Anesthesia for Liver Transplantation

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Introduction

Liver transplantation is the definitive treatment option for patients with fulminant liver failure, hepatocellular carcinoma (HCC), and end-stage liver disease (ESLD) when the limits of medical therapy have been reached. ESLD affects the majority of the body's organ systems, making liver transplantation amongst the most challenging surgeries for the anesthesiologist to manage. A summary of anesthetic considerations during liver transplantation surgery is provided in Table 72.1.

Pioneering transplant surgeon Dr. Thomas E. Starzl of the University of Colorado School of Medicine attempted the first human liver transplant in 1963, and performed the first successful (survival greater than 1 year after transplantation) human liver transplant in 1967 [1–3]. Over the past 50 years, numerous improvements in liver preservation and allocation, surgical and anesthetic techniques, and immunosuppression have improved morbidity and mortality. Approximately 7800 liver transplants were performed in the United States in 2016. The most recent data examining American transplant centers indicate greater than 90% 1-year survival and greater than 75% survival at 5 years post transplantation [4]. Despite these advances, there remains a scarcity of donor organs, and more than 14,000 candidates remain on the waiting list for liver transplant in the United States [4].

In 2002, the United Network for Organ Sharing (UNOS) established the Model for End-stage Liver Disease (MELD) score to prioritize transplant allocation. The score is calculated as a weighted average of the natural logarithms of International Normalized Ratio (INR), serum bilirubin, and serum creatinine, as the primary determinant of priority for liver allocation in the United States [5, 6]. In January 2016, this scoring system was modified by UNOS to incorporate the patient's serum sodium concentrations [7]. This modified score is called the MELD-Na. MELD-Na has been demonstrated to be a more accurate predictor of waitlist mortality than MELD score alone [8]. The MELD score was originally developed to estimate 90-day mortality after transjugular intrahepatic portosystemic shunt (TIPS) placement [9]. Subsequent evaluations of the score reveal that survival benefit increases with increasing MELD score, and that at lower MELD scores, recipient mortality risk during the first post-transplantation year is higher than for candidates who remain on the waiting list. Exception points are awarded to patients with HCC because although their liver function often remains relatively normal, transplant provides cancer cure [10–12].

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Table 72.1 Summary of anesthesia considerations in patients undergoing liver transplantation

Plan/preparation/adverse events	Reasoning/management
Preoperative evaluation (see Table 72.2)	Room-air ABG, contrast-enhanced TTE, CXR, PFTs, CT chest ECG, TTE, ± noninvasive stress testing CBC, PT, PTT, INR, fibrinogen, d-dimer Serum BUN, serum Cr, BMP
Position	Supine
Access	≥1 14- or 16-gauge IV—Rapid fluid and blood product administration Arterial line—Anticipation of hemodynamic instability, frequent blood sampling, vasoactive drug administration Central venous catheter—CVP and PAP transduction, rapid fluid and blood product administration, vasoactive drug administration
GETA	
IV induction	Even if metabolism and/or excretion are hepatic, duration of action determined by redistribution
RSI	Increased risk for regurgitation and aspiration
Maintenance	Isoflurane or sevoflurane preferred given no significant decrease in hepatic blood flow or O_2 delivery
Procedural adverse events	
Aspiration	RSI as above
Coagulopathy	Transfuse blood products to approximate goals of INR < 3.5, platelets > 20, and fibrinogen > 100 and clinical coagulation status
Hemorrhage	Transfuse pRBCs to goal of hematocrit > 25
	Rapid infuser should be available
Hypotension	Relative hypovolemia during dissection phase, euvolemia after; titrate vasopressors to effect
Hyperkalemic cardiac arrest	Apply defibrillation pads before induction; send ABGs q20–30 min during anhepatic phase; administer Ca^{2+}, dextrose, and insulin as indicated
Postreperfusion syndrome	Titrate inotropes and vasopressors to effect
Postoperative and post-discharge considerations	
Extubation	May consider if hemodynamically stable and no significant transfusion requirements

Applied Anatomy and Physiology of Liver Transplantation

Liver transplantation is divided into three phases: the dissection, anhepatic, and neohepatic phases. Each phase is characterized by different anesthetic goals, and knowledge of surgical technique critically determines hemodynamic aims and resuscitation efforts.

