Distributive failure in the microcirculation of septic patients

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Summary

Treatment of sepsis and its life-threatening complications as a result of shock and multiple organ failure remain a persisting challenge for many healthcare workers, with considerable (long-lasting) morbidity and mortality for patients, despite strenuous efforts. Since sepsis is a syndrome, that is ill-defined on the basis of frequently observed clinical symptoms that overlap numerous other disease states, and not delimitated as a clear patho-physiological entity, improvement of clinical outcome is conceived to be influenced by many factors. In that respect, the infection itself, the complex reaction of the body and the set of therapeutic interventions are all subject to further investigation. On top of that, the distributive nature of circulatory failure during sepsis has clear distinct characteristics in comparison to other forms of shock. Hypovolemic, cardiogenic and obstructive shock occur as a result of an inadequate cardiac output in relation to tissue demand, whereas septic shock is the result of distributive alterations in tissue perfusion, even in the presence of a normal or elevated cardiac output. Microcirculatory weak units become shunted, explaining patchy cellular dysoxia in the presence of apparently adequate upstream and downstream parameters of oxygen delivery. The concept of heterogeneity of blood flow under conditions of distributive shock, as in sepsis, is subject to research in this thesis. The clinical implication of this concept is clear: despite aggressive monitoring of many parameters of systemic hemodynamics in the intensive care unit, the potential culprit lesion in sepsis remains unrevealed.
In chapter 1 the concept of heterogeneity of blood flow in sepsis is elaborated in more detail with a focus on the gut. Due to the specific vascular architecture of the small intestine, the tip of the villus is more susceptible to hypoxia as a result of convexional and diffusional forms of shunting, thus becoming a microcirculatory weak unit. The ability to observe the microcirculation in-vivo with the new technique orthogonal polarization spectral (OPS) imaging, incorporated in a hand-held device, is discussed.

Before structured research with in-vivo imaging of the microcirculation is possible, the problem of quantification of the observed microcirculatory alterations has to be dealt with. Apart from the technical problem to convert complex visual images into numbers, the method must particularly be sensitive to detect heterogeneity of flow within the microcirculation. Since an automated analysis, based on software contour analysis of vessels and subsequent measurement of surface area and red blood cell velocity, was not feasible at the time, we proposed a semi-quantitative assessment of microcirculatory flow in chapter 2. After dividing the image into quadrants, flow can be expressed as a number between 0 and 3, ranging from complete stand-still to continuous. Although expressing data in a non-continuous way is a considerable disadvantage, scoring a minimum of 12 quadrants enables us to detect heterogeneity of flow. The overall microvascular flow index, an average of all the individual quadrant scores, can be obtained within a reasonable timeframe and processing this variable as (pseudo)continuous may be performed, according to statistical laws. Inter- and intraobserver variability appeared to be good for different vessels sizes in both capillary networks and repeating vascular structures, with potential applicability for the assessment of microcirculatory alterations in different organs.

In chapter 3 the dilemma of the apparent discordance between systemic hemodynamic variables and microvascular blood flow is illustrated with a clinical case-report. A patient with meningococcal meningitis and –sepsis remained persistently hypotensive, despite aggressive volume therapy, inotropes and the use of the vasopressor norepinepherine. Despite low blood pressure and oliguria, OPS-derived sublingual microcirculatory blood flow appeared to be normal. After a single bolus of terlipressin, a potent vasopressor, blood pressure and urine production were successfully restored. However, a complete shutdown of the microcirculation was observed, and the patient died with progressive metabolic acidosis.

In chapter 4 the concept of heterogeneity of blood flow, as observed within the microcirculation, is expanded to the relation between 2 microvascular beds in different organs, at different time points. In 23 patients with an abdominal sepsis and a surgical stoma the microcirculation is simultaneously observed with OPS imaging, both in the sublingual region and the intestinal region (via the stoma). Within 24 hours after the initial surgical procedure a complete discordance of flow between the 2 vascular beds was observed. After 48 hours however, a normalisation of microcirculatory flow in both microvascular beds 'restored' the correlation. These observations underline the idea that, especially under conditions of distributive shock, observed abnormalities in one organ, cannot be translated one-on-one to another organ. Even more, such correlation might be time-dependent.

If heterogeneity of flow within and between microvascular beds exists, what does this implicate for the relation between 2 different vascular compartments. In previous chapters the discordance between systemic and microcirculatory hemodynamic parameters was already subject of research. In chapter 5 the relation between a parameter of peripheral circulation, the 'big-toe-temperature', situated between the systemic circulation and the microcirculation, and sublingual microcirculatory perfusion is elaborated in 35 ICU-patients with severe sepsis. Again, a discordance between the 2 vascular compartments was observed. Although under conditions of other forms of shock a decrease in 'big-toe-temperature' is reported to be associated with severity of shock, the distributive failure in sepsis seems to blunt such correlation. Under these conditions an integrative approach of parameters to information from all relevant vascular compartments seem necessary to unravel the complete picture.

In contrast to many other parameters, microcirculatory alterations in sepsis are associated with morbidity and mortality. However, this does not automatically implicate that pro-microcirculatory strategies will lead to better patient outcome. In chapter 6 results of a prospective single centre double-blind randomised placebo controlled trial are discussed. Aim of the study was to add a specific pro-microcirculatory strategy on top of a sepsis resuscitation protocol, that incorporates reported beneficial hemodynamic interventions,

such as earl goal-directed therapy and dynamic exclusion of fluid-responsiveness. Based on earlier reports we used nitroglycerin to promote microcirculatory blood flow. Seventy patients with organ failure as a result of sepsis were included. Despite fulfilment of preset systemic hemodynamic resuscitation endpoints, sublingual microcirculatory blood flow was considerably altered at the start of the study medication. Within 24 hours microcirculatory blood flow improved significantly. However, no significant difference between placebo and nitroglycerin was observed. These unexpected findings warrant further studies that focus on situation-dependent differences in effects of nitroglycerin in sepsis and even question the presumed mechanism of action as a nitric oxide donor.

In chapter 7 another clinical model of distributive failure was explored. During cardiopulmonary bypass patients are subject to a considerable number of hemodynamic changes, associated with sublingual distributive alterations. Our aim was to investigate the relation between intestinal microcirculatory alterations and cellular dysoxia. To this extent direct observation of the rectal microcirculation in combination with rectal tonometry was performed in 26 low-risk on-pump cardiac surgery patients. In previous reports splanchnic ischemia, as detected with tonometry, was identified as a risk factor for postoperative complications in these patients. In the specific setting of this single-centre study the observed incidence of postoperative intestinal microcirculatory alterations, as well as splanchnic ischemia, was low. Extending microcirculatory in-vivo observations to the sublingual area did not disclose marked discordance of microcirculatory blood flow between the different microvascular beds.

To end this thesis chapter 8 provides an overview of the recent literature that has added to the understanding of the microcirculation as a clinical concept.