Liver Transplantation Anesthesiology

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Introduction

Liver transplantation has been widely recognized as the ultimate treatment for patients suffering from acute or chronic liver failure. As one of the most challenging noncardiac surgical procedures, successful completion of liver transplantation mandates an anesthesiology team with a special set of knowledge and skills. These include a thorough understanding of systemic manifestations of liver failure, donor types, transplant procedures, and the three stages in the transplant surgical process and related issues. Special attention should be paid to blood transfusion conservation strategies and initiation of induction immunosuppression therapy. The goal of this chapter is to describe this basic knowledge and discuss the anesthetic management of liver transplantation recipients. Practical anesthesia management is described according to the three stages of liver transplantation: Stage I (pre-anhepatic stage), Stage II (anhepatic stage), and Stage III (neo-hepatic stage).

In-depth discussions of special recipients' conditions, including acute hepatic failure (Chap. 34), porto-pulmonary hypertension and hepato-pulmonary syndrome (Chap. 35), and combined organ transplantations including the liver (Chap. 32) are found in each designated chapter in this text book.

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Recipients Presenting for Liver Transplantation

Although anesthesiology team members may be introduced to a liver transplantation recipient at a later stage of his or her lengthy pretransplantation workup, the importance of thorough review of the recipient's current medical condition cannot be overemphasized. Patients who have required intensive care prior to transplantation due to decompensating medical conditions especially demand the anesthesiology team's careful reevaluation of the conditions, which may significantly have worsened compared to existing evaluations performed several months prior to transplantation.

In general, isolated liver transplantation is indicated for those who suffer chronic noncholestatic liver disorders, cholestatic liver disorders, metabolic disorders, malignancies of the liver, acute hepatic failure, retransplantation, and miscellaneous conditions (Table 28.1). Among them, end stage liver disease (ESLD) secondary to chronic noncholestatic liver disorders is the most common indication for liver transplantation in adults, accounting for more than 60% of all transplantations performed annually [1]. In 2011, a total of 5805 adult (18+ years old) liver transplants were performed in the United States, and the etiologies, in descending order, were hepatitis C (23.5%), hepatic malignancy (20.9%), alcoholic liver disease (17.6%), cholestatic disease (9.1%), acute hepatic failure (4%), metabolic disease (2.5%), and others (22.3%) [1]. Several trends were found among liver transplantation recipients in the United States. Over the past decade, the percentage of recipients aged 50 years or older increased from 58.5 to 77.1% and the percentage of recipients aged 65 years or older increased from 7.6% in 2002 to 12.8% in 2011 [2]. The proportions of recipients with obesity (body mass index > 30) increased to 34.4% and those with diabetes also increased to 24.7%. Other notable

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Table 28.1 Indications for isolated liver transplantation

Non-cholestatic cirrhosis
Hepatitis C
Hepatitis B
Alcoholic liver disease
Autoimmune hepatitis
Cryptogenic cirrhosis
Nonalcoholic steatohepatitis
Others (hepatitis D, hepatitis A, hepatitis coinfection, chronic active hepatitis, other exposure)
Cholestatic liver disease/cirrhosis
Primary biliary cirrhosis
Secondary biliary cirrhosis (Caroli's Disease, Choledochal Cyst, other)
Primary sclerosing cholangitis (ulcerative colitis, Crohn's Disease, no bowel disease, other)
Others
Biliary atresia
Alagille syndrome
Hypoplasia
Extrahepatic
Others
Acute hepatic necrosis
Acute hepatic necrosis (hepatitis, drug, unknown etiology, other)
Hepatitis C: chronic or acute
Hepatitis B: chronic or acute
Metabolic diseases
Alpha-1-antitrypsin deficiency
Hemochromatosis–Hemosiderosis
Other hereditary disorders (Wilson's Disease, tyrosinemia, oxalosis, glycogen storage diseases, others)
Malignant neoplasms
Primary liver malignancy
Hepatocellular carcinoma (with or without cirrhosis)
Cholangiocarcinoma
Hepatoblastoma
Others (fibrolamellar hepatocellular carcinoma, hemangioendothelioma–hemangiosarcoma)
Secondary liver malignancy
Miscellaneous conditions
Budd-Chiari Syndrome, metastatic neuroendocrine tumors, cystic fibrosis, trauma, benign tumors, others)
Retransplantation
Primary nonfunctioning
Acute/chronic rejection
Hepatic artery thrombosis

conditions noted in 2011 in the United States include recipients on life support at the time of transplantation (6.6%), those with previous abdominal surgery (40.7%), and those with portal vein thrombosis (8.5%) or spontaneous bacterial peritonitis (7.6%).

Table 28.2 End-stage liver disease: systemic manifestations

Organ system/manifestation
Cardiovascular-pulmonary systems
Hyperdynamic state
Portal hypertension
Portopulmonary hypertension
Right heart failure
Hepatopulmonary syndrome
Cirrhotic cardiomyopathy
Pleural effusion
Renal-electrolytes system
Hepato-renal syndrome
Hyperkalemia
Metabolic acidosis
Hyponatremia
Hematological system
Coagulopathy
Anemia
Thrombocytopenia
Leukopenia
Spontaneous bacterial peritonitis
Gastrointestinal system
Esophageal varices
Portal hypertensive gastropathy
Mucosal dysfunction of the intestine
Nervous system
Encephalopathy
Endocrine system
Diabetes mellitus
Abnormal sex hormone metabolism
Thyroid disease
Osteoporosis
Adrenal insufficiency

Chronic Liver Failure: Etiologies, Systemic Manifestations, and Anesthetic Implications

It is important to realize that ESLD causes multiple systemic disorders (Table 28.2). Each systemic manifestation has its significant anesthetic implication during the perioperative period, thus demanding refinement in anesthetic management.

