Microcirculatory assessment in daily clinical practice – not yet ready but not too far!

Avaliação da microcirculação na prática clínica diária – ainda não disponível, mas não tão longe!

Diamantino Ribeiro Salgado[1], Raphaël Favory[2], Daniel De Backer[3]

ABSTRACT

Shock is characterized by an alteration in tissue perfusion that may lead to tissue hypoxia. Recent guidelines recommend aggressive and early resuscitation therapy, but mortality rate is still unacceptably high. Unfortunately, traditional clinical surrogates used to guide resuscitation therapy poorly correlate with microcirculatory blood flow, a key determinant of tissue perfusion. New techniques that directly assess microcirculatory perfusion at the bedside have emerged as a complement to traditional macrohemodynamic parameters. These techniques have been supported by several studies showing microcirculatory alterations in different clinical settings. In addition, these microcirculatory alterations are related with outcome and persist regardless of arterial pressure normalization, being a better predictor of organ dysfunction and mortality than global hemodynamic and laboratory parameters. These findings allowed the concept of "microcirculatory-goal directed therapy", which is now in its preliminary phase, as the impact of many interventions still needs to be assessed. Finally, microcirculation assessment has also been explored in other medical fields such as perioperative, systemic arterial hypertension, heart failure, and hyperviscosity syndromes. In this review, we shortly present the characteristics of microcirculation and the main determinants of capillary blood flow, and we discuss advantages and limitations of some recently available techniques to evaluate microcirculation at the bedside, and how they could be useful for the general clinician in daily practice.

Keywords: Shock; Resuscitation; Microcirculation/pathophysiology; Hemodynamics/physiology; Multiple organ failure/pathophysiology; Prognosis

RESUMO

O choque é caracterizado por uma alteração na perfusão tecidual que pode levar à hipóxia tecidual. Diretrizes recentes recomendam uma terapia de ressuscitação hemodinâmica precoce e agressiva nos estados de choque, mas a taxa de mortalidade ainda é inaceitavelmente alta. Os parâmetros clínicos habituais usados para orientar a terapia de reanimação correlacionam-se mal com o fluxo sanguíneo capilar, um determinante essencial da perfusão tecidual. Novas técnicas que avaliam diretamente a perfusão da microcirculação à beira do leito surgem como um complemento aos parâmetros macro-hemodinâmicos tradicionais. Estas técnicas foram testadas em vários estudos que mostraram alterações microcirculatórias em diferentes situações clínicas de choque. Além disso, estas alterações microcirculatórias estão relacionadas ao prognóstico, e persistem independentemente da normalização da pressão arterial, sendo um melhor preditor de disfunção orgânica e mortalidade do que os parâmetros hemodinâmicos globais e laboratoriais. Estes achados permitiram lançar o conceito de "terapia dirigida por parâmetros microcirculatórios", atualmente em fase preliminar, uma vez que o impacto de muitas intervenções ainda precisa ser avaliado. Finalmente, a avaliação da microcirculação também foi explorada em outras áreas que não o choque, como o período perioperatório, hipertensão arterial sistêmica, insuficiência cardíaca e síndromes de hiperviscosidade. Nesta revisão, apresentamos sucintamente as características da microcirculação e os principais determinantes do fluxo sanguíneo capilar e discutimos as vantagens e limitações de algumas tecnologias recentes disponíveis para avaliar a microcirculação à beira do leito e como podem ser úteis ao clínico geral na prática diária.

Descritores: Choque; Reanimação; Microcirculação/fisiopatologia; Hemodinâmica/fisiologia; Falência múltipla de órgãos/fisiopatologia; Prognóstico

INTRODUCTION

Circulatory shock is a common problem of different medical and surgical diseases and remains associated

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with a high mortality[1]. Resuscitation of patients with shock is a great challenge since global hemodynamic variables provide only a rough estimation of organ perfusion. Since organ function is directly related to the degree of organ perfusion, guaranteeing optimal tissue perfusion is the main objective in the shock resuscitation therapy.

