8 Anesthesia and Pain Control in Liver Surgery

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- *Anesthetic management plays a key role in the reduction of perioperative causes of mortality in liver surgery, such as bleeding and liver failure.*
- *Intraoperative reduction of the hepatic blood flow can result from changes in blood volume status and also from mechanical or pharmacological effects, and can lead to liver dysfunction.*
- *Central venous pressure lower than 5mmHg reduces blood loss during hepatic parenchymal transection.*
- *Inhalational anesthetics such as sevoflurane, desflurane, and isoflurane can maintain or even increase total hepatic blood flow; meanwhile, intravenous anesthetics have a modest impact on that.*
- *Intraoperative fluid management should not be guided exclusively by central venous pressure, and the use of colloids (such as 5% albumin) as a maintenance and replacement solution reduces extravascular translocation of fluids.*
- *Pharmacological preconditioning, mainly with the use of inhaled anesthetics, has been used to prevent ischemia-reperfusion syndrome, although its pathophysiology is not entirely understood.*

INTRODUCTION

Improvements in surgical techniques (including new technology and better understanding of anatomy, among other factors) have reduced surgical risk in hepatic resections, and the limits for liver resections have been extended.[1–6] Despite the marked reduction in the risk of blood loss and hemodynamic changes during hepatectomy, the main causes of perioperative death are bleeding and liver failure. Anesthetic care plays an important role in the reduction of perioperative morbidity and mortality.

Intraoperative blood loss is still a threatening complication during liver resection, despite the terrific reduction of this problem over the last few decades. Methods to minimize intraoperative bleeding depend on surgical techniques, and largely anesthetic management. Besides vascular clamping techniques, acute normovolemic hemodilution and low central venous pressure anesthesia have been considered crucial concerns for major hepatectomies and involve anesthetic tools. Additionally, air embolism diagnosis depends on the anesthesiologist's attention. Moreover, surgical and anesthesiological teams should act together to avoid (or minimize) the consequences of ischemia-reperfusion syndrome. Hemodynamic changes during major liver resections are not uncommon and depend on a variety of conditions such as blood loss, vascular clamping or compression, and pharmacological effects of anesthetic drugs, among others.

Thus, hepatic surgery has developed in an associative cooperation between surgical and anesthesiological teams. Surgical and anesthetic strategies should be planned together. This chapter provides an introduction to the main topics related to anesthetic approach to liver surgery.

HEPATIC BLOOD FLOW AND FUNCTIONS

The liver of an adult weighs roughly 1,500 to 1,700 grams, and receives approximately 25% of cardiac output (approximately 800 to 1,200 mL/min). Hepatic blood inflow occurs by the portal vein (75%) and the hepatic artery (25%). The arterial system is high pressure and high resistance (mean pressure similar to the aorta), while the portal vein system is low pressure and low resistance (mean pressure between 5 and 12 mmHg). The arterial blood delivers 40-50% of the total hepatic oxygen supply, and the portal vein 50-60% of that. The arterial flow experiences variations according to alterations in the portal flow (the called hepatic arterial buffer response), but the inverse does not occur (i.e., modifications in the arterial flow do not result in compensatory portal flow changes).[7,8] Temporary occlusion of the portal vein may increase arterial flow by about 30%.[7] Indeed, the increase in hepatic arterial blood flow is capable of buffering 25-60% of the decreased portal flow.[9,10] Extended liver resections induce a significant increase in the portal flow of the remnant liver (portal flow can double after resection of 60% of the liver) due to the incapacity of auto-regulation of the portal flow.[11,12] This change can result in arterial spasm (with consequences from mild cholestasis to liver failure) and portal hyperperfusion injury (represented by the so-called "small-for-size" syndrome).[13–16] Similar effects occur in the context of living liver donor transplantation with a small graft.[17,18] High portal pressure building up in the context of portal hyperperfusion shuts down the flow through the hepatic arterioles and the liver becomes de-arterialized, worsening the consequences of small-for-size syndrome.[19] Splenic artery ligation (or embolization) or portocaval (or mesocaval) shunts may lead to reduction of the portal flow, and they have been suggested as a means of minimizing the impact of small-for-size syndrome.[11,20] Pharmacological interventions to enhance hepatic arterial flow have also been tested, and include hepatic arterial infusion of adenosine, or portal vein infusion of prostaglandin E or proteolytic enzyme inhibitors.[21–23]

The liver plays a substantial role as blood volume reservoir. The liver holds approximately 500 ml of blood, or 10-15% of the total blood volume.[24] Part of this volume can be expelled following a sympathetic stimulation (by central nervous system control of the hepatic blood flow by way of the thoracic sympathetic fibers), providing additional circulatory blood if needed.

The liver is responsible for complex functions in biosynthesis, metabolism, and clearance. Important functions of the liver include synthesis of proteins involved in clotting (such as production of factors II, V, VII, IX, X, and XII), oxygen transport and immune system function, glucose homeostasis, fatty acid β-oxidation, production and excretion of bilirubin, and excretion of drugs.

Intraoperative reduction of the hepatic blood flow during a hepatectomy can result not only from changes in blood volume status, but also from mechanical or pharmacological effects, such as the use of volatile anesthetic agents (such as sevoflurane and desflurane), mechanical ventilation, positive end-expiratory pressure, hypercarbia, and vascular clamping or compression during liver mobilization. Reduction of the hepatic blood flow should be avoided, since it can result in parenchymal necrosis and liver dysfunction.

In liver disease, drug metabolism and clearance depend on the volume of distribution, liver blood flow, and hepatic microsomal activity (P450 cytochrome system). Thus, different liver disease states are related to diverse changes in drug biotransformation. Drugs frequently used in anesthetic practice (such as opioids, lidocaine, benzodiazepines, non-depolarizing muscle relaxants, and thiopental) have their half-lives increased and/or experience a cumulative effect. Monitoring of drug effects and/or titrating the drug should be considered during anesthesia of patients with liver disease.

Hemostatic changes in patients with liver disease are associated with reduction in the production of all coagulation factors (except factor VIII, produced by the endothelium), thrombocytopenia (secondary to splenomegaly due to portal hypertension), and platelet dysfunction, as well as abnormalities of fibrinogen, among other alterations. These changes lead to an increased risk of perioperative bleeding. Coagulopathy is more severe in more advanced liver disease. A prolonged International Normalized Ratio (INR), reduced levels of factors V and VII, and low counts of platelets are common findings in acute liver failure. On the other hand, a state of hypercoagulability can occur, especially in patients with cholestatic liver disease, due to an elevation of von Willenbrand Factor (vWF) and heparin cofactor II, and a decreasing of vWF cleaving protease (ADAMTS-13), plasminogen, and some anticoagulants such as protein C and S and α2 macroglobulin.