Cardiovascular and Pulmonary Systems

Patients with ESLD undergoing liver transplantation often present with hyperdynamic circulatory conditions, portal hypertension, portopulmonary hypertension, right heart failure, hepatopulmonary syndrome, cardiomyopathy, and pleural effusion. Systemic vasodilatation and formation of collateral veins (e.g., porto-systemic shunts) lead to hyperdynamic splanchnic and systemic circularity conditions.

Persistent endotoxemia, caused by shunting through porto-systemic anastomoses and enhanced endotoxin absorption from the intestine as a result of bile salt deficiency, may contribute to the vasodilation by activation of cascades of secondary mediators. Portal hypertension results from hyperdynamic splanchnic circulation with increased afterload of the portal venous system with intrahepatic cirrhosis. This leads to ascites, splenomegaly, varicose vein formation in the esophagus, portal hypertensive gastropathy, and spontaneous bacterial peritonitis. Portopulmonary hypertension can be categorized as mild (mean pulmonary arterial pressure [MPAP] 25–44 mmHg), moderate (MPAP 45–59 mmHg), and severe (MPAP $\geq$ 60 mmHg). Moderate to severe portal hypertension is associated with high perioperative mortality in liver transplantation [3] and is considered a contraindication for isolated liver transplantation unless successfully medically managed pretransplant [4]. Right heart failure can be found in patients with pulmonary hypertension. Dilatation of the right ventricle, decreased wall motion of the right ventricle, tricuspid regurgitation, and dilatation of the right atrium are hallmarks of the condition. Hepatopulmonary syndrome (HPS) is characterized by microvascular alterations and dilatation in the pre-capillary and capillary pulmonary arterial circulation. HPS is defined as a widened alveolar-arterial oxygen gradient ($AaPO_2$) on room air in the presence or absence of hypoxemia ($AaPO_2 = 15$ mmHg, or 20 mmHg in patients more than 64 years old) as a result of intrapulmonary vasodilation. HPS can be graded on the basis of the degree of hypoxemia: mild ($PaO_2 \geq 80$ mmHg); moderate ($PaO_2 = 61$–80 mmHg), severe ($PaO_2 = 50$–60 mmHg), and very severe ($PaO_2 < 50$ mmHg) [5]. Cirrhotic cardiomyopathy is a recently recognized condition and can be caused by any etiology of ESLD. It presents with systolic incompetence under hemodynamic stress, diastolic dysfunction related to altered diastolic relaxation and electrophysiological abnormalities in the absence of any known cardiac disease. The underlying pathogenetic mechanisms include abnormalities in the β-adrenergic signaling pathway, altered cardiomyocyte membrane fluidity, increased myocardial fibrosis, cardiomyocyte hypertrophy, and ion channel defects with widening of the QRS complex causing prolonged QT intervals. The clinical manifestations of this condition become relevant only in decompensated conditions or immediately after liver donor graft reperfusion with significant volume overload. Pleural effusion can be of a significant amount and may contribute to intraoperative hypoxemia due to atelectasis and decreased ventilation of the affected side of the lung.

Renal and Electrolyte Systems

Hepato-renal syndrome (HRS) [6] results from the cascade of events caused by ESLD with portal hypertension and mesenteric hyperemia; the two conditions cause relative renal hypo-perfusion, resulting in severe renal arterial vasoconstriction and progressive renal failure. Two types of HRS are observed in clinical practice [7]. Type 1 HRS is an aggressive form with a very poor prognosis, and type 2 HRS develops slowly over weeks; these patients usually have diuretic-resistant ascites and have a slightly better prognosis than those with type 1 HRS.

As a result, hyperkalemia and metabolic acidosis can be seen in patients with ESLD. Hyponatremia is also a common finding in ESLD patients. The pathogenesis is directly related to the vasodilatation and secondary neurohumoral adaptations that occur, including activation of endogenous vasoconstrictors such as antidiuretic hormone. This process leads to an impaired ability to excrete ingested water. Severity of the hyponatremia is related to the severity of ESLD.

Hematologic System

Decreased synthetic function of the liver with ESLD leads to decreased production of procoagulant factors including vitamin K-dependent factors, factor V, and factor XI. Dysfibrinogenemia is caused both by the decreased production and by increased consumption of fibrinogen due to altered production of activators and inhibitors of fibrinolysis, activation of coagulation cascade by endotoxemia, and decreased clearance of fibrinolytic proteins. Of note, traditional laboratory-based coagulation tests, including prothrombin time, partial thromboplastin time, and fibrinogen level, do not necessarily reveal the entire picture of coagulation. This point is important as the coagulation status is a fine balance between these two opposing factors [8]: procoagulants and anti-coagulants. Therefore, aggressive correction of coagulation abnormalities measured by these laboratory tests with exogenous coagulation factors and blood products occasionally results in thromboembolic complications at liver transplantation [9]. Thrombocytopenia is a common feature in ESLD. This is primarily due to hypersplenism secondary to portal hypertension, but decreased production of hepatic thrombopoietin synthesis as well as direct bone marrow suppression with alcohol exposure or hepatitis C virus also play a role. Anemia is seen due to a combination of hemorrhage from the gastrointestinal tract, decreased production of red blood cells (bone marrow suppression and/or folate deficiency), and hemodilution due to water retention. Leucopenia can be seen due to bone marrow suppression with viral hepatitis B or C, and excessive alcohol consumption. Together with leukopenia and decreased production of the compliments, patients can be prone to infections including spontaneous bacterial peritonitis.

