Liver protection in the perioperative setting

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With recent advances in surgical and anaesthetic management, clinical medicine has responded to societal expectations and the number of operations in patients with a high-risk of perioperative liver failure has increased over the last decades. This review will outline important pathophysiological alterations common in patients with pre-existing liver impairment and thus highlight the anaesthetic challenge to minimise perioperative liver insults. It will focus on the intraoperative balancing act to reduce blood loss while maintaining adequate liver perfusion, the various anaesthetic agents used and their specific effects on hepatic function, perfusion and toxicity. Furthermore, it will discuss advances in pharmacological and ischaemic preconditioning and summarise the results of recent clinical trials.

Key words: liver; hepatotoxicity; perioperative; protection; anaesthesia; volatile; preconditioning; catecholamine.

INTRODUCTION

Estimates suggest that as many as 10% of all patients with advanced liver disease will undergo surgery in the last 2 years of their lives.¹ In addition, the number of successful liver transplantations has increased dramatically over the last few years, in the USA alone the numbers have gone from 2931 procedures in 1991 to 4480 in 1999.² With a recipient survival rate of about 88%³, more and more patients with post-transplant liver dysfunction may require further surgical intervention. Even seemingly healthy patients without clinical signs of liver impairment may present with subtle liver
dysfunction, as seen in about 1 in 700 patients with a pre-test classification of American Society of Anesthesiology physical status classification (ASA-1) admitted for elective surgery. Knowledge and evaluation of pre-operative liver impairment is extremely important, as the extent of perioperative liver injury caused by ischaemia and reperfusion depends primarily on the duration of ischaemia as well as on pre-existing liver diseases, such as cirrhosis or acute hepatitis. Hepatic ischaemia and subsequent liver dysfunction is associated with a profound deterioration in prognosis. Because of the central role of the liver in the metabolic and immunological response to stress, the increased mortality seen after perioperative liver failure is most likely due to progression to multiple organ failure. Pre-existing hepatic dysfunction poses a great risk even for non-hepatic surgery, as shown by the higher blood transfusion requirements, longer hospital stays, more complications and increased mortality rate of 16.3% in patients with cirrhosis compared to 3.5% in controls. A detailed understanding of the underlying pathophysiology and thorough evaluation and pre-operative optimisation by expert anaesthetic teams is, therefore, crucial to avoid perioperative liver insults.

PRE-OPERATIVE CONSIDERATIONS AND ASSESSMENT

Because of significant inter-individual differences and the often severely reduced functional reserve capacity of patients with liver dysfunction, the pre-operative work-up needs to be tailored to the individual patient. Assessing the general health and co-morbidities, e.g. coagulopathy, renal function, volume and electrolyte status and cardiovascular function, is essential for anticipating the need for invasive cardiovascular monitoring, transfusion requirements and prolonged post-operative monitoring in high-dependency areas to minimise the risk of perioperative liver insults (see Table 1).

The healthy liver has a substantial functional reserve capacity due to the dual blood supply from portal venous (75%) and hepatic arterial (25%) blood flow. Clinical manifestations of liver insults therefore occur only after substantial damage. However, patients with advanced liver disease lose a significant amount of hepatic reserve capacity and may have an inappropriate response to surgical stress, increased risk of bleeding and post-operative hepatic encephalopathy, as evidenced by their high perioperative mortality rate.

Cardiovascular function

The systemic circulation in patients with liver cirrhosis is best characterised as hyperdynamic and dysfunctional, with increased heart rate and cardiac output, decreased systemic vascular resistance and low, normal or decreased arterial blood pressure. Cirrhotic cardiomyopathy is characterised by impaired myocardial contractility, decreased β-adrenergic receptor function and downregulation, leading to clinically significant