Dissection Phase

With the patient anesthetized and in the supine position, a bilateral subcostal incision with midline extension cephalad to the xiphoid process (Calne or "Mercedes-Benz" incision) is made. The abdomen is manually explored for evidence of metastatic HCC, other extra-hepatic malignancy, infection, or other contraindication to liver transplantation. Assuming that there are no unexpected findings that act as a contraindication to transplant, the liver is mobilized by dissection of the falciform, round, left and right triangular, and gastrohepatic ligaments in addition to ligation of any varices and/or adhesions. The porta hepatis is dissected, and the hepatic artery, common bile duct, and portal vein successively ligated. In the setting of severe portal hypertension, a temporary portacaval shunt can be created prior to portal vein ligation to help decompress varices and control variceal hemorrhage. The final steps of the dissection phase depend on the chosen technique of anastomosis—standard or piggyback—but

end with recipient hepatectomy [13, 14]. During the dissection, significant coagulopathy and surgical bleeding require active management.

Anhepatic Phase

The standard transplant technique employs a bicaval anastomosis, in which the recipient infrahepatic and suprahepatic vena cava are ligated and anastomosed to the corresponding segments of the donor vena cava in the reverse order. This technique is illustrated in (Fig. 72.1) and is associated with a shorter dissection phase, but has the disadvantage of significantly decreasing systemic venous return from the lower extremities and kidneys because the vena cava is completely clamped in the infra- and supra-hepatic positions. The decreased venous return can be offset by veno-venous bypass (VVB); this removes blood from cannulae in the femoral and portal veins and returns it to the central circulation via a cannula in the axillary or internal jugular vein. However, veno-venous bypass has its own set of risks, including vascular injury, hemomediastinum, and air or thromboembolism [13, 14].

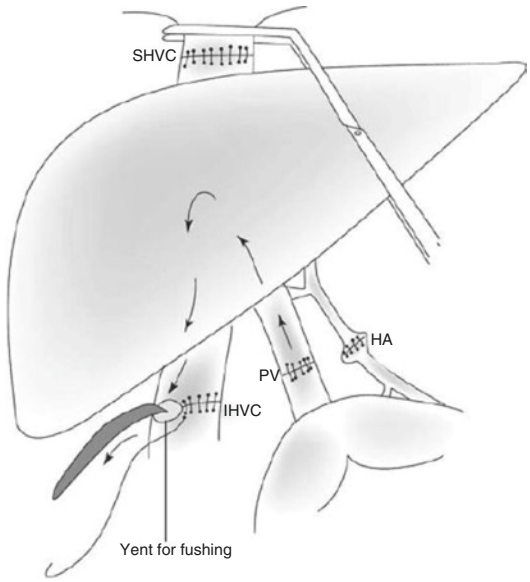

Fig. 72.1 The standard bicaval technique of liver transplantation. Initial anastomoses include the suprahepatic vena cava (SHVC), infrahepatic vena cava (IHVC), and portal vein (PV). The hepatic artery (HA) and bile duct are anastomosed after reperfusion and hemostasis. Modified from: Atlas of Organ Transplantation, Humar, Matas and Payned eds, 2009

The piggyback technique preserves the recipient vena cava and involves anastomosing the donor suprahepatic vena cava to a cuff created from the three, main recipient hepatic veins. The donor infrahepatic vena cava is ligated. This technique is illustrated in (Fig. 72.2). To access the main hepatic veins, numerous short hepatic veins connecting the caudate lobe of the liver to the vena cava must first be ligated. The liver is then lifted and rotated off of the vena cava to increase exposure. This maneuver may partially occlude the inferior vena cava and temporarily decrease blood pressure, however the ultimate result is maintenance of systemic venous return during the anhepatic phase [13, 14].

With either technique, the donor suprahepatic vena cava is anastomosed first. Immediately before the donor infrahepatic vena cava is anastomosed (standard technique) or ligated (piggyback technique), the cold storage solution and air within the donor liver are flushed to minimize the respective risks of hyperkalemia and air embolism that occur with reperfusion. Donor infrahepatic vena cava anastomosis/ligation is followed by portal vein anastomosis, at which point venous blood flow is carefully reestablished, and the donor liver re-perfused [13, 14].

