Anesthesia for liver transplantation

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1. Introduction

Liver transplantation (LT) is the replacement of a diseased liver with a healthy liver allograft. It has been recognized as the only definitive treatment of end stage liver disease. It increases both life expectancy and quality of life for patients, and it can be the definitive cure for some acquired and genetic liver diseases. Indications for liver transplantation include acute liver failure, hepatic decompensation due to chronic liver disease, primary hepatic malignancy and a variety of metabolic disorders. (1)

In 2012 a total of 6973 livers were transplanted in the European Union (EU), with live liver donations making up 3.7% of these. Globally, the percentage of live liver donations made up 18.2% of a total number of 23986. In 2013,1562 livers were transplanted within the Eurotransplant area, which includes Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia. Liver transplants had the highest quality adjusted life years (QALYs) gained with 11.5, compared to heart and lung transplants, with 6.8 and 5.2 QALYs gained, respectively. (2) The survival rates for deceased donor transplantations are approximately 86 and 72 percent for 1 and 5 years, respectively, and for living donor transplantations the survival rates are 90 and 78 percent. (3)

Because there is a lack of donors and a relative high demand for donor livers, and also because invasive testing during patient selection and preoperative screening can pose dangers, it is important to identify the patients who will benefit the most from the procedure. (1)

Advanced liver disease affects all other organ system, and it requires a skilled anesthesiologist to manage the complications that can arise before and during surgery. The surgery is divided into three phases, preanhepatic (stage I), anhepatic (stage II) and neo-hepatic (stage III), and the anesthetic management is described according to these stages, with each posing different challenges for the anesthesiologist.

2. Sažetak

Transplantacija jetre je zamjena bolesne jetre sa zdravim alotransplantatom jetre. Prepoznata je kao jedini konačni oblik liječenja terminalne bolesti jetre. Transplantacija produljuje očekivano trajanje života te može dovesti do izlječenja kod osoba s nasljednim i genetskim bolestima jetre. Indikacije za transplantaciju jetre uključuju akutno zatajenje jetre, dekompenzaciju zbog kronične bolesti jetre, primarnu malignu bolest jetre te različite metaboličke bolesti.(1)

U 2012. ukupno su 6973 jetre bile transplantirane unutar Europske unije (EU). Od toga broja 3.7% su činili živi donori. U svijetu je postotak živih donora činio 18.2% od ukupno 23986 transplantacija. U 2013. 1562 jetre su transplantirane u regijama u kojima djeluje Eurotransplant što uključuje Austriju, Belgiju, Hrvatsku, Njemačku, Mađarsku, Luksemburg, Nizozemsku i Sloveniju. Transplantati jetre imali su najviše kvalitete podešenih godina života – QALY, s 11.5 godina, u usporedbi sa transplantacijom srca i pluća, sa 6.8, odnosno 5.2 QALY-ja. (2) Stope preživljavanja za transplantacije od kadaveričnih donora su od prilike 86% i 72%, a za one od živih donora su 90% i 78%. (3)

Zbog manjka donora, relativno velike potražnje za doniranim organima te zbog invazivnog testiranja tijekom odabira pacijenata i preoperativne obrade, koji mogu predstavljati opasnost za pacijenta, od iznimne je važnosti prepoznati pacijenata koji će imati najviše koristi od transplantacije. (1)

Uznapredovala bolest jetra zahvaća sve ostale organske sustave te je potrebno imati vještog (iskusnog) anesteziologa koji će se moći nositi s komplikacijama koje se mogu razviti prije, tijekom i nakon operacije.

Operacija se može podijeliti u tri faze; preanhepatična (stadij I), anhepatična (stadij II) i neohepatična (stadij III) te je vođenje anestezije opisano u skladu s tim stadijima i svaki od njih predstavlja drugačiji izazov za anesteziologa.

3. History

Orthotopic liver transplantation, which is the placement of a liver allograft in its normal anatomical position, was first described by Francis Moore who performed trials with LT in dogs in 1958. This was followed in 1963 by Thomas Starzl et al, who performed the first liver transplantations in humans. (4) The first patient was a 3 year old boy with biliary atresia, who died during surgery due to coagulopathy and uncontrolled bleeding. The next four attempts were made in adults, who all survived the surgery, but died in the postoperative period from pulmonary embolisms that originated from the bypass tubing. (5)

