Anaesthesia for liver transplantation

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Key points

- Liver transplant outcomes continue to improve. A recent national UK audit showed 90 day survival >95%.
- Despite increasing numbers of transplants performed, the gap between supply and demand continues to grow. The UK lags behind many other high-income countries.
- Patients with end-stage liver disease exhibit multi-system pathophysiological changes.
- Potential recipients require comprehensive multi-disciplinary assessment before being placed on the waiting list. The assessment may include cardiopulmonary exercise testing and/or invasive tests, e.g. stress echocardiography or coronary angiography.
- Operative technique is developing continually, particularly regarding venous reconstruction. These developments impact upon anaesthetic technique and transfusion support.

Mortality rates after liver transplantation (LT) have steadily improved in recent years as units continue to gain more experience. A prospective cohort study of 7906 liver transplants in the UK and Ireland showed an unadjusted 90 day mortality rate for first elective LT of 10.2% for the period 1994–6,1 decreasing to 3% for 2013–4.2 Seven UK centres performed 914 LT procedures during 2013–4,3 compared with 602 in 2005–6, with much of the increase occurring after a national initiative to increase donation rates.1 3 This improvement is attributed to improved surgical techniques, better recipient selection, and advances in anaesthetic and intensive care management. However, LT remains a complex undertaking—older patients, those with progressively more severe co-morbidity, and those with previous complex abdominal surgery (including previous LT) are now considered eligible. An important remaining outcome determinant is graft quality. There are three types of grafts used commonly: donation after brain death, donation after cardiac death, and living related donation (LRD). LRD, and also split liver donation where a cadaveric graft is divided for two recipients, have helped increase graft supply, but at the cost of increased complexity.

LT remains the treatment of choice for end-stage liver disease (ESLD), and there is still a gap between supply and demand. After revision of the patient selection criteria in 2007, the number of patients awaiting LT has more than doubled, with a 12% 1 yr mortality rate on the waiting list.4 The UK annual LT rate of 11.5 per million population (pmp) furthermore still compares poorly with other high-income countries, for example, 20.7 pmp in Spain and 19.7 pmp in the USA.

This article gives an overview of the ESLD pathophysiology relevant to anaesthesia. We will also describe the preoperative evaluation and recipient selection process, and how the surgical technique impacts upon anaesthetic management and transfusion support for LT.

Pathophysiology of ESLD relevant to anaesthesia

Liver failure may be acute or chronic—we will first consider ESLD related to chronic liver disease since this is the most common group of indications for LT.

Portal hypertension

The predominant pathophysiological manifestation of ESLD is portal hypertension. This occurs both as result of increased flow and increased resistance of the portal venous system.4 Splanchnic venous congestion causes splenomegaly and varix formation in the abdomen and around the oesophagus—oesophageal variceal haemorrhage is common and related to the severity of liver disease. Increased splanchnic hydrostatic
pressure and decreased plasma oncotic pressure from hypoproteinemia lead to the formation of ascites.

Cardiorespiratory changes
Hepatic dysfunction leads to disturbed nitric oxide (NO) production and consequent peripheral vasodilatation with reduced systemic vascular resistance (SVR). A redistribution of blood occurs away from the central compartment and towards the peripheral and splanchnic venous beds. A hyperdynamic circulation therefore commonly occurs in ESLD. Over the longer term, altered volume status and the cardio-depressant properties of circulating inflammatory mediators cause cardiac remodelling, repolarization changes, and a blunted ventricular response to stress—termed cirrhotic cardiomyopathy. Dynamic outflow tract obstruction may also occur as a result of the hyperdynamic circulation. Non-selective β-blocker therapy is commonly used for the control of portal hypertension and the prevention of variceal haemorrhage; these drugs may however further blunt the ventricular stress response. Ascites-related diaphragmatic splitting is common. In addition, two specific pulmonary vascular disorders occur in ESLD: porto-pulmonary hypertension (PoPH) and hepatopulmonary syndrome (HPS).

Pulmonary hypertension
True PoPH occurs in around 4–6% of ESLD patients. Patients may also have elevated pulmonary pressures as a result of the hyperdynamic circulation alone (pseudo-PH). In true PoPH, the pulmonary vascular resistance is increased and pulmonary artery pressure (PAP) is high, despite normal pulmonary capillary wedge pressure. Severe PoPH, particularly with right ventricular pressure overload, carries a poor prognosis, although phosphodiesterase inhibitor therapy may be effective.