Neohepatic Phase

Reperfusion frequently leads to a postreperfusion syndrome (PRS), which can result in severe hemodynamic disturbance. PRS is defined as a decrease in mean arterial pressure (MAP) or heart rate (HR) of greater than 30% from baseline and may result in asystole and/or hemodynamically significant dysrhythmias. PRS incidence varies greatly in the literature from 12 to 77% [15]. Reperfusion of the liver results in a sudden load of cold, acidotic, hyperkalemic blood and preservative solution being released from the liver graft. If VVB is not used, venous blood from the portal system will also be released having been without oxygen since

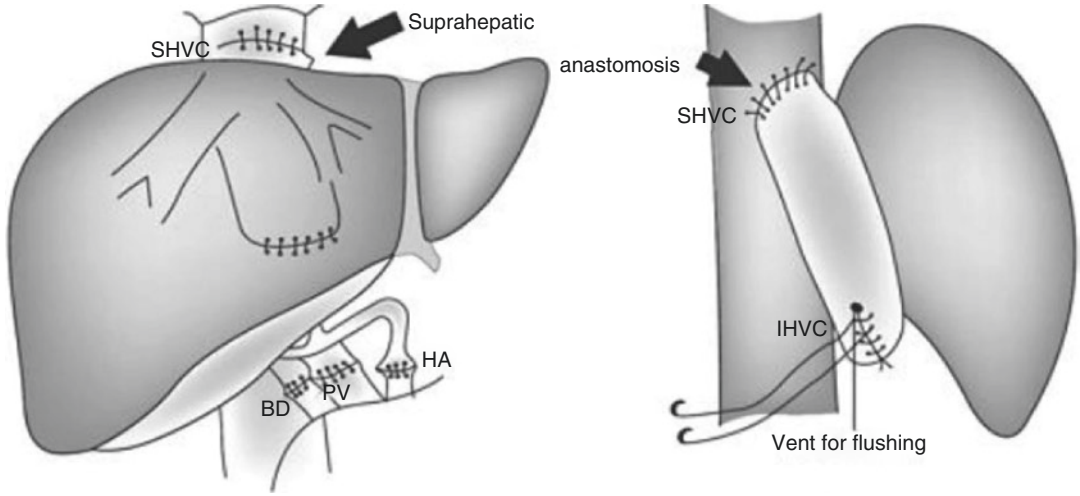

Fig. 72.2 The piggyback technique of liver transplantation. The donor suprahepatic vena cava (SHVC) is sewn to the confluence of hepatic veins returning blood to the recipient vena cava. The donor infrahepatic vena cava (IHVC) is ligated. Additionally, the portal vein (PV) is anastomosed prior to reperfusion. After reperfusion, the hepatic artery (HA) and bile duct (BD) are anastomosed. Modified from: Atlas of Organ Transplantation, Humar, Matas and Payned eds, 2009

time of clamp placement. As the byproducts of the liver graft, and products of anaerobic metabolism from the portal circulation, are delivered to the heart and lungs. The result is an increase in pulmonary vascular resistance (PVR), which can result in right heart dysfunction and cardiac arrest, particularly in patients with portopulmonary hypertension (POPH). Additionally, right heart dysfunction can prevent left heart filling and lead to notably decreased cardiac output. Often, significant vasopressor and inotrope infusions are necessary to maintain adequate systemic and coronary perfusion pressure. After the patient has been stabilized, hepatic artery anastomosis, cholecystectomy, and common bile duct reconstruction are the last steps before verification of hemostasis and closure [13, 14].

Preoperative Evaluation

Fulminant liver failure and end-stage liver disease affect multiple organ systems. Clinical manifestations are summarized by organ system in Table 72.2 and described in detail below.

Neurologic

The primary neurologic manifestation of cirrhosis and end-stage liver disease is encephalopathy, due to decreased metabolism of nitrogenous waste produced by intestinal flora. Hepatic encephalopathy is a diagnosis of exclusion, and other possible etiologies of delirium should first be ruled out. If time and circumstance allow, preoperative treatment of hepatic encephalopathy includes optimizing the patient's other comorbidities, titrating lactulose to three bowel movements per day, and administering oral antibiotics like rifaximin [16]. In fulminant liver failure, cerebral edema may increase intracranial pressure, increasing the risk of brainstem herniation. Placement of an intracranial transducer and drain has been advocated at times as means monitor intracranial pressure and drain cerebral spinal fluid. It's safety in the setting of coagulopathy has not been established and outcome improvements thus far have not been demonstrated [17]. Treatment of increased intracranial pressure may include elevation of the head, hyperventilation, hypertonic saline infusion, and osmotic diuretics such as mannitol.

