounds have generally been shown that vasopressors targeting increases in blood pressure to have a limited effect on improving microcirculation unless there was initial

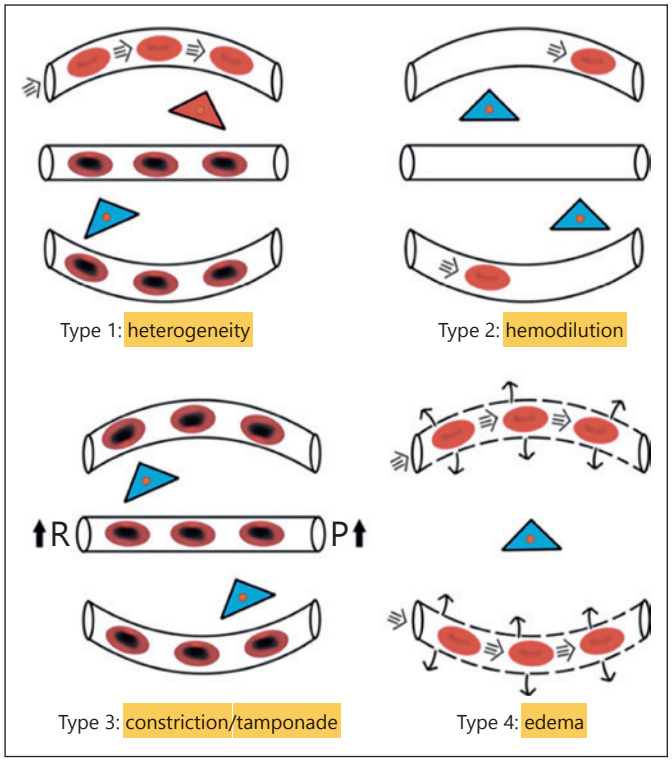

Fig. 3. Condition of microcirculatory alterations associated with loss of hemodynamic coherence and reduced oxygen capacity of the tissues. Type 1: Heterogenous RBC flow caused by RBC and endothelial cell injury induced for example by sepsis results in RBC stagnant capillaries next to perfused capillaries resulting in microcirculatory shunts and a reduction of tissue oxygen extraction capacity. Type 2: A decrease in the oxygen-carrying potential of the microcirculation due to hemodilution induced anemia resulting from a low FCD. Type 3: A stasis in the RBC flow due to increased vascular resistance (R) [37] and/or elevated venous pressure (P) [38]. Type 4: Increased oxygen diffusion distances due to edema caused by capillary leak syndrome. Adapted from Ince [67].

microcirculatory hypoperfusion; otherwise, vasopressors could actually decrease microcirculatory flow [42, 44, 45]. Vasoactive compounds having dilatory effects such as dobutamine, enoximone, and nitroglycerin, on the other hand, were much more effective in recruiting the microcirculation [40, 46, 47].

Fluids are a mainstay therapeutic option for states of hypovolemia and shock, and many studies have been conducted investigating various aspects of the response of the microcirculation to fluid administration. Studies in sepsis have shown fluid resuscitation to be effective in promoting microcirculatory flow only when such microcirculatory flow was initially low in value [48]. Such a condition was shown to occur independently of normally used surrogates of hypovolemia as indicative of fluid need such as oliguria, stroke volume, tachycardia, and low lactate [49]. In abdominal surgical patients, Bouattour et al. [50] found pulse pressure variation to identify preload dependence to be associated with reduced sublingual microcirculation, which was successfully improved by fluid administration. A consistent finding especially in cardiac surgery patients is that fluid administration leads to a Type 2 loss of hemodynamic coherence (Fig. 3) where an RBC dilution quantified by a decrease in FCD indicated a reduction in oxygen extraction capacity of the microcirculation [51], whereas a de-escalation by use of diuretic therapy leads to an increase in FCD [52]. These consistent findings of the presence of dilution anemia being caused by excessive use of fluid therapy, identified in the microcirculation as a reduction in FCD, let us to identify anemic shock as a possible fifth category of shock, which should be added to the classic four states of circulatory shock (cardiogenic, hypovolemic, obstructive, and distributive) described by Weil [53]. Blood transfusions have been shown to be an effective option for recruiting the microcirculation [54], especially in improving the diffusional component of microcirculatory oxygen transport by an increase in FCD [55].

Heart failure and cardiogenic shock have been found in a number of studies to be associated with a decrease in the microcirculatory convective flow [41, 47]. Mechanical support of the circulation by use of VA-ECMO in adult and pediatric patients has shown that the inability of VA-ECMO to improve the microcirculation was associated with adverse outcome [16, 21, 56, 57]. It is clear from the above studies that the next phase in the study of the microcirculation must be to investigate the efficacy of microcirculatory-guided resuscitation strategies. For such studies to be effective, however, a point-of-care analysis of methodology for instant bedside evaluation of microcirculatory alterations is needed.

