Microcirculatory Alterations in Sepsis

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INTRODUCTION

The microcirculation is needed for gas and nutrient exchange in tissues. A healthy microcirculation is essential for organ function [1]. Severe sepsis is a disease of the microcirculation. Yet resuscitation for severe sepsis mainly focuses on the macrocirculation and macrocirculatory parameters like systemic blood pressure.

The reasoning is that a good mean arterial pressure and cardiac output will ensure good tissue perfusion. This sounds sensible but there is evidence suggesting that recovery of the macrohaemodynamics does not always ensure recovery of the microcirculation. Then under the guise of a normal blood pressure organ function continues to deteriorate and multi-organ failure sets in [2].

It would be ideal if these changes could be detected early, before organ failure sets in and be used to guide therapy. This booklet aims to deal with the perfusional derangements and related management issues in severe sepsis.

PHYSIOLOGY OF THE MICROCIRCULATION

Structural properties

The microcirculation is made up of branching arterioles, capillaries and venules which form networks.
1) Each small artery gives rise to several arterioles which in turn divide into smaller branches. Arterioles are resistance vessels, they have circumferentially arranged smooth muscle cells, and are able to change their calibre and adjust blood flow according to local demand.
2) Capillaries are exchange vessels with a single layer of endothelium. They are fenestrated, non-fenestrated or discontinuous in different organs. Each terminal arteriole can give off 2 to 25 capillaries.
3) Venules are capacitance vessels. They are wider than arterioles and more numerous. They hold almost 70% of the circulating blood volume. [4,5]

Heterogeneity in structure

The vessels in each category are often idealized as being identical in structure. This is not true, because in reality there is great variability with regard to arteriolar tone, vessel calibre and number of branches. The point is that the normal architecture of the microcirculation is heterogeneous and uniformity in perfusion can only be ensured through local auto-regulatory mechanisms [6].

Special characteristics of the microcirculation regarding perfusion and oxygen delivery:

The microcirculation is constantly adapting to the varying needs of the tissues it supplies and ensures adequate blood flow across a wide range of pressures.

Although capillary networks vary in density and architecture and some differences in flow and oxygen supply can be expected, heterogeneity of perfusion is minimal. [3,6]

Perfusion is determined by capillary density and blood flow. Increase in capillary density does occur, but usually in response to chronic hypoxia or during training and it takes weeks. There is only a small capacity for capillary recruitment in the acute setting because normally very few capillaries are shut down [7]. The circulatory system uses convection, which is flowing fluid to transport various substances, including oxygen, around the body [6]. Oxygen loss from blood occurs as soon as it leaves the lungs. However this is not significant until blood reaches the smallest arteries. Blood velocity in larger vessels allows little time for gas exchange [8].

Blood flow is determined according to Pouiselle's law. Flow in a capillary is proportional to the driving pressure (ΔP) and to the fourth power of the capillary radius (r), and inversely proportional to capillary length (L) and blood viscosity (η):

$$Capillary\ flow = \pi\ r^4 P\ /\ 8L\eta$$

In practice changes in radius (to the fourth power) have the greatest effect on flow. [14] This is brought about by auto regulation by local tissue factors.

Once in the microcirculation oxygen relies on diffusion to reach individual cells. Molecular diffusion can only occur over short distances and, the diffusion distance of oxygen in oxygen consuming tissue is only 100μm [6].