Table 72.2 Clinical manifestations of end-stage liver disease

Organ system	Clinical manifestations
Neurological	• Hepatic encephalopathy (due to decreased metabolism of nitrogenous waste) • Elevated intracranial pressure (fulminant liver failure)
Respiratory	• Decreased functional residual capacity • Restrictive ventilatory defects • Primary respiratory alkalosis • Hepatopulmonary syndrome (liver disease, hypoxemia, and shunting due to intrapulmonary vasodilation)
Cardiovascular	• Hyperdynamic circulation (due to low blood pressure, low systemic vascular resistance, and high cardiac output) • Hypervolemia • Cirrhotic cardiomyopathy • Coronary artery disease • Portopulmonary hypertension
Hematologic	• Anemia • Thrombocytopenia • Complex coagulopathy (due to decreased synthesis of coagulation factors and proteins C and S)
Renal	• Intravascular volume depletion (due to low plasma oncotic pressure) • Chronic renal failure (due to intravascular volume depletion) • Electrolyte imbalances (e.g., hyponatremia, hypo- or hyperkalemia) • Hepatorenal syndrome
Hepatic	• Decreased synthetic function • Hypoalbuminemia, ascites, and peripheral edema • Lactic acidosis
Gastrointestinal	• Increased risk of aspiration • Ascites • Esophageal and gastric varices • GI bleeding

Respiratory

Respiratory manifestations of liver disease include decreased functional residual capacity and restrictive ventilatory defects secondary to ascites and pleural effusions (hepatic hydrothorax). Patients may also experience hypoxemia, primary respiratory alkalosis, and hepatopulmonary syndrome (HPS). HPS is defined as the triad of liver disease, PAO_2–paO_2 gradient >15 mmHg, and pulmonary arteriovenous shunting. Characteristic clinical manifestations include platypnea and orthodeoxia, which result from increased right-to-left shunting of deoxygenated blood through dependent pulmonary vascular dilatations. Preoperative evaluation for HPS should include a room-air arterial blood gas (ABG) and contrast-enhanced transthoracic echocardiogram (to evaluate for the presence of bubbles in the left atrium after five heart beats). A chest radiograph, pulmonary functions tests, and chest computed tomography (CT) should be performed to rule out other causes of hypoxemia [6].

Cardiovascular

Patients with cirrhosis have low systemic vascular resistance (SVR) and high cardiac output due to splanchnic arterial vasodilation. Patients are often hypervolemic and suffer from coexisting cirrhotic cardiomyopathy, coronary artery disease (CAD), and/or POPH. Cirrhotic cardiomyopathy is characterized by electrophysiologic abnormalities, systolic and diastolic dysfunction, and an impaired contractile response to stress due to downregulation of β-adrenergic receptors. While electrocardiogram (ECG) findings consistent with cirrhotic cardiomyopathy (QT-interval prolongation, e.g.), TTE may not reveal classic findings of the disease if systolic dysfunction is compensated due to low SVR state.

As cirrhotic patients age, the risk and surgical impact of CAD grows. Although, historically, cirrhosis has been considered "protective" with regards to incidence coronary atherosclerosis, more recent evidence suggests that this may not be the case [18, 19]. Additionally, as the demographics of potential liver transplant recipients shift more towards the elderly, the incidence and severeity of CAD may increase. The controversy surrounding incidence and evaluation are covered in greater detail elsewhere [20]. Current best practice in evaluation for CAD in liver transplant

candidates includes ECG and TTE. Screening for CAD may also include noninvasive stress testing in patients greater than 60-years-old or with a history of diabetes, hyperlipidemia, hypertension, or tobacco abuse [20–22].

The diagnostic criteria for POPH include mean pulmonary artery pressure (mPAP) > 25 mmHg at rest, pulmonary vascular resistance (PVR) > 240 dynes, and pulmonary artery occlusion pressure (PAoP) < 15 mmHg in the presence of known portal hypertension. The disease affects approximately 5–6% of patients evaluated for liver transplantation, and it portends worse survival at both two (67% vs. 85%) and 5 years (40% vs. 64%) versus isolated idiopathic or familial pulmonary arterial hypertension [23]. POPH may precipitate acute right ventricular failure in the setting of the increased cardiac output, volume, and pulmonary artery pressures that occur with PRS and as such, has been associated with significant intraoperative mortality. Older studies demonstrate up to 50% mortality with mean pulmonary arterial pressure (mPAP) 35–49 mmHg and 100% mortality with mPAP 50 mmHg or greater [24]. All patients presenting for liver transplantation evaluation should have a screening TTE with determination of right ventricular systolic pressure (RVSP) from the tricuspid regurgitant jet. Patients with RVSP $\geq$ 50 mmHg should be referred for right heart catheterization. Patients with evidence of POPH should be evaluated for initiation of pulmonary vasodilator therapy to reduce the perioperative risk of cardiovascular event. Treatment advances for POPH have resulted in improved outcomes for patients [25] and for patients those patients whose disease demonstrates reversibility, proceeding with transplantation can be safe.

