Liver transplantation (LT) is a well-accepted treatment modality for many end-stage liver diseases. The main issue in LT is the shortage of deceased donors to accommodate the needs of patients waiting for such transplants. Live donors have tremendously increased the pool of available liver grafts, especially in countries where deceased donors are not common. The main ethical concern of this procedure is the safety of healthy donors, who undergo a major abdominal surgery not for their own health, but to help cure others. The first part of the review concentrates on live donor selection, preanesthetic evaluation, and intraoperative anesthetic care for living liver donors. The second part reviews patient evaluation, intraoperative anesthesia monitoring, and fluid management of the recipient. This review provides up-to-date information to help improve the quality of anesthesia, and contribute to the success of LT and increase the long-term survival of the recipients.

1. Introduction

The first liver transplantation (LT) was performed by Starzl et al in 1963. Since then, there has been a stream of continuous improvements in surgical techniques, anesthetic management, and postoperative immunosuppressive treatment in LT, which have improved the long-term survival rate of patients who undergo LT. LT is now an accepted treatment modality in many end-stage liver diseases. The main problem in LT is the wide disparity between supply (available donors) and demand (patients needing liver grafts). To increase the pool of donors from the conventional beating heart, brainstem-dead donors, various efforts such as using marginal donor from controlled non-heart beating donor by perfusion of cold preservation solution in the femoral artery immediately after cardiac arrest, or regional extracorporeal membrane oxygenation (ECMO) perfusion of the abdominal organs after cardiac arrest, or systemic ECMO support after cardiac death—have been performed. Improvement in the surgical technique via using reduced liver graft has shortened the waiting period of pediatric recipients and eliminated death in the waiting list. The technique of split liver graft has doubled the pool of donor grafts. However, the problem of organ shortage remains. Living donor liver transplantation (LDLT) is another option to address the shortage of deceased donors. It has indeed increased the donor pool, especially in countries where deceased donors are not common. If donor shortage continues owing to the growing need for liver grafts, LDLT will play an important role in the future of LT. Because of the cultural, religious, and social differences between the West and the East, the strategy used to overcome the problem of organ shortage is also different. Western countries tend to perform more deceased donor LTs, whereas in Asia LDLT is more common. Interested readers can refer to Chen et al’s review on why LDLT flourishes in Asia. As anesthesiologists, we have to provide safe anesthesia to LT patients and resolve hemodynamic problems as they arise using the improvements in surgical techniques in LT. This review focuses more on anesthesia in living liver donors and the problems adherent to LDLT. The second part reviews the topics of patient evaluation, anesthesia monitoring, intraoperative blood loss, and blood transfusion for recipients.

2. Live liver donor

The liver is an organ that can—within a few weeks or months—regenerate to its original volume even after a large part of...
its tissue, up to 70%, has been surgically removed; the 30% remnant liver remains sufficiently functional to meet the metabolic needs of the donors.\textsuperscript{12,13} Therefore, a healthy person can donate part of his/ her liver for LT. The first successful Asian cadaveric LT was performed by Chen et al\textsuperscript{24} in 1984. Since then, the number of cadaveric LTs in Asia has remained very low.\textsuperscript{21} In 1990, the first Asian LDLT was performed in Japan,\textsuperscript{16,25} and this was quickly followed in Taiwan, Hong Kong, South Korea, China, and other Asian countries.\textsuperscript{26} Today, LDLT is a well-accepted treatment modality and has become a daily practice in treating patients with liver diseases requiring LT in Asia.\textsuperscript{7}

2.1. Beneficial aspects of LDLT

There are many advantages in LDLT when compared with deceased donor LT. First, LDLT shortens the waiting period for recipients to receive the donor graft. Second, LDLT is an elective surgery, whereas in deceased donor LT, the procedure often takes place outside of routine hours. The team members may be tired from their daily work, and the staffing levels may be low and usually with less personnel as compared with those in routine practice. The surgeons and anesthesiologists, caring for the liver transplant recipients, must prepare themselves to perform and manage a complex and prolonged surgery in patients, who may have unstable hemodynamics owing to massive blood loss from profound coagulopathy, hypothermia, complex metabolic and electrolyte disturbances,\textsuperscript{27} and nature of the surgical procedure, such as a sudden decrease in venous return and cardiac output by clamping of the inferior vena cava (IVC) with or without venovenous bypass.\textsuperscript{28,29} It is a very challenging work both physically and mentally for all the participants. By contrast, LDLT usually starts in the normal office hours, and all members of the transplant team are in good condition with high staffing level to start their daily clinical tasks. Furthermore, the recipients are usually well prepared and are in good medical shape, in that they have been optimally improved preoperatively by surgeons, anesthesiologists, hepatologists, cardiologists, and other specialists of the LT team. LDLT is not linked with the national organ allocation program, and the rank priority of grafts does not follow the MELD (Model for End-Stage Liver Disease) score as it is stated in the principle of the United Network for Organ Sharing.\textsuperscript{30} Once a suitable donor is available, LDLT can be performed, thus shortening the waiting period and eliminating potential death among the patients in the waiting list.\textsuperscript{31} The quality of the liver graft is good as it is procured from a healthy donor with stable hemodynamics without needing inotropic drugs for support during the organ procurement, and it has very short cold ischemic time, thereby minimizing preservation injury.\textsuperscript{4,24} Likewise, LDLT recipients are usually less sick and in better condition in comparison with deceased LT recipients; therefore, the outcome is similar to or even better than that of deceased LT recipients in terms of graft and patient survival.\textsuperscript{13,31,34} Emond et al\textsuperscript{35} reported that the 1-year survival rate of pediatric LDLT was 94% (compared to 88% in deceased LT). Meanwhile, Chen et al\textsuperscript{36} reported a 5-year LDLT survival rate of 98% for biliary atresia patients, 94% for patients with hepatitis B virus cirrhosis, and 90% for patients with hepatocarcinoma. LDLT started with pediatric LT using the left lateral segment\textsuperscript{13,17} and has gradually undergone an evolution to adult to adult right lobe LT.\textsuperscript{32-35}

