



Microcirculation in Patients with Sepsis: From Physiology to Interventions

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20.1 Introduction

There are a multitude of reasons why critically ill patients may have reduced cardiac output and perfusion of tissues. Patient survival depends on determining the cause of disease and treating the pathology, as well as supportive care until restoration of normal physiology. Resuscitation guidelines have long been focused on macrohemodynamic variables, such as cardiac output, as well as indirect measures of blood flow and tissue perfusion, such as lactate. In recent years, interest has been developing in the assessment and management of the microcirculation. The microcirculation is the interface between the main oxygen consumers (parenchymal cells in the tissues) and the oxygen supplier (the circulatory system). It serves to deliver nutrients and remove metabolic products in order to support normal tissue function.

For aerobic metabolism to occur there must be a constant delivery of oxygen to cells. Gas exchange occurs in the pulmonary vasculature, oxygenated blood is then circulated systemically via the cardiovascular system, and oxygen diffuses into cells at the level of the microcirculation. It is then used to make cellular adenosine 5'-triphosphate (ATP) through the process of aerobic respiration, primarily through oxidative phosphorylation in the mitochondria.

The microcirculation is a network of small blood vessels (<100 μm diameter), which consists of arterioles, capillaries, and venules. It includes endothelial cells,

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smooth muscle cells (mostly in arterioles), red blood cells (RBCs), leukocytes and platelets [1]. The microcirculation is structured such that every cell has at least one capillary adjacent to it for the purpose of passive diffusion of oxygen from the vasculature into the cell.

The early goals of resuscitation in circulatory shock are to restore global blood flow, oxygen delivery, and organ perfusion pressure with the ultimate aim of improving microcirculatory perfusion and cellular oxygen metabolism. The aim of this chapter is to outline the principles of the microcirculation, microcirculatory dysfunction in sepsis, and therapies to improve microcirculatory function and tissue perfusion.

20.2 Microcirculatory Dysfunction in Sepsis

Sepsis is characterized by macrocirculatory alterations such as relative hypovolemia, a decrease in vascular tone, myocardial depression, and a heterogeneous pattern of blood flow in the microcirculation, as well as the incapacity of cells to extract and adequately use oxygen [1].

Sepsis results in derangements in the microcirculation, with these derangements being most marked in severely ill patients. Clinical and global hemodynamic parameters do not correlate well with microcirculatory perfusion and indeed these microcirculatory abnormalities may persist after the correction of systemic hemodynamic parameters, such as mean arterial pressure (MAP) [2].

The cardiovascular system circulates blood throughout the body but it is the microcirculation in particular that actively and passively regulates the distribution of RBCs and plasma throughout individual organs (Fig. 20.1). In animal models of sepsis, lipopolysaccharide (LPS)-induced microvascular heterogeneity and increased oxygen-diffusion distances affect the distribution of RBCs and oxygen flow within the heart, leading to tissue hypoxia [3]. Endothelial malfunction and rupture of the glycocalyx can lead to microthrombi, capillary leakage, leukocyte rolling, and rouleaux formation [4]. Microcirculatory alterations increase the diffusion distance for oxygen and, due to the heterogeneity of microcirculatory perfusion in sepsis, may promote the development of areas of tissue hypoxia in close proximity to well-oxygenated zones. Improvement of tissue perfusion and oxygenation should be considered the ultimate goal of any resuscitative efforts.

20.3 Hemodynamic Reconciliation in Physiology

Septic shock is a subset of sepsis in which oxygen delivery to cells is insufficient to maintain cellular activity and support organ function. It is associated with a greater risk of mortality than with sepsis alone. It can be clinically identified by a vasopressor requirement to maintain a MAP of ≥ 65 mmHg and serum lactate level < 2 mmol/l (18 mg/dl) in the absence of hypovolemia [5]. For resuscitative measures to be effective there must be coherence between the macrocirculation and the