The rate at which oxygen exits vessels depends on its diffusion constant and also the velocity at which blood transits the vessels. Once in the arteriolar network oxygen is offloaded via radial and longitudinal gradients. The radial gradient is created between blood and oxygen consumption in tissues. This radial loss of oxygen results in a longitudinal gradient with progressively less oxygen along the length of the vessel. [8] The longitudinal gradient may have a role in regulation of blood flow. Maximal adrenergic innervations in lower order arterioles could contribute to changes in vessel diameter and blood supply. [8]
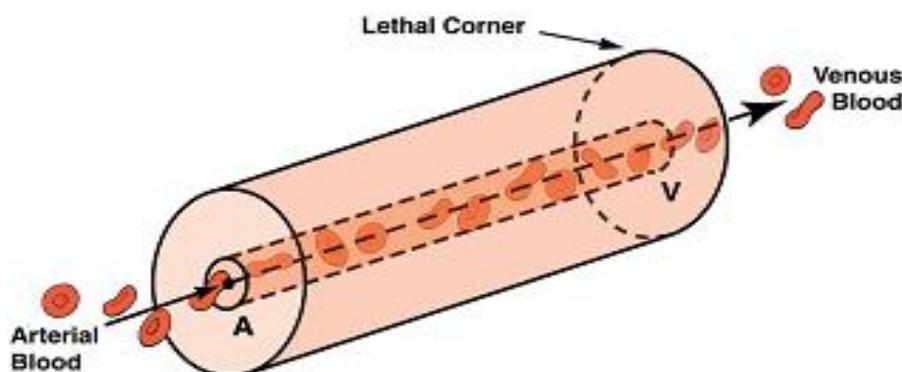
The Krogh model shows a cylindrical area of tissue around each vessel. Conceptually the radial and longitudinal oxygen loss can result in an area at the venous end, the 'lethal corner' supplied by deoxygenated blood and undergoing anaerobic metabolism. [2]

There is also a dynamic decrease in haematocrit in the microvessels compared to systemic haematocrit due to the presence of the endothelial surface layer. Individual haematocrit in different vessels can vary depending on vessel size and blood velocity. [5,8]

In summary the microcirculation shows heterogeneity with regard to blood flow, resistance and even haematocrit and oxygen supply. Despite this, autoregulatory mechanisms ensure homogenous oxygenation of tissues. [9]

Autoregulation

Changes in vascular tone are influenced by extrinsic (neural and humoral) and intrinsic factors. Intrinsic factors are myogenic (sensing stress and strain), metabolic (based on O_2, CO_2, lactate, and H+). The intrinsic factors are involved in autoregulation. These factors can have direct effects on vascular smooth muscle and indirect effects via the vascular endothelium.

There are two main theories regarding effects on vascular smooth muscle. The myogenic theory describes the increasing tension of the blood vessel wall as a response to increased blood flow. The metabolic theory explains the matching of blood flow to the metabolic activity of the tissue. A decrease in supply of oxygen releases potassium, hydrogen ions (lactic acid), phosphate, carbon dioxide, prostaglandins and adenosine. These act directly on vascular smooth muscle, causing vasodilation. This is called functional hyperaemia. A decrease in metabolites will reduce vasodilation.[14]

Properties of the endothelium:
Endothelial cell-to-cell signalling transmits information upstream about downstream hemodynamic conditions [4]. The endothelial glycocalyx is integral to the vascular barrier and involved in shear stress sensing. Endothelial cells produce nitric oxide in response to shear stress and this is an important vasodilator.

Nitric oxide is produced by nitric oxide synthetase (NOS) of which there are many isoforms. The constitutive isoforms are calcium-dependent and the inducible isoforms are calcium-independent. In the endothelium the constitutive NOS (eNOS) produces a constant, low-level of nitric oxide (NO) through the oxidation of L-arginine. NO has an important vasodilatory role by activating guanyl cyclase. [10,11] Red blood cells when sensing a decrease in oxygen saturation cause local release of nitric oxide, leading to capillary dilation at the site [9].

PATHOPHYSIOLOGY OF THE MICROCIRCULATION IN SEPSIS
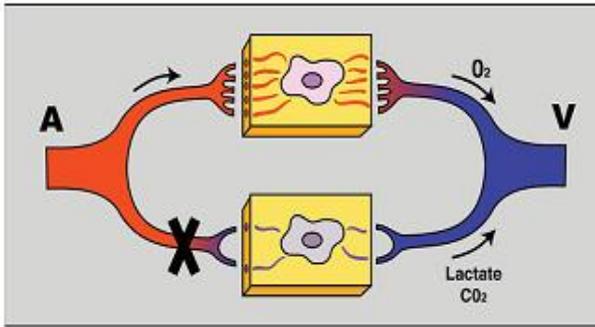
An increase in the heterogeneity of perfusion is a hallmark of sepsis. Capillaries with stopped flow are seen next to capillaries with normal flow or hyperdynamic flow. This unreliable perfusion leads to areas of hypoxia.[9]