2.2. Donor selection

The biggest ethical concern arising from LDLT is the safety of the donors, who undergo major abdominal surgeries not for their health or benefit, but risk themselves with a variable rate of perioperative morbidity and even mortality.\textsuperscript{40} The donor selection criteria may vary in different centers,\textsuperscript{41,42} but all have the same principle—to minimize the risk to the donor and maximize the benefit to the recipient.\textsuperscript{43} The evaluation process is performed stepwise in three to four steps,\textsuperscript{41,44} aiming to ensure that the potential donor is healthy enough for this procedure, and to identify and rule out the potential donor from any unsuitable condition—such as too complicated or abnormal liver vascular-, biliary anatomy and small liver volume—that may increase the risk of complications to the donor. Several formulas, such as the graft–recipient body weight ratio and graft–weight in percentage of standard liver mass, are used to ensure an adequate liver mass in the donor and the recipient.\textsuperscript{45} Failure or delay in identification of unsuitable conditions, may lead to intraoperative abandonment of the procurement procedure. This kind of aborted hepatectomy is a near-miss event, and the reported rate is about 1.1–1.2%.\textsuperscript{36}

The potential living liver donor is usually a close relative of the recipient, who must abide, if there is any, with local regulations on live organ donation.\textsuperscript{41} The donor should be a healthy adult, younger than 60 years, who is competent, and willing to donate part of his or her liver without any coercion.\textsuperscript{41,47} The complete preoperative evaluation includes medical, physical, laboratory, psychosocial, and imaging assessments by noninvasive computed tomography (CT), CT volumetry, three-detector three-dimensional magnetic resonance angiography,\textsuperscript{48} three-dimensional magnetic resonance cholangiography,\textsuperscript{49} and abdominal echo to identify and confirm that the liver is anatomically suitable to be donated and to ensure donor safety.\textsuperscript{41,50} Informed consent for donation should be obtained from the donor after explanation of the donor risk without bias.\textsuperscript{41,50} A potential donor should be excluded if the individual is a carrier of hepatitis B, or is infected with hepatitis C and human immunodeficiency virus; however, donors who are hepatitis B core antibody-positive are considered acceptable because of the high prevalence of hepatitis B infection in Asian countries.\textsuperscript{41} Perioperative active immunization and prophylaxis lamivudine given to the recipient, who will receive the hepatitis B core antibody-positive graft, may prevent de novo hepatitis B virus infection after LDLT.\textsuperscript{51} A blood group that was identical or compatible was required in the past,\textsuperscript{41} but now a donor who is ABO incompatible (ABOi) is deemed acceptable when there is no other suitable potential donor available.\textsuperscript{52-55} Operations in donors with abnormal liver function, moderate fatty liver, and infection with fever should be postponed until normalization of laboratory data and improvement of the degree of fatty liver have been attained.\textsuperscript{41,56}