Using global hemodynamic markers may not be sufficient to avoid ensuing organ failure[2]. This may at least in part be explained by the fact that organ perfusion is mostly determined by microvascular perfusion, which can be affected independently of global and/or regional perfusion. The use of some surrogates of microcirculation function to guide therapy would be more interesting than traditional classical endpoints such as vital signs[3]. However, microcirculation assessment was possible only in experimental condition until very recently. Thanks to the improvement of technology, we are now able to evaluate both anatomy and metabolism of microcirculation at the bedside[4].

In this review, we present the main techniques that have been proposed to evaluate microcirculation at the bedside and discuss their limitations and possible clinical utility for the general practitioner.

What is the microcirculation and why may it be important to monitor?

Microcirculation is defined as a network of small vessels (arterioles, capillaries, and venules) with a diameter smaller than 100 μm[5]. Microcirculation has the vital role of delivering oxygen and other essential substrates to the cells and also clearing their waste products[6] (Figure 1). Aside from these metabolic aspects, microcirculation has other physiological functions, given that it occupies the largest surface of human body endothelium, extending up to 350 m^2[7]. Hence, it plays a role in control of vascular resistance, blood coagulation, inflammatory processes and immunological barrier[7]. Thus, one may intuitively consider that organ failure is related to microcirculatory dysfunction. In fact, degrees of microvascular abnormalities have been correlated with organ dysfunction and mortality in different pathological conditions[8-11]. Additionally, microcirculatory alterations can be already detected in the very early stage of disease, and may persist regardless of macrohemodynamic status[12,13]. Interestingly, some authors have reported that microvascular variables predicted more accurately organ dysfunction and mortality than traditional hemodynamic parameters[11,14]. These findings suggest that a "microcirculatory-goal directed therapy" might be a better resuscitation strategy in critically ill patients than resuscitation based on traditional clinical parameters used in daily practice, but interventions effective in improving the microcirculation still need to be identified before this concept may be tested in a well designed clinical trial.

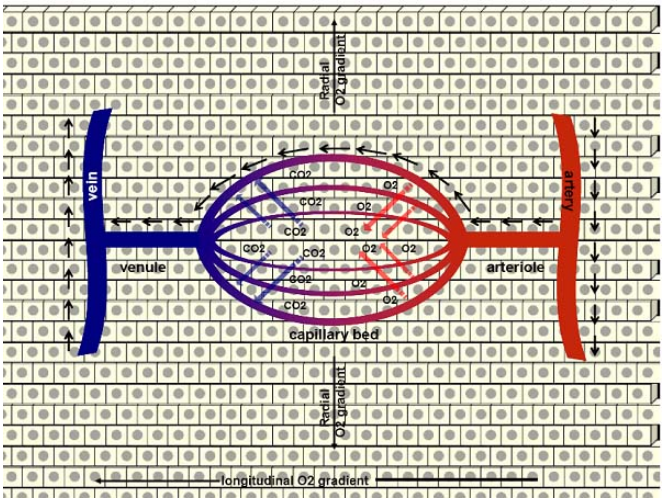


Figure 1. Schematic representation of microcirculatory network

Main regulatory mechanisms of microcirculation

Regulation of capillary blood flow and, consequently, tissue perfusion, is a complex phenomenon that includes the capillary driving pressure, arteriolar tone, hemorheology, and capillary patency[5]. Endothelial cells have the ability of sensing mechanical forces (shear stress) produced by blood flow and local stimuli, such as pH, lactate, tissue concentration of O_2 and CO_2, and neurohumoral substances. As a result, endothelium could modulate the number of well-perfused capillary, i.e., the functional capillary density, through an up and downstream crosstalk to arterioles and venules, in order to supply tissue metabolic requirements[4,15].