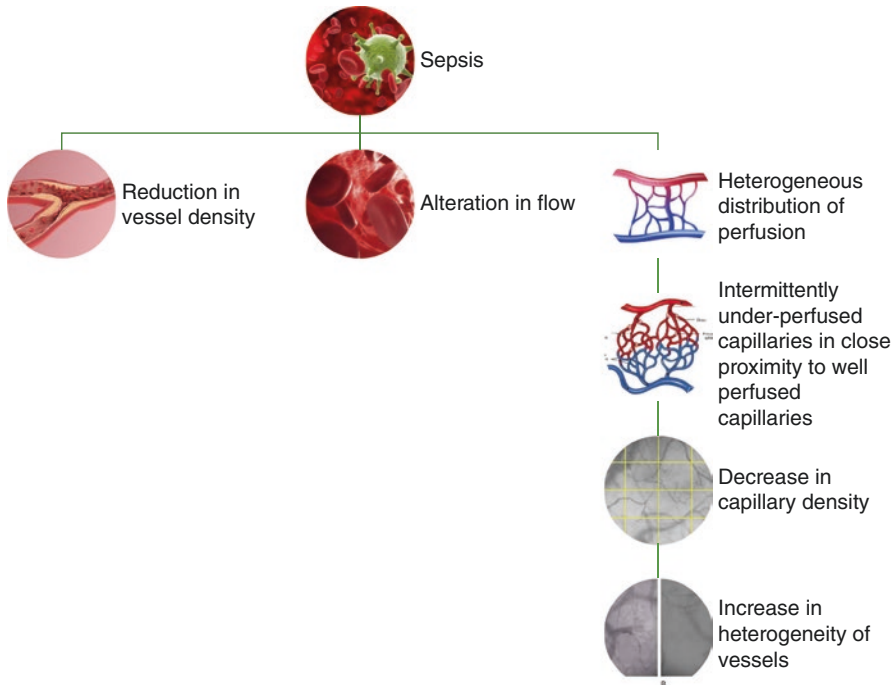


Fig. 20.1 Microcirculatory derangements in sepsis. Derangements are mainly characterized by a reduction in vessel density, alteration in flow, and a heterogeneous distribution of perfusion. Sepsis is associated with intermittently under-perfused capillaries in close proximity to well-perfused capillaries. This causes a decrease in capillary density and increase in heterogeneity of vessels

microcirculation. That is to say, normalization of systemic variables must result in a parallel improvement in perfusion of the microcirculation, oxygenation of parenchymal cells, and restoration of normal cellular activity. In many shock states, tissues can remain hypoperfused even after MAP has been restored.

The potential pathophysiologic mechanisms behind this hemodynamic incoherence during or following resuscitation include unregulated inflammation, cytokine storm, reactive oxygen species, degradation and shedding of the endothelial glycocalyx, endothelial dysfunction and increased permeability, and mitochondrial dysfunction [6].

The persistence of microcirculatory hypoperfusion after restoration of systemic variables has been shown in numerous studies and is associated with worse outcomes. Ince suggested four different types of microcirculatory alterations underlying the loss of hemodynamic coherence [7]:

Type 1 (obstructive): heterogeneous microcirculatory flow in which there are obstructed capillaries next to capillaries with flowing RBCs. Persistence of this type of microcirculatory dysfunction in the presence of normal systemic

hemodynamic variables has been associated with adverse outcomes [8]. Increased microcirculatory perfusion during resuscitation is associated with reduced organ failure in septic patients with comparable global hemodynamics [9].

Type 2 (hemodilution/anemic): reduced capillary density induced by hemodilution and anemia, in which dilution of blood causes a loss of RBC-filled capillaries and results in increased diffusion distances between oxygen-carrying RBCs and tissue cells.

Type 3 (hypoperfused): microcirculatory flow reduction caused by vasoconstriction or tamponade in which vasoconstriction of arterial vessels results in microcirculatory ischemia or raised venous pressures inducing microcirculatory tamponade.

Type 4 (distributive): tissue edema caused by capillary leak, which results in increased diffusion distances between the RBCs and tissue cells.