2.3. Donor anesthesia

Complete medical history, physical examination, preliminary laboratory, serologic tests and radiological examinations should be performed and carefully evaluated by the anesthesiologist prior to the operation. Diabetes mellitus or hypertension with regular control is accepted.\textsuperscript{41} General intubation anesthesia under standard monitors including invasive arterial blood pressure and central venous pressure (CVP) measurements is performed. It may be used with\textsuperscript{41} or without epidural analgesia.\textsuperscript{56,58} General anesthesia can be maintained with inhalational agents, balanced anesthesia, or total intravenous anesthesia.\textsuperscript{52} Live donor hepatectomy is unlike ordinary deceased total hepatectomy, in that the IVC should be preserved for the live donor. It is also different from the ordinary liver resection—there, the live donor partial hepatectomy with preservation of graft viability and adequacy, in terms of liver volume and function, is for both the recipient and the donor, is of principal importance.\textsuperscript{56} Live donor hepatectomy is, therefore, performed without control of the hepatic inflow,\textsuperscript{56,59} such as the Pringle maneuver, to protect the graft and remnant liver from ischemic injury.
Liver resection without the Pringle maneuver may be associated with difficulty in control of bleeding during parenchymal transection; as a result, it may cause blood loss, thus requiring blood transfusion, which may increase postoperative morbidity and mortality.\(^5\) The option of preoperative autologous blood donation\(^57,58\) is given to the donor in some centers to prevent transmission of infectious diseases and immunomodulation induced by allogenic transfusion.\(^52\) Intraoperative blood loss was found to be an independent risk factor for donor complications; therefore, blood loss should be minimized to prevent complications in donors.\(^54\) Intraoperative blood loss can be minimized if liver parenchymal transection is carried out with strict adherence to a meticulous surgical technique.\(^56\) The anesthesiologist can help minimize blood loss by lowering the CVP; there, the venous pressure of the hepatic vein and hepatic sinusoids is equal to the pressure of the CVP.\(^53\) Indeed, intraoperative low CVP resulted in significantly less blood loss during liver resection.\(^54,56\) Parenchymal transection under CVP of less than 5 mmHg had indeed resulted in less blood loss\(^54\) and allows easier control of inadvertent venous injury.\(^56\) Fluid restriction, forced diuresis, epidural analgesia,\(^56\) vasodilators such as morphine, nitroglycerine,\(^57\) normovolemic hemodilution,\(^58\) and normonormovolemic phlebotomy after induction of the anesthesia\(^59\) are all means to lower the CVP effectively. Autologous blood donation before the operation can prevent homologous blood transfusion and its immunological side effects\(^57,59\); however, an autologous blood donation (a kind of acute bleeding) 2 days before the operation did not affect the CVP level during hepatectomy\(^58\) but was effective in lowering CVP when phlebotomy was performed during LT.\(^60\) Nowadays, donor hepatectomy can be done with minimal blood loss. A mean blood loss of 72 mL (range 20–300 mL) was reported by Chen et al.\(^60\) Neither homologous nor autologous transfusion was required with such minimal blood loss;\(^50\) therefore, some centers have abandoned the use of autologous blood donation prior to LDLT.\(^56–58\) In other centers, where autologous blood transfusion is optionally performed, the reported mean blood loss is less than 1 L.\(^70,71\) Although a CVP of 5 mmHg is recommended,\(^64\) a too low CVP bears a potential risk of air embolism during the division of the liver.\(^64\) Such events are rare but had been reported to occur.\(^57\) In clinical practice, it is sometimes difficult to achieve a CVP of about 5 mmHg in healthy living liver donor by using fluid restriction, diuresis, morphine, and nitroglycerine.\(^65,69\) With the increasing number of living donor hepatectomies, some reports have recently shown that there is no correlation between blood loss and CVP value during hepatectomy, suggesting that it is not mandatory to reduce the CVP too aggressively.\(^65,69\) The outcome, in terms of blood loss and fluid replacement, of hepatectomy performed in living liver donor with or without placement of central venous catheter, was similar, indicating that CVP monitoring is no longer absolutely necessary in living donor hepatectomy in experienced centers.\(^55\) Stroke volume variation is a monitor of fluid therapy responsiveness. Whether a low stroke volume variation is associated with less hepatectomy bleeding is rarely reported\(^62,71\); however, its usefulness in donor hepatectomy requires further well-controlled studies. After procurement of the liver graft, the cumulative fluid deficits resulting from fluid restriction should be replaced in the donor to prevent acute renal injury.\(^56\) Most donors can be immediately extubated in the operating room and are sent to the intensive care unit (ICU) for postoperative care for safety reasons. Complications in a donor are a depressing but inevitable occurrence. Major morbidity and especially mortality in a healthy donor is a devastating event and is not well accepted by the social media. Any documented and well-publicized donor death\(^46,74,75\) certainly has a negative impact on the development of LDLT. A worldwide survey study shows that the average donor morbidity was about 24%. Within the donor morbidity group, 0.02% had postoperative liver dysfunction and liver failure requiring transplantation, and donor death was about 0.2%\(^50\) to 0.5%.\(^75\) Death of the paid donor has ever been retrospectively revealed.\(^76\)

Intravenous patient-controlled analgesia and epidural analgesia can both be performed satisfactorily in a liver donor. It seems that pain relief is better provided by the epidural analgesia in the donor.\(^77\) However, care should be taken when an epidural catheter is inserted or removed in the donor, because coagulation derangement may be encountered after liver donation.\(^78\)