The greatest endothelial body mass (approximately 110 g) lines the distal microcirculation[7], and activation of endothelial cells is an important cause of microcirculatory insufficiency[16]. A number of factors could trigger endothelium activation, including interaction with leukocytes, platelets, components of bacteria cell wall, activation of coagulation pathway, and several plasma inflammatory mediators. Once activated, endothelial cells suffer structural changes such as cytoplasmic swelling and shedding, and acquire new functions as expression and release of substances, which allow the host to face a stress[17]. However, endothelial dysfunction may occur in extreme conditions, such as severe sepsis and trauma, followed by leukocyte trafficking and fluid leakage to the interstitium, hypovolemia, hypotension, and uncontrolled coagulation, resulting in impaired

tissue perfusion, hypoxia and, ultimately, organ failure[18].

Other mechanisms may additionally play a role on the regulation of capillary blood flow. Hence, an imbalance between the effects of vasodilator and vasoconstrictor agents, such as nitric oxide (NO) and catecholamines, angiontensin II, and endothelin-1 may exacerbate the shunting area[19]. Furthermore, glycocalyx, a thin layer of glycolipids, glycoprotein, and proteoglycans that lines the luminal surface of endothelial cells, has major functions, such as control of vascular permeability, blood flow resistance, leukocyte adherence, and platelet activation. Recently, glycocalyx has gained great attention after some reports of glycocalyx disruption and endothelial dysfunction in sepsis and other inflammatory diseases[20,21]. Finally, and still controversial, mitochondrial dysfunction could be associated with signs of microcirculatory insufficiency, but whether it is a cause or a consequence of oxygen extraction deficit is still a matter of debate even though experimental data suggest that microvascular alteration precedes (and may lead to) mitochondrial dysfunction[22].

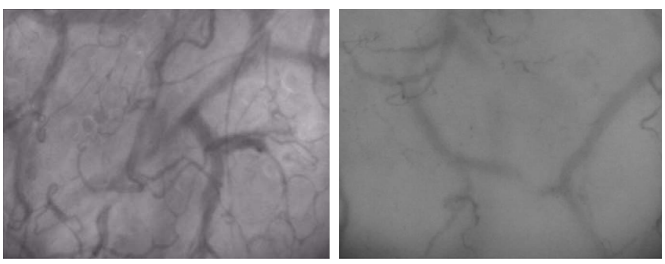
How to evaluate microcirculation at the bedside

Perfusion of microvasculature at the bedside can be essentially assessed by Laser Doppler flowmetry, intravital microscopy, and orthogonal polarization spectral (OPS) imaging techniques. Tissue oxygenation can be evaluated by transcutaneous PaO_2 and near-infrared spectroscopy (NIRS) technique.

Laser Doppler is a technique based on reflected laser light by moving erythrocytes that allows quantification of global microcirculatory blood flow in a small tissue volume of 0.5 mm^3. Laser Doppler perfusion imaging and laser speckle imaging are newer variant techniques from that former, which enable repetitive assessment of larger areas in bidimensional images[4]. However, it is important to mention that further information on microvasculature can be drawn through ischemia/hyperemia challenge tests or heating probes.

Intravital microscopy (IVM) is considered as the gold standard for *in vivo* exploration of microcirculation. In animals, this technique allows visualization of most of the vascular structures and circulating cells (red and white blood cells, platelets). When coupled with dyes, it can visualize vessels containing only plasma, the glycocalyx and it can measure oxygen tension, reactive oxygen species, nitric oxide, etc. In humans, the nailfold area is the only site where IVM can give images without dyes for thickness of nail fold capillaries allows transillumination. For safety reasons, dyes cannot be used in humans. Since this area is very sensitive to temperature changes and vasopressor agents, this technique can not be used in critically ill patients.