Initially, the immunosuppressive regimen was the same as used for renal transplantation, azathioprine and corticosteroids. The failed attempts in 1963 represented the beginning of a moratorium which lasted more than 3 years, with a return to the laboratory to improve surgical techniques and immunosuppressive therapy. In 1967 the trials were resumed. 8 pediatric patients were transplanted, all survived surgery, but all but one died within 2.5 years, from rejection due to insufficient immunosuppression, or recurrence of the underlying disease. One patient who was transplanted in 1970, whose underlying condition was biliary atresia, had a remarkable survival and was still alive in 2002. (5)

In Europe, the first liver transplantation was performed in 1971 on a 17 month old child with biliary atresia. He survived the surgery, and developed acute rejection which was reversed by steroid therapy. Unfortunately he died from uncontrolled bleeding after a liver biopsy 7 weeks postoperatively. (5)

In 1979, trials were started with cyclosporine A as immunosuppression, which greatly increased survival. By 1984, liver transplantation was no longer considered experimental, and was approved as a therapy for end stage liver disease. In 1989, 1 and 5 year survival were reported as 73% and 64%, respectively in 1179 patients. From 1990, tacrolimus was used in patients who still suffered rejection with cyclosporine. (4)

Due to the shortage of donor livers, the technique of liver reduction was developed, where a large cadaveric donor liver was divided into smaller segments that could be transplanted into several recipients. This technique has been criticized and is no

longer used as it could favour pediatric patients over adult patients, simply because one liver could be used in more pediatric patients than in adults, who need bigger grafts. In the 1990s technique of splitting the donor liver was developed, where the left lobe or left lateral segment can be transplanted to a pediatric recipient, and the right lobe to an adult recipient. (5)

4. Medical criteria determining the patient's status on the waiting list

Deciding to list a patient for liver transplantation is based on an objective measurement of hepatic dysfunction rather than on the underlying etiology. Previously, the Child-Turcotte-Pugh (CTP) score, ABO compatibility and waiting time were used to select patients eligible for transplantation. The CTP score has a maximum value of 15, and is determined by the presence of hepatic encephalopathy and ascites, bilirubin levels, albumin concentration and increase in prothrombin time.

Patients were divided into 4 categories, depending on their CTP score, need for hospitalization and intensive care, and refractory complications of portal hypertension or hepatocellular carcinoma. United Network of Organ Sharing (UNOS) Status 1 was reserved for patients with acute fulminant hepatic failure, and priority was given to this group. The other categories, UNOS status 2a, 2b and 3, were for patients with chronic liver disease, depending on severity. When deciding which patient should be prioritized, waiting time was used as a tie-breaker within a category. (6) Therefore, in this system, livers were frequently allocated to patients with less decompensated disease, but with longer waiting time. (1)

Nowadays we use the model for end stage liver disease (MELD), which is a mathematical score derived by using three variables, serum bilirubin, international normalized ratio (INR) and creatinine, with a maximum score of 40. (7) It is calculated according to the following equation:

MELD Score = 0.957 x Log (creatinine mg/dL) + 0.378 x Log_e (bilirubin mg/dL) + 1.120 x Log_e (INR) + 0.643 (8)

The model was developed in 2000, initially to predict mortality in patients undergoing transjugular intra-hepatic shunt (TIPS) procedure. It was adopted by UNOS in 2002,

to replace UNOS status 2 to 3, and by Eurotransplant (ET) in 2006 for allocation of donor livers. UNOS status 1 was unaffected. (9) A higher MELD score indicates severe disease and patients are ranked in descending order. It is only applicable for patients with chronic liver disease who are listed for elective transplantation. Patients with acute fulminant liver failure are given high urgency (HU) status in ET. (8)

MELD has been shown to accurately predict 3 month mortality in patients with chronic liver disease. (6) After implementation of MELD, the waiting list mortality decreased. However, the post-transplant morbidity increased, likely due to an increase of transplantation in patients with more decompensated liver disease. (10)

The advantages of MELD over the CTP score, is that MELD is a continuous scale, therefore waiting time is no longer an important factor, and the patients are prioritized according to their risk of dying in a defined period of time, rather than when they were listed for liver transplantation. This has implications for patients with less access to health care, who tend to be listed for transplantations later than patients with more access to health care. In addition, the MELD score does not depend on subjective variables, such as evaluation of ascites or portosystemic encephalopathy. (6) If two or more recipients have the same MELD score, the recipient with the longest waiting time will be prioritized. (8)

For patients under the age of 12, a modified version, the pediatric end-stage liver disease (PELD) score is used. It is calculated using total bilirubin, INR, albumin, with presence/absence of growth failure, and age above or below 1 year. As opposed to MELD, it has no upper limit. (7)