Gastrointestinal System

Esophageal varices and portal hypertensive gastropathy are primary abnormalities that occur due to ESLD. In general, varices can form at any portion of the alimentary tract from

the esophagus to the rectum, but the distal esophagus is the most common site for varices in ESLD. Esophageal varices result from portal hypertension and often bleed. Child-Pugh score, variceal size, and presence of red wale markings can be used to calculate a prognostic index that quantifies the risk of variceal hemorrhage [10]. An endoscopic banding procedure is occasionally performed during the pretransplantation period either to therapeutically treat bleeding varices or for prophylactic purposes. The timing of this banding procedure and the severity of the varices are important to consider for intraoperative placement of transesophageal echocardiography (TEE). Portal hypertensive gastropathy [11] has the characteristic endoscopic features of a mosaic pattern with or without red spots. It is most frequently located at the fundus and body of the stomach. Acute bleeding from portal hypertensive gastropathy is usually mild and seen in the presence of severe portal hypertension. Mucosal dysfunction of the intestine due to portal hypertension leads to malabsorption and bacterial translocation [12]. The former leads to malnutrition; the latter leads to bacteremia and spontaneous bacterial peritonitis as well as the main pathogenesis of hepatorenal syndrome due to splanchnic and systemic vasodilation.

Nervous System

Hepatic encephalopathy [13] indicates the spectrum of potentially reversible neuropsychiatric abnormalities observed in patients with liver dysfunction. There are three types of hepatic encephalopathy: Type A is associated with acute liver failure; Type B is associated with portal-systemic bypass and no intrinsic liver disease; and Type C is associated with ESLD. Therefore, hepatic encephalopathy of liver transplant patients are categorized as Type C, and are further subcategorized into those with episodic hepatic encephalopathy, persistent hepatic encephalopathy, and minimal hepatic encephalopathy. In terms of symptom severity, the West Haven criteria [14, 15] for semi-quantitative grading of mental status have been used to score the grade of clinical severity: mild (Grade 1), moderate (Grade 2—lethargy/minimal disorientation/subtle personality change), severe (Grade 3—somnolence/confusion/disorientation), or Grade 4 (coma). Several metabolic factors contribute to the development of hepatic encephalopathy, which include ammonia, inhibitory neurotransmission through gamma-aminobutyric acid receptors in the central nervous system, and changes in central neurotransmitters and circulating amino acids [16].

Endocrine System

Diabetes mellitus is seen in 15–30 % of patients with cirrhosis [17]. Insulin resistance is present in many patients with nonalcoholic steatohepatitis and chronic hepatitis C. Cirrhosis has also been linked to abnormalities in the other endocrine glands, including abnormal sex hormone metabolism, thyroid disease (hypo- and hyperthyroidism), osteoporosis, and adrenocortical dysfunction.

MELD Score

The Model for End-Stage Liver Disease (MELD) score is a grading system for evaluating the severity of chronic liver diseases for patients age 12 and older. Candidates age 11 and younger are graded with the Pediatric End-Stage Liver Disease (PELD) scoring system. The MELD system was originally developed to predict 3 month-mortality in patients undergoing a transjugular intrahepatic portosystemic shunt (TIPS) procedure [18]. It has been used for the allocation of livers to adults since February 2002 in the United States; this system better predicts liver transplantation outcome compared to the traditional Child-Pugh score. MELD score is calculated based on the three laboratory values (bilirubin, creatinine, and international normalized ratio [INR]): [19]

$$\mathrm{MELD} = 3.8\left[\mathrm{Ln\,serum\,bilirubin}\left(\mathrm{mg/dL}\right)\right] + 11.2\left[\mathrm{Ln\,INR}\right] + 9.6\left[\mathrm{Ln\,serum\,creatinine}\left(\mathrm{mg/dL}\right)\right] + 6.4$$

where Ln is the natural logarithm.

The United Network for Organ Sharing (UNOS) modifies the currently-used MELD system in two ways. In order to eliminate negative values, the lowest values of each laboratory tests is set at 1.0 (i.e., creatinine of 0.8 mg/dL is automatically changed to 1.0). Therefore, the minimum MELD score becomes 6. In order to avoid giving an unfair advantage to patients with intrinsic renal disease, the maximum serum creatinine level is set at 4.0 mg/dL, which is also the value automatically assigned to patients on dialysis. For allocation purposes, the upper level of the MELD score is capped at 40. Thus, UNOS modified the MELD score for liver transplantation allocation to range from 6 to 40. A higher MELD score indicates increased mortality in the waiting period, thus patients are prioritized for liver transplantation with a higher ranking in the waiting list of a given blood type. MELD scores are updated regularly, especially for patients with severe illness. For example, patients with MELD scores $\geq$25 have their scores updated weekly. Under the current deceased donor liver allocation system, patients with acute liver failure are exempt from the MELD-based prioritization process outlined above. Patients with acute liver failure are

prioritized as UNOS Status 1A or Status 1B. Status 1A patients have a life expectancy of hours to a few days without a liver transplant. Status 1B is reserved for very sick, chronically ill pediatric patients (age less than 18). Also, several conditions receive "Standard MELD Exceptions"; they receive a higher than calculated MELD score due to higher mortality. These conditions include hepatocellular carcinoma (HCC), hepatopulmonary syndrome, portopulmonary hypertension, familial amyloid polyneuropathy, primary hyperoxaluria, cystic fibrosis, and hilar cholangiocarcinoma. The anesthesia team should be well aware of patients' MELD scores, since patients with high MELD score have been demonstrated to have a higher incidence of complications and mortality at liver transplantation.

