Anaesthesia for liver transplantation

ABSTRACT

Liver transplantation is a complex procedure that requires a truly multidisciplinary team approach with anaesthetic involvement from the outset in order to ensure excellent outcomes. Before a patient is placed on the waiting list for a liver transplant, a thorough evaluation is undertaken and his/her suitability for transplantation discussed in a patient selection committee meeting. The perioperative management of patients requiring transplantation can be challenging because of the systemic implications of liver disease, approaches to surgical technique and the quality of the grafts used; an increase in the use of marginal donor organs to meet the organ demand poses its own unique difficulties.

Indications for liver transplantation include chronic progressive liver disease and fulminant liver failure. Both disease states have multiorgan implications. The need for liver transplantation in chronic liver disease without hepatocellular carcinoma is based on the severity of liver dysfunction and is measured by scoring systems, e.g. model for end stage liver disease (MELD) scoring, which incorporates bilirubin level, international normalized ratio and creatinine level to assess the patient's risk of dying while awaiting a transplant. In the UK sodium levels are also used to give the United Kingdom model for end stage liver disease (UKELD) score; a score of greater than 49 predicts an annual mortality risk of 9% (Barber et al, 2011) which exceeds the first year mortality risk of undergoing liver transplantation hence is used as a threshold for liver transplantation listing. Thus patients with an expected survival of 90% or less within 1 year without transplantation and >50% survival at 5 years with transplant may be listed. There have been a number of advances in perioperative care and 1-year survival in the UK is 93.4% for elective non-super-urgent liver transplantation (Zarankaite et al, 2016).

The systemic implications of liver disease, the surgical approach and increasing use of marginal grafts pose a number of challenges for the anaesthetist. In addition patients who would previously not have been considered for liver transplant – older patients, those with multiple comorbidities and extremes of body mass index – are now considered eligible. A multidisciplinary approach with anaesthetic involvement from the outset is required to achieve excellent outcomes. The selection and listing procedure and surgical management is discussed in other articles in this issue but this article outlines the assessment and perioperative anaesthetic considerations in liver transplantation.

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Anaesthetic preoperative assessment and systemic implications of liver disease

Liver disease has multiorgan repercussions, and anaesthetic assessment and preoptimization are essential. Cirrhosis is the consequence of progressive destruction and regeneration of liver parenchymal tissue. Normal portal blood flow can become obstructed as a result of fibrosis, leading to portal hypertension and porto-systemic shunting via collateral vasculature. Porto-systemic shunting impacts on the cardiovascular, pulmonary, renal and neurological systems. Alongside these changes, destruction of liver parenchyma by acute and chronic processes causes an alteration in liver synthetic function which affects coagulation, protein synthesis and metabolism.

Cardiovascular complications of end-stage liver disease

Cardiac comorbidities are common among patients presenting for assessment for liver transplantation. Historically the high cardiac output state, low systemic vascular resistance and low cholesterol levels (as a result of reduced synthetic function) of cirrhosis were thought to protect against the development of coronary artery disease but it is now recognized that the prevalence of coronary artery disease in patients with end-stage liver disease is paradoxically high. This is in part because of the increase in age of those requiring transplant, a higher prevalence of patients with metabolic syndrome and diabetes, and consequently an increase in the diagnosis of non-alcoholic steatohepatitis as the cause of end-stage liver disease, as well as an increase in prevalence of traditional risk factors for coronary atherosclerosis such as smoking and hypertension. Carey et al (1995) describe a 13.3% incidence of moderate coronary artery stenosis on coronary angiography performed on patients awaiting liver transplant. Morbidity and mortality is significantly increased following orthotopic liver transplant in those with underlying coronary artery disease, hence the importance of thorough cardiovascular

investigation. Plotkin et al (1996) showed an overall all-cause mortality of 50% and morbidity of 81% in those with significant coronary artery stenosis (>70%) undergoing orthotopic liver transplantation.

Cirrhotic cardiomyopathy is a complex condition characterized by a blunted inotropic and chronotropic response to stress as a result of downregulation of the autonomic nervous system, impaired diastolic relaxation of the myocardium and prolongation of the QT interval in the absence of other known cardiac disease. Patients with this condition may be entirely asymptomatic until put under physiological stress. This is particularly relevant during the reperfusion stage of liver transplantation when a sudden increase in preload can lead to considerable cardiac embarrassment (Rahman and Mallett, 2015).