2.4. ABO incompatibility

The four main human blood types are A, B, AB, and O. In addition to the ABO system, the Rhesus group, either positive (+) or negative (−), can also affect blood compatibility. The red blood cells of each ABO type, except the O type, carry their own type antigen: cell antigens A, B, and AB for blood types A, B, and AB, respectively. Likewise, the human immune system has developed antibodies against blood types other than its own.\(^1\) A type A person has antigen A and antibody B, a type B person has antigen B and antibody A, and a type AB individual has antigens A and B but no antibody. AB+ is known as the universal recipient, and the O type has no antigen but has antibodies A and B; therefore, O− is referred to as the universal donor. An ABO+ blood transfusion is a medical hazard; it usually results in a severe immune reaction, an acute hemolytic transfusion reaction, causing shock, kidney failure, circulatory collapse, and death.\(^80\) In the transplantation setting, ABOi was contraindicated in the past, because it may result in antibody-mediated rejection with high morbidity and graft failure.\(^81\) Today, however, it can be done with immune modulation and is well accepted in emergent LDLT when no ABO-compatible donor is available.\(^52,55\) Measurement to reduce the antibodies against the donor ABO is the key to success in organ transplantation.\(^55\) Perioperative plasmapheresis\(^82\) and the combined use of multiple immunosuppressions with\(^43\) or without splenectomy\(^54\) were measures used in ABOi living donors for kidney and liver transplantation.\(^53\) The protocols for reducing the formation of antibodies vary from center to center.\(^52\) The 5-year survival rate is about 85% in infant LDLT and 52% in adult LDLT.\(^52\) A recent report showed that using simplified intravenous immunoglobulin without local infusion therapy in the liver has improved the outcome to a level compatible to that of ABO-compatible LDLT.\(^54\) For anesthesiologists, care should be taken during blood transfusion, because the red blood cell contains the antigens of own group and the plasma contains antibodies against all blood type groups except own blood type. Therefore, when blood transfusion is required, leukocyte-poor red blood cell (LPR) or irradiated red blood cell from a person whose blood type is identical to that of the recipient’s should be given; however, when fresh frozen plasma (FFP) or platelet is required, the AB group type FFP and platelet, which contains no antibodies against the ABO system, should be given regardless of which blood group the recipient belongs to.\(^50,52\) Rhesus incompatible or combined ABO− and Rh incompatible is also allowed.\(^83\) The anesthesia management, regarding blood transfusion, is practically similar—identical red blood cells with a similar blood type to that of the recipient and AB-Rh negative FFP and platelet should be used.\(^86\)

2.5. Dual grafts

The liver vascular anatomy and its volume are evaluated and measured using imaging study before the LDLT procedure.\(^45,49\) Because the liver of the potential donor will be divided into liver graft for the recipient and remnant liver for the donor, the volume...
of each (divided) liver segment should be enough to meet the metabolic requirements of the recipient and the donor, respectively. An insufficient liver graft volume for the recipient, defined as a graft volume of less than 0.8 to 1.0% of the recipient body weight, may result in small-for-size syndrome in the recipient, which may develop to liver dysfunction, liver failure, and graft loss. Meanwhile, donors with a remnant liver volume of less than 30% of their preoperative volume may face up to four times higher risk of postoperative morbidity, including postoperative hepatic insufficiency and failure. The hepatic insufficiency can be so severe that LT for the donor may be required to treat the hepatic failure. In case of mismatch in the liver graft volume, either for the recipient or remnant liver volume for the donor, dual graft LTs may be performed. Dual graft LDLT was first introduced and performed in South Korea. It is indeed an alternative surgical technique, ensuring the safety of both the donor and the recipient. Because dual-graft LDLT is more complex, the two grafts with double- hepatic veins, -portal veins, -hepatic arteries, and -bile ducts are implanted in the recipient. The anesthesia time, especially the critical anhepatic time, with cross-clamp of the IVC, is prolonged. More intensive management with fluid resuscitation and medical support are required to maintain an acceptable hemodynamic performance.

2.6. Pregnant mother as a donor

Pregnancy is medically and ethically a contraindication for live liver donation. There was a pregnant woman in Taiwan, who was the only suitable and available donor to her 1-year-old sick child with end-stage liver cirrhosis due to biliary atresia. She had insisted on donating and saving the life of her daughter and at the same time keeping the pregnancy. The LDLT procedure was successfully performed during the second trimester of her pregnancy, and she gave birth to a healthy term baby weighing 3430 g without any complications 5 months after the donation. For pregnant women who undergo nonobstetric surgery, the reported death rate is 0.006% and the abortion rate is 5.8%. A crucial factor for anesthesia is to maintain hemodynamic stability, thus avoiding maternal hypotension, which may lead to hypoxemia and asphyxia to the fetus. Intraoperative fluid restriction is associated with force diuretic to lower the CVP to about 3.7 mmHg during the left lateral segment lobectomy to minimize the surgical bleeding. The estimated blood loss was only 40 mL. This isolated case demonstrated that live donor liver donation can be done successfully with a pregnant donor in highly experienced liver transplant centers, but this should only be done when absolutely no other donor can be found and the recipient is in urgent need of LT.

3. Anesthesia for recipients

3.1. Preoperative evaluation

Patients requiring LTs usually have severe liver diseases and multisystem disorders that pose many anesthetic challenges. The coexistence of systemic diseases or diseases related to chronic liver diseases should be evaluated before the operation. The advantage of LDLT is that systemic assessments of the recipients are performed shortly before the operation; thus, it is still possible to medically ameliorate some of the abnormal functions of the organ in a timely manner because of the elective nature of the operation. By contrast, for deceased LT, the assessments were performed mostly when the patients were placed on the waiting list for LT; thus, the results of the assessments may be out of date, and reassessments of many examinations are not feasible owing to the urgency of the operation when a suitable deceased donor suddenly becomes available.