The second consensus on the assessment of the sublingual microcirculation was published in 2018 [10]. It introduced a classification system in order to better characterize microcirculatory alterations other than solely those associated with sepsis. The types of alterations include:

- Type 1: complete stagnated capillaries (circulatory arrest, excessive use of vasopressors)
- Type 2: reduction in the number of flowing capillaries (hemodilution)
- Type 3: stopped-flow vessels are seen next to vessels with flowing cells (sepsis, hemorrhage, and hemodilution)
- Type 4: hyperdynamic flow within capillaries (hemodilution, sepsis)

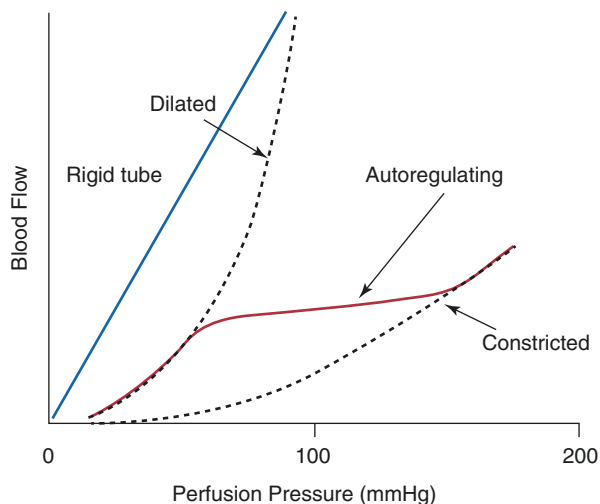
20.4 The Role of the Endothelium and Coagulation

The normal microcirculation maintains a network of perfused capillaries by auto-regulation, which is a regulatory mechanism allowing microcirculatory flow to remain independent of changes in systemic blood pressure (Fig. 20.2). The main component of this autoregulated system is the endothelial cell [1].

The endothelial glycocalyx is a negatively charged, carbohydrate-rich layer, which lines the luminal surface of the vascular endothelium [11]. It consists of proteoglycans, glycoproteins bound with sialic acid, glycosaminoglycans (GAGs), and associated plasma proteins. Proteins such as albumin, fibrinogen, fibronectin, thrombomodulin, antithrombin III, superoxide dismutase, and cell-adhesion molecules all interact with GAGs [12].

The endothelial glycocalyx controls capillary permeability and acts as a barrier [13]. Its negative charge prevents negatively charged proteins such as albumin from passing into the extravascular space, which in turn prevents fluid from passing into the extravascular space. It serves as a barrier to adhesion of leukocytes to the endothelium and indeed shedding of the glycocalyx during activation of endothelial cells may be an essential part of the inflammatory response [14]. It may also serve as a mechanosensor and mediate the release of nitric oxide in response to shear stress

Fig. 20.2 Blood flow and perfusion pressure ratio. Normal microcirculation maintains a network of perfused capillaries by autoregulation, which is a regulatory mechanism allowing microcirculatory flow to stay independent of changes in systemic blood pressure



[15]. The permeability of the vascular endothelium is of critical importance in the regulation of fluid homeostasis between the intravascular space and the interstitium and in the regulation of physiological functions of organs [16].

During sepsis, the glycocalyx is degraded by enzymes such as metalloproteinases, heparanase and hyaluronidase, which are activated as part of the inflammatory response [12]. These enzymes are activated in inflammatory states by reactive oxygen species, tumor necrosis factor (TNF)-alpha, and interleukin 1-beta (IL-1 β) [17]. Studies have found a significant reduction in the thickness of the glycocalyx in sepsis [18]. Observational studies have found an association between the levels of markers of endothelial damage and the severity of sepsis [19]. This degradation of the glycocalyx leads to vascular hyper-permeability, unregulated vasodilation, microvessel thrombosis, and augmented leukocyte adhesion [12].

Inflammatory-mediated degradation of the glycocalyx may lead to specific organ dysfunction in sepsis, such as acute respiratory distress syndrome (ARDS), acute renal failure, and hepatic dysfunction. Inflammatory cytokines, such as TNF- α , IL-1 β , IL-6, and IL-10, have been implicated in the degradation of the glycocalyx [18].