CHRONIC LIVER DISEASES

Chronic liver diseases include viral hepatitis (B and C), autoimmune hepatitis, non-alcoholic steatohepatitis (NASH), cirrhosis from any etiology, metabolic diseases (such as hemochromatosis and Wilson's disease), and cholestatic diseases (including primary biliary cirrhosis and primary sclerosing cholangitis). Patients undergoing chemotherapy can present sinusoidal injury (with oxaliplatin-based chemotherapy) and peliosis (with irinotecan-based chemotherapy). The main systemic effects of end-stage liver diseases are shown in **Table 1**.[25]

Cirrhosis may result in portal hypertension, ascites, and hepatocellular insufficiency. Portal hypertension (PH) starts

with splanchnic vasodilation (due to nitric oxide increase – shear stress), reduction of the peripheral vascular resistance and of the mean arterial pressure, and increase in the plasmatic volume, splanchnic blood flow, and cardiac output (these findings determinate the hyperdynamic status seen in cirrhotic patients).[26] PH is responsible for splenomegaly (and hypersplenism), thrombocytopenia, ascites, and esophageal varices. These findings usually occur when portal pressure is more than 20 mmHg (normal portal pressure is 5-12 mmHg). Ascites results from multiple factors, including decreased production of albumin, portal hypertension, and renal retention of sodium and water. Secondary hyperaldosteronism may manifest as hypokalemic metabolic alkalosis. Inadequate synthesis of coagulation factors produces coagulopathy. Hypersplenism worsens thrombocytopenia due to bone marrow suppression. Encephalopathy involves the activation of GABA receptors.

Cirrhotic patients usually have a hyperdynamic circulation due to a decreasing of systemic vascular resistance (SVR) and a compensatory increasing of cardiac output to maintain an adequate tissue perfusion. Other alterations may also include cirrhotic cardiomyopathy and pulmonary vascular abnormalities.[26]

Hepatorenal syndrome, hepatopulmonary syndrome, portopulmonary hypertension, and encephalopathy are conditions associated with severe cirrhosis. They are classically considered contraindications for partial liver resection, but can be present in recipients of liver transplantation (see below the topic of anesthesia in liver transplantation).

Hepatorenal syndrome (incidence of 20% in cirrhotic patients with ascites) occurs due to an unbalance among vasoconstrictor mechanisms (such as renin-angiotensin, antidiuretic hormone, and endothelin) and vasodilator mechanisms (such as prostaglandins and nitric oxide), resulting in chronic renal vasoconstriction and function deterioration. Diagnostic criteria include the association of liver failure and renal failure without other possible causes of renal failure (such as shock, sepsis, and diuretics, among others) and persistence of renal failure after correction of hypovolemia. The definitive treatment is liver transplantation.[27–29]

Hepatopulmonary syndrome (incidence of 4-17% in cirrhotic patients) is characterized by a clinical triad consisting of: i) hepatic disease and/or portal hypertension, ii) intrapulmonary vascular dilatations, and iii) abnormal arterial oxygenation (partial oxygen pressure <70 mmHg or an alveolar-arterial oxygen gradient >20 mmHg). The alveolar-arterial oxygen gradient seems to be the best parameter to assess abnormalities of arterial oxygenation. Liver transplantation is the main therapeutic option, with encouraging results.[30–33]

Portopulmonary hypertension (incidence of 5-10% among Child C cirrhotic patients) is defined by the association of cirrhosis, increased pulmonary arterial pressure and pulmonary vascular resistance. Most patients are asymptomatic and clinical manifestations of right cardiac failure appear during the evolution of the disease. Contrary to hepatopulmonary syndrome, liver transplantation does not cure portopulmonary hypertension. In fact, severe arterial pulmonary hypertension (present in portopulmonary hypertension) can represent a contraindication to liver transplantation because

Table 1. Main effects of chronic hepatic diseases.

System	Clinical manifestation	Causes
Cardiovascular	▪ Hyperdynamic circulation ▪ Portopulmonary hypertension	▪ High cardiac output (and cardiac index) ▪ Low systemic vascular resistance ▪ Arteriolar vasodilatation ▪ Cirrhotic cardiomyopathy ▪ Autonomic neuropathy
Respiratory	▪ Hypoxia	▪ Restrictive pattern (ascites) ▪ Pleural effusion ▪ Hepatopulmonary syndrome ▪ Portopulmonary hypertension
Hematologic	▪ Coagulopathy ▪ Anemia	▪ Defective synthesis of factors II, V, VII and X ▪ Thrombocytopenia (hypersplenism and/or marrow depression) ▪ Platelet dysfunction ▪ Disseminated intravascular coagulation and/or hyperfibrinolysis
Renal system, electrolyte and metabolic disorders	▪ Renal failure ▪ Hyponatremia ▪ Hypomagnesemia ▪ Hyperkalemia ▪ Hypokalemia, and/or metabolic acidosis and hypoglycemia	▪ Hepatorenal syndrome ▪ Acute tubular necrosis from sepsis ▪ Renal impairment drug (Tacrolimus/cyclosporine) related

of the poor prognosis.[30,34–36]

Encephalopathy can result from the effect of neurotoxic substances (such as ammonia) in the setting of acute liver failure (type I), portosystemic shunts (type II), or cirrhosis (type III).[37,38] Overt encephalopathy occurs in 30-45% of cirrhotic patients and the primary treatment is liver transplantation.[39]

PREOPERATIVE ASSESSMENT

Patients with no underlying liver disease tolerate resection of up to 75% of hepatic parenchyma with low rates of postoperative liver failure and mortality. Otherwise healthy patients submitted to no complex hepatectomy are assessed following routine preoperative protocols. However, patients presenting for extensive liver resection and/or those with significant comorbidities need additional assessment. Mainly hemodynamic, respiratory, and hepatic functional status should be evaluated. Patients with known cardiac diseases and those undergoing extensive hepatectomies or with predictable need for hepatic vascular exclusion or major vascular clamping should have additional cardiac tests. Stress echocardiography evaluates the contractile cardiac reserve, blood flow through the cardiac chambers and the pulmonary circulation, guiding the anesthetic management and even surgical strategy. Inadequate respiratory function should be suspected if a low saturation is measured on pulse oximetry, which provides an estimate of arterial pO_2 and could guide additional respiratory tests and perioperative adjustments. Routine liver function tests in patients with no risk factors for chronic liver disease preclude additional tests for most liver resections. Asymptomatic elevations in preoperative serum transaminase levels up to two times normal values have a minimal impact on perioperative outcomes. However, patients with acute hepatitis should not undergo elective liver resection. Obstructive jaundice is also a risk factor for morbidity and mortality. Global mortality rates for hepatectomy in patients with no underlying liver disease are less than 2-3%. Mortality rates can reach 6% for major hepatectomy and up to 15% for liver resections for hilar cholangiocarcinoma.[40] Postoperative morbidity has reached up to 40% in large series of hepatectomies. Most frequent postoperative complications include respiratory complications (such as atelectasis, pleural effusion, and pulmonary infection), biliary complications (mainly leakage), bleeding, ascites, and liver failure, among others. Many predictors of postoperative complications have been identified, including preoperative American Society of Anesthesiologists (ASA) classification, presence of steatosis, extent of liver resection, simultaneous extrahepatic resection, and perioperative blood loss and transfusion.[1,40]