The altered flow patterns are due to microvascular plugging and auto-regulatory dysfunction [5,9]. Injury to the endothelial glycocalyx leads to uncovering of adhesion molecules and increased interaction of leucocytes with the endothelium. Leucocyte rolling and adhesion to endothelial cells is observed in sepsis. There is also increase in platelet rolling and adhesion. Coagulation pathways are triggered leading to fibrin deposition on the endothelium and formation of microthrombi. [7]

Microvascular plugging is caused by microthrombi and red and white blood cells that become less deformable during sepsis. [5,7]

Autoregulation is lost via many mechanisms. Endothelial injury and destruction of the endothelial glycocalyx disturbs cellular signalling pathways. Smooth muscle cells loose adrenergic sensitivity and tone. The balance between vasodilators and vasoconstrictors in the microcirculation is lost. The nitric oxide system plays a central role in the microcirculation. This system is disturbed in sepsis. The inducible isoform (iNOS) is heterogeneously expressed leading to variable vasodilation and shunting. [5,7] NO reacts readily with molecular oxygen or superoxide (which is also produced by iNOS) to form $ONOO^-$ which causes damage to DNA and cell membranes [8].

This loss of auto–regulation leads to an independence (or disconnection) of microcirculation from the rest of the circulatory system. This is the reason that a good blood pressure cannot reliably improve microcirculatory dysfunction. [2,5]

Heterogeneity in perfusion

The diffusion distance of oxygen depends on the density of capillary and arteriolar supply. If this distance exceeds a critical point, anaerobic metabolism will likely occur. [2] Global tissue hypoxia, seen as a low mixed venous O_2, means the venular ends of capillaries contain de-oxygenated blood. This is explained by the 'Krogh model'. [2]

However a high or normal SvO_2 does not exclude tissue dysoxia from occurring. One explanation for this phenomenon is abnormal cellular O_2 utilization – cytopathic hypoxia. An alternate explanation is microcirculatory shunting. When microcirculatory units are shut down the area for gaseous exchange is reduced.

Blood is redirected to capillaries that are still open, but these are exposed to supranormal amounts of oxygen. Then at the venous end the result is venous hyperoxia and an elevated serum lactate. [2]

An interesting development in attempting to define microcirculatory dysfunction in sepsis is observation of flow abnormality via Orthogonal Polarization Spectral (OPS) Imaging. Shunting is a key component of the distributive shock seen in sepsis.

This condition occurs in the presence of normal or even supranormal levels of cardiac output. In other types of shock, like hypovolaemic or cardiogenic shock, the decrease in cardiac output causes a uniform decrease in flow which is observed in arterioles, capillaries and venules. [9]

Classification of microcirculatory flow abnormalities

Class I abnormality:
All capillaries are stagnant with normal or sluggish venous flow. This is seen in septic patients where high-dose vasopressors are required to achieve a normal blood pressure.

Class II abnormality:
Empty capillaries are seen next to capillaries with continuously flowing red blood cells. The reduced capillary density causes regional hypoxia. The perfused capillaries have red blood cells with high haemoglobin saturation, which shows poor oxygen off-loading caused by a reduction in capillary surface area for gaseous exchange. These changes are observed in patients who have had cardiac bypass with extracorporeal circuits, or extracorporeal membrane oxygenation (ECMO).

Class III abnormality:
Capillaries with stagnant blood cells next to capillaries with normal flow. Septic patients, sickle cell patients and critically ill malaria patients showed these abnormalities. The malaria patients who were comatose had normal hemodynamics in combination with high lactate levels.