In 15-20% of patients, the MELD score is of limited usefulness because the score cannot accurately predict survival. (Hepatology 2016). MELD exceptions were developed to more accurately predict patient mortality. Exceptions include hepatocellular carcinoma (HCC), hepatopulmonary syndrome, portopulmonary hypertension, familial amyloid polyneuropathy, cholangiocarcinoma, cystic fibrosis, metabolic disease, hepatic artery thrombosis and primary hyperoxaluria. These patients will be assigned a higher MELD score than their laboratory values suggest, and will receive an increase in points every three months. (11)

4.1 Indications for liver transplantation

In 2015 7127 LTs were perfomed in the US, and the etiologies were hepatitis C (26.2%), alcoholic liver disease (25.9%), cholestatic disease (8.3%), malignancy (7.2%), acute liver failure (1.9%) and others/unknown (30.6%). A reduction in patients presenting for transplantation with Hepatitis C infection was reported, and it is no longer the most common etiology for transplantation. This is likely due to introduction of effective antiviral therapy in 2014. The number of recipients in the category others/unknown has increased, likely due to an increase in non-alcoholic fatty liver disease. (12)

In adults the most common indications are cirrhosis, primary biliary cirrhosis and primary sclerosing cholangitis. The main indications in the pediatric population are primary biliary atresia, followed by metabolic disorders, such as alpha-1 antitrypsin deficiency, Wilson's disease, tyrosinemia and Crigler-Najjar type-1 syndrome, and fulminant hepatic failure, cryptogenic cirrhosis, neonatal hepatitis and malignancy. (13)

A list of medical indications for liver transplantation is provided in table 1.

Table 1: Medical indications for liver transplantation.

Medical indications for liver transplantation	
Viral	Hepatitis C Hepatitis B
Autoimmune liver disease	
Alcohol-related liver disease	
Inherited/metabolic liver diseases	Hereditary hemochromatosis α-1-Antitrypsin deficiency Nonalcoholic fatty liver disease Tyrosinemia Type IV glycogen storage disease Neonatal hemochromatosis Amyloidosis

	Hyperoxaluria Urea cycle defects Amino acid defects
Cholestatic liver disease	Primary biliary cirrhosis Primary sclerosing cholangitis Biliary atresia Alagille syndrome Progressive familial intrahepatic cholestasis Cystic fibrosis Bile duct loss
Malignancy	Hepatocellular carcinoma Cholangiocarcinoma Fibrolamellar carcinoma Epithelioid hemangioendothelioma Hepatoblastoma Metastatic neuroendocrine tumor
Polycystic liver disease	
Vascular disorder	Budd-Chiari syndrome
Fulminant hepatic failure	
Retransplantation	

from : Fox A, Brown R. Is the Patient a Candidate for Liver Transplantation?. Clinics in Liver Disease. 2012;16(2):435-448.

4.2 Contraindications for liver transplantation

Contraindications for LT are divided into absolute and relative and are presented in table 2.

Table 2: Contraindications to liver transplantation.

Contraindications to liver transplantation	
Absolute contraindications	Relative contraindications
Severe cardiopulmonary disease	Advanced age
Other outstanding malignancy	Obesity
Hepatic malignancy with vascular invasion or beyond transplantable criterion	Psychiatric disease
Extrahepatic malignancy	HIV infection
Active infection	Surgical challenges: prior extensive intra-abdominal surgeries, extensive vascular thrombosis
Active substance abuse	
Poor psychosocial support	
Poor compliance	

from Fox A, Brown R. Is the Patient a Candidate for Liver Transplantation?. Clinics in Liver Disease. 2012;16(2):435-448.

5. Preoperative evaluation

Before any surgery it is essential to perform a preoperative evaluation to assess a patient's risk of perioperative morbidity and mortality, and to optimize the patient for the procedure. In patients without comorbidities, it is enough to do a thorough history and physical examination with focus on risk factors for cardiovascular and respiratory diseases. (14) However, ESLD adversely affects all organ systems, and due to the shortage of donor livers and the effects of ESLD on perioperative morbidity and

mortality, it is important to identify patients who will most benefit from LT. Pre-LT evaluation has two main objectives, to assess the risk for perioperative morbidity and mortality, and to estimate long term survival. (15) According to the American Association for the study of liver diseases (AASLD) typical evaluation of patients undergoing LT should include a careful history and physical examination, cardiopulmonary assessment, laboratory studies to confirm the etiology and severity of liver disease, creatinine clearance, laboratory studies to determine the status of hepatitis B and C virus, Ebstein Barr virus, cytomegalovirus, and HIV infection, and abdominal imaging to determine hepatic artery and portal vein anatomy and the presence of HCC. (16)