<table>
<thead>
<tr>
<th>Table 1. Pre-operative assessment.</th>
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<tr>
<td>Cardiovascular function: ECG, echocardiography, exercise/pharmacological stress-test</td>
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<tr>
<td>Pulmonary function: Detailed pre-operative blood gas analysis (right heart catheterisation)</td>
</tr>
<tr>
<td>Renal status: Electrolytes, urea and creatinine</td>
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<tr>
<td>Coagulation profile: INR, platelet number and function</td>
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<td>Hepatic function: Liver function tests, Child–Pugh score</td>
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ECG, electrocardiography; INR, international normalised ratio.
Cardiac dysfunction and a limited contractile reserve to meet perioperative haemodynamic challenges. Moreover, the response to exogenous norepinephrine and other potent vasoconstrictors, such as angiotensin II and vasopressin, is blunted in patients with liver cirrhosis.\textsuperscript{16,17} Thus, intraoperative cardiovascular stability maintaining adequate end-organ perfusion may be difficult to achieve and detailed pre-operative assessment of the functional reserve is warranted. Pre-operative echocardiography and either an exercise or pharmacological stress-test should be performed routinely. A 12-lead ECG may detect rate-corrected Q-T interval (QTc) prolongation, which is frequent in patients with cirrhosis and may predict severe arrhythmias and sudden cardiac death.\textsuperscript{18}

**Pulmonary function**

Two distinct pulmonary vascular disorders are known to occur in chronic liver disease – the hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH). The exact pathophysiological mechanisms are not known, but both are characterised by pulmonary vascular remodelling at different sites of the pulmonary microcirculation. Several pathophysiological abnormalities have been reported within the HPS, including diffuse or localised dilatation of pre- or post-capillary pulmonary vessels, increased intrapulmonary arterial–venous shunting and portal–venous anastomoses.\textsuperscript{19} The development of HPS does not seem to correlate uniformly with the degree of underlying liver impairment, but the clinical features of exertional dyspnoea, cyanosis and increased pulmonary arterial–venous shunting are seen in up to 15% of patients with chronic hepatic disease\textsuperscript{20} and may have deleterious effects on the attempt to maintain adequate perioperative liver perfusion and oxygenation.

The incidence of POPH, however, is about 10 times lower than that of HPS.\textsuperscript{19} Advanced POPH presents clinically with exertional dyspnoea, chest pain and syncope and the diagnosis is based primarily on pulmonary haemodynamic criteria obtained via right heart catheterisation, as defined at the third World Symposium on Pulmonary Artery Hypertension.\textsuperscript{21} Moderate and severe POPH can substantially increase the risk associated with liver transplant, increasing perioperative mortality to >50% with a pulmonary artery pressure of 35–45 mmHg and a pulmonary vascular resistance of >250 dynes/s/cm\textsuperscript{5}.\textsuperscript{22} The European Respiratory Society recommends screening for POPH with transthoracic Doppler echocardiography and right heart catheterisation.\textsuperscript{19} Since patients with cirrhosis present with a variable PaO\textsubscript{2} response to 100% inspiratory oxygen, detailed pre-operative blood gas analyses may help in understanding the underlying mechanism of hypoxia: if there is no improvement in PaO\textsubscript{2} under inhalation of 100% oxygen intra-pulmonary shunting is likely; a moderate increase of PaO\textsubscript{2} (>300 mmHg) does not rule out arteriovenous communications; a normal response with PaO\textsubscript{2} > 500 mmHg can exclude intra-pulmonary shunting,\textsuperscript{23} making ventilation–perfusion mismatching or dilated alveolar capillaries more likely as the main factors responsible for arterial hypoxaemia.\textsuperscript{24}

**Renal assessment and electrolyte status**

Hepatorenal syndrome (HRS) is the renal disease most strongly associated with severe liver disease.\textsuperscript{25} HRS, a functional renal failure with histologically normal kidneys, is a diagnosis of exclusion, as it is caused by alterations in renal blood flow due to a reduction in effective intravascular volume from splanchnic vasodilatation.\textsuperscript{26,27} It usually presents with uraemia and oliguria in patients with advanced cirrhosis and ascites\textsuperscript{27} and may be
exacerbated by perioperative fluid shifts and intravascular hypovolaemia. Electrolyte abnormalities, such as hyponatraemia, are common in patients with advanced liver disease, because of HRS, fluid retention, massive ascites and large-volume paracentesis. Symptomatic and severe hyponatraemia (<125 mEq/l) must be treated and corrected carefully to avoid central pontine myelinolysis.