The Orthogonal Polarization Spectral (OPS) imaging technique is a relatively new non-invasive method developed for the assessment of the human microcirculation, ideal to study microcapillaries under thin mucosa layer such as those of tongue, conjunctiva, and serosa. This device consists of a small videocamera attached to a light source with filters that capture images by a probe connected to a personal computer via an optic fiber connector and a videocard. The examined tissue is illuminated with polarized light (wavelength of 548 nm which is both deoxy and oxyhemoglobin light absorption) allowing the best imaging of microvessels. Within the tissue, up to depth of almost 300 μm, the light is depolarized and reflected to the camera. OPS was validated in several animal experiments by comparison with fluorescence intravital microscopy. Sidestream Dark-Field (SDF) is a further development of OPS technique based on slightly different principles with another wavelength and isolation of emitting and illuminating light. This allows a better resolution and clarity in the same kind of hand-held microscope easy to use at the bedside[23]. In humans, OPS and SDF have been successfully applied to investigate the microcirculation of the tongue, skin, liver and the brain (Figure 2). Several measurements can be obtained from these images[24], including functional capillary density (density of perfused capillaries), total vessel density, and a semi-quantitative estimation of the flow patterns. Although semi-quantitative, these scores have a good reproducibility for flow estimation through different sites[12-14,25-27], with good agreement of flow measurements with software in experimental conditions[28], even though the analysis may sometimes be more complex in the gut[29]. Some software for image analysis are currently available,



A B

Figure 2. Sidestream Dark Field imaging pictures of sublingual capillaries from patients with normal (A) and abnormal (B) microcirculation. A clear difference in the capillary density could be observed at the static image, while differences in the flow patterns (greater frequency of no flow or intermittently perfused vessels) could be detected only in the dynamic sequences

but the technical procedure is somewhat still semi-automatic and allows only measurements of flows lower than 1 mm/sec.

NIRS is a non-invasive method assessing tissue oxygenation using near-infrared spectroscopy (Figure 3). It is a special form of reflectance spectroscopy. It allows measuring, most of the time

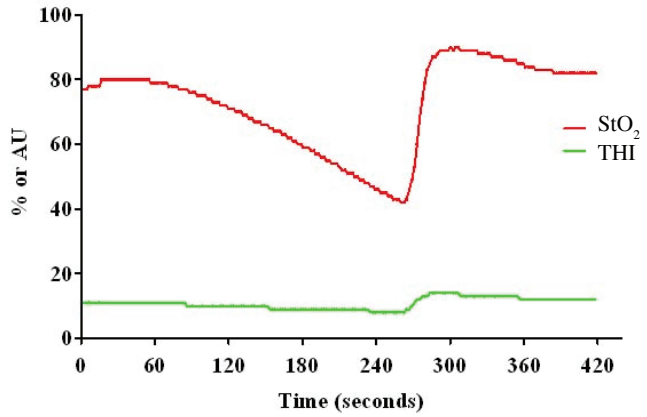


Figure 3. Schematic representation of StO_2 and THI (total hemoglobin index) curves during a dynamic occlusive test with Near-infrared Spectroscopy (NIRS) technique. AU, arbitrary units for THI curve

at the thenar eminence, the tissular saturation of oxygen (StO_2). This term, although widely used, is appropriate as the technique mostly measures hemoglobin oxygen saturation measured in a volume of illuminated tissue with a near infrared wavelength. Hence it measures the saturation of hemoglobin in blood vessels (predominantly vessels with a diameter less than 1 mm, thus concerning more micro- than macrocirculation[30] comprised in a piece of tissue, but not the O_2 saturation of the tissue itself. The distinction between arterial, capillary and venous compartments of oxyhemoglobin measured is obviously not possible and the StO_2 value represents a weighted average of StO_2 in all these vessels. Different manufacturers use different equations so that both depth and proportion of arterioles and venules may vary, which may influence the StO_2 value and makes comparison between studies sometimes difficult. The thenar site is chose because it is less sensitive to edema, but other sites may be studied as well. Of note, the StO_2 will vary according to the site used for a given patient at a given time. A correlation between central venous oxygen saturation ($ScvO_2$) and StO_2 has been challenged[31-32]. Dynamic testing with a three minutes ischemic period with a tourniquet gives more interesting information than basal measurement of StO_2. Indeed, the descending slope of the StO_2 signal is mostly influenced by tissue oxygen consumption and the amount of blood in the tissue while the ascending slope (after the end of ischemia up to hyperemic phase) reflects maximal recruitability of the microcirculation, an index of microvascular responsiveness.