Portopulmonary hypertension and the hepatopulmonary syndrome

The prevalence of portopulmonary hypertension in those awaiting orthotopic liver transplantation is approximately 6%. Although the exact aetiology is unknown, in end-stage liver disease there is a reduction in the hepatic clearance of vasoactive substances leading to remodelling of the pulmonary vasculature. Pulmonary hypertension may develop with eventual right ventricular dysfunction. Portopulmonary hypertension is defined by portal hypertension (15 mmHg) and mean pulmonary artery pressure >25 mmHg or transpulmonary gradient >10 mmHg and pulmonary vascular resistance >240 dyn/s/cm^5. An elevated right ventricular systolic pressure (>50 mmHg) on transthoracic echo would trigger the decision for right heart catheterization studies. Portopulmonary hypertension with mean pulmonary artery pressure of 35–50 mmHg poses a higher risk for patients undergoing liver transplantation, with a longer post-liver transplantation period of ventilation and length of hospital stay, while a mean pulmonary artery pressure greater than 50 mmHg remains an absolute contraindication to liver transplantation in most centres. Portopulmonary hypertension patients with mean pulmonary artery pressure of 35 mmHg or more should be treated aggressively to improve the mean pulmonary artery pressure, pulmonary vascular resistance and right ventricular function (Aldenkortt et al, 2014; Krowka et al, 2016).

In hepatopulmonary syndrome vasoactive substances cause hypoxia as a result of intrapulmonary shunting of blood by intrapulmonary vascular dilatation. Diagnostic criteria for hepatopulmonary syndrome include a history of chronic liver disease, an alveolar–arterial oxygen gradient of >15 mmHg and right to left shunting on contrast-enhanced echocardiography. The shunt fraction may be quantified with a 99mTc macroaggregated albumin scan. The severity of hepatopulmonary syndrome is determined by the degree of hypoxaemia. Based on the European Respiratory Society Task force recommendations (Rodríguez-Roisin et al, 2004), severity is graded by partial pressure of oxygen (PaO_2) as:

- Mild (PaO_2 ≥80 mmHg)
- Moderate (PaO_2 = 60–79 mmHg)
- Severe (PaO_2 = 50–59 mmHg)
- Very severe (PaO_2 <50 mmHg).

Between 15 and 30% of those with liver disease have intrapulmonary vascular dilatation with associated hypoxaemia (Abrams et al, 1995). Most patients are asymptomatic, but may present with dyspnoea and platypnoea (shortness of breath relieved by lying flat). Orthodeoxia (a fall in arterial oxygen on standing upright) can be confirmed with arterial blood gas measurement on standing and lying, and correction of hypoxia with blood gases on and off 100% oxygen. It is essential to diagnose hepatopulmonary syndrome as it is a significant cause of poor outcomes in patients with end-stage liver disease but can be reversed by liver transplantation.

Cardiovascular evaluation of liver transplant patients

Cardiovascular investigations in the preoperative setting include an electrocardiogram to assess for electrophysiological abnormalities and a transthoracic echocardiogram to assess underlying systolic and diastolic ventricular function, valvular abnormalities, pulmonary artery pressure and to exclude a pericardial effusion. Further testing is dependent on local institutional protocols but, in line with American College of Cardiology/American Heart Association (Fleisher et al, 2014) and European Society of Cardiology (Kristensen et al, 2014) guidelines, should include non-invasive stress testing such as a dobutamine stress echocardiogram (high negative predictive value) to assess for myocardial ischaemia if there are multiple risk factors for coronary artery disease.

For those patients deemed intermediate or high risk for coronary artery disease, a coronary angiogram is advocated in consultation with a cardiologist.

Cardiopulmonary exercise testing

An individual's risk of morbidity and mortality postoperatively can be gauged with the estimation of preoperative functional performance. The severity of pre-existing cardiac or respiratory disease and the functional ability of individuals to manage the extra metabolic demands caused by stress can be estimated with the use of cardiopulmonary exercise testing. This is an objective way of assessing functional status and involves the patient performing exercise on standardized equipment while inspired and expired gases, electrocardiogram, non-invasive blood pressure and oxygen saturations are measured continuously. The anaerobic threshold is the point when carbon dioxide production increases beyond oxygen consumption, signifying a dominance of anaerobic over aerobic metabolism, and is a marker of cardiorespiratory fitness. Patients with impaired aerobic capacity as measured by low peak oxygen consumption (VO_2peak) and a low anaerobic threshold (<9 ml/min/kg) have prolonged

hospitalization after liver transplantation, and a higher postoperative mortality (Epstein et al, 2004; Prentis et al, 2012; Bernal et al, 2014).