Patients with underlying chronic liver disease, especially cirrhosis, are at increased risk for morbidity and mortality and need specific preoperative anesthetic assessment. As cited above, general anesthesia reduces cardiac output, induces splanchnic vasodilatation, and causes a reduction in hepatic blood flow. Thus, cirrhosis represents an additional risk, especially in hepatic surgery. Anesthesia in patients with end-stage liver disease should be designed to maximize hepatic perfusion and hepatic oxygen delivery, and to prevent and treat the cirrhosis associated complications, such as coagulopathy, portal hypertension, and encephalopathy.

The severity of hepatic dysfunction can be evaluated by a variety of methods, such as Child-Pugh score (**Table 2**) and the Model for End-Stage Liver Disease (MELD) score (**Figure 1**), both scoring systems that have been reliably correlated with postoperative mortality rate in cirrhotic patients undergoing liver surgery. Other criteria, such as portal hypertension, have been evaluated as risk predictors in cirrhotic patients. This issue is also discussed in **Chapter 5** (Liver Function Assessment Before and After Hepatic Resection) and **Chapter 6** (Surgical Approach to Patients with Cirrhosis). Cirrhosis may result in specific organ dysfunction, such as respiratory, renal, or circulatory dysfunction. Arterial blood-gas measurements and Doppler echocardiography are useful to recognize pulmonary hypertension. Abnormal preoperative serum creatinine concentration demands additional renal function studies.

Child-Pugh score (**Table 2**), initially designed to stratify

Table 2. Child-Pugh score.

Parameter	score		
	1	2	3
Ascites	None	Mild	Moderate or severe
Encephalopathy (grade)	None	1-2	3-4
Bilirubin (µmol/L)	<35	35-50	>50
INR	<1.8	1.8-2.3	>2.3
Albumin (g/L)	>35	28-35	<35

The sum of the five scores is used to assign a "Child-Pugh grade" of A (5-6 points), B (7-9 points) or C (10-15 points). INR: International Normalized Ratio.

risk of surgical treatment of portal hypertension, is classically used as a predictor of mortality after abdominal surgery in cirrhotic patients. A study before the development of laparoscopic surgery demonstrated an increase in mortality rates after abdominal surgery, from 10% in Child A to 31% in Child B, to 76% in Child C cirrhosis.[41] The Child-Pugh score has also been demonstrated to be a useful tool to stratify operative risk in liver resections in cirrhotic patients. Extent of hepatic resection in a cirrhotic patient is generally delimited by Child-Pugh classification: Child A patients may tolerate resections of up to 60% of hepatic parenchyma (such as a right hepatectomy), Child B patients tolerate only segmentectomies, and Child C patients tolerate only tumor enucleation.

The MELD score is calculated based upon serum creatinine, total bilirubin, and prothrombin time levels (**Figure 1**). It was originally designed to estimate long-term survival in cirrhosis. In patients with cirrhosis, the preoperative MELD score has been identified as a risk factor for morbidity and mortality after liver resection. Delis et al.[42] reported a nil mortality rate in patients with MELD ≤9 versus a 15.3% mortality for MELD >9 (P<0.001). Another recent study in cirrhotic patients stratified the risk of irreversible postoperative liver failure according to MELD score (MELD scores <9, 9-10, and >10 were associated with 0.4%, 3.8%, and 20.3% irreversible postoperative liver failure, respectively). Additionally, preoperative serum sodium level ≥140 mEq/L identified low-risk patients.[43] On the other hand, Schroeder et al.[44] found that Child-Turcott-Pugh (CTP) score and physical scores of the American Society of Anesthesiologists (ASA) were superior to MELD in predicting outcomes after elective liver resections. MELD score seems to be an accurate predictor of early outcomes after hepatectomy in cirrhotic patients, but not in patients without cirrhosis.[45,46]

Another sign of chronic liver disease, the presence of portal hypertension, was once considered a contraindication for liver resection. However, recent studies suggest that in Child A patients, the presence of portal hypertension does not increase the risk of mortality, but does increase the risk of morbidity.[47] In comparing patients with same MELD score, the presence of portal hypertension showed no effect on the mortality, in a retrospective study.[48] A recent study in patients with Child A cirrhosis demonstrated that severe clinically significant portal hypertension (and also a preoperative neutrophil:lymphocyte ratio (NLR) ≥2.8) was an independent risk factor for liver failure after hepatic resection.[49]

Acute hepatitis and other manifestations of end-stage liver disease, such as encephalopathy, hepatopulmonary syndrome, hepatorenal syndrome, and portopulmonary hypertension, are also well-established contraindications for partial hepatectomy. They should be treated accordingly, if possible, before hepatectomy, but in most cases the definitive treatment is liver transplantation.

MELD SCORE

3.78 x $\log_e$ **serum bilirubin** (mg/dL) +
11.2 x $\log_e$ **INR** +
9.57 x $\log_e$ **serum creatinine** (mg/dL) +
6.43

NOTES:
- If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0
- Any value less than 1 is given a value of 1

Figure 1. Formula to calculate MELD (Model for End-Stage Liver Disease).

LOW CENTRAL VENOUS PRESSURE (CVP)

Many studies have demonstrated that a low CVP (below 5 mmHg) reduces blood loss during hepatic parenchymal transection,[50–52] and the anesthesiologist team plays a crucial role. The intravenous fluids administration (pre- and intraoperatively until the end of hepatic resection and hemostasis) should be limited to keep systolic blood pressure over 90 mmHg and a diuresis of at least 0.5 mL/kg/h.[53–55] Active dehydration can be obtained with diuretics such as furosemide or manitol. Vasoactive agents, such as intravenous nitroglycerin, and intravenous morphine are also used to reduces CVP in case of fluid restriction is ineffective.[56] Intravenous fluid administration (using crystalloid or colloid) is used to increase the intravascular volume and CVP just after the parenchymal cross section.