Transcutaneous oxygen pressure ($TcPO_2$) has been used as a surrogate of arterial blood gazes in neonates since a long time. It has been used in adults where $TcPO_2$ has been found to be correlated with PaO_2 during normovolemia and hypoxemia and more with cardiac output during hypovolemic low flow shock[33]. Similarly, $PtcCO_2$ was observed to track the course of arterial carbon dioxide tension ($PaCO_2$) during adequate cardiac output, but it became flow-dependent during low flow shock. As it gives the average value of PO_2 in the sampled volume and is mostly influenced by arteriolar PO_2, it does not measure tissue or microvascular oxygenation. Moreover, the heating period of electrode and the calibration are major concerns for bedside monitoring.

CLINICAL UTILITY

Sepsis

Microcirculatory studies in sepsis have greatly contributed for the understanding of the main mechanisms of cellular metabolic dysfunction. Severe sepsis and septic shock are particularly susceptible to microcirculatory alterations (Figure 3), which are more marked than in other types of shock[34]. Many factors could predispose microcirculatory defects in sepsis, including an increased secretion of inflammatory cytokines, endothelial and coagulation activation, hemorheological dysfunction, glycocalyx alterations, and high levels of vasoconstrictive substances and altered NO secretion[35].

Several experimental and clinical studies have reported sepsis-associated microcirculatory insufficiency. Using OPS technique, our group demonstrated reduced sublingual capillary perfusion in patients with severe sepsis and septic shock, and that the persistence of those abnormalities was associated with higher mortality[11-12]. Other authors also showed that these abnormalities are present very early in the sepsis, and that their evolution in response to resuscitation procedures was associated with changes in organ failure scores[13-14].

Until this moment, microcirculatory assessment was useful mostly to understand the pathophysiology of sepsis (a distributive shock) and to identify patients who may have persistent tissue perfusion abnormalities after correction of global hemodynamic variables, highlighting that resuscitation protocols based on macrohemodynamic parameters are not enough to prevent sepsis-associated organ failure and mortality. However, it is still uncertain whether the implementation of a "microcirculatory-goal

directed resuscitation therapy" will prove to be useful in sepsis. Before conducting such study, we need to better define how therapeutic interventions may affect the microcirculation in different clinical contexts (see below).

Heart failure

Heart failure is a common medical problem responsible for a significant burden on health care sources, high morbidity and mortality rates, despite a continuous improvement in pharmacological therapies[36]. Patients with decompensated heart failure and cardiogenic shock typically present increased systemic vascular resistance, high cardiac filling pressure, low cardiac output, and SvO_2. In addition, the incidence of microcirculatory abnormalities (Figure 3) is elevated in these groups of patients and independently correlated with a higher risk of death[9]. Vasodilators are a mainstay therapy for heart failure as they reduce afterload, improve heart performance, and reduce cardiac-related death. Furthermore, vasodilators could also act on microcirculation reducing shunt areas and improving organ perfusion. Recently, den Uil et al. demonstrated that nitroglycerin, a known vasodilator with NO donor properties, was able to reverse microcirculatory abnormalities in patients with acute heart failure[37]. However, whether correcting microcirculatory dysfunction will be associated with the improvement of patient outcome in a microcirculation-guided approach still remains to be proved.

Head trauma and subarachnoid hemorrhage

Near Infrared Spectroscopy has been used to detect intracranial subdural and epidural hematomas[38] with a sensitivity of 0.87, whereas it was not useful to detect postoperative hematomas. The group of Ince in Nederlands reported interesting findings using the OPS technique in subarachnoid hemorrhage where they look at microvessels during neurosurgery procedures. Functional capillary density was decreased following SHA[39]. More importantly, microvascular spasms could be noticed during the surgery while vasospasm was not yet detected by usual techniques. Another study[40] showed increased contractile responses of the cerebral arterioles in the presence of subarachnoid blood (and induced by hypocapnia), suggesting increased microvascular tonus.

