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Factors influencing splanchnic microcirculation in animal models of endotoxaemia

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ABSTRACT

Even though severe sepsis and septic shock therapy has improved in recent years, mortality remains high (22-50%). Disturbances in splanchnic organ homeostasis and increases in gut permeability have long been presumed to contribute to systemic inflammation and multiple organ dysfunction syndrome in critical illness and septic shock. In recent years, microcirculatory dysfunction has been highlighted as an important player in the development of sepsis-induced organ failure. This thesis investigated splanchnic microcirculatory changes in endotoxaemia, and the microcirculatory effects of ethyl pyruvate, endothelin (ET) receptor antagonists, and a norepinephrine-induced increase in perfusion pressure. Laser Doppler flowmetry (papers I-IV) and sidestream dark field microscopy (paper IV) were used to evaluate the microcirculation.

In papers I-III a 5-hour model of porcine endotoxaemia was used. In this model, the systemic haemodynamic response to endotoxin was hypodynamic, with decreasing cardiac index (CI), hypotension, and systemic acidosis. Splanchnic regional blood flow and microcirculatory perfusion deteriorated, and ileal mucosal acidosis measured with air tonometry developed in parallel.
Although intervention with the resuscitation fluid Ringer's ethyl pyruvate solution (REPS) temporarily improved systemic haemodynamics, no major differences in haemodynamic parameters or splanchnic perfusion were found compared to standard therapy with Ringer's acetate (RA).
The mixed ET_A/ET_B receptor antagonist tezosentan did not increase superior mesenteric artery flow (SMAF), but microcirculatory perfusion in the ileal mucosa and ileal mucosal acidosis was still improved. Tezosentan also increased portal vein flow compared to controls, but no significant improvement of hepatic microcirculatory perfusion could be demonstrated. Selective $endothelin_A$ receptor antagonism with TBC3711 failed to improve splanchnic regional blood flow, splanchnic microcirculatory perfusion or ileal mucosal acidosis.

A 25-hour model of endotoxaemic shock in sheep, mimicking the hyperdynamic circulation seen in septic patients, was used in paper IV. After 24 hours of endotoxaemia, CI was increased and systemic hypotension had developed. Although SMAF also increased, microcirculation in the ileal mucosa and muscularis was disturbed, ileal mitochondrial complex I activity decreased, and ileal mucosal acidosis developed. Increasing perfusion pressure with norepinephrine after 24 hours of endotoxaemia did not significantly alter SMAF, ileal microcirculation, ileal mitochondrial enzyme activity or ileal mucosal acidosis.

In conclusion, gut microcirculatory alterations have a weak correlation to systemic and regional indices of flow and pressure in endotoxaemia, strengthening the hypothesis that monitoring and therapies directed towards the microcirculation could be of value in sepsis. The ET system is involved in the development of gut microcirculatory dysfunction in endotoxaemia, and mixed ET receptor antagonism is necessary to counteract the effects of ET in this context. Resuscitation with REPS does not appear to have initial positive haemodynamic or microcirculatory effects compared to RA.

Key words: Microcirculation, endotoxin, sepsis, pig, sheep, endothelin, ethyl pyruvate, gut, liver, splanchnic circulation, shock, tonometry, norepinephrine

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