The cardiopulmonary evaluation in patients presenting for LT is complex. Cardiac events are common in these patients, occurring in 25-70% of patients in the intra- or postoperative period, and it has a significant effect on prognosis. Patients undergoing LT should be assessed for common conditions, such as coronary artery disease, hyperdynamic circulatory state and cirrhotic cardiomyopathy, as well as obstructive or restrictive lung disease, hepatopulmonary syndrome, and pulmonary hypertension. (15) (16)

The prevalence of coronary artery disease (CAD) in LT candidates ranges from 2,5-27%, and due to the poor physical status of these patients may not experience common symptoms of CAD. In the perioperative period there is an increase in metabolic and oxygen demands of the myocardium, and coronary blood flow may be insufficient if coronary artery occlusion is present. CAD impacts morbidity and mortality both during LT and postoperatively. Therefore, it is essential to detect silent CAD. Stress testing should be performed in patients with coronary risk factors, and drug stress testing is preferred as these patients given the poor physical status in LT candidates. Given a positive stress test, coronary angiography should be performed. (15)

A 12-lead electrocadiography (ECG) should be performed in all LT patients. Cirrhotic cardiomyopathy, a common conditions in patients with ESLD, presents with a long QTc interval. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4782417/) It can also be detected by echocardiography. Although the prevalence of valvular heart disease is

expected to be low, the severity of valve dysfunction is predictive of perioperative complications. (15)

A careful pulmonary evaluation should be perfomed, even in asymptomatic patients. A routine preoperative evaluation of pulmonary function should include a thorough history and physical examination, arterial blood gas analysis, chest x-ray, pulmonary function tests (PFTs) as spirometry, and a Doppler echocardiography to estimate pulmonary artery pressure and exclude increased pulmonary vascular resistance. (17) A positive Doppler echocardiography should be followed up by right heart catheterization for some patients. (16)

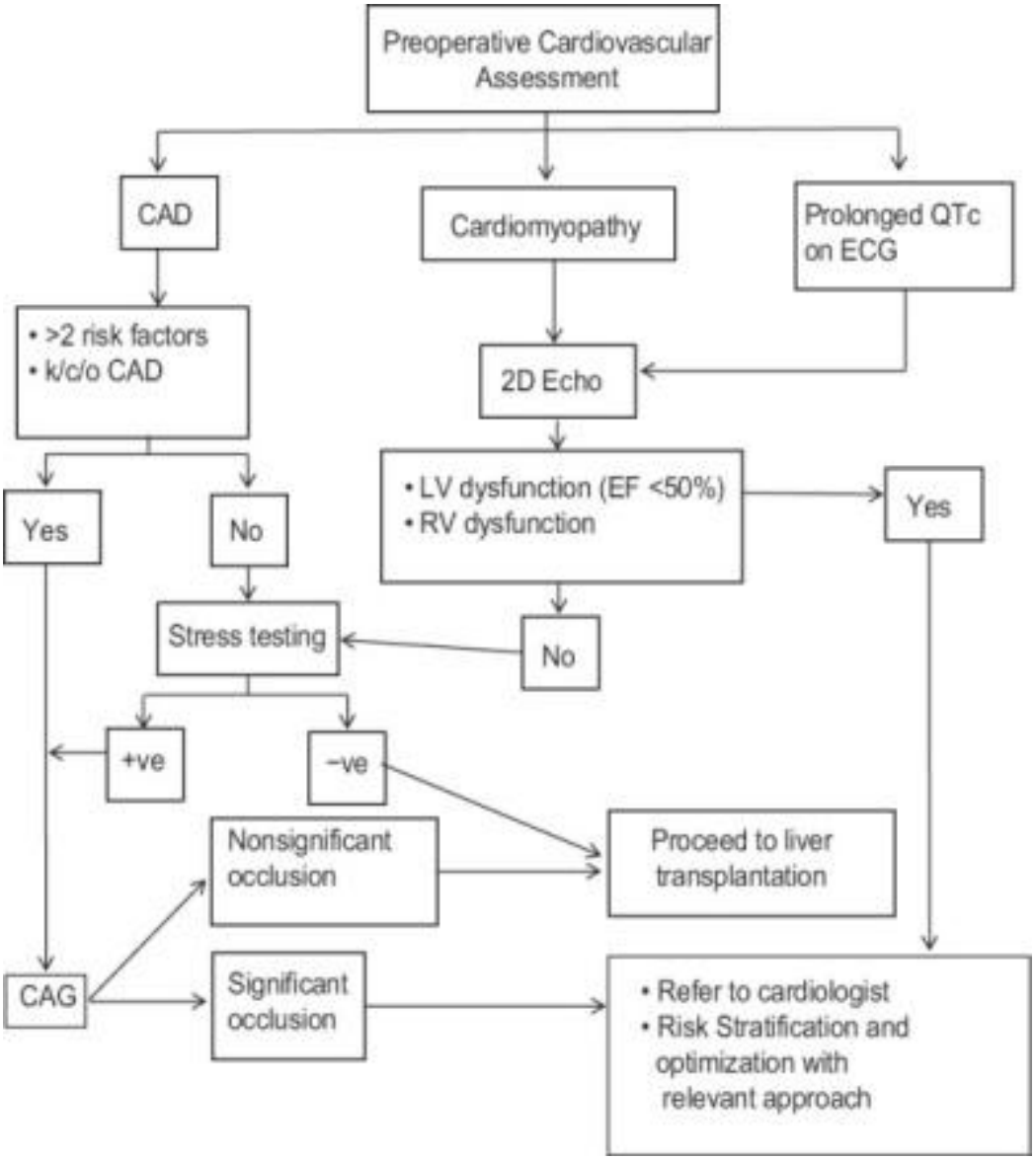
Patients with chronic kidney disease have poor survival after LT, whereas patients with hepatopulmonary syndrome drastically improve after transplantation. Patients should undergo a thorough evaluation of renal function prior to transplantation, and certain patients with chronic kidney disease may be considered for a combined liver-kidney transplantation. (16)

