Variability of splanchnic blood flow measurements in patients with sepsis – physiology, pathophysiology or measurement errors?

Splanchnic blood flow and sepsis

Impaired tissue oxygenation, especially in the splanchnic region, may play a central role both in the pathogenesis of multiple organ dysfunction and in the development of complications in various groups of intensive care patients [1, 2]. In severe inflammation such as SIRS, septic infection, and septic shock, the metabolic demand for oxygen in the splanchnic region is increased [3, 4, 5]. This is explained in part by an increased hepatic metabolism [6, 7]. In patients with normal or hyperdynamic hemodynamics, hepato-splanchnic blood flow is higher than normal, but the increase in oxygen consumption is disproportionate to the increase in blood flow. Hence, splanchnic oxygen extraction has to be increased. It is therefore evident that splanchnic tissue perfusion is at risk, should any deterioration of systemic oxygen transport occur. This is clinically relevant especially in septic shock, where early myocardial depres-

sion is common [8, 9]. During experimental cardiac tamponade, endotoxin infusion appears to impair the hepatic microcirculatory blood flow: while mesenteric and liver blood flow increased similarly, the liver capillary blood flow increased less than the intestinal mucosal blood flow [10]. In addition, the critical oxygen delivery required to maintain oxygen uptake constant is higher in the liver as compared to the intestine.

Assessment of splanchnic blood flow

The aim of monitoring hepato-splanchnic perfusion is to detect, prevent, and reverse tissue hypoperfusion. This may help to improve the outcome of these patients. The available methods to evaluate splanchnic perfusion include among others dye-extraction methods, ultrasound and laser Doppler flowmetry, tonometry, and spectrophotometry. Both the appropriate use of each method and the correct interpretation of the measurements are of fundamental importance.

In critically ill patients estimation of splanchnic blood flow is usually based on hepatic uptake of substances, which are metabolized by the liver and distributed in the plasma [11, 12, 13]. Indocyanine green dye has become the most often used substance. However, estimated hepatic blood flow calculated from systemic indocyanine green clearance correlates poorly with blood flow obtained using hepatic vein catheterization and the Fick principle [12]. In case of normal liver function, pharmacokinetic modeling improves the accuracy substantially. Because vasoactive drugs change acutely the hepatic extraction of indocyanine green, the use of methods without hepatic venous catheterization is not valid.
Variability of physiological signals in critically ill patients

When effects of drugs or other interactions on the splanchnic perfusion are assessed, it is important to measure the respective blood flows under steady state conditions. In addition, when constant dye infusion methods are used, stable blood concentrations during the measurements are mandatory. Most investigators measure the blood dye concentrations three times per measurement period in intervals of 5 min to prove stable conditions. In the August issue of this journal, Dr. Sakka and coworkers assessed the variability of splanchnic blood flow in eight sedated, mechanically ventilated patients during a stable 4-h period [14]. By using the continuous indocyanine green method they found a standard error of 31% for repeated measurements with 5-min distances and of 26% for average values with 2-h distances. In contrast, coefficients of variation for triplicate cardiac output measurements using the thermodilution method were low (between 3% and 4%). The high variability of the splanchnic blood flow measurements could neither be explained by unstable indocyanine green concentrations (coefficients of variation between 4% and 6%), nor by inaccuracies in hematocrit (coefficient of variation 2%). The pumps for the infusion of the indocyanine green solution were calibrated. The authors conclude that splanchnic blood flow may exhibit significant variability in patients with sepsis, even when systemic hemodynamic parameters are stable. They suggest that this spontaneous variability could explain the non-uniform behavior of changes in splanchnic blood flow in response to therapeutic interventions such as vasoactive drugs; for instance, treatment of hypodynamic septic shock with norepinephrine and dopamine had little effect on systemic oxygen transport but was associated with major changes in splanchnic blood flow and oxygen transport [15]. Regional changes were unpredictable from systemic changes. In patients with pancreatitis, dobutamine had inconsistent effects on splanchnic blood flow: in individual patients, splanchnic blood flow even decreased [16]. In patients with septic shock, low-dose dopamine increased splanchnic perfusion in patients with low fractional splanchnic blood flow but not in patients with high fractional splanchnic blood flow [17]. Therefore, if the variability of splanchnic blood flow is high, small effects of drugs may not become apparent, and effects attributed to the infusion of drugs may have occurred just by chance.

The physiologic variability of hemodynamic and respiratory variables is well known in healthy subjects [18, 19]. Heart rate and blood pressure variability are signs of an intact autonomic nervous system. In patients with cardiovascular disease a strong association has been found between impaired heart rate variability and both all-cause and cardiovascular mortality rates [20, 21, 22]. Age and heart rate are the major determinants of the selected heart rate variability measures [23, 24]. Heritable factors have also been proposed [25]. In diabetic patients, heart rate variability is reduced and inversely associated with plasma glucose levels [26]. In septic patients, cardiac variability and sympathovagal balance are impaired [27].

Splanchnic blood flow demonstrates circadian variation [28]. By using magnetic resonance velocity mapping, Lycklama a Nijeholt and co-workers found an intra-individual variability for portal vein flow measurements of approximately 7% [29]. The variability did not increase after a meal and was independent of the technique used (Echo-Doppler measurements vs magnetic resonance velocity mapping). Some of the variability in regional (and potentially systemic) blood flow measurements can be explained by movement of the diaphragm during the respiratory cycle: in a recent study venous return from the legs was monitored using an ultrasonic flow recorder placed over the femoral veins in ten subjects [30]. Quiet inspiration was associated with a fall in femoral venous blood flow of 65% of the end-expiratory value. Between-subjects variability could be largely explained by differences in abdominal pressure swings. The amount of fall in femoral blood flow during inspiration varied in proportion to the diaphragmatic contribution to tidal volume. Isovolume belly-in maneuvers and external compression of the abdomen also caused cessation of femoral blood flow. In line with the findings of Dr. Sakka and co-workers, there is some evidence from animals studies that splanchnic hemodynamic parameters could exhibit a more pronounced variability as compared to systemic hemodynamics [31]: in conscious rats a major oscillation at around 160 mHz was present in the mesenteric, but not in hindquarter circulation. Cross-spectral analysis performed between mean arterial pressure and mesenteric blood flow indicated that fractional changes in flow were twice as much as those in mean arterial pressure. We have measured the variability of gastric mucosal PrCO₂ in 40 patients and systemic hemodynamic parameters in 100 patients with acute respiratory or circulatory failure during the first 24 h after admission to the intensive care unit [32]. We found at the most a slightly higher coefficient of variation for gastric mucosal PrCO₂ (15%) as compared to heart rate (6%), mean arterial pressure (9%), and thermodilution cardiac output (10%). Using the same technique as Dr. Sakka and colleagues, Uusaro reported a coefficient of variation of 7% for splanchnic blood flow in 136 critically ill patients. In the subgroup of patients with septic shock the coefficient of variation was 9%. This is well below the variability of splanchnic blood flow reported in the study by Dr. Sakka and co-workers. In septic patients and in healthy volunteers challenged with endotoxin, heart rate variability is de-