20.5 Assessment of the Microcirculation

20.5.1 Microcirculatory Targets

Macrocirculatory parameters such as MAP are poor predictors of cardiac output. The sympathetic response to stress and neural adaptation tends to initially maintain the MAP in the face of decreasing flow [20]. It is thus a poor indicator in the early assessment of shock. Indeed systemic hemodynamic variables do not indicate the onset of shock but rather indicate the onset of cardiovascular decompensation. Measures of microvascular flow enable the earlier detection of shock (Fig. 20.3).

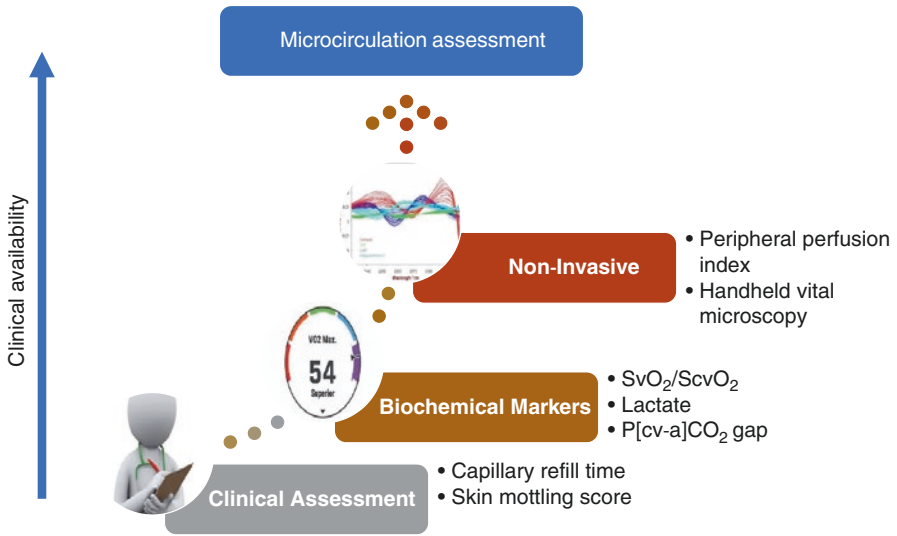


Fig. 20.3 Measures of microvascular assessment classified by their availability in clinical practice. SvO₂ mixed venous oxygen saturation; ScvO₂ central venous oxygen saturation; P[cv-a]CO₂ gap central-venous-arterial CO₂ difference

20.5.2 Clinical Assessment

20.5.2.1 Capillary Refill Time

The capillary refill time (CRT) is defined as the time required for a distal capillary bed (i.e., the nail bed) to regain its color after pressure has been applied to cause blanching [21]. Historically the upper limit of normal was quoted to be 2 s; however more recent studies have suggested the upper limit of normal for capillary refill time to be 3.5–4.5 s [22, 23]. It does however vary with factors such as age and temperature, and is subject to inter-observer variability.

Hernandez et al. reported that CRT and central-to-toe temperature difference (Tc-toe) were more significant predictors of successful resuscitation than normalization of metabolic parameters such as central venous oxygen saturation (ScvO₂) and central-venous-arterial CO₂ difference (P[cv-a]CO₂ gap). In their study, the presence of normal values of both CRT and Tc-toe at 6 h was independently associated with successful resuscitation [24]. This suggests that noninvasive measures of peripheral perfusion such as CRT and Tc-toe may be used as surrogates for more invasive techniques in the assessment of peripheral perfusion.

Patients with persistently abnormal peripheral perfusion as measured by CRT following initial resuscitation have been shown to have a higher likelihood of developing complications such as organ failure and decreased survival [25].

20.5.2.2 Skin Mottling

Skin mottling is defined as a bluish skin discoloration that typically manifests near the elbows or knees and has a distinct patchy pattern. It is the result of heterogeneous small vessel vasoconstriction and is thought to reflect abnormal skin perfusion [21]. The mottling scoring system (from 0 to 5), based on mottling area extension from the knees to the periphery, is a simple and reliable tool used for the assessment of peripheral perfusion (Fig. 20.4). Higher skin mottling scores have been found to be predictive of mortality in patients admitted to the intensive care unit (ICU) [26].

20.5.3 Biochemical Markers

Biochemical markers are used to indicate global perfusion in both the intensive care and the nonintensive care setting. Mixed venous oxygen saturation (SvO_2), $ScvO_2$, plasma lactate, and $P[cv-a]CO_2$ gap are commonly used measurements for this purpose.



