7. Summary

The liver and kidney are an important organs involved in a number of biosynthetic, biotransformative, detoxifying, endocrine and immune processes and therefore it is understandable that its dysfunction is associated with adverse outcome of critically ill patients. Hepatic and renal dysfunctions in critical illness are relatively common and occur usually as a component of multiple organ dysfunction syndrome (MODS). Several mechanisms have been proposed to explain the development of MODS. Among these, 1) the hypoxic component resulted from an inadequate oxygen supply to tissues, and 2) cytotoxic effects of various mediators are believed the key elements in the pathophysiology of MODS. From these complex causes of injury are probably the most therapeutically attainable the hemodynamic disturbances and maintenance of adequate organ perfusion pressure using vasopressors is one of the cornerstones of treatment of critically ill patients. Blood flow through organs is autoregulated over a wide range of mean arterial pressure (MAP). There is an agreement that under physiological conditions minimum value of MAP necessary to ensure this autoregulation is about 60-65 mm Hg. Therefore MAP > 65 mmHg has been recommended as a goal for the vasopressor therapy in sepsis. In critical condition, however, vasoplegia and altered vascular reactivity may result in a shift of the autoregulatory threshold to higher values. In this context, some clinicians advocate a higher MAP than generally recommended (i.e. MAP > 65 mmHg) presuming that it may further increase regional blood flow. But not only perfusion pressure may change the perfusion of this important region. It is well known that enteral nutrition (EN) in healthy volunteers increases total hepatosplanchnic blood flow (HSBF). However, whether this mechanism is preserved in acute stress state is not known. EN in such circumstances may even be harmful. No harmful side effects of EN have been found in post-cardiac surgery patients requiring inotropic support. However, the comparable data on the effects of EN in sepsis has not been completed. Turning mechanically ventilated patient from supine to prone position (PP) is often used in the management of acute lung injury (ALI). Although no significant alterations of systemic hemodynamic were demonstrated, PP could theoretically endanger HSBF due to a decrease in venous return, increase in intra-abdominal pressure and decrease of left ventricular volume. Although the prevention of MODS associated organ dysfunction would be obviously the best treatment modality, it is not always attainable in a clinical realistic scenario and then organ function support/replacement is necessary. As the treatment with liver support systems is not clinically common, continual renal replacement therapies (CRRT) are used in critically ill patients very often. In spite of clear CRRT life saving capability, it could have serious unfavorable side effects. The extracorporeal circuit (EC) of CRRT induces per se the activation of various cascades during the contact with the blood (i.e. behaves bioincompatible) and so potentially contributes to patients disease severity. Moreover treatment of critically ill patients with CRRT is often complicated by hemodynamic instability.

For reasons mentioned above we conducted experimental and clinical studies pursuing the effects of: (A) norepinephrine induced manipulations with perfusion pressure (B) EN and (C) PP on hepatosplanchnic blood flow, metabolism and energy balance (D) heparin rinse and (E) citrate anticoagulation on EC biocompatibility/thrombogenicity and (F) effects of continuous venovenous hemofiltration-induced cooling on global hemodynamic, hepatosplanchnic oxygen and energy balance. The main findings of our studies were that (A) in hyperdynamic, "normotensive" (i.e. with MAP > 65 mmHg) porcine bacteremia, norepinephrine-induced increase in perfusion pressure exhibited neither beneficial, nor deleterious effects on liver blood flow, intestinal macrocirculatory blood flow and ileal mucosal microcirculation; (B) the initiation of low dose post-pyloric EN in patients with severe sepsis led to increase of systemic and kinetics and gastric mucosal energy balance; (C) prone position in A LI patients compromises neither hepatosplanchnic perfusion nor gastric mucosal energy balance; (D) heparin rinse before the CRRT has no beneficial effect on thrombogenicity and biocompatibility of EC; (E) although citrate anticoagulation successfully overcomes thrombogenicity of EC it does not completely eliminate EC induced complement activation; (F) mild core cooling induced by of continuous venovenous hemofiltration may not affect hepatosplanchnic oxygen and energy balance in septic critically ill patients, even though it affects global hemodynamic (increases MAP).

In conclusion, our studies showed that (A) in hyperdynamic experimental sepsis with MAP > 65 mniHg a "better" perfusion pressure achieved by titrating norepinephrine to restore near- normal

MAP neither improved nor adversely affected perfusion of the liver and the gut- it suggests that the perfusion of these organs was, at least in our model, within their autoregulatory range; (B) EN may not be harmful even in hemodynamicaly compromised critically ill septic patients; (C) prone position in ALI patients is safe procedure concerning hepatosplanchnic perfusion and energy balance; (D,E) heparin preprocedural EC rinse and citrate anticoagulation are not able to reduce the bioincompatibility of the CRRT; (F) beneficial hemodynamic effect of mild CRRT induced core cooling is not probably followed by adverse hemodynamic and metabolic consequences in hepatosplanchnic region.