The PELD system is calculated using parameters including bilirubin, INR, albumin, growth failure, and age (less than 1 year old or not).

Other Recipient Conditions

The following recipient conditions warrant special anesthetic considerations from the anesthesiologist team. Fulminant hepatic failure is defined as acute liver necrosis without any preexisting liver disease. This condition is one of the MELD-exempt conditions; the severity and priority for liver transplantation would be gauged with another grading system (i.e., King's College Criteria [20]). In addition to rapidly progressing coagulopathy, renal failure, metabolic acidosis, and respiratory failure, increased intracranial pressure can be an important challenge to successful perioperative anesthetic management (Chap. ##). Patients with hepatopulmonary syndrome or portopulmonary hypertension also receive MELD-exception treatment. Severe intraoperative hypoxemia or acute right heart failure could be major challenges in the care of these patients during the peri-transplantation period. These conditions are discussed further in Chap. ##. Emergent retransplantation is indicated for a primary nonfunctioning liver graft. Primary nonfunctioning is defined as an aggravated form of reperfusion injury resulting in irreversible graft failure without detectable technical or immunological problems [21, 22]. It is the most common reason for early retransplantation [23], with a reported incidence of 4–8 % [24]. These patients present at the ICU after recent liver transplantation with or without hepatectomy of the nonfunctioning liver graft. These patients are transferred from the ICU to the operating room with full monitoring and vascular accesses and the retransplantation is performed with a minimal dissection stage; however, a prolonged "anhepatic state" due to graft failure often causes severe coagulopathy and metabolic derangement including hyperkalemia and metabolic acidosis. Retransplantation for chronic rejection is often associated with adhesion and a prolonged dissection phase with surgical bleeding and incurred risk of massive transfusion. Budd-Chiari syndrome is a rare cause of portal hypertension and liver failure, which often results from hypercoagulable states induced by polycythemia vera, essential thrombocytosis, and myeloid metaplasia [25, 26]. These patients can present for liver transplantation with or without porto-systemic shunt surgeries or transjugular intrahepatic porto-systemic shunts (TIPS). Intraoperatively, establishment of vascular accesses could be challenging and a thorough review of the preoperative venography is important for planning.

Types of Liver Grafts and Their Implications

A liver transplantation involves the whole liver or a reduced-sized liver (a split graft or a liver segment). Transplantation of the latter would allow two liver recipients to receive a liver from one deceased donor or allow for living donor liver donation. A reduced-size liver transplant may result if the donor liver is too large for the recipient. Liver grafts can be donated from either deceased or living donors. The former can be categorized into donation after brain death (DBD) donors and donation after circulatory (or cardiac) death (DCD) donors. Living donor grafts consist of right lobe donations for mainly adult recipients or left lobe donations for mainly pediatric recipients. In 2011 in the United States, 5805 adult liver transplants were performed, which included transplant of 5351 livers from DBD donors, 266 from DCD donors, and 188 from living donors [1]. Concerns about donor safety has decreased the enthusiasm for living donor liver transplantation in the United States, and recently the number of donations from living donors plateaued at about 250 annually. For deceased donors, extended (or expanded) criteria donation (ECD) liver grafts have been utilized increasingly due to the shortage of donors with standard criteria donation (SCD). The definition of ECD has been defined well in kidney transplantation; however for liver transplantation, the criteria are not necessarily unanimous and are defined per transplantation center [27].

The course of anesthesia for liver transplantation is often dictated by the category and the quality of the donor liver graft. For example, living donor liver transplantation for an adult recipient usually takes place alongside donor hepatectomy; therefore, coordination of the timing of two operations (donor and recipient) is important. In general, the cold ischemic time in living donor liver transplantation is markedly shorter than that in deceased donor liver transplantation. Liver transplantation using ECD graft [28, 29] or grafts with higher donor risk indexes [30] may result in primary

nonfunctioning and delayed functioning. These conditions can present with significant hemodynamic derangement post re-perfusion with refractory coagulopathy and lactic acidosis.

Surgical Methods and Their Anesthetic Implications

Discussion with the transplant surgical team regarding the surgical method of the liver transplantation is crucial as each surgical team and institution has its own method. Basically, the liver graft is implanted either with preservation of the retrohepatic inferior vena cava (IVC) (the so-called "piggyback" method) or the traditional retrohepatic caval resection (the so-called "standard" method). The piggyback method, first described by Tzakis et al. in 1989 [31], has become widely adopted and is the contemporary technique of choice for liver transplantation [32]. This technique preserves the venous return from the lower body via the IVC with application of a side clamp on the IVC to exclude the hepatic vein for circulatory system for hepatectomy of the diseased liver. In such a way, the venous stasis of the lower body and the kidneys is avoided and the preload of the heart during the anhepatic stage can be maintained. On the other hand, the retrohepatic caval resection technique was described as the original method of liver transplantation hepatectomy [33]. Clamping at the supra-hepatic IVC as well as at the infrahepatic IVC are required to exclude the liver from the circulation for hepatectomy, which often results in venous stasis in the lower body as well as the kidneys; venous return is compromised and the preload of the heart is decreased. When venous collateral vessels are well established, this drawback can be minimized. Prior to the procedure, the surgical team may test hemodynamic conditions with a test application of the IVC clamp. Therefore, the anesthesiology team should prepare for potential hypotension after the application of the IVC clamping, which requires inotropes with judicious usage of volume infusion. Alternatively, to minimize the drawbacks associated with the IVC clamping as well as minimize the venous stasis of the portal system, veno-venous bypass (VVB) was developed [34] and has been used in selected centers. The idea is to insert drainage cannula both in the portal vein and the femoral vein and return the venous blood to the upper body venous system using a centrifugal pump. Traditionally, the return cannulas are placed in the axillary vein with a surgical cut down technique; however, the percutaneous technique using the internal jugular vein is advocated to avoid wound complications by axillary cut down (infection, seroma, or nerve damage). The anesthesiology team may be asked to place the return cannula via the internal jugular vein and play a major role in the VVB initiation and termination [35].