Class IV abnormality:
Hyperdynamic flow is seen in some capillaries next to capillaries with stagnant cells. Venules also show hyperdynamic flow. This is seen in resuscitated hyperdynamic septic patients.
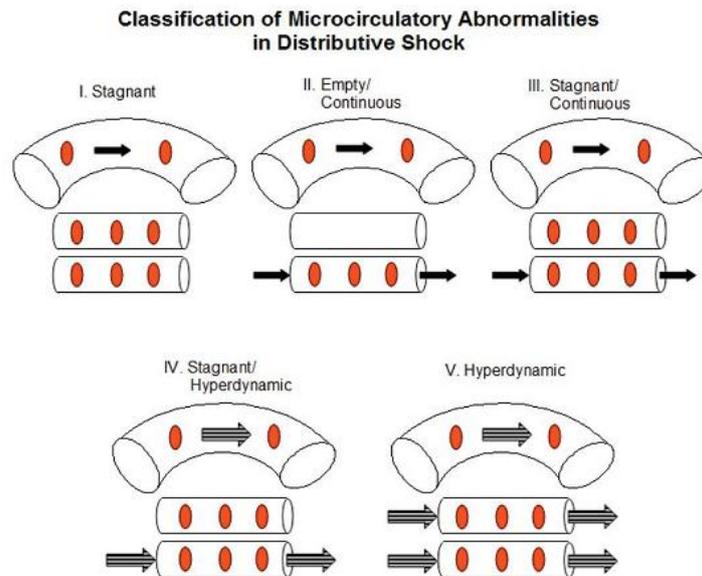
Class V abnormality:
Hyperdynamic flow is seen at all levels of the microcirculation. Blood cells travel at such high velocities that individual cells cannot be distinguished from each other. Interestingly, this type of abnormality is seen in extreme exercise. The pathogenic nature of class V abnormalities in septic patients still has to be determined. [9]

Classifying microcirculatory flow abnormalities in distributive shock

Class	Capillary hemodynamics	Disease states observed in
I	Stagnant	Pressure guided resuscitation from sepsis
II	Continuous/capillary fall-out	On-pump CABG surgery, ECMO
III	Continuous/stagnant	Resuscitated sepsis, reperfusion injury, sickle cell crises, malaria
IV	Hyperdynamic/stagnant	Resuscitated sepsis
V	Hyperdynamic	Resuscitated sepsis, exercise

CABG, coronary artery bypass grafting; ECMO, extracorporeal membrane oxygenation.

Elbers PWG, Ince C: Critical Care 2006

Classification of Microcirculatory Abnormalities in Distributive Shock

A classification system for categorizing sublingual microcirculatory flow abnormalities seen in distributive shock as observed by OPS/sidestream dark-field imaging. Each class consists of a venule with two capillaries. In this way, the heterogeneity of the capillary flow is described by showing the two most characteristic types of flow seen. Solid arrows depict normal flow whereas the striped arrows represent hyperdynamic flow. No arrow depicts stagnant flow (examples of real-time films of each class of abnormality can be downloaded from our web site [43]).

Elbers PWG, Ince C: Critical Care 2006

ASSESSMENT OF PERFUSION

Tissue perfusion and washout of waste end-products is the goal of the circulatory system. There are three points at which these can be monitored – the macrocirculation, the microcirculation and the end-products of metabolism and down-stream markers. Firstly macro-hemodynamic measures can be monitored using parameters like mean arterial pressure and instituting cardiac output monitoring. I have mentioned the disconnection between macro-circulation and microcirculation, so poor perfusion can persist despite normalisation of macro-hemodynamic variables.

The other parameters traditionally monitored are the end-products of metabolism and downstream markers, these include: lactate, base deficit, pH, CO_2 and mixed venous saturation. The modalities that are used to monitor the microcirculation itself, allow either direct visualisation of the microcirculation or indirect assessment by measuring tissue oxygenation. [5]

Assessment of the microcirculation

There is still no single objective, reliable method of assessing the microcirculation [5]. In practice the device used can only tell you about the microcirculation in one area at a time. This can be generalised to the rest of the body if the pathology can be reasonably though to be affecting other microvascular beds in the same way. However this is an extrapolation. At best this extrapolation can indicate the minimal alterations that have occurred. [3]

Direct assessment

Intravital microscopy uses trans- or epi-illumination, to observe superficial layers of thin tissues. Fluorescent dyes can be used for a higher contrast and specific cells can be labelled for visualization, but the dyes are potentially toxic. In humans it can only be used on the eye, skin and the nail fold.