Hyperviscosity and tumoral syndromes

Fluorescein angiography has allowed retinal microcirculation assessment[41] in patients suffering from hyperviscosity syndromes: Waldenström syndrome, cryoglobulinemia and plasmocytoma. An increase in arteriovenous transit time was noticed in patients who had a two-fold increase in plasma viscosity. Unexpectedly, no change in the microvascular sublingual flow could be detected by the OPS imaging technique in patients during Sickle Cell Disease in painful crisis[42].

OPS has been used to assess the effects of antivascular tumor treatment in a model of hamster and has been used evaluation of oral squamous cell carcinoma in humans[43].

A recent case report[44] showed images of stopped flow in a leukemic patient which disappeared when white blood cell count was normalized. We failed to observe similar findings in several patients with leukocyte counts above 100,000 /mm^3 (unpublished observations), thus the role of microvascular evaluation in patients with leukostasis remains to be evaluated.

Perioperative setting

Microcirculatory response to surgery

Several factors can impact microcirculation during and after surgical intervention: hypoperfusion related to intraoperative important blood losses, inflammation due to incision and manipulation of mesentery, inflammation, sympathetic stimulation (arteriolar constriction and decrease in microvascular flow). Endothelium integrity can be altered, leading to capillary leak, and leukocyte rolling and adhesion are enhanced after surgery. TNF-α seems – at least in animal models – to be a pivotal mediator implicated in these abnormalities. Selectins, vascular adhesion molecule 1, intercellular adhesion molecule 1 also seem to contribute to this microvascular dysfunction. Leukocyte trapping, vasoconstriction, and tissue edema at microcirculatory beds may cause increase in the radial oxygen gradient leading to tissue hypoxia and organ dysfunction. A good review of this topic is found elsewhere[45].

Cardiopulmonary bypass

Bauer et al. looked after the effects of cardiopulmonary bypass (CPB) on sublingual microcirculation. Functional capillary density (FCD) decreased whereas there were no effects on vascular diameter or velocity. This FCD normalized one hour after discontinuation of CPB and was correlated with hemoglobin concentration and body temperature. Rolling of leukocytes was increased threefold one hour after discontinuation of CPB[46]. Other reports suggest that these abnormalities may persist for a longer period of time[47].

Major surgery

Microvascular abnormalities can also be observed in patients undergoing high risk surgery. Recently, Jhanji et al.[27] reported that patients who presented

complications after major abdominal surgery had perioperative and early postoperative sublingual microcirculation abnormalities. Interestingly, global oxygen transport, lactate levels, transcutaneous oxygen pressure, and even cutaneous red cell flow measured by laser-doppler flowmetry could not identify patients who would develop complications. This is in line with data showing that global hemodynamic parameters are not correlated with macrohemodynamic ones. Unfortunately, the latter are sometimes the only accurate data we may probably have to assess severity or to perform a therapeutic intervention. The field of perioperative assessment of microcirculation is wide open and gives promising perspectives.

How to treat microcirculatory dysfunction

Global hemodynamic optimization is a prerequisite for good microcirculation. Nonetheless, we can still find microcirculatory abnormalities even after relatively stabilized global hemodynamic parameters. Some conditions could particularly be considered during the treatment of microcirculatory abnormalities.

Anesthetic agents

Anesthetic agents can impact microcirculation. In experimental conditions, halogenated gases, benzodiazepines, opiate agents, and propofol have been shown to alter microcirculation[48-49]. In humans, the impact of these agents has been less well studied. Two recent studies reported microcirculatory alterations after commonly used sedative-anesthetics agents; Lamblin et al. found worsened microcirculation responses after sedation with midazolam and/or sulfentanil in critically ill patients[50]. In addition, propofol was associated with reduced capillary perfusion density in patients during general anesthesia[51]. Compared to abnormalities described in severe pathological processes such as sepsis, these abnormalities are usually minor. However, it is possible that these further deteriorate the microcirculation in these patients, and this may be one of the reasons why sedation holidays have been shown to improve the outcome.