Intraoperative Anesthetic Management

Induction and Maintenance of General Anesthesia and Anesthetic Agents of Choice

The recipients' preoperative condition is reviewed and examined for any further changes; any sign of deterioration of the condition compared to the pretransplantation workup should be investigated. Judicious use of anxiolytics is recommended to avoid oversedation prior to the induction of general anesthesia, as the bioavailability of benzodiazepine usually high due to low serum albumin. Given the urgency of the transplantation and possible delayed gastric emptying due to ESLD, the patient should be treated as if they have a full stomach and rapid sequence induction to secure the airway is warranted; however, routine use of succinylcholine in this scenario should be avoided due to a concern for acute hyperkalemia associated with this agent. Intravenous induction agents including propofol or etomidate can be safely used. When post induction hypotension is a concern, the latter agent may be preferred. Potential adrenal suppression with etomidate may be mitigated by the glucocorticoid administration for immunosuppression regimen. Maintenance of anesthesia can be easily achieved with the balanced technique using inhalational agents, nondepolarizing muscle relaxants, and opioids. If fast track anesthesia is planned to remove the endotracheal tube early in the postoperative period, the rapid offset agents can be selected, including sevoflurane or desflurane, rocuronium if sugammadex as a reversal agent is available, and remifentanil infusion.

Several inotropes of choice (epinephrine, dopamine, or norepinephrine) should be prepared for any unexpected hemodynamic changes. Vasopressin should also be available in case of refractory hypotension. A cell salvage device and a rapid infusion system should also be available in the operating room and ready for use if indicated. Prophylactic antibiotics (a third generation cephalosporin of choice) should be given prior to the skin incision and timely re-dosing during the operation. In case of massive bleeding, the timing of re-dosing should be shortened to maintain the effective plasma concentration of antibiotics. For intraoperative fluid maintenance, any isotonic-potassium and glucose-free crystalloids should be adequate. Excessive usage of normal saline solution should be avoided, since a sudden increase in serum sodium level may result in acute central pontine myelinolysis [36].

Vascular Accesses and Monitoring

The degrees of cardiovascular and pulmonary system involvement in ESLD as well as the invasiveness of the surgical transplant method dictate selection of invasive

hemodynamic monitoring. However, each transplantation institution has its own institutional guidelines based on its philosophy and historical practice [37]. These institutional practices can vary significantly from a minimalist approach (one arterial line, several large bore intravenous lines with or without central venous line) to a maximalist approach (two arterial lines, two central lines with a pulmonary arterial [PA] catheter with continuous cardiac output measurement and TEE). The advocates of two arterial lines (one radial arterial line and the other via a central arterial system: contralateral side of the brachial artery or the femoral artery) are based on observations that a central arterial line would better represent the central arterial pressure than a radial artery, especially under hypotensive conditions, would serve as a failsafe measure during the surgery, and would allow continuous monitoring during phlebotomy via the other arterial line. The two central lines may assure the two independent rapid infusion sites of blood and fluid at the time of hemodynamic disaster, while allowing placement of a PA catheter. A PA catheter provides direct measurement of right-sided pressures as well as pulmonary arterial pressure, which is crucial when the recipient has preexisting pulmonary arterial hypertension. The catheter can provide continuous monitoring of pulmonary arterial pressure postoperatively in the ICU. TEE can be especially useful to evaluate right ventricular function that demonstrates pulmonary hypertension to rapidly diagnose the potential cause of cardiac collapse (hypovolemia, myocardial depression, and clot/air embolism), and to evaluate the performance of VVB. If VVB placement using the axillary cut down technique is anticipated, a venous access on the ipsilateral side of the arm should be discouraged, since infusion via the distal site of the same side of the axillary cut down will be obliterated.

These invasive monitors should be placed under a well-established safety protocol. Ultrasound-guided insertion of the central lines would be recommended and the tube transducing method [38] assures the venous site prior to the insertion of a dilator. Use of a smaller diameter arterial catheter may minimize postoperative hematoma formation. The arterial puncture of the femoral artery should be performed with great caution since the site is prone to postoperative hematoma formation, which could occasionally warrant surgical evacuation and pseudoaneurysm repair. A TEE probe can be safely placed and maintained intraoperatively; however, insertion of a probe into a patient who had recent banding of esophageal varicose veins can result in gastrointestinal bleeding. A recent review of the complications associated with invasive monitoring, including VVB cannulation, showed a relatively low incidence overall; however, vascular complications at the femoral vascular sites (arterial and venous) were rather striking [39].

Stage I (Pre-anhepatic) Management

The anesthesia team should be aware that there are three distinctive stages in liver transplantation. Each stage is defined by surgical feature, which inevitably demands specific anesthetic management and could potentially lead to specific complications. Stage I starts at the surgical incision and ends with the termination of the blood flow to the recipient's diseased liver.