Hematologic

Anemia, thrombocytopenia, and coagulopathy are common hematologic manifestations of cirrhosis and ESLD. Anemia is frequently due to gastrointestinal blood loss and/or malabsorption of folic acid and vitamin B12. Thrombocytopenia is similarly multifactorial in etiology and may be due to decreased production of thrombopoietin and/or splenic sequestration. Coagulopathy is primarily mediated by decreased hepatic synthesis of coagulation factors and anticoagulation proteins C and S. In practice, the coagulopathy is complex as these patients may be clinically coagulopathic, or may be predisposed to pathologic thrombus formation (portal vein thrombus, e.g.). Preoperative evaluation of hematologic manifestations should include a complete blood count and clotting tests (prothromin time, activated prothrombin time and international normalized ration, fibrinogen, and d-dimer). Due to these factors, as well as portal hypertension, ESLD patients are at significant risk of massive and rapid blood loss during liver transplantation. Red blood cell and plasma transfusion products must be readily available as the patient enters the operating room.

Renal

Low plasma oncotic pressure due to hypoalbuminemia may cause intravascular volume depletion despite a state of increased total body water. This intravascular volume depletion decreases glomerular filtration rate (GFR), and in susceptible patients, leads to acute or chronic renal failure. Electrolyte abnormalities are common, especially hypervolemic hyponatremia and hypokalemia. Hepatorenal syndrome is an especially ominous complication of both fulminant and chronic liver failure and is the result of splanchnic arterial vasodilation, followed by renal arterial vasoconstriction and ultimately renal failure. Preoperative evaluation of renal function should include serum BUN, serum creatinine, and a basic metabolic panel. Depending on the severity of renal failure, preoperative hemodialysis (HD) or intraoperative continuous renal replacement therapy (CRRT) may be indicated.

Hepatic

Fulminant acute liver failure and cirrhotic ESLD disrupt both the synthetic and metabolic functions of the liver. INR is typically used to track

synthetic function of the liver. While increases in INR do correlate with coagulopathy, the relationship is not linear. Procoagulant therapy should be guided by clinical coagulopathy and not laboratory values alone.

In addition to decreased synthesis of procoagulation factors and anticoagulation proteins C and S, there is decreased synthesis of albumin. This results in low plasma oncotic pressure, ascites and peripheral edema. Decreased metabolism of lactic acid may result in lactic acidosis, which may be profound during the anhepatic phase of liver transplantation.

Gastrointestinal

ESLD patients are at risk for regurgitation and aspiration due to increased abdominal pressure from ascites and altered mental status from hepatic encephalopathy. Additionally, due to their portal hypertension, these patients often have esophageal and gastric varices. Concomitant coagulopathy puts these patients at increased risk of GI bleeding when the esophagus is instrumented with naso- or oro-gastric tubes or transesophageal echocardiogram (TEE) probe. Risk/benefit analysis should be undertaken prior to these procedures.

Intraoperative Anesthetic Considerations

Pre-incision

Given the uncertain volume status and low SVR states of end-stage cirrhosis, an arterial catheter should be considered prior to induction of anesthesia, particularly in unstable patients or those in fulminant failure. In the setting of ascites and deceased lung compliance, consideration should be given to a rapid sequence intubation. Establishment of general endotracheal anesthesia followed by maintenance with a volatile agent and narcotic. Paralysis should be maintained with an aminosteroid or a tetrahydroisoquinoline derivative neuromuscular blocker. Although propofol and most other intravenous induction agents are metabolized and/or excreted by the liver, their duration of action is primarily determined by redistribution, rendering them safe to use for induction. Higher doses of neuromuscular blockers may be required to achieve optimal intubating conditions due to the enlarged extracellular fluid compartment resulting in an increased volume of distribution. After intubation, an arterial line should be placed if not done before induction. Additional vascular access should be secured, including at least one 14- or 16-gauge IV, and a large central venous catheter with multilumen access. A rapid infuser needs to be available, and defibrillation pads should be applied early in anticipation of possible cardiac arrest upon reperfusion. Given the importance of assessing cardiac performance, consideration should be given to placement of a pulmonary artery catheter or TEE probe unless contraindicated. Packed red blood cells (pRBCs) and fresh frozen plasma (FFP) should be available in the operating room due to the high risk of significant bleeding (coagulopathic and surgical), At the authors' institution, liver transplantation is started with 10 units of pRBC and 10 units of FFP in the operating room prior to incision. Additional pRBCs, FFP, cryoprecipitate, and platelets are ordered and administered based on laboratory values and clinical coagulopathy. Common laboratory investigations intraoperatively include blood gases, platelet counts, PT, PTT, INR, and thromboelastography.