Despite its clear benefits during liver resection, a low CVP carries some disadvantages that are inadequate organ perfusion, insufficient volume reserve in case of bleeding, and possible increased risk of air embolism. The latter increases in cases of resection of tumors close to major hepatic veins. It is worth noting that when a liver resection is performed using total vascular exclusion, a low CVP is not required. On the contrary, a volume expansion to a CVP of more than 14 mmHg is usually necessary for cross-clamping of the inferior vena cava while maintaining adequate circulation and blood pressure.[57]

Air embolism with clinical expression is very uncommon on hepatic surgery,[58] although intracardiac air bubbles are frequently identified during hepatic parenchymal transection when transesophageal echocardiography is used. Intraoperative signs of air embolism include: i) decrease in end-tidal carbon dioxide, and decrease in both arterial oxygen

saturation (SaO_2) and tension (PO_2), along with hypercapnia; ii) tachyarrhythmias; iii) electromechanical dissociation; iv) pulseless electrical activity; v) ST-T changes; and vi) sudden hypotension. Massive air embolism can result in death of the patient.

The consequences of air embolism can be minimized by placing the patient in a 15 degree Trendelenburg position and with the use of 1.0 fraction of inspired O_2 (FiO_2). Also, the use of hepatic vascular exclusion can be used in patients with high risk for air embolism.[59] The presence of a patent oval foramen (10% to 25% of patients) presents the risk of embolism into the systemic circulation with more severe consequences, such as cerebral or cardiac ischemia. Similar processes may occur in the presence of hepatopulmonary syndrome due to intrapulmonary shunts.

HEMODYNAMIC CHANGES

Some intraoperative events may compromise hemodynamics during elective liver resection, such as intraoperative bleeding, liver vessel occlusion, air embolism, and surgical liver mobilization.

The risk of intraoperative bleeding during liver resections has decreased over time. Recent series report a low percentage of – or even no – blood transfusion. Intraoperative bleeding is anticipated in situations such as repeat surgery, combined organ resection, large tumors, vascular reconstruction, and increased portal pressure. Patients with cirrhosis but no ascites, no hepatocellular insufficiency, no acute alcoholic hepatitis, and a normal coagulation have a prognosis similar to that of patients with no underlying chronic liver disease.[60–62]

During surgical liver mobilization it is possible that the inferior vena cava or portal vein may be compressed or twisted. This occurrence should be suspected when a combined reduction of the systemic arterial pressure and expired PCO_2 occurs. Surgeons should be advised of these findings to, if possible, replace the liver to the anatomical position.

Vascular clamping. Vascular clamping is largely used in major liver resections and is partially responsible for the reduction of intraoperative bleeding. The existence of numerous portosystemic anastomoses (between the splanchnic system and the superior and inferior vena cava system) explains the few variations in the splanchnic venous resistance and cardiac preload during portal clamping.

Vascular control techniques include inflow vascular clamping (total or selective, continuous or intermittent), and inflow plus outflow vascular clamping (total or selective vascular exclusion) (**Figure 2**).

Total inflow vascular occlusion (**Pringle maneuver**) reduces cardiac output by 10- 20%, due to a reduction in the venous return. The decrease in the preload is also responsible for reduced central venous pressure and backflow hepatic bleeding. On the other hand, the Pringle maneuver leads to increase of the systemic vascular resistance (by up to 40%) and mean arterial pressure (10-30%), due to a sympathetic activation by baroreceptors in the hepatic pedicle.[63,64] The blockage of the autonomic nervous plexus on the hepatic pedicle by lidocaine infiltration prevents the arterial pressure from increasing.[65] These hemodynamic changes quickly return to baseline values following unclamping.

A normal liver tolerates continuous ischemia by inflow occlusion for up to 60 minutes (30 minutes when cirrhosis is present). Reperfusion delivers mediators responsible for the ischemia-reperfusion injury. Intermittent pedicular clamping minimizes this syndrome and allows longer and yet undetermined cumulative periods of clamping.

Total Vascular Exclusion (TVE) of the liver results in important hemodynamic changes. Complete clamping

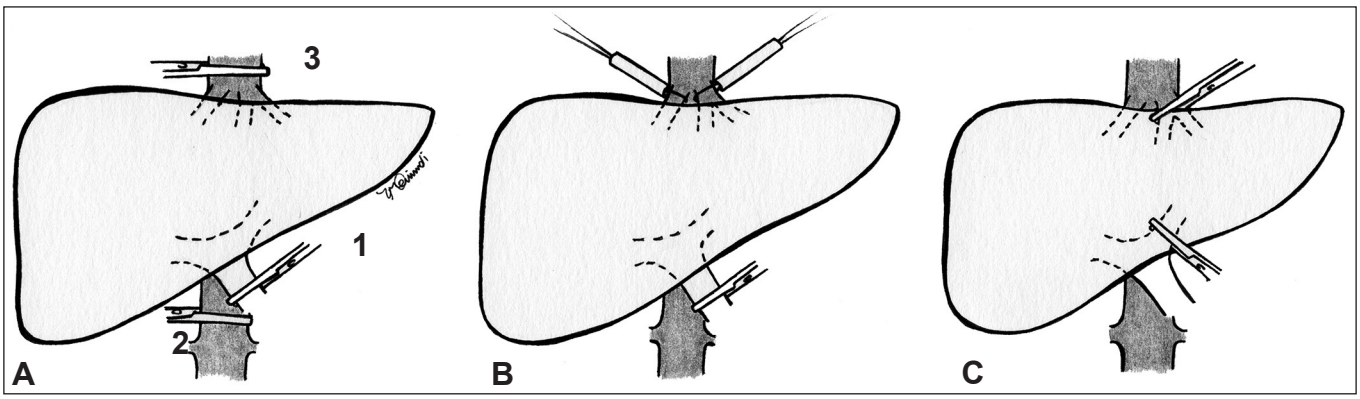

Figure 2. Schematic representation of vascular clamping techniques in liver surgery. **A**) Clamping of hepatic pedicle (1), infrahepatic vena cava (2), and suprahepatic vena cava (3) is used for classical total vascular exclusion of the liver. Clamping of only (1) represents Pringle Maneuver. Clamping of only (1) and (2) can be used to occlude inflow and reduce central venous pressure and backflow. **B**) Total vascular exclusion of the liver without vena cava occlusion. This technique demands ligature of all direct branches to retrohepatic vena cava. **C**) Unilateral vascular exclusion, allowing continuous inflow and outflow on the opposite side.

of the inferior vena cava and portal vein leads to a 40-60% reduction of venous return and cardiac output.[66,67] Despite a compensatory 80% increase in systemic vascular resistance and a 50% increase in heart rate, the cardiac index is reduced by half.[55,68,69] Intravenous fluids infusion can be used before hepatic TVE to prevent abrupt decrease in cardiac output. Colloids are preferred because they additionally improve splanchnic circulation and reduce bowel edema. Vasoactive drugs (vasopressin or norepinephrine) can be used if volume loading is inadequate to maintain acceptable blood pressure. If the mean arterial pressure and/or the cardiac debit decrease more than 50% even after three to five minutes of TVE, the TVE is interrupted. Hemodynamic intolerance, despite volemic load and vasoactive drugs, is observed in 5-20% of patients.[67,70] Venovenous bypass can be used in these cases (**Figures 3** and **4**). Declamping after TVE is generally well tolerated, with rapid normalization of hemodynamics parameters. Acute volemic overload with pulmonary edema can occur with declamping if large endovenous volumes are needed for an adequate tolerance to TVE of the liver.