Osteoporosis is a common finding in ESDL, particularly in postmenopausal women and patients with cholestatic disorders such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis, therefore all patients should screened for osteoporosis due to the risk of pathological fractures in the postoperative period. (16)

Because of the immunosuppressive regimen that is necessary to facilitate transplantation, patients with a history of extrahepatic malignancies are at an increased risk of recurrence, and should therefore be evalutated by an oncologist prior to LT. (16)

It is good to include the anesthesiologist in preoperative evaluation early enough to enable optimizing the patient and tailoring a good anesthesia plan for every patient.

Figure 1: Preoperative cardiovascular assessment. (18)



6. Diseases related to chronic liver disease

6.1 Portal hypertension

Portal hypertension represents a common complication of chronic liver disease, and it is the main cause of hospitalization, LT and mortality among patients with cirrhosis. The most common cause of portal hypertension in the western world is cirrhosis, however around 10% of cases are due to non-cirrhotic causes, such as schistosomiasis and idiopathic portal hypertension. Portal hypertension has two components, a structural and a dynamic component. The structural changes, caused by fibrotic changes in the liver architecture, accounts for the biggest increase in pressure. The dynamic component accounts for around 30% of the increased portal pressure, and is caused by increased local production of vasoconstrictors and decreased availability of vasodilators. (19) As the resistance increases, development of collateral vessels and a hyperdynamic circulatory state further aggravates portal hypertension. (20)

Portal hypertension is defined by a hepatic venous pressure gradient (HVPG) of more than 10 mmHg, (19) and is predictive of development of complications. (21) A normal HVPG is below 5 mmHg, and values between 5 and 9 represent subclinical portal hypertension. (19) HPVG is the difference between the wedged and the free hepatic pressures, and represents the pressure gradient between the hepatic vein and the intra-abdominal portion of the inferior vena cava. (21)

Clinical manifestations of portal hypertension include development of collateral circulation, such as esophageal varices and abdominal wall collateral vessels, portal hypertensive gastropathy, spontaneous bacterial peritonitis, ascites, hepatic hydrothorax, hepatopulmonary syndrome, portopulmonary hypertension, cirrhotic cardiomyopathy and hepatic encephalopathy. (19)

At levels above 10 mmHg, the patient is at increased risk of developing esopageal varices and HCC. Above 12 mmHg, the risk of variceal bleeding increases, and at 16 mmHg the risk of mortality is increased. With levels above 30 mmHg, there is risk of spontaneous bacterial peritonitis. (19)

