Diagnosis and Treatment of the Septic Microcirculation

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Introduction

Shock has typically been classified into four types: Hypovolemic, cardiogenic, obstructive, and distributive. The first three categories are associated with a decrease in cardiac output, leading to tissue hypoxia. Distributive shock, such as septic shock, results from abnormal distribution of normal or increased cardiac output, secondary to microcirculatory dysfunction. Severe disruption of the microcirculation during sepsis results in a pathologic heterogeneity in microvascular blood flow that occurs as a consequence of the shutdown of weak microcirculatory units. This implies that oxygen transport is shunted from the arterial to the venous compartment, leaving the microcirculation hypoxic, and is the main pathogenic feature of distributive shock. Such a scenario results in maldistribution of microvascular blood flow and a mismatch between oxygen delivery and oxygen demand in different tissues that seems to be the first step in the progression to organ failure [1].

In shock profiles other than sepsis, where the microcirculation is not affected to such an extent, optimization of systemic hemodynamic parameters would likely ensure adequate oxygenation of tissues. In severe sepsis, however, regional hypoperfusion can persist even after correction of global hemodynamic and oxygen-derived variables [2]. This disparity between systemic and regional tissue oxygenation makes it difficult to define monitoring and treatment endpoints.

The microcirculation can be assessed at the bedside using new imaging techniques, namely orthogonal polarization spectral (OPS) imaging and sidestream dark field (SDF) imaging. During resuscitation and treatment of septic shock, these techniques allow for evaluation and verification of whether the treatment strategies implemented really improve the microcirculation in an attempt to correct tissue dysxia. In fact, some studies have been published recently that evaluate the effectiveness of different treatments on the microcirculation using these techniques.

The present chapter focuses on the pathophysiology of the distributive defect of septic shock at the microcirculatory level, as well as discussing new evidence regarding the effects of vasopressors and vasodilators on the microcirculation during septic shock.

Normal Microcirculation

Microcirculatory function is the main prerequisite for adequate tissue oxygenation and, thus, also organ function. The roles of the microcirculation include transporting oxygen and nutrients to tissue cells, ensuring adequate immunological function
and, in disease, delivering therapeutic drugs to target cells. The microcirculation network consists of the smallest blood vessels (<100 μm diameter), where oxygen release to the tissues takes place, and includes arterioles, capillaries, and venules (microcirculatory units) [3]. This network accounts for 10 billion capillaries and the highest endothelial surface in the body (more than 0.5 km²). The main cell types in the microcirculation are the endothelial cells, smooth muscle cells (mostly in arterioles), red blood cells (RBC), leukocytes, and platelets. The endothelial cells have a key role in microcirculatory functioning, participating in blood flow regulation, controlling coagulation and immune function, and releasing nitric oxide (NO) in response to shear stress and possibly also hypoxia [4]. NO is an important factor in maintaining the integrity of blood flow through the microcirculation by regulating resistance vessel diameter (relaxing smooth muscle cells in proximal arterioles), blood rheology (regulating RBC and leukocyte deformability), interactions between blood elements and the vascular wall (regulating leukocyte-endothelial adhesion and platelet adhesion and aggregation), and blood volume (increasing vascular permeability during endotoxemia) [5].

Microvascular oxygen delivery cannot be predicted from systemic or even regional oxygen delivery. First, microvascular hematocrit is lower than systemic hematocrit due to the Fahraeus effect (dynamic reduction of hematocrit due to axial migration of erythrocytes near the center of the vessel). Second, the distribution of hematocrit is nonlinear at vascular branch points. Third, microvascular P0₂ (partial oxygen pressure) is also lower than systemic PO₂ and is heterogeneously distributed. Hence, oxygen delivery is heterogeneously distributed throughout the microcirculation network [6].

The structure and function of the microcirculation is highly heterogeneous in different organs, and is closely related to the functional role played by a particular organ as a whole. The number of capillaries per unit mass of organ or tissue (capillary density) may be related to the organ’s metabolic requirements (muscles, heart, brain) or to other functional requirements (skin, intestinal mucosa, kidney) [7]. This marked heterogeneity of the microcirculation leaves the network particularly vulnerable to hypoxic insult.

The microcirculation normally insures adequate oxygen delivery to meet the oxygen demands of every cell within an organ. A strict regulatory mechanism is in place to achieve this, with multiple signaling pathways interacting at different levels. In this way, oxygen transport to tissues with high oxygen need is augmented and oxygen transport to tissues with low metabolic activity is restricted [8]. This regulatory mechanism allows microcirculatory flow to occur independent of changes in systemic blood pressure, a mechanism called autoregulation [7]. In general, driving pressure, arteriolar tone, hemorheology, and capillary patency are the main determinants of microcirculatory blood flow.

Regional flow is determined by large vessels (medium-sized arterioles), which are mainly controlled by the sympathetic nervous system. In contrast, local distribution of blood flow to tissues is regulated by the microcirculation. When terminal arterioles are vasodilated, perfusion of the capillaries increases; when terminal arterioles are vasoconstricted, the number of recruited capillaries decreases. These vessels are primarily under local control, and the endothelial cells play a central role in this [4]. It has been proposed that these cells can regulate arteriolar smooth muscle tone upstream by sensing shear stress and different regulating substances (acetylcholine, catecholamines, prostaglandins, endothelin, bradykinin, thromboxane, adenosine, nitrosothiols and ATP) downstream in the capillary network. Endothelial cell-to-cell