Hepatic selective vascular exclusion, i.e., inflow and outflow occlusion of one hemiliver (or individual sectors) without caval clamping, has similar hemodynamic effects to the Pringle maneuver and it is well tolerated in most cases.

HEPATIC BLOOD FLOW

Total hepatic blood flow tends to reduce during liver surgery (**Table 3**). During controlled ventilation, portal flow decreases because of an increase in splanchnic vascular resistance with hypocarbia. Positive end-expiratory pressure decreases blood flow, probably by increasing hepatic venous pressure and by a vasoconstrictive response in the preportal vasculature. Most inhalational anesthetics (such as halothane and enflurane) induce additional decrease of hepatic blood flow, but others (such as sevoflurane, desflurane and isoflurane) can maintain or even increase total hepatic blood flow.[71] Halothane induces the most profound reductions in hepatic blood flow and hepatic oxygen delivery.[71] Intravenous anesthetics have a modest impact on hepatic blood flow. Induction agents (such as etomidate and thiopental) decrease hepatic blood flow, either from increased hepatic arterial vascular resistance or from reduced cardiac output and/or blood pressure.[72] On the other hand, ketamine has little impact on hepatic blood flow, and propofol increases hepatic arterial and portal flow by a possible vasodilator effect.[73–75] Epidural anesthesia results in a 25% to 35% decrease in the hepatic blood flow, despite a constant cardiac output.[76] Treatment with norepinephrine to compensate systemic hypotension aggravates the decrease on hepatic blood flow.[77] Combined epidural and general anesthesia is suggested as a useful strategy to keep a low

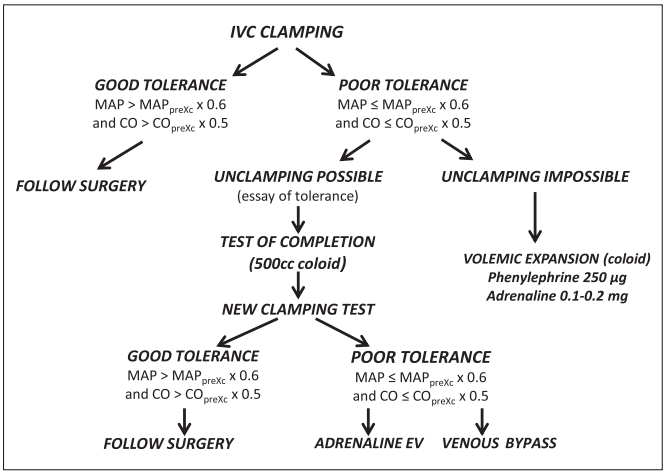

Figure 3. Approach according to hemodynamic tolerance of total vascular exclusion of the liver. IVC: inferior vena cava; MAP: mean arterial pressure; CO: cardiac output; preXc: before IVC clamping. (Adapted from Dilly et al.[69])

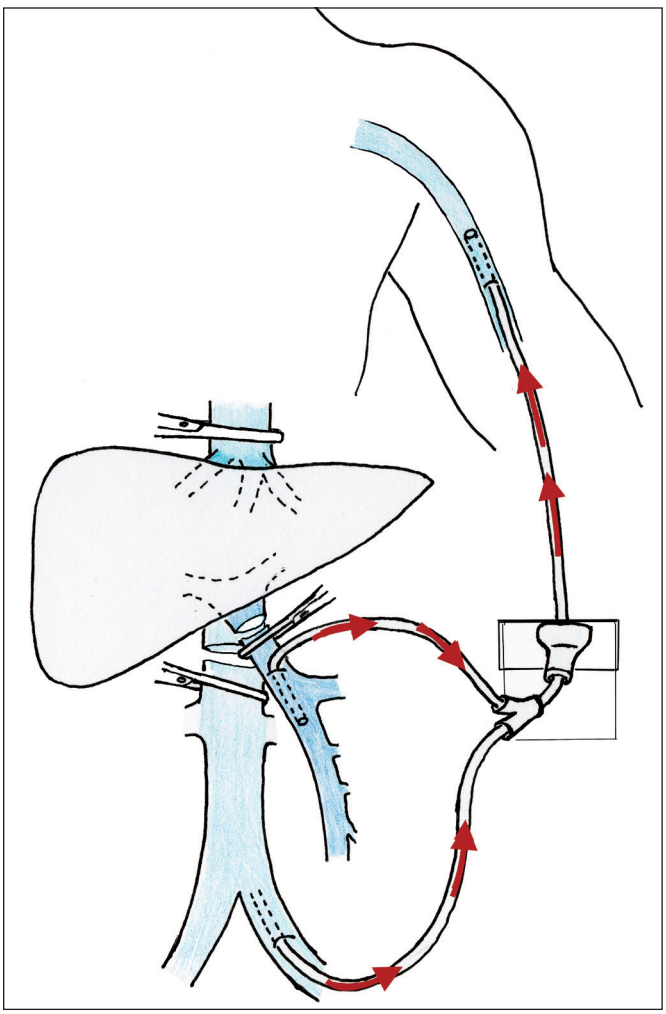

Figure 4. Schematic representation of venous bypass during total vascular exclusion of the liver. The blood from the inferior vena cava and portal vein is directed to superior vena cava.

central venous pressure during liver resection. Epidural anesthesia promotes redistribution of blood flow, decreasing venous return and portal venous pressure, and consequently the hepatic congestion.[78] Also, combined inhalatory and intravenous anesthesia is a useful strategy to minimize the need inhalation drugs.

Techniques to reduce blood loss during hepatectomy, such as the Pringle maneuver, total hepatic vascular exclusion and low PVC are worth while to diminish perioperative blood transfusion and morbidity, but the also have some risks. Studies have shown that low CVP can reduce blood loss and transfusion but also is associated with higher rates of perioperative renal failure.[64]

Fluid management should not be guided by CVP values since this method is not able to estimate volemic status, nor responsiveness to fluid tests.