Haematology and rebalanced haemostasis

Preoperative anaemia is an independent risk factor for poor outcome in patients undergoing major non-cardiac surgery (Musallam et al, 2011). Patients with end-stage liver disease may be anaemic for a variety of reasons and preoptimization of anaemia on listing for orthotopic liver transplantation is essential. Low haemoglobin levels, mean cell volume and a low ferritin level are indications for iron therapy. Oral iron is low cost and has been a long-standing treatment, but patient compliance can be problematic. Adequate absorption of oral iron can also be variable, particularly in the face of inflammation or malignancy. Inflammation leads to upregulation of hepcidin, an endogenous inhibitor of gastrointestinal iron absorption. Parenteral iron is effective in the treatment of iron deficiency and with significantly lower side effects than oral preparations (Tolkien et al, 2015). Newer parenteral preparations can be administered over 15 minutes and have a good safety profile.

Portal hypertension can lead to splenomegaly and sequestration of platelets, rendering patients thrombocytopenic, a relatively common feature of end-stage liver disease. However, there is an increase in the concentration of von Willebrand factor, which may contribute to adequate platelet function.

In-vitro tests of coagulation, including prothrombin time, international normalized ratio and activated partial thromboplastin time, are generally found to be deranged in the end-stage liver disease population. This is caused by a reduction in hepatic synthesis of clotting factors. They can be used in scoring systems (as above) to predict outcome, but they are not good predictors of bleeding risk in patients with liver disease (Mallett et al, 2013). Thrombin generation, both in vivo and in vitro, is downregulated by thrombomodulin. On assessment of prothrombin time, thrombomodulin is not factored in and hence the validity of tests such as prothrombin time for assessing the risk of bleeding is questioned. These conventional tests of coagulation poorly reflect the coagulation system as a whole. The haemostatic system in cirrhosis is actually rebalanced with a reduction in both procoagulant and anticoagulant factors such as antithrombin and protein C. Studies have shown thrombin generation (the final enzyme of coagulation) in plasma from patients with cirrhosis to be as much as that from healthy people (Tripodi et al, 2005). Therefore, bleeding in this population can be attributed to other causes such as endothelial dysfunction or vascular changes associated with portal hypertension. However, because of the relative deficiency of both pro- and anticoagulant factors, the balance of haemostasis in end-stage liver disease is fragile and these patients can be easily tipped into either a hypo- or hypercoagulable situation.

Renal and electrolyte disturbance

There is a significant increase in risk of postoperative cardiovascular events and risk of mortality linked to identification of renal impairment before orthotopic liver transplantation. A meta-analysis suggested a 7-fold increase in the risk of death in patients with cirrhosis and renal impairment, with 50% of patients dying within 1 month of a diagnosis of renal impairment (Fede et al, 2012). The aetiology of renal impairment includes sepsis, hypovolaemia and hepatorenal syndrome.

For a diagnosis of hepatorenal syndrome there must be a history of acute or chronic liver failure and portal hypertension, a reduced glomerular filtration rate, minimal proteinuria (<0.5 g/day) and an absence of a history of infection, nephrotoxic drug use and hypovolaemia. There must be no sustained improvement in renal function with intravenous fluid challenges. The pathogenesis of hepatorenal syndrome is related to a reversible renal vasoconstriction thought to be caused by a decrease in renal perfusion pressure, an increase in renal sympathetic activity and an increase in humoral and renal vasoactive mediators (Dagher and Moore, 2001).

In cirrhosis, renal dysfunction is often the result of hypovolaemia, use of nephrotoxic drugs or bacterial sepsis, and management is centred on optimizing fluid management and treating these underlying causes. Blood pressure (and hence renal perfusion pressure) should be optimized; management of abdominal compartment hypertension should be resolved by paracentesis. Renal replacement therapy or support can be considered as a bridge to either liver transplantation (and therefore relief of hepatorenal syndrome) or hepatic recovery.

Deranged electrolytes are common in liver disease and require careful correction because of the risks associated with rapid fluctuations in concentration. Hyponatraemia is seen in association with portal hypertension, ascites and diuretic use. The correction of sodium should be no greater than 12 mmol/litre in 24 hours to prevent the development of central pontine demyelination.

Hyperkalaemia results from either an increased potassium load or from reduced clearance. Preoperative optimization of hyperkalaemia is essential as there are predictably transcellular potassium shifts and an increased potassium load at reperfusion of the donor liver. Severe hyperkalaemia may introduce myocardial depression, arrhythmia and cardiac arrest.