6.2 Central nervous system

Patients with cirrhosis frequently have neurologic signs and symptoms, and the most common neurologic manifestion is hepatic encephalopathy. Hepatic encephalopathy is a spectrum of reversible neuropsychiatric abnormalities ranging from mildly altered mental status to coma and death. Subclinical hepatic encephalopathy is detected only by psychomotor testing, and is usually characterized by subtle clinical symptoms. (22) The severity of overt hepatic encephalopathy is graded from I to IV based on clinical symptoms, where grade I represents changes in behavior, mild confusion, slurred speech and disordered sleep. Grade II is characterized by lethargy and moderate confusion. Grade III is marked confusion, stupor, incoherent speech and asleep but arousable, and patients with grade IV hepatic encephalopathy are comatose and unresponsive to pain. The mechanism is not clear, but current theories suggest a combination of gamma-amino butyric acid (GABA) potentiation by ammonia and chronic low grade glial edema may be responsible for the symptoms. (22)

Patients who develop encephalopathy due to acute liver failure have a poor prognosis, with rapid progression of symptoms and mortality from 70% to 80%. However, in clinical practice, the more common form is chronic encephalopathy associated with end stage liver disease. For these patients the 1 year survival after the first episode of encephalopathy is 40%, and at 3 years the survival is 15%. These patients usually have slower progression and milder symptoms, and it is typically triggered by precipitating causes such as gastrointenstinal bleeding, infection, electrolyte disturbances or constipation, among others. Treatment is aimed at removal of the precipitating factors, and for patients with chronic encephalopathy, protein restriction can be effective. (22)

6.3 Cardiovascular system

Liver cirrhosis is associated with a spectrum of cardiovascular abnormalities, including hyperdynamic circulations and cirrhotic cardiomyopathy. (23) The mechanism of hyperdynamic circulation in cirrhosis is peripheral and splanchnic vasodilation, due to an increased production and activity of vasodilators such as nitric oxide, carbon monoxide and endogenous cannabinoids, as well as decreased

reactivity to vasoconstrictors. Early on, the decreased vascular resistance is compensated for by an increase in cardiac output. However, later on, an increase in cardiac output can no longer compensate for the decreased systemic vascular resistance. This leads to underfilling of the arterial circulation, and thereby decreased effective blood. To maintain effective arterial blood volume and arterial pressure, several vasoconstrictor systems are activated, such as the renin-angiotensin-aldosterone system, sympathetic nervous system and antidiuretic hormone. Activation of these systems causes sodium and water retention, which is the main mechanism behind the development of ascites. (24)

Liver dysfunction not only adversely affects the circulation, but also cardiac contractility. The main clinical features of cirrhotic cardiomyopathy aresystolic and diastolic dysfunction and electrophysiologic abnormalities (25), in the absence of other causes of cardiac dysfunction. Systolic dysfunction is mostly latent and is unmasked by physical or pharmacologic stress. Systolic dysfunction in cirrhotic patients is caused by alterations in beta-adrenergic signaling pathways, increased cholesterol content in the myocadial cell membranes which may alter ion channel functions, enhanced endocannabinoid signaling which has a negative inotropic effect, and NO overproduction, which has a toxic effect on the myocardium. (26)

Myocardial hypertrophy and fibrosis due to activation of the RAAS as well as subendothelial edema and increased interstital collagen deposition leads to diastolic dysfunction. This is characterized by decreased ventricular relaxation and inadequate ventricular filling, increased atrial pressure and prolonged isovolumetric relaxation. (26) It can be seen on Doppler echocardiography as a decreased E/A ration. (24)

The electrophysiological abnormalities in cirrhotic cardiomyopathy comprise of chronotropic incompetence, electromechanic uncoupling and prolonged QT interval. (26) Chronotropic incompetence is an inability to increase the heart rate with increased demands, which lead to exercise intolerance (27) and electromechanical uncoupling is an asynchrony between the electrical and mechanical activity of the heart. QT prolongation is present in around 60% of patients with cirrhosis. These phenomena are correlated to the severity of liver disease. (26)

6.4 Renal system

Renal failure is a common complication of cirrhosis. Renal failure in these patients is related to the circulatory changes mentioned previously. Prolonged activation of vasoconstrictor systems brought on by splanchnic vasodilation and low systemic vascular resistance leads to severe renal vasoconstriction which may progress to a severe reduction in GFR and renal insufficiency, known as hepatorenal syndrome (HRS). (24) HRS exists as two types. Type 1 is characterized by a rapid onset with doubling of serum creatinine concentration within two weeks. It is associated with severe multiorgan dysfunction, and it carries a poor prognosis with a very low short term survival rate. Type 2 has a slower and more progressive onset. (28) These patients have diuretic resistant ascites and slightly longer survival.(29) Activation of vasoconstrictor systems lead to retention of sodium and water, therefore HRS is rarely present in the absence of ascites. (28)

HRS can be precipitated by factors that further impair renal circulation, such as hypovolemia due to gastrointestinal bleeding, large volume paracentesis without adequate plasma expansion and bacterial infections. A clear relation has been established between spontaneous bacterial peritonitis and development of HRS. (30)