Fig. 20.4 Mottling score showing stage 5 mottling. Mottling score defined by five areas over the knee is developed to evaluate tissue perfusion at bedside

20.5.3.1 SvO₂ and ScvO₂

Using the SvO₂, the Fick equation can be used to calculate the cardiac output [27]:

$$\text{SvO}_2 = \text{SaO}_2 - (\text{VO}_2 / \text{cardiac output} \times \text{Hb} \times 1.34)$$

where Hb is the hemoglobin concentration, SaO₂ the arterial oxygen saturation, and VO₂ whole-body O₂ consumption.

When the SaO₂, VO₂, and hemoglobin remain constant, decreasing values of cardiac output result in decreases in SvO₂ secondary to increases in the oxygen extraction rate. Normal values for SvO₂ range from 70% to 75%. The measurement of SvO₂ requires a pulmonary arterial catheter; however, ScvO₂ can be obtained from a central venous catheter and although oxygen levels vary slightly it can be used as a surrogate.

20.5.3.2 Lactate

Lactate is perhaps the most commonly used biochemical indicator of resuscitation in sepsis. It is the most easily measurable and interpretable and can be done rapidly with point-of-care testing. In contrast to SvO₂ and ScvO₂ it does not require central venous access.

Lactate is a product of anaerobic metabolism and thus indicates inadequate oxygen delivery to or metabolism by the tissues. It is included in the most recent definition of septic shock. The combination of a lactate level >2 mmol/l and vasopressor requirement to maintain MAP >65 mmHg in the absence of hypovolemia has been associated with mortality of >40% [5]. Lactate clearance as a target of resuscitation has been shown to be non-inferior to using ScvO₂ monitoring [28].

20.5.3.3 Central-Venous-Arterial CO₂ Difference

The P[cv-a]CO₂ gap can be used as an adjunct in the assessment of the macro- and microcirculation. Using a central venous catheter, the ScvO₂ can be measured and used as a surrogate for global tissue hypoxia, and the P[cv-a]CO₂ gap can be calculated and used as a surrogate for the cardiac index. Persistence of a PCO₂ gap >0.8 kPa (6 mmHg) after 24 h of treatment has been associated with a higher mortality [29].

CO₂ is 20 times more soluble than O₂ and thus as a result is a more sensitive marker of hypoperfusion. Where there is a barrier to O₂ diffusion as a result of hypoperfused or nonfunctional capillaries, CO₂ will still flow into the venous system. In the context of a patient with a ScvO₂ >70% and persistently elevated lactate, the PCO₂ gap may be elevated reflecting a barrier to O₂ diffusion at the level of the microcirculation.

20.5.4 Peripheral Perfusion Index

The peripheral perfusion index is based on the analysis of the pulse oximetry signal. It is the ratio between the pulsatile blood flow and non-pulsatile static blood flow in peripheral tissues. It is a noninvasive method that uses the ubiquitous pulse oximeter for its calculation. In a 2002 study by Lima et al. [30], a cutoff of <1.4 was suggested to predict poor peripheral perfusion and a peripheral perfusion index <0.2

predicted ICU mortality in septic patients following resuscitation, with accuracy similar to lactate [31].

20.5.5 Handheld Vital Microscopy

Handheld vital microscopes were introduced clinically in the 1990s and investigations of their use have played a key role in understanding the microcirculation in sepsis. They allow single RBCs to be visualized in the capillaries. The third and most recent generation of handheld vital microscopes is based on a mode of dark-field microscopy called incident dark-field (IDF) imaging. This device gives improved resolution and an increased number of capillaries can be seen in comparison to the previous generation, which was based on sidestream dark-field (SDF) imaging [32].

The most common anatomical location imaged is the sublingual circulation. Microcirculatory abnormalities visualized include increased heterogeneity of perfused vessels, proportion of perfused vessels, total density of small microvessels, and microvascular flow index (MFI) [27]. Currently the clinical relevance of microvascular alterations is expressed in terms of proportion of perfused vessels and MFI [10].