Citrate metabolism occurs in the liver, and therefore can be deranged in end-stage liver disease. As a consequence, citrate delivered to the perioperative patient within blood transfusions can lead to ionized hypocalcaemia. Baseline calcium levels should therefore be checked before orthotopic liver transplantation.

Intraoperative management

There is a significant variation in the conduct of anaesthesia during orthotopic liver transplantation between centres within the UK and beyond, and it is unclear whether

one particular method of anaesthesia leads to better outcomes than others. Preoperative checks, with the use of the World Health Organization checklist, should be performed before induction of anaesthesia. Standard monitoring including 5-lead electrocardiogram, oxygen saturation measurement and non-invasive blood pressure monitoring is instituted. In general, anaesthetic induction is in a cardio-stable manner with the use of drugs such as short-acting opioids (e.g. fentanyl), benzodiazepines (e.g. midazolam) and anaesthetic induction agents (e.g. propofol). Non-depolarizing muscle relaxants are used to enable the patient's airway to be secured. Maintenance of anaesthesia is continued with inhalational anaesthetics.

Appropriate venous access and methods of invasive monitoring are promptly introduced. A multi-lumen internal jugular line together with a large bore central or peripheral rapid infusor line is sited for measurement of central venous pressure, intraoperative infusion of drugs and rapid infusion of fluid and blood products. Radial arterial line insertion allows for beat-by-beat blood pressure monitoring and sampling of blood for point of care analysis at each stage of the operation. In some centres, a pulmonary artery catheter is placed to permit cardiac output and pulmonary artery pressure monitoring where there are concerns around pulmonary hypertension. Alternative semi-invasive methods of cardiac output monitoring using pulse contour analysis such as LiDCO and FloTrac may also be considered. Perioperative transoesophageal echocardiography permits the assessment of intravascular volume status, right ventricular dysfunction, regional wall motion abnormalities indicative of cardiac ischaemia and may detect the formation of thrombi or emboli.

There must be meticulous attention to positioning of the patient, padding of pressure areas and protection of lines from manipulation post-application of sterile drapes.

Point of care tests including arterial blood gas analysis and viscoelastic tests such as thromboelastography are used in many centres to guide electrolyte and blood product management.

Viscoelastic tests of whole blood dynamic clot function allow evaluation of the kinetics of clot formation including initial formation of a clot and the maximal strength of the clot, thus providing a better picture of the interaction between clotting products, blood cells and platelets as well as the degree of fibrinolysis (*Figure 1*). Viscoelastic tests can also be modified to give an indication of fibrinogen concentration and an assessment of platelet function. Point of care testing-based management of coagulation reduces blood transfusion rates as well as perioperative blood loss (Agarwal et al, 2013). Variations in haemostatic profiles on thromboelastography are demonstrated in *Figure 1*.

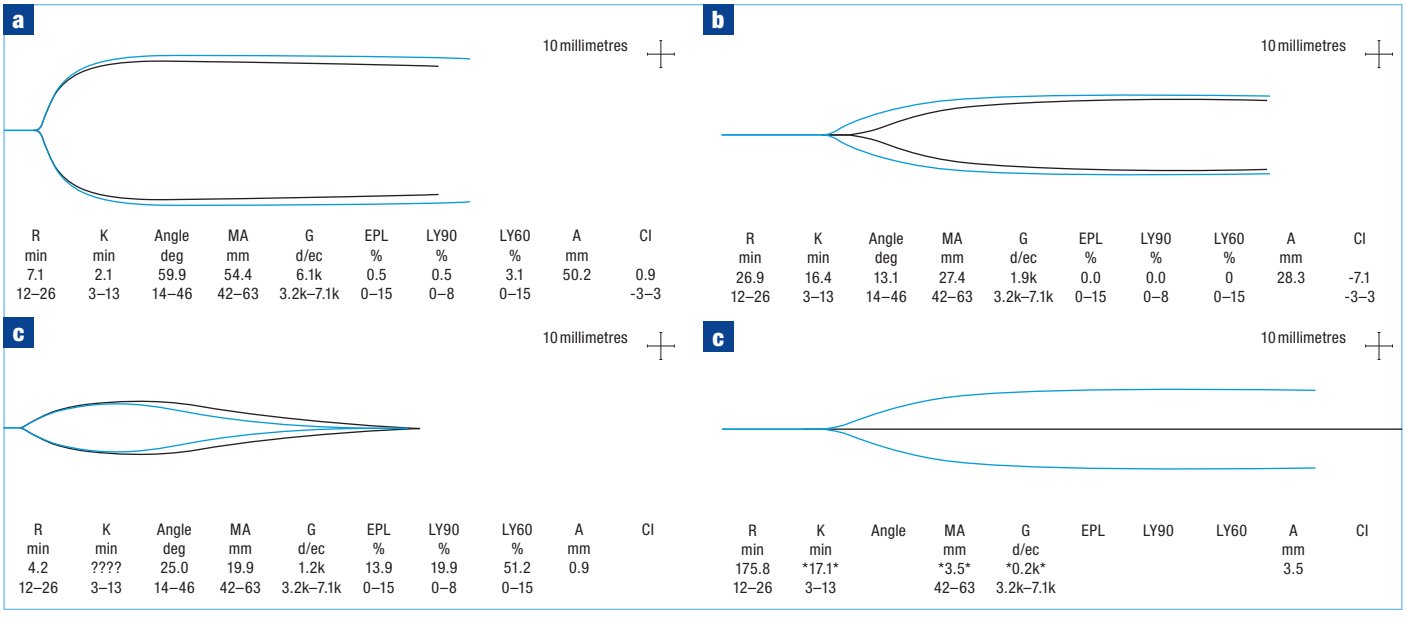
Cell salvage is used routinely in liver transplantation (hepatocellular carcinoma is not considered to be a contraindication) and has reduced the transfusion of allogeneic blood.