Microcirculatory alterations and hypoxemia have been reported in patients with chronic kidney disease and patients on hemodialysis. Studies using the BOLD technique for measuring renal tissue oxygenation showed that chronic kidney disease patients with renal hypoxemia had a 3 times more likely chance to develop the need for renal replacement therapy or show a 30% or more increase in serum creatinine [58]. During the course of hemodialysis and fluid withdrawal, microcirculatory flow is reduced as shown in several HVM studies [59, 60]. This effect could be reversed following renal transplantation [59]. In a large cohort of hemodialysis patients, Meyring-Wosten et al. [61] identified, by mea-

surement of arterial and venous oxygen saturation, states of "prolonged intradialysis hypoxemia," a condition they found to be associated with all-cause hospitalization and mortality. De-escalation following volume overload can be accomplished by hemodialysis or by diuretic therapy. Campos et al. [62] showed how arterial saturation can improve upon volume removal during hemodialysis. In an HVM study volume overloaded post-cardiac surgery patients receiving diuretic therapy were shown to be successful in increasing sublingual FCD, thereby improving the diffusive capacity of the microcirculation [52].

In states of inflammation and infection, such as in sepsis, blood purification of inflammatory mediators can be accomplished by the use of specialized cytokine removal filters, such as Cytosorb, in line with continuous replacement therapy. In a propensity score weighted retrospective clinical trial, we showed that such an approach was successful in improving 28 day mortality in severely ill septic ICU patients [63]. In an HVM study, Zuccari et al. [64] showed that the use of such Cytosorb filters were associated with a reduction in cytokine levels in parallel with a recovery of microcirculatory alterations associated with sepsis.

New Directions in the Clinical Monitoring of the Microcirculation

There is general agreement in the literature that the ultimate expectation of achieving an adequate hemodynamic resuscitation target is when there is a normalization of tissue perfusion (e.g., [65]). However, there is no clarity about what is precisely meant by "tissue perfusion." It is presumed that tissue perfusion must be equivalent to the promotion of the flow of RBCs in the microcirculation with the aim of promoting tissue oxygenation to sustain cell viability needed to support organ function. However, the most common resuscitation procedure being fluid resuscitation may increase convection but at the expense of diffusion of oxygen due to the increase in diffusion distance between the RBCs reducing the oxygen extraction capacity of the tissues [66, 67]. Thus, a technique such as a laser Doppler is inadequate in measuring these variables because it only measured the flux. Near-infrared spectroscopy is equally inadequate because it only measures approximate hemoglobin oxygen saturation instead of actual delivery of oxygen availability. Thus, what is needed is a metric combining cellular RBC transport as well as RBC availability which represent the 2 primary determinants of microcirculatory oxygen transport: RBC convection and diffusion capacity, the latter consisting of the density of RBC-filled capillaries (FCD) and the capillary hematocrit [1]. To measure both microcirculatory convection and diffusion capacity, direct visualization of the microcirculation is mandatory (for identification of single RBC). In addition, these functional microcirculatory parameter values have to be directly calculated at the bedside in a point-of-care manner. Only then can clinicians titrate resuscitation compounds to optimize microcirculatory perfusion and oxygen transport values. HVM meets the requirements to allow clear visualization of flowing RBCs in the microcirculation and our recently introduced clinically validated automatic analysis software called MicroTools [35] allows instant calculation of all of the required parameters to quantify microcirculatory oxygen transport values thus fusing capillary hematocrit, FCD, and the flow of RBC into one parameter defining the determinants of microcirculatory oxygen transport variables has led us to introduce a new resuscitation target variable we call tissue "RBC perfusion". We expect this parameter, which can be instantaneously measured using HVM in conjunction with MicroTools, to provide a gold standard as a microcirculatory resuscitation target. A current research in our group in a large international multicenter database has gathered microcirculatory measurements in various patient categories, and therapeutic interventions will provide the validation of the use of tissue RBC perfusion as this new resuscitation target.

Conclusion

Over the last several decades, much progress has been made in our understanding of microcirculatory (dys-) function in various clinical conditions due to the introduction of HVM for bedside observations of the microcirculation. Over the years, technological advances have led to improvements in the development of hardware related to HVM as well as development of fully automated software (MicroTools) for analysis of images to provide functional microcirculatory parameters. It is expected that direct visualization of the microcirculation and performing point-of-care analysis of functional parameters will identify patients at risk where apparent resuscitation targets have been met based on the normalization of systemic hemodynamic variables and possibly provide new microcirculatory-based resuscitation targets in conjunction with systemic hemodynamic targets [68].

Disclosure Statement

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Author Contributions

G.G., M.H., and C.I.: design of the work, revising the manuscript critically for important intellectual content.

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