Coagulation profile

The liver plays a pivotal role in the coagulation process and coagulopathy is a prominent feature of acute and chronic liver failure. All coagulation factors are produced in the liver, except von Willebrand’s factor, which is produced in endothelial cells. The coagulopathy in liver disease results from impaired production of coagulation factors, alterations in vitamin K metabolism, a low grade disseminated intravascular coagulation, enhanced fibrinolytic activity and/or alterations in platelet number or function. An increased pre-operative prothrombin time is associated with post-operative liver decompensation and perioperative mortality. The coagulation profile should be assessed pre-operatively and coagulopathy corrected, depending on the surgical procedure and the expected blood loss. As hyperthermia inhibits the enzymes of the coagulation cascade and thus further aggravates intraoperative blood loss, strict normothermia should be maintained using warmed fluids or warm-air devices. Portal hypertension is the most common cause for thrombocytopenia in liver disease and platelet sequestration in the spleen can increase from the normal 30% to as much as 90%. In addition, qualitative platelet dysfunction, including inhibition of platelet aggregation and alterations in platelet membrane composition, can impair perioperative haemostasis. Thus, care should be taken when considering neuraxial anaesthesia in patients with severe liver disease, as platelet function might be impaired despite a normal platelet count. Pre-operative assessment and correction of coagulopathy is important to minimise intraoperative blood loss and transfusion requirements. Application of vitamin K, infusion of fresh frozen plasma or cryoprecipitate can normalise coagulation factors and platelet transfusion may be indicated for low platelet numbers or abnormal intrinsic platelet function.

Quantified risk stratification

Patients with chronic liver disease have a reduced hepatic reserve capacity to cope with perioperative stress and are at increased risk for post-operative liver failure, coma or death. Thus, the decision to perform surgery in these patients needs to be made on the basis of the individual risk profile and the proposed surgical intervention. Comorbid conditions associated with perioperative morbidity and mortality need to be identified and assessed, as discussed in detail elsewhere. Two risk stratification schemes have been designed to assess the perioperative risk of patients with chronic and advanced liver disease – the Child–Pugh score (1984) and, more recently, in 1999, the Model of End-Stage Liver Disease (MELD). The Child–Pugh score (see Table 2) was originally derived from patients undergoing portosystemic shunting for variceal haemorrhage, but subsequent studies have shown its usefulness in estimating risks for patients with liver disease undergoing hepatic or non-hepatic surgery. On average, patients with a Child–Pugh class A score have a 10% perioperative morbidity and mortality rate with intra-abdominal surgery, those with a class B score about 30% and about 82% with class C. Patients with a Child–Pugh class B or C score were considered candidates for liver transplant until the Mayo Clinic developed a revised
model in 1999. This Model of End-Stage Liver Disease (MELD) was designed to overcome the ambiguity and interobserver variability due to the subjective parameters of the Child–Pugh score. Initially aiming to predict 3-month mortality in patients with chronic liver disease, it as been used since 2002 by the United Network for Organ Sharing (UNOS) to prioritise patients awaiting liver transplantation. The MELD score is based on biochemical parameters rather than the subjective assessment of clinical features and is calculated from the patient’s serum creatinine (Crea), bilirubin (Bil) and international normalised ratio (INR):

\[
\text{MELD Score} = 10 \times 0.957 \ln(\text{Crea}) + 0.378 \ln(\text{Bil}) + 1.12 \ln(\text{INR}) + 0.643
\]

Even though the MELD score is a more objective predictor of post-operative mortality than the Child–Pugh score, it is principally used to select patients for liver transplantation and the Child–Pugh score remains the best validated predictor of perioperative morbidity and mortality in patients with liver impairment.

