

The most common cause of death in patients with sepsis/septic shock is deterioration of the function of multiple organs, termed multiple organ dysfunction syndrome. Although our understanding of mechanisms involved in the pathophysiology of sepsis-induced tissue damage has improved substantially, therapy of these syndromes still remains largely supportive. The hallmark of sepsis is an overwhelming systemic production of both pro- and anti-inflammatory mediators leading to generalized endothelial and epithelial damage, microcirculatory-mitochondrial distress, altered endocrine and coagulation homeostasis and cellular immune hyporesponsiveness. Therefore, the hypothesis that modulation of this excessive immunological and biological response to infection might improve patient outcome appears reasonable. Hemoelimination techniques represent biologically plausible way to provide non-specific removal of soluble pro- and anti-inflammatory mediators, although the concept of blood purification in sepsis remains a matter of considerable debate. The aim of this thesis was to elucidate effects of 1) high volume hemofiltration (HVHF) and 2) coupled plasma filtration adsorption (CPFA) in a long-term, hyperdynamic porcine septic shock model, which fulfils the criteria for human sepsis. We hypothesized that both HVHF and CPFA may exert beneficial effects via a „pleiotropic“ effects including both systemic and regional hemodynamics and microcirculation, oxygen kinetics, tissue energy metabolism, coagulation and endothelial systems. Moreover, the mechanism(s) by which HVHF exerts its potentially beneficial effects were explored. In these mechanistic studies the main outcome variables were selected physiological parameters, providing biological insight for future (clinical) studies. In addition, in a separated study we verified the hypothesis, that the cooling of blood entering the extracorporeal circuit to 20°C and following rewarming of blood before it enters the organism could assure the sufficient anticoagulation and circuit patency during continuous veno-venous hemofiltration. This method would allow performing of renal replacement therapies without any other anticoagulation. The main results of this thesis were: a) early HVHF proved superior in preventing the development of septic hypotension. However, neither of tested hemofiltration doses was capable of reversing the progressive disturbances in microvascular, metabolic, endothelial and lung function; b) in a very similar model of septic shock the early CPFA treatment failed to prevent from progression of sepsis to septic shock and was not capable of reversing the sepsis-induced disturbances in various biological pathways and organ systems. Hence, both the efficacy and safety of this method require further rigorous experimental validation in clinically relevant models; c) regional cooling of blood in the CRRT extracorporeal circuit to 20°C for 6 hours makes it possible to perform the procedure without the need to use any anticoagulant with no blood clotting in the extracorporeal circuit. The method of selective incircuit blood cooling seems to be a feasible alternative strategy for anticoagulation during CRRT.