Laser Doppler detects a shift in frequency of laser light upon encountering flowing erythrocytes. It can be used on skin, muscle, gastric mucosa and rectum. Velocity of flow in a small area, 0.5 to 1mm^3, of microcirculation is calculated. Flow measurement given is an average of the velocities in all the vessels (arterioles, capillaries and venules) in the measured volume.

Limitations: only a small area can be investigated, the type of microvessel, direction and heterogeneity of flow, and any changes in haematocrit are not taken into account. The advancement on this technique is scanning Laser Doppler which allows two dimensional visualization of the microcirculation.

Orthogonal Polarization Spectral (OPS) Imaging is a non-invasive method for direct visualization of microcirculation using green polarized light. The light reflected back from the surface is still polarized and filtered out. While light from deeper tissues is depolarized and absorbed by red blood cells on its way to the main optical lens. High contrast images of microcirculation are formed and red blood cells seen as black and gray bodies.

Tissues with a thin epithelial layer, such as mucosal surfaces can be studied. It is incorporated in a hand held microscope, and most frequently used on the sublingual area. Limitations: movement artefacts from breathing and presence of secretions like blood and saliva. Patients need to be cooperative or sedated so they do not bite the device. Internal organs are not investigated.

The assessment is semi-quantitative and not an exact measurement of red blood cell flow velocity in individual vessels. A score based on average flow over 12 quadrants (three regions X four quadrants per region), is made from the flow impression of vessels with a particular area in a given quadrant. The flow score is from 0 to 3 and its relationship with actual flow is not known. Selecting the exact same site as before is also difficult on repeated measurements.
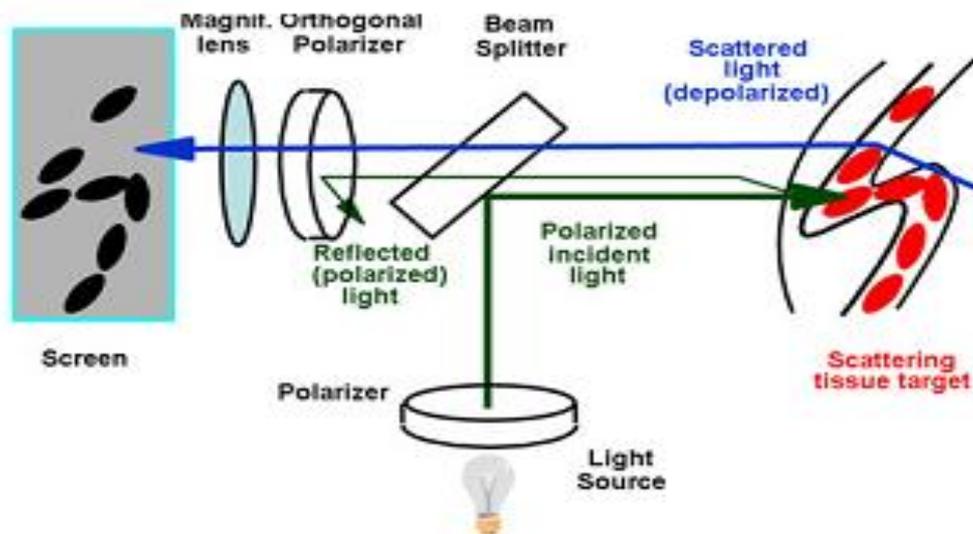
De Backer et al. Int Care Med 2010