### ANAESTHETIC CONSIDERATIONS AND INTRA-OPERATIVE MANAGEMENT

Patients with advanced liver disease are much more likely to suffer from hepatic decompensation due to anaesthesia and surgery. In a study of 733 patients with cirrhosis who underwent surgery, the perioperative mortality within 30 days was 11.6% and the complication rate was 30.1%, considerably higher than in patients without liver dysfunction. Post-operative pneumonia was the most frequent complication, with risk factors including a high Child–Pugh score, diagnosis of cirrhosis, ascites, elevated serum creatinine, pre-operative gastrointestinal bleeding and intraoperative hypotension.

Not only chronic liver impairment but also acute hepatitis increases the susceptibility for ischaemia following hypoperfusion, perhaps because of the hypermetabolic state. Hepatic blood supply is complex and is regulated on different levels. Alterations in blood flow on each of these levels can reduce hepatic nutritive blood supply and thus contribute to subsequent hepatocellular injury; reduction in cardiac output or systemic vascular resistance or an increase in right atrial pressure may all reduce hepatic blood flow. The splanchnic blood supply is highly variable and does not necessarily

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<table>
<thead>
<tr>
<th>A. Classification</th>
<th>Points</th>
<th>Albumin (g/dl)</th>
<th>Bilirubin (mg/dl)</th>
<th>INR</th>
<th>Ascites</th>
<th>Encephalopathy</th>
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<tr>
<td></td>
<td></td>
<td>&gt;3.5</td>
<td>&gt;2.0</td>
<td>&lt;1.7</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>B. Interpretation</td>
<td>Points</td>
<td>Class</td>
<td>1-year survival (%)</td>
<td>2-year survival (%)</td>
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<tr>
<td></td>
<td></td>
<td>A</td>
<td>100</td>
<td>85</td>
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<td></td>
<td></td>
<td>B</td>
<td>81</td>
<td>75</td>
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<td></td>
<td></td>
<td>C</td>
<td>45</td>
<td>35</td>
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INR, international normalised ratio.
increase even with stable or increased cardiac output.\textsuperscript{36,37} Hence, the regional macro and micro circulation is also actively modified to ensure an adequate nutritional blood supply. This so called ‘hepatic arterial buffer response’\textsuperscript{38} is partly mediated by locally released adenosine.\textsuperscript{39} Moreover, the endothelium itself is actively involved in the regulation of sinusoidal blood flow and various mediators such as nitric oxide, endothelin and carbon monoxide have already been identified.\textsuperscript{40–43} Interaction of the different anaesthetic agents with these microcirculatory mediators might partly explain the varying hepatotoxic effects of volatile anaesthetics and the subsequent perioperative liver insults.

General anaesthesia aggravates the already dysfunctional cardiovascular status present in many patients with chronic liver disease, further reducing the hepatic blood flow, especially that of the hepatic artery. Of the inhaled volatile anaesthetics, halothane and enflurane appear to reduce hepatic artery blood flow the most because of systemic vasodilatation and negative inotropic effects.\textsuperscript{44,45}

**Volatile agents**

It is commonly accepted that all volatile anaesthetics have the potential to impair liver function.

**Halothane**

Halothane is associated with a risk for autoimmune hepatitis following exposure, with a reported incidence of about 1:6000–1:35000.\textsuperscript{46} A mild hepatic reaction is characterised by moderately increased liver enzymes, transient jaundice and a low mortality. Fulminant halothane-associated hepatitis, however, is associated with repeated exposure to halothane and the development of severe liver failure with high mortality. Specific circulating IgG antibodies were found in patients with fulminant hepatic failure after halothane exposure and these antibodies were shown to react with cell surface antigens of hepatocytes making them more susceptible to antibody dependent cell-mediated toxicity.\textsuperscript{47} In addition, a genetic susceptibility factor has been proposed, which would predispose certain patients to halothane hepatitis\textsuperscript{48} and thus makes an individual prediction about the safety of halothane very difficult.