ANESTHETIC MANAGEMENT

Liver resections are performed under general anesthesia with endotracheal intubation and controlled ventilation. Rapid sequence induction is used in patients with ascites or other risk factors for regurgitation. Maintenance of anesthesia is mainly by volatile halogenated combined with intravenous agents. Volatile anesthetics with low hepatic metabolism, such as isoflurane and sevoflurane, have low effect on hepatic blood flow and can be safely used. These drugs are also used to induce pharmacological hepatic preconditioning before continuous vascular clamping. However, postoperative hepatitis was associated in various degrees with inhalators anesthetics, mainly with halotane.

Chronic liver disease may impair the clearance, prolong the half-life, and potentiate the clinical effects of several drugs. Dosage and administration of these drugs should be adjusted accordingly in patients with liver dysfunction. Opioids, such as morphine and meperidine, have significantly reduced metabolism and prolonged half-life (almost doubled) in patients with cirrhosis. Alfentanil, but not fentanyl nor remifentanil, has the half-life prolonged in cirrhotic patients.[79–82] Thiopental, despite a small hepatic extraction ratio, has elimination half-life unchanged in cirrhosis due to its large volume of distribution, similarly to etomidate.[83] Propofol elimination is unchanged with chronic liver disease, but the mean clinical recovery times may be longer after discontinuation of infusions.[84] On the other hand, the half-life of midazolam is prolonged due to reduced clearance and reduced protein binding with cirrhosis, resulting in a prolonged duration of action and an enhanced sedative effect.[85] Steroidal muscle relaxants, such as vecuronium, mivacurium, and rocuronium, have prolonged half-lives (and consequently prolonged neuromuscular blockade) due to decreased clearance in patients with hepatic dysfunction.[86,87] Atracurium and cisatracurium have metabolism independent of hepatic function (Hofmann elimination) and can be used without modification of doses in cirrhotic patients.[88,89]

Effects of mechanical ventilation can have an impact on

Table 3. Factors affecting hepatic blood flow during anesthesia.

Hepatic blood flow	Factor	Mechanism involved
Decrease	Halothane and enflurane	Hepatic arterial constriction, increase hepatic vascular resistance (respectively)
	Thiopental and etomidate	Arterial blood flow and cardiac output reduction
	Regional anesthesia (spinal and epidural)	Systemic hypotension
	Mechanical controlled ventilation	Reduction of preload and cardiac output
	PEEP	Reduction of sympathetic tonus
	Hypoxia	Sympathetic activation
	Hypocapnia	Direct effects
	Alkalosis	Direct effects
Increase	Dopamine (renal dose)	Direct effects
	Propofol	Splanchnic vasodilatation
	Isoflurane	Increase in microvascular blood velocity
	Hypercapnia	Direct effects
	Acidosis	Direct effects
No significant effect	Ketamine	
	Sevoflurane and desflurane	

hepatic blood flow. Controlled positive pressure ventilation and positive end-expiratory pressure may reduce venous return and cardiac output, with compromise of the hepatic blood flow. Also, hyperventilation with hypocarbia reduces hepatic blood flow.

Intraoperative fluid management. The use of colloids (such as 5% albumin), rather than crystalloids, as a maintenance and replacement solution reduces extravascular translocation of fluids. Crystalloids should be limited to a minimum. Fresh-frozen plasma is used as maintenance fluid in patients requiring coagulopathy correction. Red blood cells are usually transfused if the hematocrit falls below 25%. In cirrhotic patients, the judicious use of vasopressin (2-5 U/hour) combined or not with norepinephrine restores peripheral vascular resistance and systemic blood pressure.[57] Any intraoperative decrease in systemic arterial pressure should be rapidly treated to preserve liver blood flow and, therefore, minimize postoperative liver impairment, especially in cirrhotic patients. On the other hand, infused fluids should be restricted until parenchyma sectioning is completed, to keep a low central venous pressure.[50]

Monitoring. Invasive hemodynamic monitoring (such as measure of CVP, continuous invasive arterial pressure, pulmonary artery catheterization, intraoperative echocardiogram) depends on the complexity of hepatic resection and patient's health status. Minor resections can be safely performed with no invasive hemodynamic monitoring. On the other hand, complex resections with TVE and/or veno-venous bypass might benefit from more invasive monitoring.

Other parameters such as urinary output, core temperature, electrolytes and, if available, coagulogram must be monitored

STRATEGIES TO PREVENT HETEROLOGOUS BLOOD TRANSFUSION

Blood loss is a major concern in hepatic surgery and transfusion of red blood cells is required in about 25-30% of patients.[90] It is the main intraoperative complication during hepatic resections. Intraoperative blood loss and perioperative blood transfusion are associated with a higher rate of postoperative morbidity and recurrence, and poorer long-term survival in patients with malignancies. Heterologous blood transfusion can raise the risk of nosocomial infections and lead to Transfusion Related Acute Lung Injury (TRALI).

Besides low central venous pressure and vessel occlusion techniques, other methods are useful to minimize blood loss and allogenic blood transfusion, such as intraoperative blood salvage, preoperative autologous blood donation, and intraoperative isovolemic hemodilution. The use of antifibrinolytic agents such as aprotinin, aminocaproic acid, and tranexamic acid is still controversial.[91] Conditions like hypothermia, acidosis, and hypocalcemia can disturb hemostasis and should be prevented and treated. Risk of red blood cell transfusion and auto donation, use of erythropoietin, and blood-saving devices and others ways to reduce perioperative blood transfusions are discussed in **Chapter 9** (Morbidity and Mortality after Liver Surgery).

ISCHEMIA-REPERFUSION SYNDROME

The reperfusion of the liver after a long period of ischemia (such as by vascular clamping) induces a diversity of hepatic lesions called ischemia-reperfusion (IR) syndrome, but its pathophysiology is not entirely understood yet. Cirrhotic and steatotic livers seem to be particularly susceptible to this injury.[92,93]

Several interventions have been developed to minimize IR injury. Ischemic preconditioning consists of a short period of ischemia followed by a short period of reperfusion, prior to a prolonged ischemia and reperfusion.[92,94] This strategy demonstrated no advantage compared to intermittent clamping.[95,96] The pharmacological preconditioning, mainly with the use of inhaled anesthetics, has also been used with the same goal.[97]

POSTOPERATIVE ANALGESIA

Postoperative pain management in patients with liver cirrhosis is challenging and is often inadequate due to the lack of therapeutic efficacy or the high incidence of adverse effects.[98] Severe complications from analgesia in cirrhotic patients include hepatic encephalopathy, hepatorenal syndrome, and gastrointestinal bleeding. Analgesics should be started with the minimum effective dose and should be titrated slowly with avoidance of polypharmacy. Adverse effects must be monitored, especially sedation and constipation. The first-line drug to mild pain is paracetamol, which is safe at doses of 2-3g/day. Tramadol is a safe option for moderate to severe pain. Non-steroidal anti-inflammatory (NSAI) agents are contraindicated because they can cause acute renal failure and/or gastrointestinal bleeding. Opioids should be used with caution to prevent encephalopathy. The opioids with the best safety profile are fentanyl and hydromorphone, with methadone as an alternative.[98,99] Patient-controlled analgesia (PCA) with morphine (1 mg with 7 min of refractory period) and paracetamol is often used.