HRS is a diagnosis of exclusion. It can only be diagnosed in the setting of cirrhosis with ascites, in the absence of shock with serum creatinine >113mml/L, no improvement of kidney function 2 days after volume expansion and diuretic withdrawal, no current or recent treatment with nephrotoxic drugs and in the absence of parenchymal kidney disease. (31) Spontaneous recovery is rare, and the only effective treatment for HRS is LT. (30)

The main differential diagnosis is acute tubular necrosis (ATN). ATN should be suspected if renal failure develops immediately after administration of nephrotoxic drugs, or in the setting of hypovolemic or septic shock. (30)

6.5 Electrolytes

Hyponatremia frequently develops in patients with advanced cirrhosis. Activation of vasoconstrictor systems causes retention of sodium and water as a compensatory mechanism for the low effective circulatory volume. With disease progression, the

kidneys are unable to eliminate solute free water. This leads to non-osmotic release of ADH, leading to plasma dilution, further aggravating the hyponatremia. (32) Currently, treatment is limited to conventional therapies like sodium restriction. Althought vasopressin antagonists are available, their role in treatment of patients with liver failure is questionable. (33) Hyponatremia correlates with the severity of liver disease, serves as a prognostic factor for patients with liver failure,* and is included in calculation of the MELD score.

Hypokalemia can be caused by various reasons such as use of diuretics, hyperaldoseronism due to activation of RAAS, or secondary to hypomagnesemia in alcoholic liver disease. (34)

6.6 Pulmonary system

Portopulmonary hypertension (POPH) is a form of pulmonary artery hypertension (PAH) which is associated with portal hypertension. The prevalence in patients undergoing LT is estimated to be 8,5%, as opposed to 2-5% in the general population with portal hypertension. The main clinical symptom of POPH is dyspnea on exertion, and other symptoms include fatigue, generalized weakness, ligh-headedness and orthopnea. (35) It is not related to the etiology or severity of liver disease, but female sex and presence of autoimmune disease are risk factors for development of POPH. (36)

Patients with POPH present with mean pulmonary artery pressure (mPAP) >25 mmHg at rest, mean pulmonary capillary wedge pressure (mPCWP) <15 mmHg and pulmonary vascular resistance (PVR) >240 /dyne/sec/cm-5 in association with clinical portal hypertension with or without significant chronic liver disease. Diagnosis is suggested by transesophageal echocardiography (TEE), and confirmed with right heart catheterization. Every patient undergoing LT should be screened for POPH with TEE.

The survival of untreated POPH is very poor, with 54% mortality within a year of diagnosis, and 5 year survival as low as 14%. In some patients with successful LT there can be resolution of POPH with time, (35) however in other patients it persists or worsen. (36)

Hepatopulmonary syndrome (HPS) is defined by intrapulmonary vascular dilatation (IVPD) and hypoxemia in combination chronic liver disease or portal hypertension. IVPD can cause a right to left shunt resulting in hypoxemia. (36) The most prominent symptom is dyspnea at exertion or at rest. Patients may experience platypnea-orthodeoxia syndrome, with worsening dyspnea when moving from recumbent to upright position due to worsening of right-to-left shunting and thereby a decrease in oxygenation. (37)

The diagnostic criteria for HPS are chronic liver disease with alveolar-arterial oxygen pressure gradient (aDO2) ≥ 15 mmHg, or ≥ 20 mmHg, or or ≥ to the age-adjusted value, as well as intrapulmonary vascular dilatation at contrast-enhanced transesophageal echocardiography(CT-TEE) or Technetium macroaggregated albumin lung perfusion scan (99m-TcMAA). IVPD is found in 40-60% of patients with liver disease, but only 15-30% have hypoxemia and therefore meet the diagnostic criteria for HPS. Patients diagnosed with HPS qualify for MELD exception points. Medical treatment for HPS is disappointing, and the definitive treatment for HPS is LT. HPS increases perioperative mortality, but 5 year survival is similar in patients with and without HPS. (36)

6.7 Coagulation

The liver is essential in coagulation, as it is the site of synthesis for procoagulant factors, anticoagulant factors, and fibrinolytic proteins. (38) Chronic liver disease is characterized by a decrease in most procoagulant factors, with the exception of von Willebrand factor and factor VIII. It was previously believed that patients with liver failure were „autoanticoagulated“, but newer research has shown that there is also a reduction in naturally occurring anticoagulants such as protein C and antithrombin, and therefore a paralell reduction in both procoagulant and anticoagulant factors. (39)