Hepatopulmonary syndrome
The prevalence of HPS in patients with ESLD is as high as 20%. The condition is characterized by disordered pulmonary capillary vasodilatation and ventilation–perfusion mismatch. Less commonly, subpleural arteriovenous communications may also occur. Its pathogenesis involves release of hepatic endothelin-1, with consequent pulmonary endothelial NO production. Patients with HPS present with hypoxia, and also exhibit orthodeoxia, a decrease in arterial oxygen saturation on standing up, when reduced systemic pressure permits increased right-to-left shunt. The diagnosis is confirmed through bubble echocardiography. The presence of HPS is an additional risk factor for early post-transplant mortality, but if LT is successful, the condition resolves over time.

Haematological changes
ESLD impacts significantly on the haematological system, and the severity of pre-transplant liver disease [e.g. as reflected by the Child–Pugh or model for end-stage liver disease (MELD) score] is strongly predictive of the need for perioperative transfusion support. Before operation, anaemia is common because of splenic red cell sequestration, malnutrition, and chronic bleeding. Hypersplenism and immunoglobulin-mediated platelet destruction cause thrombocytopenia. Platelet aggregation and adhesion may be inhibited, even where the platelet count is normal. Impaired synthesis of pro-coagulant factors and anti-coagulant proteins and fibrinolytic factors occur. The result is that coagulopathy is common in ESLD but is often not reflected well in standard laboratory tests. The rebalancing of coagulation homeostasis may make some patients hypercoagulable and at risk of thrombosis; again this is often only revealed on functional testing.

Pathophysiology of acute liver failure
Acute, or ‘fulminant’, liver failure (ALF) occurs when a previously normal liver fails over days or weeks. The pathophysiology of ALF is related to toxin release from the necrotic liver and adverse metabolic effects of rapid liver function loss. Microcirculatory changes and decreased SVR cause a clinical picture similar to that of septic shock. Encephalopathy and cerebral oedema occur and increased intracranial pressure is often the mode of death. In addition, the immune system is affected and sepsis may consequently complicate the course of ALF.

Preoperative evaluation and recipient selection
Process
Potential LT recipients are assessed, before being placed on the waiting list, by a multi-disciplinary team (MDT) consisting of:

- hepatologist,
- transplant surgeon,
- anaesthetist,
- intensive care physician,
- transplant co-ordinator,
- other health and social care professionals as required, e.g. psychologist, social worker, dietitian, or substance misuse specialist.

The hepatology assessment concentrates mainly on establishing whether there is a solid indication for transplant. The rest of the MDT assessment usually follows only at the request of a hepatologist. The surgical and anaesthetic assessments concentrate, respectively, on the technical feasibility and overall risk of transplantation. Intensivists are involved in the assessment of the overall risk of transplantation in some centres. Assessment, investigation, and counselling are often achieved by means of a short elective inpatient stay, with outpatient services offered where practicable. Individual patient decisions are made at MDT meetings in accordance with regularly updated national selection policies.

The team decision balances the strength of the indication, life expectancy without transplant, expected surgical risk, and risk from comorbidity. Patients thought unlikely to survive for at least 5 yr after transplant are not usually considered. The MDT also advises on graft selection, since not all types of graft are suitable for all recipients.

Patients awaiting LT require relative prioritization to ensure equitable access to a limited supply of organs. The MELD score is derived from the patient’s serum bilirubin, creatinine, and international normalized ratio (INR) of the prothrombin time, is predictive of survival without LT. It is extensively used in North America, including for decisions about graft allocation. The UK Model for End-Stage Liver Disease (UKELD) score is used in recipient selection and prioritization in the UK. It is derived from the patient’s serum sodium, creatinine, bilirubin, and INR. A UKELD of 49 or greater predicts a 1 yr mortality rate of >9% without transplant; this is currently the lowest UKELD within the listing criteria. A UKELD score of 60 predicts a 50% chance of 1 yr survival. Recipients may thus also be prioritized according to their UKELD score. Patients with primary liver tumours do not exhibit the biochemical changes in the above scoring systems while they may still benefit from LT. The Milan criteria are...
commonly used to select such patients for LT. Those with a single tumour of 5 cm or less, or up to 2–3 tumours all between 1 and 3 cm in diameter, are usually considered to qualify. If a centre wishes to register a patient who does not satisfy any of the above criteria for transplant, a request may be made for consideration by a national appeals panel.