One should be cautious when using sedatives in order to perform good quality recordings for videomicroscopic techniques as well as for laser Doppler flow. Whenever possible, doses of these agents should be kept constant during evaluation of the microcirculation.

Anticoagulants

As microvascular abnormalities coincide with activation of coagulation in various conditions including sepsis, a link between the two has been suggested. Although it is difficult to dissociate both factors, microthrombosis is infrequent but this does not rule out the implication of activated coagulation pathways in microvascular dysfunction. As various agents with anticoagulant properties have been used in the therapy of patients with sepsis, several studies have evaluated the impact of these agents on the microcirculation.

All animal studies assessing the effects of activated protein C on microcirculation reported a beneficial effect[20,52-53]. We showed evidence of a beneficial impact on perfused capillary proportion as early as four hours after the beginning of activated protein C infusion in septic patients with an on/off pattern[54]. Interestingly, it seems that the anticoagulant properties of the drug may not be implicated in these microvascular effects. Improvement in white blood cell rolling and adhesion as well as preservation of glycocalyx may also be implicated[20,52-53].

Other anticoagulants may also improve the microcirculation. In endotoxin shock, antithrombin also blunted microcirculatory abnormalities[55]. Here the mechanism may also be independent of anticoagulant properties, as the drug was shown to inhibit white blood cell rolling and, more importantly, infusion of a modified antithrombin with preserved anticoagulant properties but deprived of its site of ligation to endothelium failed to affect microvascular perfusion and white blood cell rolling. Finally, hirudin, a pure thrombin inhibitor, impairs microvascular perfusion in septic animals, suggesting that anticoagulation alone may not be effective in improving the microcirculation[56].

Anti-inflammatory drugs

Since activation of inflammatory mechanism are closely related to microcirculatory abnormalities, one would considerer that drugs with anti-inflammatory effects could be beneficial to treat or prevent these capillary disorders. For example, pre-treatment with dexametasone in an experimental rodent model of sepsis was able to prevent hypotension, vasodilation, and arteriolar vasomotion dysfunction after LPS administration[57]. In a very recent prospective study, Büchele et al. demonstrated that a stress dose of hydrocortisone was associated with improvement of capillary perfusion defects in septic shock patients, and this effect was already present after the first hour of steroid treatment[58].

Vasodilators

Topical application of acetylcholine has been shown to totally reverse microvascular abnormalities in patients with sepsis[12,20] as well as in patients with severe heart failure[9]. One may thus ask whether systemic vasodilator agents also improve the microcirculation.

Angiotensin-converting enzyme (ACE) inhibitors had been shown to improve endothelium-dependent vasodilation via a NO-dependent mechanism in a rabbit model of endotoxin shock[59]. However, no effect could be seen in endothelial histological injury or tissue factor expression in this same model.

Nitroglycerin effects on microcirculation derangements had been tested in heart failure[37] and sepsis[60]. In acute heart failure, low doses of nitroglycerin (33 μg/min) increased perfused capillary density (assessed by SDF) for about 15%[37].

Verapamil was shown to induce significant arteriolar dilatation, increase microvascular flow and functional capillary density, and decrease arteriolar transmural PO_2 difference of the awake hamster window chamber preparation[61].

At this stage, it is quite difficult to suggest that vasodilator agents should be used to treat the diseased microcirculation. The impact of induced hypotension cannot be neglected. This was well illustrated in an experimental study by Nakajima et al.[62]. In that study, the authors observed that arginine, a NO donor, increased microvascular perfusion in septic animals when blood pressure was normalized with vasopressor agents, but not when it was given alone in hypotensive animals. In addition, the long-term effects of these agents, which often also have important cellular and metabolic effects, cannot be neglected.

Fluids

In sepsis, diminished intravascular volume associated with increase in interstitial fluid has been advocated to impair tissue oxygenation and transport of energy substrates to cells.