The MFI is used to characterize the velocity of microcirculatory perfusion. The screen is divided into four quadrants. The average flow of RBCs is then calculated and described as absent (0), intermittent (1), sluggish (2), or normal (3) [33]. An MFI <2.6 in combination with tachycardia >90 beats per minute (bpm) has been shown to be an independent risk factor for increased in-hospital mortality [34].

Handheld vital microscopes can also be used to measure the perfused boundary region of the microcirculation, which is calculated as the dimensions of the permeable part of the glycocalyx allowing penetration of circulating RBCs. This provides an index of glycocalyx damage [4]. The perfused boundary region has been shown to be increased in critically ill patients compared with healthy controls reflecting decreased thickness of the endothelial glycocalyx [35]. The perfused boundary region has been shown to be reproducible and have good inter-observer reliability, which makes it a promising tool for guiding resuscitation and decision-making in sepsis.

Monitoring of the microcirculation during resuscitation can help to verify whether interventions have been successful in restoring perfusion and oxygenation of the tissues and in restoring hemodynamic coherence.

20.6 How We Can Modify the Microcirculation in Sepsis

Microvascular perfusion is directly related to the driving pressure (difference between pressure at the entry and exit site of the capillary) and the radius of the vessel (to the fourth power) and inversely related to blood viscosity. Intravenous fluids are a mainstay of supportive care in sepsis and may help to increase microvascular perfusion by increasing the driving pressure, decreasing the blood viscosity, or affecting the interaction between circulating cells and the endothelium [36].

Volume expansion with fluid has been shown to improve microcirculatory perfusion in the early (<24 h) but not in the late (>48 h) phase following the diagnosis of severe sepsis [36]. It is not conclusive yet whether colloids or crystalloids are superior in improving the microcirculation.

Assessment of microcirculatory variables such as MFI may be helpful in determining the need for fluid therapy. A study by Pranskunas et al. [37] examined macrohemodynamic variables, such as oliguria, MAP, ScvO₂ and hyperlactatemia, and MFI, as a tool to select ICU patients eligible for fluid therapy. In patients with an MFI of <2.6, fluid therapy resulted in a significant increase in median MFI as well as a reduction in the median number of clinical signs of impaired organ perfusion. In contrast, in patients with an MFI >2.6 at baseline, fluid challenge did not increase the median MFI nor did it result in a reduction in the number of clinical signs of impaired organ perfusion. This suggests that in patients with a normal or near-normal MFI, causes other than microcirculatory flow were to blame for persistent organ dysfunction. Since none of the macrohemodynamic variables were able to discriminate an MFI <2.6, direct assessment of microcirculatory flow may help guide decisions regarding administration of fluids [37].

A study by Hanson et al. [38] looked at liberal fluid resuscitation in severe falciparum malaria. Severity of disease in terms of lactic acidosis correlated with the degree of erythrocyte sequestration as visualized by orthogonal polarized spectroscopy (OPS) rather than hypovolemia. Liberal administration of fluid did little to improve erythrocyte sequestration; however, it did increase the risk of potentially lethal complications of fluid overload and increased capillary permeability. In addition to suggesting against liberal fluid administration in severe falciparum malaria the results also suggest that direct visualization and assessment of the type of microcirculatory dysfunction may guide decisions about whether administration of fluid may be futile and lead to complications rather than resolution.

Further to that, hypervolemia has also been associated with microcirculatory dysfunction and increased degradation of the glycocalyx in sepsis. In a study in patients undergoing on- and off-pump coronary artery bypass surgery, increased levels of atrial natriuretic peptide (ANP) preceded elevation of inflammatory cytokines and shedding of the glycocalyx [39]. Chappell et al. also observed increased levels of ANP and shedding of the glycocalyx in response to volume loading and hypervolemia [40]. ANP has been shown to independently induce shedding of the endothelial glycocalyx in pig hearts as evidenced by increased levels of syndecan-1 and histologically visible degradation of the glycocalyx on electron microscopy. It in turn led to increased vascular permeability [41].

In a study of patients with severe sepsis, high levels of syndecan-1 were associated with the risk of intubation following large-volume fluid resuscitation compared to patients with low levels of syndecan-1. This may reflect the increased vascular permeability following degradation of the glycocalyx leading to increased risk of respiratory failure [42].