### Preoperative evaluation

Cardiopulmonary events are the leading cause of non-graft-related deaths in LT, and the assessment therefore includes detailed evaluation of cardiovascular function and physiological reserve. Most centres have pre-defined routine investigations for potential transplant recipients (Table 1). Functional testing is also recommended for LT candidates. In patients placed on the waiting list, investigations are repeated periodically if the patient waits for more than 6 months, or if their condition changes.

#### Echocardiography

Screening echocardiography is indicated in order to quantify ventricular function, valvular anatomy, the presence or absence of outflow tract obstruction, and estimate PAP.13

Dobutamine stress echocardiography (DSE) has been recommended over other pharmacologically stressed imaging modalities13 and is presumed to replicate the physiological changes seen during LT. It has good negative but poor positive predictive value for postoperative cardiac events. High rates of chronotropic incompetence (an inability to achieve target heart rate with pharmacological stimulation) limit the usefulness of DSE. However, chronotropic incompetence itself has also been found to predict all-cause poor outcomes.13

#### Cardiopulmonary exercise testing

An increasing body of literature supports the use of cardiopulmonary exercise testing (CPET) for risk stratification in major non-cardiac surgery. In ESLD, functional capacity predicts survival both with4 and without15 LT. Consequently, CPET now forms part of the routine preoperative evaluation in some LT centres. In ESLD, poor skeletal muscle function, the presence pleural effusion or ascites, or β-blocker therapy may influence the result. However, the data may still be useful and effusions are sometimes electively drained in order to allow assessment of the patient’s underlying physiological reserve. More research is needed to determine how (if at all) information obtained at CPET should be integrated into recipient selection, graft allocation, or both.

#### Coronary angiography

The liver–transplant-specific literature on coronary angiography, revascularization, or both is scant, but patients with coronary artery disease (CAD) have worse outcomes from LT than those without.16 Candidates with a positive non-invasive test should therefore be considered for coronary angiography. An individual decision must be made in consultation between the LT MDT and a cardiologist, which balances procedure risk against possible benefit, both from LT and from optimal management of the patient’s CAD. In ESLD, coronary artery bypass has poor outcomes but coronary stenting (with a bare-metal stent if LT is to be considered) may be beneficial.16

#### Evaluation of the pulmonary circulation

Screening trans-thoracic echocardiography should include PAP estimation where possible; however, the value is usually over-estimated. Mild to moderate PoPH is not a contraindication to LT, but patients may nevertheless benefit from specialist referral and phosphodiesterase inhibitor therapy. Severe PoPH (mean PAP >50 mm Hg), particularly with evidence of RV failure, is a contraindication to LT as the early post-transplant mortality rate is unacceptably high. Where severe PH is suspected, patients are usually subjected to right heart catheterization to confirm or refute the diagnosis of PoPH before being considered for LT. PoPH usually does not resolve, even after successful LT.

#### Intraoperative management

A recipient is ‘called in’ when a suitable graft becomes available and up-to-date investigation results are obtained as necessary. There is usually adequate notice for the patient to be starved, while the organ is retrieved and transported.

#### Conduct of anaesthesia

LT is performed under balanced general anaesthesia with the use of invasive monitoring, and facilities available for the rapid

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### Table 1 Screening investigations

<table>
<thead>
<tr>
<th>Blood tests</th>
<th>Urea, creatinine, serum electrolytes</th>
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<tbody>
<tr>
<td>Full blood count, prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen level</td>
<td></td>
</tr>
<tr>
<td>Liver function test (LFT)</td>
<td>Spirometry</td>
</tr>
<tr>
<td>Chest X-ray (CXR)</td>
<td>Spirometry</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Cardiac evaluation</td>
</tr>
<tr>
<td>Cardiac evaluation</td>
<td>12-lead ECG</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing (CPET)</td>
<td>Cardiopulmonary exercise testing (CPET)</td>
</tr>
<tr>
<td>Respiratory evaluation</td>
<td>Abdominal ultrasound—assess liver, presence of ascites</td>
</tr>
<tr>
<td></td>
<td>Abdominal magnetic resonance imaging (MRI)—liver anatomy</td>
</tr>
<tr>
<td></td>
<td>Doppler ultrasound to determine patency of portal vein/hepatic artery (if not adequately shown on MRI)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Psychosocial assessment</td>
<td>Nutritional assessment, including assessment of muscle mass and strength (hand grip strength)</td>
</tr>
</tbody>
</table>
administration of salvaged blood, donated red cells, and other components. Large-bore peripheral access is obtained before induction and central venous and arterial cannulae are usually placed asp. The indications for rapid sequence induction are as usual. Anaesthesia is usually maintained with a volatile agent. The exception is ALF, where controversy exists over whether volatile agents worsen intracranial pressure, even where hypercapnia is avoided.