3.2. Diseases related to chronic liver disease

It is known that liver disease per se may affect many vital organs.

3.2.1. Portal hypertension

Portal hypertension with a pressure higher than 12 mmHg is common in patients with liver cirrhosis. The normal portal flow is about 1000–1200 mL/min, but it may fall to about 400 mL/min in a cirrhotic patient. This drastic reduction of portal flow leads to the formation of portosystemic collaterals that divert portal blood into the systemic circulation. Liver dysfunction associated with portosystemic shunt subsequently affects the central nervous system, cardiopulmonary, renal function with electrolyte imbalance, gastrointestinal, hematologic, and coagulation systems.

3.2.2. Central nervous system

Hepatic encephalopathy in acute liver failure may have brain edema associated with high cranial pressure. The necessity of intracranial pressure monitoring remains controversial. Although it is indeed effective in guiding the therapy, severe intracranial bleeding as a complication has been noted. High intracranial pressure can be treated by osmotic therapy using hypertonic saline and mannitol. Hypertonic saline should be used with caution when dealing with a patient who has brain edema with hypotension. A too-rapid correction of hyponatremia may result in central pontine myelinolysis, a neurological complication with high mortality from osmotic demyelination syndrome. The effectiveness of decreased intracranial pressure when using the molecular adsorbent recirculating system, a detoxifying liver support system, is still a controversial issue in LT.

3.2.3. Cardiovascular system

Almost 70% of patients with end-stage liver disease are in circulatory hyperdynamic state, characteristic with high cardiac output and low systemic vascular resistance, and tachycardia with normal or slight decrease in blood pressure. As cirrhotic cardiomyopathy, diastolic dysfunction, and coronary artery disease (CAD) may be encountered in LT recipients, the heart function should be carefully evaluated. Because intraoperative hemodynamic instability is a feature of the LT procedure, which results from massive bleeding, sudden decrease in venous return during IVC clamping in the anhepatic phase and sudden return of cold, acidic, hyperkalemic, and unknown vasodilator products from the cold ischemic liver graft to the heart, many of these may cause postreperfusion syndrome (PRS) and cardiac events during the procedure, especially at the reperfusion phase. The incidence of cardiac arrest during deceased donor LT procedure is reported to be 3.3 to 5.5%, with a high mortality of about 50%. The incidence of cardiac arrest in LDLT is about 1.0%. Both figures are remarkably higher in comparison with that of noncardiac and non-LT surgery, whose incidence was about 0.01 to 0.043%. Preoperative assessments of the heart performance and ischemic CAD are necessary. Electrocardiography, treadmill, thallium scan, and cardiac echo are usually performed. When the results of the treadmill and thallium scan are suspected for CADs, coronary CT angiography or even heart catheterization is necessary. The benefit of heart catheterization is that the presence of CAD can be immediately confirmed and treated with percutaneous coronary intervention. This measure has reduced the perioperative mortality rate through reductions in the incidence of both fatal and nonfatal myocardial infarctions in LT. Cardiopulmonary exercise testing is an important clinical tool to evaluate exercise capacity.
and exercise intolerance, and to predict the outcome of the patients. Cardiopulmonary exercise testing is a sensitive and specific predictor for short-term survival of patients in the waiting list for LT and after LT.

3.2.4. Renal system

Renal dysfunction is common in patients with liver cirrhosis; it poses various problems in LT, resulting in high postoperative morbidity and mortality. The outcome of LT is better when renal function can be improved in end-stage liver disease patients with chronic renal disease prior to transplantation. However, not all renal diseases are improvable; combined liver and kidney transplantation is therefore, performed. Both kidney and liver grafts are usually from the same deceased donor. In the living donor setting, kidney and liver grafts are recommended to come from two different live donors. It should be noted that combined liver and kidney transplantation is associated with more blood transfusions and has a relatively high frequency of postoperative complications that moderately impair short-term survival. Furthermore, pre-transplant renal impairment is a predictor of cardiac event(s) after LT. A complete cardiac assessment is indicated when renal impairment is found before the operation.

3.2.5. Electrolytes

Electrolyte imbalance, such as hyponatremia, ionized hypocalcemia, and hyperkalemia, are common in LT. Hyponatremia observed in liver disease may associate with hepatorenal syndrome, portal hypertension, and ascites. It can cause brain damage and even death; therefore, a slow corrective action is required, keeping in mind that the rise of serum sodium should be less than 12 mEq/L in 24 hours in preventing central pontine myelinolysis. Hyperkalemia, defined as serum potassium higher than 5 mEq/L, is easily encountered during the LT procedure. It can be induced by increased potassium load, decreased renal excretion, and increased transcellular potassium shift. Severe hyperkalemia may induce myocardial depression, cardiac arrhythmia, and cardiac arrest. Because this is an urgent condition, prompt recognition and effective treatment are crucial. Correct acidosis, diuresis, insulin with glucose, hemodialysis, and autotransfusion are all measures to treat hyperkalemia. Because citrate is metabolized in the liver, citrate metabolism is hindered in liver disease; blood transfusion may induce ionized hypocalcemia. Routine and repeated checking of serum sodium, ionized calcium, and potassium during the LT procedure is required.