Apart from its use as a colloid, albumin may have other beneficial effects on the microcirculation. Sphingosine-1-phosphate (S1P) is an important plasma phospholipid for the maintenance of vascular permeability [43]. S1P suppresses the activity of metalloproteinase, which in turn protects against the loss of syndecan-1 and

degradation of the glycocalyx [44]. RBCs are an important source of S1P and albumin may attenuate the degradation of the glycocalyx by acting as a carrier of S1P from RBCs to the endothelium [45].

Transfusion of RBCs has been shown to improve the microcirculation independently of the macrocirculation and the hemoglobin level in hemorrhagic shock patients [46]. A systematic review by Nielsen et al. failed to find a benefit of RBC transfusion in most critically ill patients. However, they identified a number of studies that found that patients with abnormalities in tissue oxygenation or microcirculatory indices do demonstrate improvement following transfusion [47].

Venous vasodilators have been theorized to improve microcirculatory flow by dilating postcapillary venules, thereby increasing capillary flow, and decreasing transcapillary pressure and extravasation into the tissues. In vasoplegic shock, the macrocirculation is vasodilated whilst the microcirculation is vasoconstricted [7]. Studies on the effect of nitroglycerin on the microcirculation in septic shock have yielded conflicting results. Spronk et al. found that it did improve microcirculation [48], whilst Boerma et al. in a larger randomized controlled trial found that it did not improve the microcirculation compared with the placebo group [49]. In this study, both the placebo group and the nitroglycerin group achieved significant improvements in the microcirculation [49]. The median MFI of the nitroglycerin group improved from 1.67 to 2.71, and the placebo group went from 1.42 to 2.71. It may be that other resuscitative efforts were sufficient to improve the MFI to values approaching normal. Nitroglycerin may however be of use in septic shock if its use is decided based on the type of microcirculatory dysfunction and the resuscitation status of the patient, and it is titrated in combination with technologies that can monitor, directly assess, and quantitatively analyze the microcirculation.

Increasing the arterial blood pressure with increasing doses of vasopressors has not been found to improve MFI, proportion of perfused vessels, vessel density, or heterogeneity index [50, 51]. There may be a dissociation between increases in arterial pressure produced by vasopressor agents and improvement in microvascular perfusion and delivery of vital substrates. This is probably due to shunting between postcapillary venules and precapillary arterioles and due to a sustained increase in SvO₂ (as commonly happens in the initial stages of septic shock).

Finally, in critically ill non-bleeding patients, transfusion of fresh frozen plasma (FFP) resulted in a decrease in the levels of syndecan-1 and factor VIII, suggesting an improvement in the endothelium. This was accompanied by, and perhaps a result of, an increase in ADAMTS13 levels and a decrease in von Willebrand factor levels [52].

20.7 Conclusion

The microcirculation is the vital interface at which oxygen is delivered to cells. Without a functioning microcirculation the restoration of aerobic metabolism is impossible. Increased understanding of microcirculatory dysfunction helps to explain the persistence of tissue hypoxia despite restoration of normal macrohemodynamic parameters.

The importance of the microcirculation in critical illness is becoming increasingly clear. With newer and more sophisticated monitoring techniques, the microcirculation can be used to guide resuscitative efforts towards more targeted therapies. In addition to clinical examination and biochemical markers as methods of assessment, handheld vital microscopes allow direct visualization of capillaries and a number of indices and classifications have been developed that show good inter-observer reproducibility. As these devices become more widely available they may become routinely used in the management of sepsis and other conditions that affect systemic hemodynamics.

Despite the advances in our understanding of microcirculatory dysfunction there remains a deficit in knowledge regarding how best to treat it. For example, both hypo- and hypervolemia seem to negatively affect the microcirculation and the endothelial glycocalyx, and the type of fluid that is best for restoring perfusion and maintaining endothelial integrity remains to be established. As more clinical studies adopt handheld vital microscopy and investigate treatments based on microcirculatory status we may see that the management of hemodynamics in sepsis becomes more nuanced and individualized.

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