Orthotopic LT requires recipient hepatectomy followed by multiple vascular anastomoses and bile duct reconstruction. The portal venous system supplies circa 70% of hepatic blood flow. Venous anatomy is usually reconstructed first to achieve reperfusion, followed by arterial and biliary tree reconstruction. ‘Reperfusion syndrome’ occurs after revascularization of the graft. It presents as severe cardiovascular instability and may be accompanied by asystole or significant arrhythmias (usually secondary to sudden hyperkalaemia) and development of significant fibrinolysis requiring treatment.

The surgical phases, and common anaesthetic problems encountered, are detailed in Table 2.

Venous reconstruction technique and anaesthetic implications

Surgical practice has changed considerably over the last decade, particularly with regard to venous reconstruction. The classic technique (Fig. 1a) involves resection of the intrahepatic portion of the recipient’s inferior vena cava (IVC) with hepatic veins in situ. A section of donor IVC is left attached to the graft liver and used to bridge the gap (IVC replacement). During portal vein and IVC cross-clamping, a significant decrease in venous return occurs as fluid is sequestered in the gut and lower limbs, reducing the effective circulatory volume. The liberal use of resuscitation fluid may cause fluid overload when caval flow is restored. Engorgement of the vulnerable graft is a particular concern, with consequent delayed function or non-function. Venovenous bypass (VVB) may be used to maintain venous return when IVC replacement LT is performed. Bypass cannulae are placed in the IVC (usually via a femoral vein) and portal vein, and blood is mechanically pumped to the superior vena cava (SVC), either via a surgically placed or percutaneous cannula. This gives optimal operating conditions and ameliorates the haemodynamic changes described above. However, there is morbidity and mortality related to the technique itself, and no convincing evidence of improved patient outcomes. Consequently, considerable variation in practice exists between centres.

A newer surgical technique (Fig. 1b) involves side-clamping of the IVC, with a cavotomy and implantation of donor liver left attached to a patch or segment of IVC with cava-cavostomy if necessary—known as ‘piggy-back LT’. Piggy-back LT usually leaves an effective recipient caval diameter of around 50% of normal even during the anhepatic phase. This preserves some venous return, decreases bleeding, and shortens the graft warm ischaemic time, although the evidence is equivocal regarding whether recipient outcome is improved. Surgical porta-caval shunt placement, if used, further preserves venous return and decreases bleeding, resulting in shorter intensive care unit (ICU) stay. VVB is thus used increasingly selectively. It is considered when prolonged portal clamping is anticipated, when IVC replacement is needed, or to limit fluid shifts in patients with PoPH, who are at risk of RV overload after reperfusion, in Budd–Chiari syndrome, or in re-do LT.

Haemodynamic monitoring

Traditionally, pulmonary artery catheters (PAC) were widely used in LT. Less invasive cardiac output monitors (e.g. the various pulse contour analysis devices) have now replaced the PAC in many centres, except where significant concern over pulmonary hypertension exists. However, this occurs rarely in view of the fact that patients with severe PoPH at preoperative assessment are unlikely to be considered transplantable.

There is increasing interest in the use of intraoperative transoesophageal echocardiography (TOE) during LT. TOE allows direct evaluation of ventricular size, filling, and muscle function.

Table 2 Surgical phases of liver transplant procedure and common anaesthetic problems