3.2.6. Pulmonary system

The pulmonary complications associated with liver disease include pleural effusion, hepatopulmonary syndrome with intrapulmonary shunts, and pulmonary hypertension. Mild to moderate pulmonary hypertension with a pulmonary systemic arterial pressure <60 mmHg or a mean pulmonary arterial pressure of <45 mmHg seems to have no impact on the outcome of the procedure, but severe pulmonary hypertension—defined as a systolic pulmonary artery pressure of >60 mmHg or a mean pulmonary artery pressure >45 mmHg—is associated with high perioperative mortality. LT patients with pulmonary hypertension require intraoperative pulmonary arterial catheter monitoring and transesophageal echocardiography (TEE) for assessing right ventricular function, and rapidly acting vasodilators, such as epoprostenol and nitric oxide, to treat the pulmonary hypertension should be available. Patients with severe pulmonary hypertension are at the greatest risk for a pulmonary hypertensive crisis with right heart failure at the time of reperfusion.

Hepatopulmonary syndrome is characterized by hypoxemia and pulmonary vascular dilatation. Preoperative hepoxemic patients should undergo contrast echocardiography to confirm the diagnosis of hepatopulmonary syndrome. Although it is an independent risk factor for mortality, the long-term LT survival rate is acceptable.

3.2.7. Coagulation

Patients with acute or chronic liver insufficiency have different degrees of coagulopathy, mostly associated with thrombocytopenia. The mechanism is attributable to a reduced production of most of the coagulation factors, protein needed for fibrinolysis, and thrombopoietin, which is required to form platelets in megakaryocytes. Thrombocytopenia is not only due to decreased platelet production, it may also be a result of increased turnover and sequestration in the enlarged spleen. Results of clinical tests such as prothrombin time, activated partial thromboplastin time, and platelet count are usually abnormal in patients with liver disease. Whether it should be routinely and prophylactically treated prior to the invasive procedure has recently come under debate.

The prophylactic correction of coagulation defects with fresh frozen plasma and platelet has not reduced the intraoperative blood loss; on the contrary, it has been related to worse surgical outcomes. Some investigators have recommended that abnormal coagulation parameters should not be prophylactically treated unless there are clinical signs that hemostatic defects such as microvascular oozing without clot formation are not surgically controllable.

3.3. Intraoperative anesthetic management

The role of the anesthesiologist is to provide safe general anesthesia and maintain an acceptable hemodynamic performance, ensuring sufficient perfusion to the vital organs of the patient. Standard anesthesia monitoring according to the American Society of Anesthesiology should be met (https://www.ingelking.com/read/manual-clinical-anesthesiology-chu-fuller-1st/chapter-8/standard-asa-monitors).

3.3.1. Hemodynamics

Because hemodynamic instability is common in LT, additional hemodynamic monitoring is required, which may include direct arterial pressure measurement, pulmonary arterial catheter or other cardiac output measurement devices, TEE, and CVP. The pulmonary arterial catheters are mostly used in new centers when they start their LT programs; however, only 30% of experienced transplant centers used it routinely. Its use is indicated when the patient is known to have pulmonary hypertension. TEE is not routinely used, but is very useful when hemodynamic performance becomes very unstable and particularly when this occurs for unknown reasons. TEE provides accurate information regarding the left and right heart function, and helps identify the cause of the hemodynamic instability. Identification of the cause of hemodynamic instability is crucial because the therapeutic intervention and possible prevention depend on the etiology of the instability. TEE can be safely used during LT, even in patients with known esophageal varices. It seems not to increase the incidence of intraoperative variceal bleeding.

Hemodynamic instability can be encountered at any point during the LT procedure and has multifactorial etiologies. Blood loss is probably the main cause; indeed, the unpredictable blood loss and transfusion is still the key problem for surgeons and anesthesiologists in LT. Massive blood loss requiring massive blood transfusions of more than 100 U of red blood cells or even death from uncontrollable surgical bleeding was common in the past. Nowadays, blood loss and the blood products required have been reduced, but still vary widely from no blood transfusion to...
overload. The proper treatment is surgical intervention to eliminate
pressure and vital organ perfusion. Vasopressin, a drug that
may be supported by using pure alpha agonist drugs to increase the
decrease in venous return owing to a hepatic out
by insuf
ventricle when assessed by TEE, all the obtained parameters from
CVP, low wedge pressure, and low cardiac output with empty
saver can help maintain hemodynamic stability and prevent
hypothermia. Such prevention measures are necessary because hypothermia itself may cause coagulopathy, even in patients with
normal coagulation profiles. Furthermore, stable hemodynamics may be supported by using pure alpha agonist drugs to increase the
systemic vascular resistance, which subsequently improves blood
pressure and vital organ perfusion. Vasopressin, a drug that
selectively reduces the blood flow to the splanchnic organ, may reduce intraoperative blood loss during LT.