The operative procedure, which is described in more detail in a linked article in this issue, is divided into phases and each phase has its own challenges for the anaesthetist.

Dissection phase (phase I)

The dissection phase begins at knife to skin and ends upon clamping of the blood vessels supplying the native liver. On opening the abdomen, ascites is drained and large volume shifts may occur. Adhesions are broken down, biliary and vascular structures are identified and the liver is mobilized

Figure 1. Examples of thromboelastography traces. a. Normal trace. b. Hypocoagulable trace, long r time (reduced clotting factors), low MA (hypofibrinogenaemia and/or thrombocytopaenia). c. Fibrinolysis. d. Heparin effect – black trace is caused by endogenous heparinoids reversed by heparinase in green trace thromboelastogram. EPL = estimated per cent lysis; G value = clot strength; k = constant – time taken for trace to reach 20 mm amplitude; Ly60 = per cent lysis at 60 minutes; Ly90 = per cent lysis at 90 minutes; MA = maximum amplitude; r time = reaction time.



in preparation for removal. There may be significant blood loss during this phase, particularly in patients with severe portal hypertension, intra-abdominal varices and venous congestion.

To limit surgical bleeding during the dissection phase excessive fluid administration should be avoided. Fluid can be titrated to a lower central venous pressure and the use of vasopressors and octreotide rather than fluid is advocated to maintain normotension. This avoids splanchnic pooling and congestion but this must be balanced with achieving an appropriate preload in anticipation of the next phase.

Anhepatic phase (phase II)

The anhepatic phase commences when the blood supply to the native liver is occluded and ends when reperfusion of the donor liver occurs. A caval replacement technique (resection of the intrahepatic inferior vena cava and caval bypass) with clamping of the inferior vena cava can lead to haemodynamic disturbance with a reduction of preload by up to 50%. Caval preservation with side-to-side anastomosis ('piggy back' technique) causes considerably less haemodynamic instability and intraoperative blood loss.

The lack of a functioning liver in the anhepatic phase can cause a significant derangement in physiology. An absence of clotting factor including fibrinogen and anticoagulant factor synthesis leads to a coagulopathic state or even a prothrombotic state if the haemostatic balance is tipped. Hyperfibrinolysis may be induced by an increase in tissue plasminogen activator concentrations and its inhibitors and is usually seen towards the end of stage II and early stage III. Tissue plasminogen activator is released by the new graft and mesenteric vessels particularly on reperfusion, possibly in response to ischaemia. Fibrinolysis can be limited with the use of antifibrinolytics such as tranexamic acid, and replacement of fibrinogen with concentrate (Xia and Steadman, 2005). Antifibrinolytics are used routinely in some centres and in other centres only with evidence of fibrinolysis on thromboelastography and surgical bleeding.