<table>
<thead>
<tr>
<th>Phase</th>
<th>Surgical details</th>
<th>Common anaesthetic problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-anhep</td>
<td>Inverse T or extended/bilateral subcostal incision</td>
<td>Haemorrhage from dissection, varices, and adhesions</td>
</tr>
<tr>
<td></td>
<td>Mobilization of the structures around the liver and porta hepatitis</td>
<td>Haemorrhage exacerbated by pre-existing coagulopathy</td>
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<tr>
<td></td>
<td>Hepatic artery and bile duct divided</td>
<td>Cardiovascular instability from ascitic decompression</td>
</tr>
<tr>
<td>Anhepatic</td>
<td>Portal vein and hepatic veins divided</td>
<td>Low SVR state causes hypotension, exacerbated by maldistribution</td>
</tr>
<tr>
<td></td>
<td>Explantation of native liver</td>
<td>of blood away from central compartment towards splanchic</td>
</tr>
<tr>
<td></td>
<td>IVC preparation for implantation</td>
<td>circulation</td>
</tr>
<tr>
<td></td>
<td>New liver inserted. Caval and portal anastomoses fashioned</td>
<td>Over-treatment with fluid, blood components, or both may cause</td>
</tr>
<tr>
<td></td>
<td></td>
<td>splanchnic congestion and exacerbates bleeding</td>
</tr>
<tr>
<td>Neo-hepatic</td>
<td>Graft reperfusion</td>
<td>No production of clotting factors, fibrinogen deficiency, and</td>
</tr>
<tr>
<td></td>
<td>Hepatic artery anastomosis</td>
<td>worsening coagulopathy</td>
</tr>
<tr>
<td></td>
<td>Biliary reconstruction</td>
<td>Progressive hypocalcaemia</td>
</tr>
<tr>
<td></td>
<td>Good graft function suggested by production of bile, decreasing serum lactate,</td>
<td>Absent citrate/lactate metabolism, reduced gluconeogenesis,</td>
</tr>
<tr>
<td></td>
<td>normalization of serum calcium and resolution of CVS instability</td>
<td>increasing serum lactate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Worsening metabolic acidosis</td>
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<tr>
<td></td>
<td></td>
<td>Surgical haemorrhage</td>
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<tr>
<td></td>
<td></td>
<td>Hypotension and further decrease in SVR</td>
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<tr>
<td></td>
<td></td>
<td>Sudden preload increase at reperfusion</td>
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<tr>
<td></td>
<td></td>
<td>Abrupt K+ increase at reperfusion with possible arrhythmia or</td>
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<tr>
<td></td>
<td></td>
<td>cardiac arrest</td>
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</table>
It may also detect thrombus or air embolus as a cause for haemodynamic instability. The drawbacks are that the technique requires specific expertise and that it has major resource implications in terms of personnel availability and equipment. Concern also exists that TOE may cause harm in patients with vulnerable oesophageal varices.

Transfusion support and fluid management

As described above, preoperative coagulopathy is common. It often worsens further during the anhepatic phase, at reperfusion, or during haemorrhage, which may occur at any stage of the operation. After reperfusion, hyper-fibrinolysis may occur and variable heparin-like substances are released from the previously ischaemic graft. The result is that coagulation disturbances in LT are complex, often not adequately reflected in standard laboratory tests, and evolve rapidly. Transfusion management and measures to decrease blood loss are thus primarily based on clinical judgement, aided by timely coagulation tests. Point-of-care coagulation monitoring, e.g. with thrombo-elastography or rotational thrombo-elastometry, is widely used.

The use of intraoperative cell salvage is strongly advocated. Particularly during the pre-anhepatic phase, excess fluid administration is avoided and the maintenance of low central venous pressure advocated, as is the case for liver resections, to limit surgical bleeding. Transfusions of fresh-frozen plasma (FFP), cryoprecipitate, and platelets are commonly required to treat coagulopathy, but there is no consensus regarding dosage, the optimal threshold for treatment, or both. Practice is to an extent variable according to location: coagulation factor concentrates are widely used in mainland Europe, but FFP use is widespread in the UK, for reasons of cost and availability.

Postoperative care

Fast-tracking LT patients

Traditionally, patients were admitted to the ICU for a period of stabilization while remaining sedated and ventilated. Early extubation where possible is increasingly practiced in some centres. Potential advantages include improved early graft blood flow due to negative intrathoracic pressure during spontaneous ventilation, reduced ICU stay, and decreased incidence of nosocomial infections. A scoring system based on observational data uses nine readily available operative and recipient factors such as age at transplant, BMI, gender, MELD score, pre-transplant length of stay in hospital, transplant numbers, total number of packed red cells transfused, operation time in minutes, and use of vasopressor in the last hour of operation. A high score suggests a higher probability of successful fast-tracking. Patient and graft survival were significantly better in fast-tracked patients compared with patients who were ventilated on ICU. As yet, no randomized evidence supports the practice.

Common complications after LT

Patients are closely monitored for early signs of liver dysfunction, renal dysfunction, and immunosuppressive drug levels. Table 3 shows the common complications seen after LT.

Acknowledgement

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Declaration of interest

None declared.
MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to BJA Education.

References