Commentary

Gut oxygenation in sepsis: still a matter of controversy?

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Abstract

Part of Stephan Jakob's exhaustive review paper in the present issue of *Critical Care* deals with the notion that intestinal cellular energetics are deranged in sepsis, in terms not only of inadequate tissue perfusion but also of impaired mitochondrial respiration and/or coupling (i.e. organ dysfunction in sepsis may occur as a result of 'cytopathic hypoxia'). This suggests that efforts to improve outcome in septic patients by manipulating systemic oxygen delivery and regional blood flow are doomed to failure. That suggestion remains largely speculative, and experimental and clinical results presented here consistently demonstrate that there is still a place for treatment of abnormal perfusion in the context of early severe sepsis and septic shock.

Keywords cytopathic hypoxia, haemodynamics, oxygen delivery, sepsis, shock

In his review paper published in the present issue of *Critical Care*, Stephan Jakob [1] deals with the difficult and broad topic of splanchnic ischaemia in critical care. The presentation is exhaustive, including the still controversial issue of inadequate gastrointestinal flow in septic states. As mentioned in that review, several lines of evidence support the notion that cellular energetics are deranged in sepsis, in terms not only of inadequate tissue perfusion but also of impaired mitochondrial respiration and/or coupling (i.e. organ dysfunction in sepsis may occur as a result of 'cytopathic hypoxia') [2]. If this is correct then the therapeutic implications might be enormous. It would imply that efforts to improve outcome in septic patients by monitoring and manipulating cardiac output, systemic oxygen delivery (DO_2) and regional blood flow are doomed to failure, and that the focus should rather be on developing pharmacological strategies to restore normal mitochondrial function and cellular energetics. This is largely speculative, however, and the controversy remains regarding whether there is a deficit in regional DO_2 or whether the deficit resides in the inability of tissue cells to utilize available oxygen adequately.

A deficiency in the ability of tissues to extract oxygen is a prominent feature of the pathology of sepsis, and this is especially true at the level of the gut [3]. This deficiency manifests as a condition in which, despite apparent correction of global variables of DO_2, signs of regional dysoxia are present (e.g. elevated lactate levels and enhanced gastric carbon dioxide level – a surrogate marker for decreased perfusion that is determined tonometrically). Several investigators have reported that tissue oxygenation is impaired in experimental models of sepsis. For example, we investigated the effects of acute endotoxaemia on tissue partial oxygen tension (PO_2) [4]. We took sequential measurements in a single group of dogs at baseline during a 1-hour infusion of lipopolysaccharide, and then during a 2-hour infusion of dextran solution. Infusion of lipopolysaccharide resulted in a marked decrease in systemic DO_2, but this parameter was normalized by resuscitating the animals with a colloid solution. In contrast, the distribution of intestinal mucosal PO_2 remained low despite a marked increase in mesenteric DO_2. Those findings were reproduced by Hasibeder and coworkers [5] and Tugtekin and coworkers [6], and the development of tissue hypoxia following injection of lipopolysaccharide was attributed by those authors to impaired microvascular control of nutritive flow.

Temmersfeld-Wollbrück and coworkers [7] employed microlightguide reflectance spectrophotometry for direct assessment of the microvascular oxyhaemoglobin and its

DO_2 = systemic oxygen delivery; EGDT = early goal-directed therapy; NO = nitric oxide; PO_2 = partial oxygen tension; $ScvO_2$ = central venous oxygen saturation.

partial distribution in the mucosa of the upper gastrointestinal tract, and noted profound differences between healthy control individuals and patients in septic shock. The latter group was characterized by overall lowered levels of mucosal oxygenation, concomitant with apparent heterogeneity of regional oxyhaemoglobin, and the appearance of small descrete areas of tissue that were severely hypoxic. To our knowledge, that important study was the first to reproduce findings in humans that had been observed in animal models, indicating that during septic shock abnormal microcirculatory oxygenation occurs in the gastrointestinal tract, despite more than adequate systemic oxygen derived parameters. Interestingly, the mucosal to arterial carbon dioxide gap was increased when mucosal oxyhaemoglobin was decreased.