An improvement in the OPS imaging is the sidestream dark-field (SDF) imaging. Green light is emitted from the sides of the device and light reflected by superficial layers stays peripherally. Light reflected from the depths of tissues reaches the optical lens and can be viewed. In comparison to OPS it offers improved image quality, relative technical simplicity, and does not require a high-powered light source. [3]
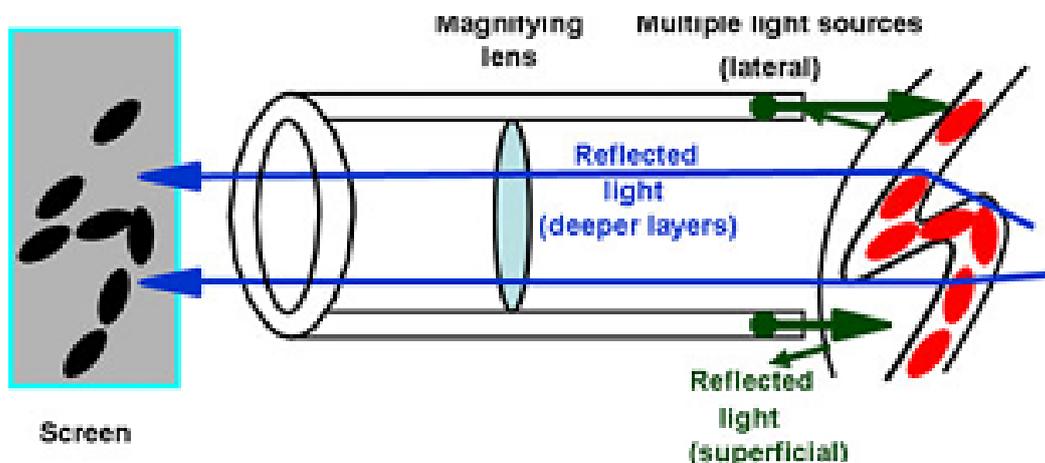
De Backer et al. Int Care Med 2010

Indirect assessment

Evaluation of tissue oxygenation:
Here oxygen tension or saturation is measured in a section of tissue. These are near infra-red spectroscopy (NIRS), pO_2 electrodes, reflectance spectroscopy. The latter two are not used clinically due to their limitations.
Near infra-red spectroscopy calculates tissue oxygen saturation (StO_2) by measuring fractions of oxy- and deoxyheamoglobin. It is influenced by adipose tissue thickness an oedema, so it is usually placed in the thenar eminence. The dynamic response of StO_2 to brief period of forearm ischemia is clinically relevant.

The rapid recovery of StO_2 after an occlusion test shows the microcirculation is still able to increase blood flow after a brief period of ischemia i.e. some degree of autoregulation is still present. Here fluid resuscitation and increasing blood pressure could improve perfusion.

End-products of metabolism and downstream markers:
Lactate:
Lacate is commonly monitored as a marker of tissue hypoperfusion. However it is a global marker of tissue hypoxia and is also non-specific for anaerobic metabolism. Despite this studies have shown an elevated serum lactate (>4mmol/L), even with normal macro-haemodynamics and no clinical markers of organ dysfunction, carries a worse prognosis.

Lactate clearance of less than 10% (over 2-6hrs) also has a higher mortality, because it shows sustained organ hypoperfusion. Therefore repeated lactate levels are useful in assessing the adequacy of circulatory resuscitation. [13,2]

Venous oxygen saturation (SvO_2):
Venous oxygen saturation is a global parameter that is often used to gauge if oxygen supply is meeting oxygen demand in sepsis. It is measured using a pulmonary artery catheter (location of maximum venous mixing) and this is an invasive procedure. It can be misleading because a high venous saturation can occur with shunting and cellular hypoxia. The venous saturation measured via central venous catheter is about 5% -18% higher than via pulmonary artery catheter. Studies show conflicting data about using mixed venous saturation as a resuscitation end-point. [13, 3]

PCO_2 derived measurements:
Washout of CO_2 from the microcirculation depends on adequacy of blood flow. Tissue CO_2 is measured by electrodes and probes in inserted or in contact with tissue. Gastric tonometry has largely been abandoned but sublingual and buccal PCO_2 monitoring is currently still being developed. [3]

Microdialysis dialysis:
Microdialysis measures different soluble molecules in the extracellular fliud. These molecules equilibrate through a semi-permeable membrane of hollow fiber, which is perfused with saline at a constant rate. Lactate and pyruvate are measured. The lactate/pyruvate ratio is used to detect tissue hypoxia. It cannot detect whether the hypoxia is due to altered flow or other causes of tissue hypoxia and it cannot detected alterations in perfusion before it caused cellular hypoxia. [3]

Summary of techniques:
The ability to directly visualize the microcirculation by the bedside using OPS and SDF is a remarkable development but still has many limitations.