During this stage, the surgical team performs dissection of the liver and its hilum, which may take longer in those who undergo redo-liver transplantation, have histories of upper abdominal surgery, or have histories of recurrent spontaneous bacterial peritonitis. A large amount of surgical bleeding can be encountered when recipients have severe portal hypertension with numerous porto-systemic venous shunting in the abdominal walls and peritoneal tissues. On the other hand, the duration of this stage can be very short for those who undergo redo liver transplantation for primary nonfunctioning due to completed dissection with minimum adhesion. Therefore, the primary goal of anesthetic management during Stage I is to maintain the volume status. A potential risk of sudden surgical bleeding during Stage I should be determined preoperatively to plan vascular accesses and to prepare blood products. When the risk is high, a rapid infusion device should be prepared. Maintenance of low central venous pressure (CVP) may reduce venous bleeding during hepatectomy [40, 41], although the evidence for using low CVP in liver transplantation is conflicting [42, 43]. For patients with severe portal hypertension, octreotide infusion may be indicated to reduce the portal venous pressure.

Aggressive normalization of the coagulation abnormality based on traditional laboratory-based coagulation tests and/or point of care coagulation tests (thrombelastography or thromboelastometry) may not be warranted or even could be detrimental [44]. On the other hand, a systematic review indicates that the benefit of prophylactic use of tranexamic acid and aprotinin both reduced the need for allogeneic blood products in liver transplantation. No increased risk for hepatic artery thrombosis, venous thromboembolic events, or perioperative mortality was observed for any of the investigated drugs [45]. Currently, aprotinin is not used due to widely publicized concern for thromboembolic complications observed in the field of cardiac surgeries [46].

Stage II (Anhepatic) Management

Stage II starts when blood circulation to the diseased liver is terminated, which is achieved by clamping the portal vein, the hepatic artery, and the hepatic vein. Hepatic venous

drainage to the systemic circulation is achieved either by application of a spoon-clamp at the junction of the hepatic vein to the IVC or by application of straight clamps both above and below the retrohepatic IVC. The former clamping technique is required for the surgical team to perform the retrohepatic caval preservation technique or the piggyback technique. Stage II ends when the liver graft is reperfused in the recipient's circulation system. During this stage, the surgical team performs a hepatectomy of the recipient's diseased liver, ensures hemostasis of the liver bed, establishes the venous outflow of the liver graft, and anastomoses one of the two blood inflows to the liver graft (the portal venous system or rarely the hepatic arterial system). In a few selective cases with severe intra-operative hemodynamic instability, the application of VVB is still justifiable and it is initiated to aid the surgical procedures at this stage [47]. Occasionally, VVB is initiated to aid the dissection procedure when the surgical team encounters difficulty.

During Stage II, the patient is anhepatic, which is the hallmark of this phase. Despite preexisting dysfunction of the diseased liver, complete loss of whatever liver function remains leads to striking changes in the recipient's system. Coagulopathy is often observed due to accumulation of tissue plasminogen activator (tPA) and other anti-coagulation products, including a heparinoid product [48] which is normally metabolized by the liver. Drug metabolism relying on hepatic function ceases. The level of serum lactate is elevated. Hemodynamic changes at the time of initiation of the stage can be profound. In this setting, aggressive correction of coagulation derangement should not be indicated, since the changes are temporary phenomena and accumulated tPA and other endogenous anti-coagulants will normally be quickly metabolized after liver graft reperfusion. Sudden hemodynamic derangement should be anticipated at the temporal termination of the hepatic venous drainage, which often results in decreased cardiac output because of the reduced preload. This is especially commonly observed at the clamping of the IVC for the standard procedure or overzealous side clamping of the IVB for the piggyback procedure. Well-developed collateral venous circulation formation due to long standing ESLD may minimize this incidence; otherwise, VVB should be indicated when the patient cannot tolerate the clamping of the IVC. Sequestration of the venous blood in the portal venous system may lead to hypotension. In this case, porto-systemic shunting with a temporal surgical shunting procedure or porto-systemic VVB can be performed. Of note, the hypotension occurring in this stage is better treated with aggressive administration of vasopressors rather than fluid replacement, since aggressive volume administration may result in volume overload at graft re-perfusion, which could lead to right heart failure, or venous congestion of the liver graft which is detrimental for its function. Preparation for graft reperfusion at Stage III should be initiated; serum potassium level should be aggressively managed to less than 4 mEq/L, metabolic acidosis should be corrected, and inotropes should be readily available.

Stage III (Neohepatic) Management

Stage III starts at graft reperfusion and ends at completion of the liver transplantation procedure. This stage is further subdivided into the time period within 5 min after the graft reperfusion and the rest of the period, since the initial 5 min after the graft reperfusion is the most volatile period regarding hemodynamic condition. After completion of anastomosis of hepatic outflow and one of the hepatic inflows (mainly the portal vein, rarely the hepatic artery), the surgical team is ready to reperfuse the liver graft. During the graft reperfusion, all the sequestrated venous blood in the portal venous system and in the venous system in the lower body returns to the heart if VVB has not been used. Preservative solution with high potassium concentration remained in the liver graft and endogenous metabolites with accumulated in the vascular system of the liver graft during cold and warm ischemic stages are also returned to the heart. Sudden overloading of the heart with this venous volume, potassium, and endogenous metabolites can result in systemic vascular dilatation with depressed cardiac function as well as pulmonary vascular constriction; systemic arterial hypotension, decreased cardiac output, bradycardia, and pulmonary arterial hypertension are often observed and even prolonged sinus arrest or pulseless electrical activity cardiac arrest could occur [49]. The systemic hypotension associated with liver graft reperfusion is coined as post reperfusion syndrome (PRS). PRS, first described by Aggarwal et al. in 1987 [50], is a syndrome of cardiovascular collapse related to systemic vasodilatation due to the release of vasoactive substances from the reperfused liver, acidosis, hyperkalemia, hypercarbia, and hypothermia. The original definition of PRS is prolonged hypotension (over 1 min) which occurs within 5 min after the reperfusion of the liver graft. Hypotension is defined as the decrease of systemic mean arterial pressure of more than 30 % from base line pre-reperfusion.