The type and the volume of fluids used to resuscitate patients are very important. We should not only focus on its volume restoring properties but also on endothelium, microvasculature, and inflammation. Even though starches improved microvascular perfusion in short-term animal studies[63], the VISEP study[64] nicely illustrated that repeated and high doses of starches may have deleterious effects on renal function and coagulation.

Hypertonic fluids could be beneficial because they can increase cardiac output (preload effect and positive inotropism), promote arterial vasodilation (hyperosmolarity), and reduce tissue edema (osmotic gradient) and may consequently decrease the oxygen diffusion distances. Use of hypertonic solutions has been reported to improve microvascular perfusion in numerous pathological conditions[65].

Red blood cells transfusion has been shown to have variable effects on sublingual microcirculation[66]. Interestingly, these seem to have favorable impact on the microcirculation when it is markedly altered prior to transfusions while it may even impair the microcirculation when it is close to normal at baseline. This illustrates why a direct evaluation of the microcirculation may be useful, as these divergent effects on tissue perfusion were not noticed by classical monitoring tools.

Catecholamines

Dobutamine has been shown to have beneficial microcirculatory effects in patients suffering from septic shock[67]. There was a significant increase of cardiac output and oxygen transport, but mean arterial pressure remained constant. The capillary density increased as well as the proportion of perfused capillaries. This increase was inversely correlated to a decrease in lactate levels, but not with cardiac output or mean arterial pressure. However, dobutamine did not recruit all capillaries, and the global impact of this drug was quite limited.

Vasopressor agents may theoretically have potentially detrimental effects on the microvascular bed mediated by vasoconstriction. Vasopressin and norepinephrine similarly altered microvascular perfusion in non-hypotensive animals[68]. On the contrary, both agents failed to impair microvascular perfusion when they were administered to correct hypotension in septic animals[62].

Limitations and pitfalls

Although these technologies are attractive and interesting at a first glance, there are some limitations that must be taken into account. For SDF images, the video capture is one of the most important steps where problems may occur. For example, presence of secretions, control of movement, correct adjustment of focus and light intensity must be done systematically in order to obtain good quality images. In addition, great care should be taken to prevent pressure artifacts, as these would lead to spurious flow stagnation even in the large venules[24]. Finally, the images are analyzed offline and this process is time-consuming, preventing real time assessment of therapies at the bedside. It has recently been shown that bedside evaluation can satisfactorily evaluate the microcirculation[69], thus opening some opportunities for wider use at the bedside.

Regarding NIRS, StO_2 measurement without occlusion test are of limited value as these represent the average of the hemoglobin oxygen saturation in all vessel segments (arterioles, venules, and capillaries) in the analyzed tissue volume, and the relative contributions of each part could not be determined. Secondly, NIRS is not a direct measure of microcirculatory blood flow, and, therefore, the observed elevation of tissue StO_2 does not necessarily

reflect a local increase in delivery after provocative ischemic test. Thirdly, the quality of measurements may be influenced by temperature and thickness of subcutaneous tissue.

Laser Doppler technique which measures the average blood flow in small tissue volume is unable to differentiate the contribution of each microcirculatory segment and also does not detect hematocrit changes. A more comprehensive review of microcirculatory technical limitations can be found elsewhere[70-71].

CONCLUSIONS

Hemodynamic shock is a common emergency situation faced by the general physician. Early goal-directed resuscitation based on macrohemodynamic parameters has been proven useful but still insufficient, since vasodilatory septic shock mortality continues unacceptably high. One possible explanation is the persistence of microcirculatory and mitochondrial dysfunction that were shown dissociated from traditional vital signs and clinical surrogates of tissue perfusion. Thanks to relatively simple techniques, which allow assessment of functional and anatomical microcirculation at the bedside, a new horizon is now open to explore innovative shock resuscitation strategies – the concept of microcirculatory/mitochondrial-goal directed therapy. In addition, these techniques could be useful in other clinical settings such as perioperative, cardiogenic shock, arterial hypertension, head trauma, hyperviscosity syndromes.

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