In contrast to the findings described above, a number of studies suggest that tissue PO_2 values are normal or even elevated in endotoxaemia or sepsis. For example, Hotchkiss and coworkers [8] estimated tissue PO_2 values in a number of organs in rats rendered septic by caecal ligation and perforation. They did not find evidence of tissue hypoxia in skeletal muscle, cardiac muscle, liver and kidney in septic rats. VanderMeer and coworkers [9] investigated the effects of endotoxaemia on intestinal mucosal PO_2 in pigs, and did not identify a decrease in mucosal PO_2. Further results from the same group suggest that sepsis might be associated with 'cytopathic hypoxia', a situation in which impaired production of ATP exists despite adequate availability of oxygen in the vicinity of mitochondria within cells. This, according to those authors' main hypothesis, followed sepsis induced nitric oxide (NO) over-production, resulting in lower levels of oxidative phosphorylation [10].

In an *in vitro* model of intestinal epithelium [11], incubation with the NO donors sodium nitroprusside, S-nitroso-N-acetylpenicillamine, or 1% NO gas reduced ATP levels and reversibly increased the permeability of intestinal epithelium. Data regarding the effects of sepsis on tissue levels of adenine nucleotides (i.e. ATP and ADP) are plentiful but, largely because of conflicting findings, they are difficult to interpret [12,13]. One crucial issue has recently been addressed [14]. In an *in situ* isolated flow-controlled gut loop, it was observed that epithelial injury (as assessed by nuclear chromatin condensation) and mitochondrial swelling occurred 2 hours before any increase in NO production (as assessed by nitrotyrosine and inducible NO synthase immunoprevalence), suggesting that lipopolysaccharide-induced ileal injury and NO dysregulation were clearly dissociated in that preparation, with injury preceding nitric oxide (NO) overproduction.

It was recently confirmed in a clinical trial [15] that impaired tissue perfusion plays an important role in the development of multiple organ failure and death during severe sepsis. The purpose of that study was to evaluate the efficacy of early goal-directed therapy (EGDT) before admission to the intensive care unit; EGDT involved adjustments to cardiac preload, afterload and contractility in order to balance DO_2 with oxygen demand. The evaluation was conducted by monitoring continuous central venous oxygen saturation ($ScvO_2$; targeting a level >70%). Interestingly, $ScvO_2$ was lower than a mean value of 50% in patients who arrived at the emergency department with severe sepsis or septic shock; this serves as a reminder that, before fluid loading is started, severe sepsis and septic shock are associated with severely depressed haemodynamics (as has been demonstrated in lipopolysaccharide animal models). The patients were randomly assigned to receive either 6 hours of EGDT ($n = 130$) or standard therapy (which differed only in the fact that $ScvO_2$-based therapy was not used; $n = 133$) before admission to the intensive care unit. There were no significant differences between the groups with respect to baseline characteristics. During the interval from 7 to 72 hours, the patients assigned to EGDT had a significantly higher mean $ScvO_2$, a lower lactate concentration, a lower base deficit and a higher pH than did the patients assigned to standard therapy ($P < 0.02$ or $P = 0.02$ for all comparisons). In-hospital mortality was 30.5% in the group assigned to EDGT, as compared with 46.5% in the group assigned to standard therapy ($P = 0.009$).

These experimental and clinical results consistently demonstrate that there is a place for treatment of abnormal perfusion in the context of early severe sepsis and septic shock. They do not exclude, however, that altered oxygen utilization can follow at a later stage. Whether EGDT acts by improving gastrointestinal perfusion specifically remains unknown, but success with this strategy suggests that treating altered tissue perfusion remains an appropriate objective, at least during early sepsis.

Competing interests

None declared.

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