The anesthetic management of this critical stage is preparation for such cardiac dysfunction and timely management of cardiac conditions. For preparation, aggressive treatment of serum potassium should be initiated during Stages I–II. The methods include insulin and glucose administration, loop diuretics, treatment of metabolic acidosis with bicarbonate (50 mEq IV) or tromethamine infusion. A 100-mL of the latter solution contains tromethamine 3.6 g (30 mEq) in water, which is hypertonic 389 mOsmol/L and pH 8.6 (8.4–8.7). This solution does not contain sodium ions, which is beneficial for unwanted sodium load for recipients with

hyponatremia. Intravenous administration of calcium chloride (1–2 g) should be considered immediately prior to the graft reperfusion for cardiac membrane stabilization. In order to decrease exogenous potassium load, allogeneic red blood cells can be processed with a cell salvage device. Uncontrollable hyperkalemia, when encountered, should be aggressively treated with intraoperative hemodialysis using the existing hemodialysis catheter or newly established central venous access. "Pretreatment" to counteract the anticipated cardiac depression can be initiated prior to graft reperfusion using infusion of inotropes (e.g., epinephrine), intravenous calcium chloride (1 g), intravenous bicarbonate (50 mEq), and intravenous methylene blue (100 mg). Maintaining 100 % inspiratory oxygenation concentration to increase oxygen stores in the system and decreasing inhalation agent to minimize vasodilator effect of the agent should be considered.

At graft reperfusion, further aggressive treatment should be indicated upon any initial sign of cardiac dysfunction: bolus administration of epinephrine and vasopressin and/or atropine (0.4–1 mg). When cardiac arrest occurs, the surgical team should initiate immediate cardiac compression. This is achieved best by direct cardiac massages via the incision of the left diaphragm. For differential diagnosis of cardiac arrest, TEE is very useful. When intracardiac clots are witnessed, heparin administration (3000–5000 IU) via the central line to prevent further expansion of the clot can be considered. A low-dose administration of recombinant tissue plasminogen activators (0.5–4 mg) has been reported to be effective in the treatment of pulmonary thromboembolism in liver transplantation [51].

When stable hemodynamic status is achieved after reperfusion of the liver graft, the surgical team proceeds to complete the other inflow vessel anastomosis. At this stage, close monitoring of the coagulation status is very important, since reasonable surgical hemostasis should be achieved prior to reconstruction of the biliary system following the vessel anastomosis. Coagulation status monitoring at 30 min after the graft reperfusion should best guide further coagulation management, since a reasonable improvement of coagulation parameters is expected at this stage. Conversely, poor graft function should be anticipated when ongoing coagulopathy is observed at coagulation monitoring at 30 min post reperfusion.

At the end of the procedure, a return VVB cannula, if it was used, is removed and a purse string stich is applied at the insertion site to minimize hematoma formation. If the patient's condition is stable, the liver graft is functioning, and the blood transfusion is minimal, fast track anesthesia can be considered and early termination of the mechanical ventilation and removal of the endotracheal tube can be achieved either in the operating room or the ICU [52].

Strategies for Blood Transfusion Conservation

Complications related to allogeneic blood transplantation in liver transplantation have been documented. Therefore, it is prudent for the anesthesia team to exercise conservation strategies to minimize exposure of the patients to allogeneic blood products. A number of strategies have been demonstrated to achieve the goal. These include maintenance of low CVP, acute hemodilution and autologous blood return, and cell salvaging. The theoretical rationale for maintaining low CVP is to minimize surgical venous bleeding with reduction of systemic venous pressure. This technique seems to be particularly useful during Stage I. The techniques include phlebotomy and pharmacological systemic vasodilation with an inhalational agent as well as veno-dilators [53]. Acute hemodilution and autologous blood return at the beginning of Stage I can achieve not only reduction of the CVP but also preserve autologous blood for auto-transfusion in a later stage of transplant surgery. The rationale of this technique is that platelets and coagulation factors can be well preserved in the autologous blood and aid hemostasis upon auto-transfusion. This technique can be indicated only for patients with hemodynamic stability and higher hemoglobin levels. Red blood cell (RBC) salvage using a cell salvage device is a well-established technique and has widely been used. Contraindications for the technique include infected materials in the surgical field and malignant lesions. Some studies, however, suggest the properly washed shed blood were free from malignant cells [54]. By combining these strategies, some transplantation centers have achieved non-RBC transfusion liver transplantation [53].

Point-of-care coagulation monitors have been widely used to diagnose coagulopathy or fibrinolysis and to direct transfusion therapy [55]. Unlike the conventional plasma coagulation tests (including prothrombin time, partial thromboplastin time, INR, platelet count, or fibrinogen level), these point-of-care coagulation monitoring devices can provide the anesthesiology team with relatively whole blood coagulation conditions [56], except for temperature (the default temperature of 37.0 °C at the measurement) and endothelial function (the cup and the torsion pin are made of steel) in a relatively short period of time. Currently, thromboelastometry and thromboelastography are widely available as point-of-care coagulation monitors. Thromboelastometry (ROTEM, TEM®, Tem Innovations GmbH, Munich, Germany) is an established method testing viscoelastic hemostasis in whole blood [57]. Its multiple assays can provide information regarding extrinsic and intrinsic coagulation conditions as well as heparin effect, fibrinolysis, and fibrinogen contribution. Thromboelastography has also been used widely [58] and provides information on the activity of the plasma coagulation system, platelet function, and

fibrinolysis [59]. Recently, several new TEG variants have been utilized to provide faster assessment of coagulation condition as well as estimation of fibrinogen level.