**Enflurane**

Enflurane has also been linked to post-operative liver damage\textsuperscript{49}, however, the exact mechanism remains unclear and controversy exists over whether enflurane is the causative agent.\textsuperscript{50,51} This might be partly explained by cross-sensitisation between enflurane and halothane, which has been shown for the protein products of enflurane metabolism.\textsuperscript{52}

**Isoflurane**

Isoflurane, an isomer of enflurane, undergoes only a minimal biotransformation of 0.2%. Although this rate of biotransformation is thought to be minimal, several authors consider isoflurane to be the cause of a wide spectrum of hepatic injuries, ranging from post-operative transaminitis to fulminant hepatic failure and death.\textsuperscript{53–57} Isoflurane has been shown to have a positive effect on hepatic blood supply, possibly due to direct vasodilatation in the hepatic vascular bed.\textsuperscript{58} The exact mechanism is still being investigated,
but isoflurane, just like sevoflurane, has been shown to induce an upregulation of haem oxygenase-1 (HO-1). This enzyme catalyses the conversion of haem to biliverdin IX$_{a}$, free iron and carbon monoxide$^{59}$ and thus decreases portal vascular resistance and may, therefore, exert hepatoprotective effects. Induction of HO-1 seems to be an individual feature of isoflurane and sevoflurane, since upregulation of HO-1 could not be seen with desflurane.$^{60}$

**Sevoflurane**

The metabolism of sevoflurane is rapid, with fluoride appearing in the plasma within minutes of administration.$^{61}$ Although sevoflurane is also metabolised by cytochrome P450 (about 2–5%), this does not result in the formation of fluoroacetylated neoantigens.$^{61}$ Sevoflurane causes a slight decrease in portal blood flow in animals, but in humans no difference in indocyanine green clearance has been shown and it appears to be as safe as isoflurane.$^{62}$

**Desflurane**

Desflurane increases hepatic blood flow, but there is no significant difference between it and isoflurane.$^{63}$ Desflurane is metabolised by cytochrome P450 to only a very small degree (0.02%) and the reported hepatotoxicity in three patients was very low compared to that of other volatile anaesthetics.$^{64}$

The autoimmune antibody response that induces hepatic necrosis is directed at neo-antigens on trifluoroacetylated proteins. These are the products of cytochrome P450-dependent biotransformation.$^{65}$ The production of antibodies should be related to the relative degree of metabolism of each volatile agent (apart from sevoflurane)$^{66}$, that is: halothane (15–40%) $>$ enflurane (2.5%$^{67}$) $>$ isoflurane (0.2%$^{68}$) $>$ desflurane (0.02%$^{69}$). Therefore, the formation of auto-antibodies should occur proportionately less frequently with isoflurane and desflurane.

**Regional anaesthesia**

Both general and regional anaesthesia cause reversible sympathectomy with peripheral vasodilatation and exacerbation of hypotension. No significant difference in liver function and hepatic perfusion was seen between general anaesthesia using isoflurane and spinal anaesthesia, provided the mean arterial pressure was maintained within normal limits.$^{70}$ However, patients requiring vasopressors for more significant haemodynamic disturbances were excluded from that study. Because of the increased risk for spinal haematoma in patients with liver dysfunction and the better titration of volatile anaesthetics, isoflurane, sevoflurane$^{71}$ or desflurane might be the more appropriate agents for anaesthesia in patients with pre-existing liver impairment.