Evaluation of images needs to be consistent and this will probably require development of software. The sublingual area seems to be the most suitable for the hand-held device, but what about the rest of the microcirculation.

A more integrated approach using muscle StO_2 and tissue capnometry with SDF would target different areas. However there are still many technical hurdles to overcome. [12]

THERAPEUTIC INTERVENTIONS FOR THE MICROCIRCULATION

Hemodynamic resuscitation:
Hypotension and hypovolemia lead to poor capillary filling and perfusion. Therefore fluid resuscitation and vasopressors are still a mainstay of management in sepsis. [7]

Intravascular resuscitation:
Fluids can improve microvascular perfusion, increasing the proportion of perfused capillaries. The effects can be seen mostly in the early phase of sepsis, within 24h of diagnosis, but after 48h no improvement was made even when cardiac output increased. Whether these effects will persist or be transient, and also whether this effect can be "saturable" requires further study. Pottecher et al. suggested this "saturable" effect, when they observed the first bolus of fluids improved micro-vascular perfusion, whereas the second had no effect even though cardiac output increased further.

The effects of red blood cell transfusions also seem to be quite variable. In one trial, although the effects in the entire population were negligible, transfusions did improve micro-vascular perfusion in patients with the most severely altered microcirculation at baseline. [7]

Vasopressors:
Vasopressor agents also have variable effects. Correction of severe hypotension and achieving a minimal perfusion pressure restores micro-vascular perfusion. Dubin et al. assessed the change in mean arterial pressure from 65 to 75 and 85 mmHg in 20 patients with septic shock.

There was huge inter-individual variability, some patients reached their maximal micro-vascular perfusion at 65 mmHg, and others reached it at 75 or 85 mmHg. Sublingual microcirculatory assessment showed, interestingly, that the increase in arterial pressure was found to beneficial in the most severe cases but detrimental in patients with close to normal microcirculation at baseline. [7]

This demonstrates the disconnection between global hemodynamics and microcirculation and also huge individual variability in the microvascular response to therapeutic interventions. [7] Since the response of the micro-circulation cannot be predicted, microcirculation-oriented resuscitation requires monitoring of the microcirculation. [12]

Vasodilators:

Vasodilating substances may have a role in manipulation of the microcirculation. Spronk et al. gave nitroglycerin to a small series of patients and reported a rapid improvement in the microcirculation. Subsequently Boerma et al. performed a randomized trial with 70 patients and did not show any advantage of giving nitroglycerin over placebo. The trials did have differences in methodology but at this stage nitroglycerin administration is still controversial and cannot be recommended. Nitroglycerin is not selective and can dilate both perfused and non-perfused vessels, thereby possibly worsening shunting. [7]

NO synthetase inhibitors:

The up-regulation of iNOS in sepsis is associated with refractory hypotension, impaired vascular response to adrenergic stimulation and capillary leak. It also impairs mitochondrial function. However NOS inhibitors have not consistently been shown to improve perfusion in the microcirculation and their role as therapy in severe sepsis is not clear. The suggestion is that the specific inducible isoform needs to be targeted. [5]

Steroids:

The use of steroids in sepsis is a non-specific way of modulating the systemic inflammatory response. It can preserve the endothelial glycocalyx and attenuate rolling of leucocytes, thus protecting the endothelium. It may have a role in inhibiting iNOS. Recommendations, at this point however, suggest that only septic shock patients whose blood pressure is responding poorly to fluid resuscitation and vasopressor therapy should receive steroid therapy. [5,7]

Statins:

Statins are cholesterol-lowering agents but also have pleotropic effects. They appear to have an anti-inflammatory and anti-oxident activity during sepsis. They increase expression of eNOS, along with a down-regulation of iNOS. Together, this increases NO levels, restoring the auto-regulatory functions. [5]

CONCLUSION

Pathological changes to the microcirculation appear early in sepsis. These changes are present even when central blood pressure has normalised. The monitoring of the microcirculation is important, but methods need to be integrated and made more user friendly. Therapies targeting the microcirculation are also still under investigation. Further development in these areas will not only improve our understanding of severe sepsis but also assist in our management of these patients:

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