Special Agents Administered at Transplantation

Glucocorticoid is a very common agent to be started intraoperatively; it is administered intravenously (methylprednisolone of 500 mg–1 g) immediately prior to or at the time of graft reperfusion. Anesthetic implication of intraoperative glucocorticoid administration is mainly hyperglycemia. The standard initial immunosuppressive regimen for most liver transplant recipients is tacrolimus and mycophenolate mofetil, commonly in conjunction with glucocorticoid. By 1 year after transplant, most patients are no longer taking glucocorticoid and are taking tacrolimus with or without mycophenolate mofetil. With these immunosuppressive regiments, acute rejection occurs in less than 20% of recipients during the first year.

Currently, induction agents for lymphoid depletion have infrequently been used in liver transplantation; however, they have an important role as calcineurin inhibitor-sparing agents in the immediate post-transplant period. These induction agents include polyclonal antibodies (e.g., antithymocyte globulin and antilymphocyte globulin) and monoclonal antibodies such as muromonab-CD3 (or OKT3) which is directed against the CD3-antigen complex on mature T-cells or humanized monoclonal antibodies against the interleukin-2 receptor (e.g., basiliximab and daclizumab). Other experimental induction agents may also be used, including belatacept, which is a high-affinity fusion protein that binds CD80/86 on antigen-presenting cells; efalizumab, which is a humanized monoclonal antibody against leukocyte function-associated antigen-1; or alemtuzumab, which is a humanized monoclonal, complement-fixing, anti-CD52 antibody that is expressed on the surface of immune cells. If these induction agents were used in the operating room, the anesthesiology team should be vigilant for potential complications associated with these agents including fever, rash, hypotension, bronchospasm, pulmonary edema, or thrombocytopenia. Premedications with corticosteroid, histamine 1 receptor blocker, histamine 2 receptor blocker, and acetaminophen should be administered prior to the initiation of these agents. Any side-effects should be promptly treated with termination or slowing-down of the infusion rate of an induction agent.

Hepatitis B hyper immunoglobulin is often indicated for patients with hepatitis B receiving hepatitis B-negative donor graft. This product is made from human plasma; therefore, the patient should be watched for any sign of allergic reaction.

Octreotide is occasionally indicated for recipients with severe portal hypertension to decrease portal venous pressure and flow during transplantation. The reported hemodynamic impact of this agent includes increase of systemic and pulmonary vascular resistance and resultant increase of systemic and pulmonary arterial pressures with bradycardia and decreased cardiac output.

Recognition and Formation of a Liver Transplantation Anesthesiologist Team

Recruitment of dedicated liver transplantation anesthesiology team members has been advocated to increase the consistency of the practice and potentially safer transplantation results [60]. A number of large transplantation centers have adopted such a practice [61]. Unfortunately, anesthesiologists or intensivists are not specifically mentioned or recognized in the statement in the glossary of the Health Resources and Services (HRHS) Administration Organ Procurement and Transplantation Network (OPTN) web site (http://optn.transplant.hrsa.gov/resources/glossary.asp). The stated definition of "Transplant Team" only includes clinical transplant coordinators, transplant physicians (mainly indicates hepatologists), transplant surgeons, financial coordinators, and social workers. As an effort to establish the transplantation anesthesiology team, a proposal has been created and is under review with the American Society of Anesthesiologists (ASA) (Table 28.3) [62].

Table 28.3 Guidelines for director of liver transplant anesthesia Committee of Origin: Transplant Anesthesia (Approved by the ASA House of Delegates on October 21, 2009)

Liver transplant programs shall designate a Director of Liver Transplant Anesthesia.
The Director of Liver Transplant Anesthesia shall be a Diplomate of the American Board of Anesthesiology (or hold an equivalent foreign certification). Applicants who are not Board certified shall attain this status within 2 years of their approval as Director of Liver Transplant Anesthesia.
The Director of Liver Transplant Anesthesia shall have one of the following:
1. Fellowship training in Critical Care Medicine, Cardiac Anesthesiology and/or Pediatric Anesthesiology that includes the perioperative care of at least 10 liver transplant recipients, or
2. Within the last 5 years, experience in the perioperative care of at least 20 liver transplant recipients in the operating room and/or intensive care unit. Experience acquired during postgraduate (residency) training shall not count for this purpose.
The Director of Liver Transplant Anesthesia shall earn a minimum of 8 h of ACCME Category I CME credit in transplant-related educational activities within the most recent 3-year period.

(Adapted from United Network for Organ Sharing. Attachment I to Appendix B of UNOS Bylaws: XIII. Tranplant Programs. Available at https://www.unos.org/wp-content/uploads/unos/Appendix_B_AttachI_XIII.pdf; accessed 9/15/2015.)

Conclusions

The liver transplantation anesthesiology team should be well-trained and specialized to provide safe and reliable management. Since patients with ESLD present with various degrees of systemic manifestations and these conditions have significant implications in anesthetic course, preoperative evaluation and planning of anesthesia management is crucial. Occasionally, transplantation-specific procedures should be requested, including VVB management and TEE placement and evaluation. Intraoperative coagulation management should be stage-specific. Intraoperative compilations sometimes require the anesthesiology team's best abilities to treat cardiac demise and massive bleeding and its treatment with transfusion.

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