Regional analgesia. Thoracic epidural analgesia (with bupivacaine or ropivacaine, combined or not with morphine) provides excellent analgesia for liver resections and reduces the need for systemic opioids. Placement of

epidural catheter represents a low-risk procedure; however, coagulation disturbances (due to cirrhosis or anticoagulant drug administration) are contraindications to insertion and removal of epidural catheters. Thus, patients with preoperative severe coagulation disturbances and those with probable prolonged postoperative coagulopathy secondary to the surgical procedure (including factors such as amount of remnant liver, perioperative blood loss, liver ischemia, and hemodilution) and the presence of underlying liver disease should not receive epidural catheters.

STEROID ADMINISTRATION

Some studies have demonstrated that preoperative steroid administration can reduce surgical stress and has a positive impact on liver function after liver resection.[100] Methylprednisolone (30 mg/kg or 500 mg preoperatively) or hydrocortisone (500 mg preoperatively, followed by 300 mg, 200 mg, and 100 mg on postoperative days 1, 2, and 3, respectively) can be used intravenously in cirrhotic or non-cirrhotic patients undergoing liver resection.[101–103]

In a review article, steroids significantly reduced post-operative blood levels of bilirubin, as well as inflammatory markers such as interleucine-6 and C-reactive protein. There was no evidence supporting a risk difference in infectious complications and wound healing between study groups. In conclusion, perioperative steroids seem to have a favorable impact on postoperative outcomes after liver resection.[104]

ANTIBIOTICS

Perioperative antibiotic prophylaxis is warranted, even in case of resection of non-complicated tumors, because of the long operating times, large remnant dead spaces, and areas of devitalized tissue. However, postoperative routine antibiotic administration has been shown to be unnecessary following liver resection.[105–107]

Bacterial translocation from the gut to the systemic circulation is the main responsible for peritoneum inoculation following major liver resection.[106] Thus, intravenous cefazoline (2g before induction of general anesthesia with 1g every 4h throughout surgery) is recommended.

Biliary obstruction, even when not associated with clinical infection, should be considered as a potential source of sepsis and it requires antibiotic therapy In this case, piperacillin (with or without tazobactam) combined with an aminoglycoside or with a fluoroquinolone are adequate choices.[3,105] Further antibiotic administration depends on the results of bacteriological examination of intraoperative bile samples.

Cirrhotic patients with ascites are likely to have translocation of intestinal enterobacteria to the systemic circulation. A 24h prophylaxis by a third generation cephalosporin or fluoroquinolone is warranted in these cases.[2,108]

FAST-TRACK LIVER SURGERY

Fast-track surgery (FTS), or enhanced recovery after surgery (ERAS), combines several techniques applied pre-, intra-, and postoperatively, with the goal of accelerating recovery. Fast-track programs include the selective use of drains, strict control of fluids, use of regional anesthesia, early removing of nasogastric tube (at the end of the surgery) and urinary tubes, early oral intake and deambulation (6-8 h after the surgery if no contraindication), and opioid-sparing analgesia (multimodal analgesia). These measures can be used collaboratively to reduce complications and the length of hospital stay in digestive, orthopedic, and cardiovascular surgery.[109–112] In liver surgery (including liver transplantation), fast-track or ERAS programs have been used with satisfactory results, causing in reduction of length of hospital stay without compromising morbidity, mortality, or readmission rates.[113–120] Both anesthesiological and surgical teams should be habituated to these protocols, since their application requires combined strategies and must be planned even prior to hospitalization.

ANESTHESIA FOR LIVER TRANSPLANTATION

PREOPERATIVE ASSESSMENT

Most liver transplantations are performed in the context of chronic liver failure. Prognosis in cirrhotic patients can be estimated using scores such as Child-Turcotte-Pugh and Revised Model for End-Stage Liver Disease (MELD). However, anesthetic perioperative management must take in account not only the liver function but also the usual associate comorbidities.

Disorders that are usually contraindications for partial hepatectomy are common in liver transplant recipients. **Cardiac diseases** comprise coronary artery disease (present in up to 25% of liver transplant recipients[121]) and cirrhotic cardiomyopathy. Cirrhotic cardiomyopathy is characterized by abnormal cardiovascular response to stress and it is present in up to half of patients undergoing liver transplant. Systolic and diastolic dysfunction, prolonged QT, and electrical and mechanical dyssynchrony are present. Despite a normal or increased myocardial contractility at rest, these patients have inotropic and chronotropic incompetence.[122] **Pulmonary disorders** include hepatopulmonary

syndrome (8-24% of end-stage cirrhotic patients) and portopulmonary hypertension (2-10% of end-stage cirrhotic patients). Hepatopulmonary syndrome is characterized by pulmonary vascular dilatation and a decreased systemic arterial oxygenation (PaO_2 <80 mmHg or alveolar arterial gradient >15 mmHg) in association with chronic liver disease. Portopulmonary hypertension is characterized by increased mean pulmonary artery pressure (>25 mmHg) and pulmonary vascular resistance (>240 dyne/s/cm^{-5}), and normal or decreased pulmonary artery wedge pressure (<15 mmHg). The most serious **renal disorder** is hepatorenal syndrome (18-40% of end-stage cirrhotic patients), defined as increased serum creatinine (>1.5 mg/dL) without other possible causes of renal failure.[123]

INTRAOPERATIVE MANAGEMENT

Liver failure is responsible for a decrease in metabolism and protein binding of drugs. The sensitivity of the microsomal enzyme induction accelerate the biotransformation (inhalational anesthetic agents and barbiturates) and the impairment of hepatic blood flow leads to a decreasing in the biotransformation with longer half-lives for some drugs (such as meperidine, lidocaine, diazepam, and thiopenthal).