**Haemodynamic management**

Patients with chronic liver disease have a reduced functional reserve capacity and are at greater risk of ischaemia and hypoperfusion, and therefore require tighter control of arterial blood pressure. However, macrohaemodynamic variables, such as mean arterial pressure and systemic vascular resistance, do not necessarily reflect nutritional organ blood supply, and oxygenation as well as microcirculatory blood flow cannot be reliably predicted from those variables.$^{72}$ Vasoactive agents may, therefore, elicit their effects at
various levels, hindering detailed intra- and perioperative monitoring. Furthermore, vasoactive agents do not just alter cardiac output and systemic vascular resistance and thus oxygen delivery; they also modify regional oxygen consumption. Studies addressing the local nutritional blood supply have identified marked differences between physiological and pathophysiological conditions, although they have mainly been performed in septic patients or in animal models. It is, therefore, difficult to find detailed data about various vasoactive agents in patients with liver impairment and extrapolation of the results to a clinical setting needs to be done with great care.

**Volume therapy**

Intraoperative haemodynamic management is dictated by the surgical approach. Maintaining a low central venous pressure (CVP) between 2 and 5 mmHg limits the distension of hepatic veins and has been shown to reduce intraoperative blood loss during liver surgery. Once haemostasis is achieved, euvoalaemia should be restored by fluid replacement, as the low-CVP approach exposes the patient to the risk of inadequate organ perfusion and reduces the volume reserve for meeting haemorrhagic challenges.

**Epinephrine and norepinephrine**

In a recent study Krejci et al. compared the effects of phenylephrine, epinephrine and norepinephrine on various splanchnic vascular beds in septic pigs, including blood flow through the superior mesenteric artery, microcirculatory blood flow in the intestinal mucosa of the stomach, jejunum and colon and the microcirculatory blood flow on the surface of the liver. Despite normovolaemia and an increased mean arterial pressure of about 20 mmHg above baseline, infusion of both epinephrine and norepinephrine had detrimental effects on regional mesenteric and microcirculatory blood flow in the jejunal mucosa. Blood flow in other organs (e.g. stomach, colon, liver and kidney) remained virtually unaffected despite an increased mean arterial blood pressure following epinephrine infusion. These results are similar to a report from de Backer et al. who found that epinephrine could impair splanchnic circulation in patients with septic shock and that the effect of epinephrine differed with the degree of underlying sepsis. For hepatosplanchnic blood flow measurement, indocyanine green clearance combined with hepatic vein catheterisation was used, thus representing metabolic variables rather than direct mucosal blood flow. These results imply that the effects on splanchnic perfusion do not only differ between vasoactive agents but are also dose dependent.

**Dopamine, dobutamine and dopexamine**

The effects of dopamine or dobutamine versus dopexamine on systemic, regional and local blood flow were studied in a porcine septic shock model, which showed no selective beneficial effect, improving microcirculatory blood flow only by increasing cardiac output. In patients with sepsis, dopexamine failed to selectively increase splanchnic blood flow and in a prospective, randomised controlled, double-blinded multicentre trial, dopexamine did not improve outcome after major abdominal surgery, had no effect on organ dysfunction, duration of intensive care unit or hospital stay and actually decreased gastric mucosal pH.

The data on dopamine are very controversial, showing detrimental effects on gut mucosa perfusion in septic patients in one study, but improvements in splanchnic blood flow in septic patients in another. Interestingly, the effects of dopamine on
splanchnic blood flow may actually differ according to basal splanchnic perfusion, as seen in the small human study by Meier-Hellmann et al.\textsuperscript{81} Whether dobutamine has a specific effect on splanchnic mucosa is still debated. Cross-over studies in patients with septic shock comparing the combination of dobutamine and norepinephrine with epinephrine alone, showed a favorable effect of dobutamine/norepinephrine, with improved splanchnic blood flow and oxygen uptake, higher gastric pH and lower portal vein lactate concentration.\textsuperscript{82} A selectively beneficial effect of dobutamine, however, could not be confirmed in adequately fluid resuscitated septic patients, with an unaltered splanchnic oxygen consumption and a parallel increase in splanchnic blood flow and cardiac index being recorded.\textsuperscript{83}