PRS, defined as a severe deterioration of blood pressure associ-ated with bradycardia, may occur immediately after reper-fusion. It usually responds well to small dose intravenous adrenaline. Duration of the cold ischemic time is found to be an independ-ent risk factor forPRS; therefore, its occurrence is relatively rare in LDLT owing to the short cold ischemic time. All additional hemodynamic monitoring measures mentioned above are very helpful and reliable in managing LT anesthesia, except in hepatic outflow obstruction in the reperfusion phase. When repeated severe hypotension is associated with tachycardia, low CVP, low wedge pressure, and low cardiac output with empty ventricle when assessed by TEE, all the obtained parameters from anesthesiology monitoring indicate that it is hypovolemia. However, this clinical picture of hypovolemia is relative and not caused by insufficient fluid administration. The real cause is the sudden decrease in venous return owing to a hepatic outflow obstruction that results from a too-heavy liver allograft or kitting of the hepatic vein anastomosis. The diagnosis does not rely on anesthesia monitoring; it is suspected when the liver allograft is engorged and hard. The hemodynamics can be improved when the liver is lifted or repositioned by surgeons. The final diagnosis is confirmed by Doppler ultrasound with low or absence of flow velocity. The treatment definitely does not call for fluid resuscitation; blind correction of the observed abnormal parameters will lead to fluid overload. The proper treatment is surgical intervention to eliminate the outflow obstruction.

When a patient has refractory cardiopulmonary dysfunction from massive blood transfusion or other causes, ECMO support is a therapeutic option to rescue the patient.

3.3.2. Blood transfusion

The indication for red blood cell transfusion shows little varia-tion in different centers: the transfusion threshold is mostly set at a hematocrit level of 18–21%, and the goal is to maintain a postoperative hematocrit of 27–30%. It is reported that a low hematocrit level reduces the incidence of hepatic artery thrombosis (HAT) after LT.

Allogenic blood transfusion may not only transmit infectious diseases, but also induces a variety of immune modulations inducing alloimmunization, transfusion-associated graft-versus-host diseases, and immunosuppression, which may increase the rate of postoperative infection, respiratory distress syndrome, multiple organ failure, and increased recurrence of malignant tumors. Likewise, immunologic responses from blood transfusion may reduce the graft and patient survival in LT. Most of the immunological side effects mentioned above are believed to result from donor-derived leukocytes. Elimination of the allogenic leukocyte from the red blood cell and thrombocyte concentrates by filtering it is clinical requirement. Clinical investigations have indeed shown that the administration of leukocyte-depleted or leukocyte-poor red blood cell can reduce postoperative infections, morbidity, mortality, and duration of hospitalization. LPR is now universally implemented in the UK and other European countries, but not worldwide because of its high cost. In the LT setting, LPR and leukocyte-poor platelets are administered when blood trans-fusion is indicated. In some centers, irradiated LPRs are used as a precautionary measure to prevent graft-versus-host disease. Transfusion-associated graft-versus-host disease is a rare but almost lethal complication of the transfusion in immune-compromised patients. It is induced by donor leukocyte from the transfused blood products. Irradiation of blood products before transfusion is able to prevent such complications. A recent report showed that irradiation of LPR products may not be necessary and not beneficial in liver transplant recipients with regard to the rates of rejection and infection. The consequences of massive blood and rapid transfusion of banked blood may lead to citrate intoxication and hyperkalemia. Electrolytes should be routinely checked and appropriately corrected. Both ionized calcium and potassium disarrangements may result in cardiac arrest. The reported incidence rate of cardiac arrest during the LT procedure is 3.3% to 5.5%. The incidence is almost 100-fold higher when compared with that of noncardiac and nontransplantation proce-dures (which have a rate of 0.01%). Although closed chest cardiac massage can be immediately initiated by surgeons, external cardiac defibrillation of the heart under sterile conditions is very difficult to pull off because of the nature of the procedure. The outcome of CPR (cardiopulmonary resuscitation) in LT is usually poor, with a mortality rate of more than 50%. Evidence shows that the initial closed chest cardiac massage of LT patients usually shifted to open chest cardiac massage through the diaphragm and internal defibrillation.

3.3.3. Monitoring and treatment of coagulopathy

Although the indications and end point of red blood cell replacement are clear, there is still no consensus reached regarding the monitoring and management of intraoperative abnormal coagulation data. Conventional coagulation tests, such as prothrombin time, activated partial thromboplastin time, platelet count, bleeding time, fibrinogen, and fibrin degradation products, usually yield abnormal results in end-stage liver disease, but the provided information does not adequately reflect the clinical hemostasis status as made evident by our inability to predict intra-operative blood loss. The conventional coagulation tests measure only the quantity of the procoagulant factors of the complex hemostatic system. In fact, the complex hemostasis system contains pro- and antihemostatic pathways. Both pathways can change simultaneously in chronic liver disease, but the change of the antihemostatic pathways is usually not well reflected in the routine coagulation test. Patients with end-stage liver disease may be in hemostatic balance or rebleeding condition despite routine coagulation test are abnormal. Clinically, such abnormal coagulation data are still able to provide good hemostatic function as observed in many patients with end-stage liver disease who undergo major surgeries, such as LT in pediatric as well as adult patients, without requiring any blood product trans-fusion. However, the rebalance hemostasis condition is
unstable; it may change from an unknown reason toward a hypo- or hypercoagulation situation, as evidenced by occurrence of both bleeding and thrombotic complications in some patients.142,194,196