Induction of anesthesia may be performed using thiopental, ketamine or midazolam, with minimal effects on hemodynamics. Succinylcholine should be avoided in cases of renal dysfunction with increase potassium levels. Muscle relaxants can be used safely. Atracurium has organ-independent elimination, and the duration of action of vecuronium and rocuronium can be used for the assessment of allograft function.[124,125]

Surgery in the recipient is divided in three phases: pre-anhepatic (or hepatectomy) phase, anhepatic phase, and neohepatic phase (**Table 4**). The main risk during **hepatectomy phase** is blood loss, and a low central venous pressure is helpful to minimize blood transfusion. During **anhepatic phase** preload can be severely restricted if venous clamping is necessary and a hyperfibrinolytic state may occur (due to increased tissue plasminogen activator without plasminogen activator inhibitor and alpha 2 antiplasmin) along with the preexisting coagulopathy. The **neohepatic phase** is characterized by organ reperfusion and coagulopathy (hyperfibrinolysis, dilutional coagulopathy, platelet dysfunction, hypothermia, and hypocalcaemia). The thromboelastography can be very useful, mainly during the anhepatic and neohepatic phases, allowing the accurate diagnosis of the coagulopathy and its adequate correction.

Ischemia-reperfusion injury results from a microcirculatory failure and production of reactive oxygen species, and it is associated with primary graft dysfunction. Ischemic and/or pharmacological preconditioning and antioxidants drugs have been tested to minimize the effects of ischemia-reperfusion syndrome. Particularities of anesthetic

Table 4. Anesthesia guidelines for liver transplantation at the University of Wisconsin.

Surgical phase	Anesthetic goals and procedures
Preanhepatic phase	- Anesthesia induction and invasive monitors - Antibiotic and baseline labs (including TEG) - **CVP <5 cmH_2O** (restrictive IV fluid – phlebotomy if Hgb>10g/dL) - BP > 60 mmHg (Norepinephrine or vasopressin) - CO >5 L/min (Dopamine or epinephrine) - Hgb>7 g/dL, platelets > 40,000/µL, MA on TEG > 45 mm, fibrinogen > 100 mg/dL - Mannitol 0.5 g/kg IV over 1h, prior to anticipated clamping - Just before clamping: - IV heparin 3,000 to 5,000 U, if TEG is normal of hypercoagulable; - Increase CVP to 10 cmH_2O with IV fluids; - 25% albumin in severe hypoalbuminemia
Anhepatic phase	- **CVP around 5 cmH_2O** (IV fluids) - Hb>7 g/dL - BP > 60 mmHg and CO > 5 L/min (Norepinephrine or vasopressin) - Correction of base deficit (Bicarbonate infusion) and hypocalcemia (IV calcium chloride)
Neohepatic phase	- BP > 60 mmHg (Vasopressin in bolus when systemic vascular resistance decline) - Heart rate > 60/min (Epinephrine in bolus) - **CVP 5-10 cmH_2O** (euvolemia) - BP > 60 mmHg (Norepinephrine or vasopressin) - CO >5 L/min (Dopamine or epinephrine) - Hgb > 7g/dl, platelets > 40,000/µL, fibrinogen > 100 mg/dl - Correction of coagulopathy: protamine, platelet transfusion, and ε aminocaproic acid according to TEG variations

TEG: Thromboelastogram; CVP: Central Venous Pressure; Hgb: serum hemoglobin; BP: Blood Pressure; CO: Cardiac Output; MA: Maximal Amplitude. (Modified from Hannaman and Hevesi [125])

management according to each surgical phase in the liver transplant recipient are described in **Table 4** (modified from Hannaman and Hevesi[126]).

LIVING LIVER DONORS

Adult-to-adult living donor liver transplantation (LDLT) has been used to minimize the scarcity of organs. The volume of liver to be resected from the donor must be enough to supply the needs of receptor; however, the donor remnant liver must also have adequate volume and function for the safety of the donor. This balance is frequently difficult, and donor safety must be the priority. Adequate volumetric and functional hepatic evaluation is crucial, but appropriate surgical and anesthetic techniques are crucial to optimize postoperative donor liver function. Besides a sufficient hepatic volume with adequate blood inflow, blood outflow, and biliary drainage, parenchymal injury should be avoided.

Despite efforts to avoid perioperative complications in liver donors, a significant number die. Control of postoperative pain is more difficult in donor patients, probably due to a neuroplasticity effect, along with various psychological factors, resulting in an exaggerated pain perception. Caution should be taken with the use of epidural analgesia since postoperative coagulation is unpredictable.

ANESTHESIA FOR ENDOCRINE TUMORS

Surgery for carcinoid tumors exposes a risk of carcinoid crisis. Efforts during the perioperative period are to avoid blood pressure variation and inadequate analgesia. An optimal analgesia with regional anesthesia avoids stressors such as pain, which could launch a carcinoid crisis. However, the potential hypotension and need of vasoconstrictors could lead to an exaggerated response. Intravenous or inhalation techniques for general anesthesia are used, in both the goal is maintain stability with adequate depth of anesthesia and analgesia. Drugs with potential for histamine release, such as morphine and atracurium, should be avoided.

Octreotide (in a dose of 300 mcg subcutaneously) before surgical resection of endocrine tumors, especially in patients with a history of carcinoid syndrome, may prevent a carcinoid crisis. Octreotide can also be used during a carcinoid crisis, in addition to plasma infusion, to restore hemodynamic instability, because usual fluid resuscitation is not efficient in this condition and the use of calcium or catecholamine can aggravate the clinical condition.

LAPAROSCOPIC LIVER RESECTION

Recent studies have demonstrated that laparoscopic liver resections (minor and major hepatectomies) are safe and have some advantages in selected patients. However, the use of laparoscopic access is associated with a high incidence of gas embolism during liver resections. The combination of low CVP, high pneumoperitoneal pressure, and opening of hepatic venous branches during parenchymal transection might favor gas embolism. However, a recent study comparing laparoscopic liver resections with different CVP/intra-abdominal pressure gradients demonstrated a similar incidence of gas embolism among groups.[127] Also, the definition of clinically significant air embolism is not clearly defined. The passage of air bubbles through cardiac chambers during hepatectomy is commonly identified by intraoperative echocardiography, but few of these patients exhibit clinical signs of severe gas embolism. More studies are necessary to elucidate the true frequency of clinical gas embolism and the effect of pneumoperitoneal and central venous pressures.[128]

SUGGESTED READING

Eipel, C., Abshagen, K. & Vollmar, B. Regulation of hepatic blood flow: The hepatic arterial buffer response revisited. *World J. Gastroenterol.* **16**, 6046-6057 (2010).

This paper reviews the relevance of a hepatic blood flow regulatory mechanism called the buffer system.

Koch, D. G. & Fallon, M. B. Hepatopulmonary syndrome. *Clin. Liver Dis.* **18**, 407–420 (2014).

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