\textbf{Vasopressin}

Vasopressin plays only a minor role in physiological blood pressure regulation. In the past few years clinical studies have shown that vasopressin can rapidly restore blood pressure in septic shock. However, the effects of vasopressin on splanchnic and hepatic blood flow are controversial and the subject of much discussion. In septic rats, vasopressin induced severe abnormalities in gut mucosa blood flow\textsuperscript{84} and this finding was confirmed in patients with septic shock; vasopressin altered the blood flow distribution pattern in the splanchnic area compared to norepinephrine, decreasing total splanchnic blood flow and doubling the pCO\textsubscript{2} gap.\textsuperscript{85} Preliminary results of the completed Vasopressin and Septic Shock Trial (VASST) were recently presented at the Society of Critical Care Medicine's 36th Critical Care Congress: data from 779 patients in septic shock, receiving either norepinephrine or vasopressin, were analysed. Overall, no difference in 28-day survival between groups could be found. However, a subgroup analysis showed improved survival with vasopressin in patients with less severe hypotension.

\textbf{Phosphodiesterase inhibitors}

Phosphodiesterase inhibitors used in septic patients showed promising results in a study from Kern et al.\textsuperscript{86} An increase in hepatosplanchnic oxygen consumption, an increased lignocaine metabolism and a decreased release of hepatic tumour necrosis factor (TNF)-alpha were found, all indicating an improvement in hepatosplanchnic function and anti-inflammatory properties after 12 hours of enoximone treatment. In a septic porcine model, olprinone showed beneficial effects in restoring systemic and hepatic circulation\textsuperscript{87}, suggesting a dose-dependent increase in splanchnic blood flow.

\textbf{Levosimendan}

This pyridazinone-dinitrite with both inotropic and vasodilating effects has been shown to selectively increase blood flow to the duodenum and to decrease splanchnic vascular resistance.\textsuperscript{88} Beneficial effects of levosimendan on gastric mucosa oxygenation, which were at least partially independent of systemic effects, were shown by Schwarte et al. in an animal model.\textsuperscript{89} Few clinical trials have directly compared vasoactive agents and the use of surrogate endpoints, such as indocyanine green clearance, makes it very difficult to make recommendations with regard to the best choice for perioperative liver protection. Moreover, increased mean arterial pressure and/or cardiac output do not equate with regional or microcirculatory nutritive blood flow. The majority of evidence, however, suggests that vasopressin and epinephrine have adverse effects on splanchnic perfusion.
and that the combination of norepinephrine and dobutamine might be preferable. Newer agents, such as levosimendan and olprinone, appear to selectively improve splanchnic perfusion and their potential for perioperative liver protection warrants further research. The recommended approach to anaesthetic use is given in Table 3.

### PRECONDITIONING

Ischaemia and reperfusion injury is a major cause of morbidity and mortality following liver surgery and transplantation. Iatrogenic occlusion of the supplying blood vessels, with the aim of reducing blood loss in hepatic trauma or resection, induces warm ischaemia, similar to haemorrhagic, cardiogenic or septic shock. Cold hepatic ischaemia is an integral component of liver transplantation. Liver tolerance for ischaemia is poor and the safe ischaemia time is not known. In addition to the direct ischaemic insult, hepatic injury occurs during reperfusion. The exact mechanisms, such as the activation of local macrophages and the production of reactive oxygen intermediates and pro-inflammatory cytokines, are still being investigated. The oxidative stress related to hepatic reperfusion injury has long been recognised, but is beyond the scope of this review and is discussed elsewhere in more detail.33,90