Owing to a lack of metabolic function when anhepatic, levels of citrate and lactate build up, causing acidosis. Circulating citrate ions mop up any ionized calcium, leading to a significant reduction in levels of calcium available for homeostasis. There is also a reduction in gluconeogenesis and glucose uptake. Regular point of care testing allows monitoring and management of the derangement of electrolytes such as calcium and glycaemic control.

Slow intravenous calcium can be delivered to replace a reduced circulating calcium concentration. Methylprednisolone 1 g is administered before reperfusion of the new liver to protect the graft from ischaemic reperfusion injury but also to start immunosuppression. In preparation for the reperfusion phase, potassium concentration should be <4.0 mmol/litre – this may require the use of Actrapid (insulin) and glucose, loop diuretics, beta-2 agonists or bicarbonate boluses and in extreme cases haemofiltration. Profound metabolic acidosis is addressed with the use of bicarbonate solutions if necessary.

Reperfusion phase (phase III)

On completion of the vascular anastomoses, the reperfusion phase begins. The donor liver is perfused with the recipient's blood and there is a sudden release of perfusion fluid into the systemic circulation. This fluid has a high potassium and acid load; it is cold and may contain microemboli, all of which predispose to a subsequent post-reperfusion syndrome.

Post-reperfusion syndrome is defined by severe haemodynamic instability with persistent hypotension (>30% decrease in mean arterial pressure within 5 minutes of reperfusion sustained for at least 1 minute) in association with asystole or other significant arrhythmia (Aggarwal et al, 1987). Physiological changes suggestive of post-reperfusion syndrome include severe systemic hypotension, bradyarrhythmia, increased central venous pressure and increased pulmonary artery pressure. It is a difficult condition to predict, with age of the liver donor seeming to be the only identifiable predictor. With an increase in use of marginal grafts to accommodate the increased demand for liver transplantation, this syndrome is likely to be encountered more often (Ramsay, 2008; Siniscalchi et al, 2016).

Management at reperfusion includes close collaboration with surgeons for the timing of release of the clamp. A pre-emptive bolus of calcium chloride is given to counteract acid and potassium and hence prevent potassium-related cardiac arrhythmia, and hypotension is managed with vasopressor support. Reduced systemic vascular resistance and hypotension can continue for over an hour, hence continuing vasopressor infusion. There may be a requirement for bridging bicarbonate boluses to manage acidosis until the new liver begins to function. Once the new donor liver begins to function, lactate metabolism commences and bicarbonate production increases which buffers excess acidaemia. Clotting factor and fibrinogen production are reinstated and coagulopathy improves. Initial features of primary graft dysfunction include continuing coagulopathy, worsening metabolic acidosis and an absence of bile production. Primary graft dysfunction can be an early indicator of primary graft non-function, the incidence of which is up to 7% (Mor et al, 1992), and may necessitate early re-transplantation.

Primary graft dysfunction is more common in marginal or extended criteria grafts and those with a prolonged cold ischaemia time. These grafts may present significant haemodynamic changes, coagulopathic changes (particularly marked fibrinolysis) and metabolic derangement. The anaesthetic challenges of managing these grafts in patients with multiple comorbidities and high MELD scores are manifold and donor–recipient matching is crucial.

Postoperative management

The key management goals postoperatively include consideration of early extubation, management of coagulopathy, limitation of risks of thrombosis in hepatic vasculature and monitoring of graft function. The postoperative care of patients on the intensive care unit is covered in another article.

Conclusions

The thorough assessment of patients before orthotopic liver transplantation is key in the preoptimization of individuals and planning anaesthetic management. Liver disease has repercussions for many organ systems and an understanding of the physiological consequences of end-stage liver disease and its impact on risk is vital. Each phase of liver transplantation has pitfalls that must be recognized and acted upon early. Tools such as cardiac output monitoring, point of care testing and viscoelastic testing have assisted with the successful perioperative management of patients. Future challenges lie with the increase in use of marginal donor grafts to meet the ever-increasing recipient demand. **BJHM**

Conflict of interest: none.

KEY POINTS

- Liver transplantation is a multidisciplinary intervention with anaesthetic involvement from the outset.
- One-year survival following liver transplantation is currently greater than 90%.
- Liver disease has multiorgan repercussions and anaesthetic assessment and preoptimization are essential.
- There is a significant variation in the conduct of anaesthesia between centres within the UK and beyond, and it is unclear whether one particular method of anaesthesia leads to better outcomes than others.
- Increasing use of extended criteria or marginal grafts poses increasing challenges for the anaesthetist.
- The operative procedure is divided into phases and each phase has consequences that the anaesthetist has to be aware of and prepared for.

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