Dissection Phase

After incision is made, the peritoneal cavity should be assessed for the presence of ascites. If more than 5 L of ascites is drained and/or there is evidence of intravascular volume depletion, consideration should be given to replacement of fluid losses with albumin; overall volume status goal during dissection is however, relative hypovolemia as a means to reduce blood loss. The decision for transfusion of blood products is based primarily on clinical assessment of volume status and coagulopathy. Good communication regarding

on-going bleeding and coagulopathy between surgical and anesthetic teams is of critical importance. Although no specific guidelines exist, at the authors' institution, blood products are transfused based on the clinical impression of coagulopathy and on-going bleeding to approximate goals of hematocrit >25%, INR <3.0, platelets >20,000–30,000/mL and fibrinogen > 100 mg/dL. Crystalloid should be minimized in the setting of low plasma oncotic pressure, although this practice is mostly empiric, not evidence based. Patients may become hypotensive due to further decreases in SVR from inhalational anesthetics and/or fluid shifts. If a vasopressor is needed to maintain MAP goals, norepinephrine is typically first-line, followed by vasopressin. Patients with end-stage liver disease may demonstrate resistance to α-adrenergic agonists like phenylephrine, limiting their usefulness [22].

Anhepatic Phase

The primary goal of the anhepatic phase is to optimize the patient for reperfusion. During this phase, ABGs are sent every 20–30 min, and dextrose and insulin should be co-administered as necessary to achieve a goal potassium concentration < 4 mEq/L. In the presence of acidosis or a base deficit, sodium bicarbonate may also be administered. Calcium chloride or calcium gluconate are administered for the dual purposes of repletion of calcium chelated by citrated blood products and cardiac membrane stabilization prior to reperfusion. Special attention should be paid to the volume status, with the goal of adequate intravascular volume to re-perfuse the donor liver [21].

Neohepatic Phase

Given the relatively high concentration of potassium in the cold storage solution in the donor liver, the surgical team may flush the new liver with blood into the surgical field before unclamping the portal vein. The flush decreases the risk of hyperkalemia and cardiac arrest by washing the preservation solution from the donor liver. The University of Wisconsin liver preservation solution, with a potassium concentration of 120 mmol/L, is a significant donor-related mechanism of hyperkalemia following reperfusion. ECG changes, especially peaked T waves, may accompany reperfusion and necessitate immediate treatment of hyperkalemia. Replacing the portal clamping may also be exercised to prevent progression to hyperkalemic cardiac arrest. Additionally, significant bradycardia may result within the first 5 min as the cold storage solution stuns the right heart. Cytokine release syndrome may follow 12–15 min after reperfusion and should be treated aggressively with vasopressors and inotropic agents. PRS may last for several hours with a low SVR state. Additionally, this is typically a period of increased coagulopathy due to a combination of surgical loss, depletion of pre-existing recipient procoagulant factors, and lack of new factors being formed by the reperfused donor organ. As synthetic function resumes, the coagulopathy will also improve, but this process may take several hours. Significant transfusion of blood products is often required until function in the donor graft returns. Extreme cases of coagulopathy and blood loss may require extreme measures such as recombinant Factor VII administration.

After hemostasis of the large vascular anastomoses, immunosuppression is typically given. Intraoperative immunosuppression is institution-specific but often includes steroids, specifically methylprednisolone.

The final portion of the case includes the last vascular anastomosis—the hepatic artery. Cholecystectomy and bile duct anastomosis follow. Assuming adequate hemostasis, the patient's abdomen is closed, and the patient can be transported to the ICU for monitoring and continued management. At large liver transplant centers, more patients are being considered for early extubation. If the patient is hemodynamically stable and transfusion requirements were not significant, extubation in the OR can be successfully performed.

Summary

Patients with ESLD have significant manifestations of their cirrhosis that impacts every major organ system. Liver transplantation surgery, despite significant advancements, still involves significant blood loss and hemodynamic derangements. It is critical for the Anesthesiologist caring for these patients to be very familiar and experienced in managing these aspects of liver transplantation.

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