The recent discovery, in animal studies, of the promising endogenous cellular protective mechanism known as ischaemic preconditioning, has led to several clinical trials. The hypothesis that a short period of ischaemia, prior to subsequent prolonged clamping during the main surgical procedure, could reduce hepatic injury and improve outcome was investigated. In a recent prospective randomised study, Azoulay et al.91 investigated whether a 10 min period of prior ischaemic preconditioning in 60 patients requiring major hepatectomy would protect them against hepatic ischaemia–reperfusion injury. The results were disappointing, as ischaemic preconditioning in the clinical trial did not prevent ischaemia–reperfusion injury, nor did it have any impact on important clinical outcomes such as morbidity, length of hospitalisation and in-hospital mortality.91,92 In another prospective, randomised clinical trial with 100 patients undergoing major liver resection, Clavien et al.93 demonstrated an age-related beneficial effect of ischaemic preconditioning on post-operative aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. Interestingly, only patients younger than 60 years and those with steatosis benefitted – older patients and those with cirrhosis did not. Again, no benefit could be found in terms of morbidity, length of ICU or hospital stays, possibly due to the small sample size. This lack of improvement and the marked difference between age-groups indicates that the protocol for preconditioning might need to be tailored to the individual subgroup of patients. Furthermore, the positive effects seen in the surrogate endpoints (e.g. blood loss94, liver enzyme levels95 or ATP content97) used in animal and clinical studies, as summarised elsewhere90, need to be translated into clinical outcome and confirmed in larger trials.

### Table 3. Recommended anaesthetic approach.

- Isoflurane or sevoflurane (may exert hepatoprotective effects)
- Dobutamine and noradrenaline for haemodynamic control
- Volume therapy directed at minimising blood loss (low central venous pressure (CVP) in liver resection) while aiming at euvoilaemia
POST-OPERATIVE CARE

Hospital mortality after elective liver resection is about 1% in patients without underlying liver disease and about 10% in patients with pre-existing disease. In a study on 478 patients, Belghiti et al. reported a post-operative complication rate of 22%, with pulmonary infection being the most frequent (11.9%), and abdominal abscess with or without biliary fistula (7.1%), haemorrhage (2%) and renal failure (0.7%) occurring less frequently. A hyperdynamic state with increased cardiac output and augmented splanchnic blood flow persists for at least 3 post-operative days after liver resection, with the development of mild-to-moderate pulmonary oedema and an incidence rate of transient ascites of about 50%. Because of an incidence rate of about 8% for major post-operative complications and 3% for re-operation, patients undergoing major liver resection or with significant pre-operative liver impairment should be closely monitored for the early detection of post-operative complications.

PERSPECTIVE AND FUTURE RESEARCH

Hepatic ischaemia and reperfusion injury is associated with high morbidity and mortality. One cornerstone of perioperative liver protection is to minimise the liver insult by optimising hepato-splanchnic perfusion and avoiding possible hepatotoxic agents. In addition, recent research has provided interesting data about ischaemic or drug-induced preconditioning and thus prevention of liver damage. Induction of hepatic enzymes (e.g. HO-1) has been shown to reduce hepatic reperfusion injury. Gene expression is up-regulated in response to a variety of stimuli, including isoflurane, sevoflurane, oxidative stress, hypoxia and other triggers. The exact mechanisms remain unclear and are subjects for further research, but specific preconditioning, whether ischaemic or pharmacological, and thus induction of protective mechanisms, e.g. haem oxygenase, might be able to limit subsequent liver injury. Despite promising results in animal studies, current regimens of ischaemic preconditioning have yet failed to improve morbidity and mortality in the clinical setting. Future research needs to be directed towards optimising ischaemic protocols, i.e. length of ischaemia, continuous versus intermittent, in order to translate positive effects on surrogate parameters into clinical outcome.

Practice points

- Pre-existing liver impairment increases susceptibility to ischaemia and affects non-hepatic organ systems, thus warranting detailed pre-operative assessment
- Maintenance of adequate hepatic perfusion and oxygenation is crucial for perioperative protection
- The volatile agents isoflurane or sevoflurane increases hepatic blood flow; using these agents in combination with norepinephrine and dobutamine for the maintenance of perfusion pressure may potentially provide benefits
REFERENCES


Research agenda

- Microvascular regulation of blood supply warrants further research – can possible drug interactions be identified?
- Might certain anaesthetic agents selectively improve hepatic blood supply and oxygenation?
- What are the exact mechanisms of preconditioning and how do we improve morbidity and mortality?
Liver protection in the perioperative setting