Thrombotic events such as portal vein thrombosis and HAT in pediatric patients during surgery were indeed detected by Doppler ultrasound after reperfusion of the new liver allograft.197 Whether abnormal coagulation data should be corrected before the operation and whether thromboelastography (TEG) should be used to monitor intraoperative coagulation profiles are debatable issues.150,151,193,195,199,200 TEG, a device used to assess the coagulation factors, platelet function, clot strength, and fibrinolysis at the same time, provides a complete picture of hemostasis; hence, it can deliver a more targeted treatment.194 However, clinical analysis showed that there is no correlation between preoperative coagulation profiles191,195,201 and TEG,196 and intraoperative blood transfusion requirement can be identified. Some investigators even found that the monitoring of coagulation techniques is not important in directing blood product transfusion during LT.151,193 Indeed, no evidence-based literature has compared blood loss based on the presence or the type of coagulation monitoring in a double-blind fashion.151 Furthermore, it is possible that the surgical technical factors, which are usually ignored or are technically too difficult to include in multivariate analysis causing serious loss,163,200,201 rather than patient-related factors, are more important for the control of bleeding in the LT setting.202 Some clinicians found that prevention of bleeding is more important than monitoring. The blood loss can be reduced by lowering the intravascular volume during dissection of the diseased liver by restricting the fluid administration,193 or more aggressively, by performing phlebotomy of 500–800 mL blood without volume replacement to lower the CVP together with vasopressor infusion to support the blood pressure in patients undergoing LT. With such methods, almost 79% of LT can be done without blood transfusion.150 Coagulation factors, such as platelet and FFP, should be used with caution. Although platelet is an important element of normal hemostasis, it has also a nonhemostatic function that plays a role in inflammation, angiogenesis, tissue repair and regeneration, and ischemia/reperfusion injury.203,204 Platelet transfusion has a negative impact on the outcome of cardiac surgery143,144 and LT due to acute lung injury.143,144 Likewise, although the reason remains unclear, intraoperative transfusion of any amount of FFP significantly decreased the 1-year survival rate following LT,150 and it is also found to be the only predictive factor for postoperative relaparotomy to check the bleeding.52 Postoperative bleeding and thrombotic events are potential risk complications of all surgical operations. Both events can be encountered in end-stage liver disease patients despite the abnormal coagulation profiles.194,200 In the LT setting, the incidences of preoperative portal venous thrombosis (PVT) were 2.8% in pediatric patients and 1.8% in adult patients357 despite profound coagulation defects.194 The rate of postoperative HAT had been reported to be as high as 42% in pediatric patients after LT.208 It decreased, after the incorporation of microscopic reconstruction of the hepatic artery, to approximately 4.4%, with a range of 0–20%.357 The incidence of PVT after LT was reported to be lower than that of HAT, which has been known to occur.209,210 Mechanical factors and hypercoagulopathy probably contribute to these thrombotic events.194 Because the outcomes of HAT and PVT with possible graft dysfunction are usually more serious209,214 than postoperative bleeding, the latter can be easily managed with blood product transfusion or surgical intervention. Therefore, preoperative and intraoperative prophylactic correction of the coagulopathy in patients undergoing LT is not recommended when there is no uncontrollable bleeding.199,194,215 It is also a preferred practice to send patients to the ICU with light prolongation of INR (international normalized ratio) of about 1.5 to 2
times.149,152 Early or immediate extubation is a trend in LT.312–316 Clinically, it is safe and improves the clinical result; it is also cost-effective by shortening the length of ICU stay.312–316

4. Conclusion

Deceased LT as well as LDLT is a complex and challenging procedure for surgeons and anesthesiologists. Live donor hepatectomy is usually performed without control of the hepatic inflow, but when it is carried out with strict adherence to a meticulous surgical technique and control of the intravascular volume by the anesthesiologist, it results in minimal blood loss without requiring blood transfusion. For the recipient, the amount of blood loss and blood transfusion has decreased in comparison with past levels; however, intraoperative bleeding is unpredictable and is still the main key problem in LT. The general consensus is reached in the use of red blood cells—from the threshold to the end target of hemotocrit—but controversy remains in the use of coagulation factors, such as FFPs, platelets, and cryoprecipitates. How and what is the best way to monitor the status of hemostasis, should the abnormal coagulation data be prophylactically corrected, and what is the appropriate amount and the target end point in treating coagulopathy during LT by using coagulation factors is still uncertain. Further research in this field is warranted.

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B. Jawan et al.