Assessment and preservation of liver function in hepatic ischemia and reperfusion
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Chapter 10

Summary and conclusions
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The effects of liver I/R injury are still a major concern during extensive liver resections in which clamping of the afferent vessels are necessary to minimize blood loss. Although extensive research has been conducted over the past decades to elucidate the mechanisms involved in I/R injury, these complex mechanisms, involving several pathways, are not yet fully understood. Animal studies are still an important part of current research, especially when mechanistic issues are investigated. Rodents have often been used for these studies, but, although rodents are well suited for these experiments, comparison of these studies becomes very difficult.

In Chapter 2, an overview is presented of the rat animal models used in literature, in regard with anesthetic methods, rat gender and strain. In total, 9 different animal models, 11 different anesthetics (single or combined) and 5 different rat strains have been used as described in 105 articles. Applied ischemia times vary largely as well as reperfusion times, use of systemic heparin and body temperature control. In all, there seems to be no consensus on the rat model to be used in liver I/R research. An attempt is made to reach such consensus by proposing a standardised rat model based upon literature reports. We strongly believe that a consensus as such, will benefit the liver I/R research community.

Liver I/R research has been conducted not only in rats but in many other animal species. Each species has its own species-specific differences in anatomy and susceptibility to liver I/R injury. Chapter 3 describes experimental liver I/R models in several animal species and their specific differences.

The influence of temperature on liver I/R injury has been well established already. In the transplantation setting, decreasing temperature of the organ extends the limits of storage time until 24 hours depending on species and the organ transplanted. However, the influence of small fluctuations in (body) temperature is less defined. Although in humans, temperature control is a major concern during operations, in animal experiments, control of body temperature is seldom performed routinely. During any type of anesthesia, it is not uncommon to find a drop in body temperature up to several degrees when no special measures have been undertaken. In Chapter 4, the influence of a decrease or an increase in body temperature of 1°C on liver I/R injury was investigated. We showed that a slight drop in body temperature significantly protected the liver from I/R injury, whereas a slight increase tripled the amount of liver injury. Therefore, the influence of temperature on outcome in liver I/R experiments, or in any other type of experiment involving liver ischemia, should not be underestimated and it is thus advisable to maintain the
body temperature of rats during the experiments on 37°C exactly. This condition is quite easily achieved by placing the rat in supine position on a warm heating pad and adjust the temperature using a lamp.

A condition which is also commonly encountered during liver I/R research in rats is the development of acidosis and hypoxia due to respiratory failure. Almost all anesthetic compounds suppress the respiratory system to some extent. However, insertion of a tracheal tube is seldom used to facilitate spontaneous respiration, let alone tracheal intubation and active ventilation. According to literature data, the resulting acidosis and hypoxia can influence the outcome of the experiment. In Chapter 5, the influence of acidosis and hypoxia on liver I/R injury was investigated in four groups of rats: 1) no acidosis and normoxia, maintained by controlled ventilation, 2) acidosis and normoxia, maintained by passive supply with oxygen, 3) no acidosis and hypoxia, maintained by bicarbonate administration without respiratory support and 4) acidosis and hypoxia, i.e. without respiratory support or pH correction. We showed that that influence of acidosis was deleterious under normoxic conditions but protected the liver from I/R injury under hypoxic conditions. These findings cannot be neglected in liver I/R research and therefore, respiration should be facilitated and cautiously controlled during anesthesia.

The role of complement activation in liver I/R research still is unclear, although it has be identified as an important mechanism in liver I/R injury. Although at first, most authors referred to the alternative pathway as the main activator of complement in liver I/R, the classical pathway has more recently also been shown to play a role in this activation. The molecular mechanisms of the observed activation of complement during liver I/R have not been defined, but a contribution of CRP mediated activation has been suggested. In Chapter 6, purified human C1-inh was administered using different dosages and at different time points in an in vivo rat model of partial liver ischemia. Furthermore, a possible role of CRP mediated complement activation was investigated. We found that administration of C1-inh before induction of ischemia as compared to administration at the end of the ischemic period resulted in less hepatocellular injury after 24 h of reperfusion, which was significantly lower when compared to albumin treated, control rats. Furthermore, our data strongly suggest a role of CRP-mediated complement activation in liver I/R injury. The amount of C1-inh necessary to decrease liver I/R injury seems to be no more than 100 IU/kg bwt.

The decrease in intra operative and postoperative complications has improved the outcome of major liver surgery over the last decades. The reduction of intra-operative blood-loss by clamping the afferent vessels to the liver, with or without clamping of the supra-hepatic and
infra-hepatic caval vein, significantly contributed to this achievement. A further decrease in postoperative morbidity and mortality can be accomplished by reducing procedure related liver injury, such as I/R injury. The objective of Chapter 7 was to decrease liver I/R injury by means of a mild decrease in core liver temperature of 10°C, achieved by in situ hypothermic perfusion of the liver during ischemia.

To this end, liver ischemia was induced by total hepatic vascular exclusion with concomitant in situ perfusion by way of the hepatic artery, using hypothermic (4°C) Ringer-glucose (cold perfused group, core liver temperature maintained at 28°C), normothermic (38°C) Ringer-glucose (warm perfused group), or without in situ perfusion (control group). We found that a mild decrease in liver temperature during ischemia significantly attenuated hepatocellular I/R injury while the sinusoidal endothelial cells remained viable without loss of function.

Microcirculatory disturbances are an early event of I/R injury. Since intrahepatic tissue oxygenation depends on oxygen delivery by the liver microvasculature, the tissue distribution of oxygen reflects the microcirculatory status of the liver. Also, during reperfusion, reactive oxygen species (ROS) are formed, contributing to liver I/R injury. In Chapter 8, the influence of mild cooling of the liver during ischemia on microcirculation and ROS production was investigated. We concluded that the protective effect of mild cooling against liver I/R injury was associated with sustained hepatic (arterial and portal venous) flow and preservation of microcirculatory integrity. Oxidative stress occurred during the initial phase of reperfusion and was abrogated in part by in situ hypothermic perfusion. Therefore, clinical application of this intervention for salvaging the remnant liver during partial hepatectomy under compromising conditions, deserves further investigation.

Despite all advances made in recent years, the major cause of mortality after liver resection has remained failure of the remnant liver. Thus, it is important to estimate total and local liver function before planning partial resection of the liver in order to predict function of the remnant liver. At present, the indocyanine green (ICG) clearance test is considered to be one of the most reliable function tests although it only gives an estimate of global liver function. A similar function test, hepatobiliary scintigraphy, is capable of providing segmental information of functional liver mass. In Chapter 9, pre-operative assessment of liver function with both the ICG clearance test and hepatobiliary scintigraphy were compared in 30 patients undergoing partial liver resection for liver tumours. Both liver function tests were comparable with regard to liver uptake. Only hepatobiliary scintigraphy however, could provide information about local excretatory liver function. Despite pre-operative biliary drainage in patients with hilar bile duct
tumours, hepatobiliary scintigraphy could still show decreased liver function of the tumour-affected side of the liver. This provided useful information on the functional status of the future remnant liver segments.