All stages in hemostasis may be abnormal, including primary hemostasis, coagulation and fibrinolysis. INR is included in calculation of the MELD score, and it is linked to the severity and prognosis of liver disease, it is not a good marker for the risk of bleeding in these patients, because it does not accurately reflect the changes in both the procoagulant and anticoagulant systems. Acute events, such as infection,

variceal bleeding and uremia may lead to changes in hemostasis and predispose to bleeding. (40)

This imbalance between pro- and anticoagulants may explain why patients with liver disease, despite a bleeding diathesis, are not protected from events such as peripheral-vein thrombosis, portal vein thrombosis, atherothrombosis and progression of liver fibrosis. (39)

7. Intraoperative anesthetic management

There are three distinct stages in in liver transplant surgery which the anesthetic team need to be aware of. The stages are each defined by a surgical feature, are characterized by specific complications and require different anesthetic considerations. These stages are the preanhepatic or dissection stage, the anhepatic stage, and the neohepatic or reperfusion stage. (29)

7.1 Monitoring

LT causes major fluid shifts, electrolyte disturbances, hemodynamic instability and metabolic derangements. Cardiac events are the leading cause of non-graft related death, therefore emphasis is placed on hemodynamic monitoring. The type of monitoring differs according to the preoperative status of the patients, as well as between transplantation centers. Standard monitoring includes ECG, peripheral oxygen saturation (SpO2), end tidal CO_2, central venous pressure (CVP) and arterial blood pressure (ABP). (41)

As previously mentioned, ESLD is characterized by high cardiac output (CO), decreased systemic vascular resistance, and depletion of intravascular volume. In addition, during the different stages of LT there are hemodynamic changes that need to be recognized and managed. (42) Routine monitoring includes ECG, pulse oximetry, capnograph and temperature monitoring. Direct arterial blood pressure, central venous and pulmonary artery pressure monitoring should also be in place. (13) For invasive arterial artery pressure, both radial and femoral artery cannulation can be used, but the femoral artery is sometime problematic during clamping of the aorta. Until recently, pulmonary artery catheter (PAC) was used to monitor cardiac filling pressures and guide fluid therapy, but these filling pressures have little positive

predicting value in predicting hemodynamic instability. Nowadays CO can be measured in selected cases through the PAC using intermittent thermodilution. Continuous monitoring of CO is also possible using a heating coil within the PAC. This eliminates the need for bolus injections and provides an average CO reading over time, as opposed to intermittent readings. Due to the risk of arrhythmias, and the inaccuracy of readings if the PAC is placed incorrectly, its use is declining, and is now reserved for patients with suspicion of PPH. (43) Additionally, during the reperfusion stage, return of cooled blood to the systemic circulation as well as infusion of large amounts of fluids may cause inaccurate estimation of CO. (44)

For the most of the patients less invasive hemodynamic monitoring devices are used. Devices that provide a continuous estimate of stroke volume (SV) and CO through analysis of the shape of the arterial pulse wave from a peripheral arterial catheter are commercially available, and can be used to guide fluid and inotrope therapy.

TEE provides direct visualization of the function and volume status of the heart, and in hemodynamic instability, and can be used to immediately diagnose air or thromboembolism, as well as measurement of CO. However, it's use in LT is limited due to the high prevalence of esophageal varices in LT candidates. (43) While grade 4 esophageal varices is a true contraindication, TEE has been safely performed in grade I and II varices. (44)

Traditionally, coagulation has been monitored using conventional coagulation tests (CCTs), such as prothrombin time (PT), activated partial thromboplastin time (APTT), platelet count and plasma fibrinogen leves. Even with all of these together, it may not provide a complete picture of the coagulation status, and therefore anesthesiologists use a combination of CTTs with point of care (POC) devices such as thrombelastography or rotation thrombelastometry. These tests measure and graphically display changes in viscoelasticity of the blood. They are repeated frequently during the course of LT and are used to guide blood product replacement. (44)

Acute fulminant hepatic failure (AFHF) increases the risk for increased ICP, and in addition, ICP tends to vary significantly during the course of LT. ICP should be monitored, however, due to the coagulopathy associated with AFHF, traditional invasive ICP monitoring is associated with a risk of intracranial hemorrhage. Newer

noninvasive methods of ICP monitoring are becoming increasingly popular, such as Transcranial Doppler (TCD), which measures the blood flow velocity in the middle cerebral artery (MCA), and Optic Nerve Sheath Diameter (ONSD), which measures changes in the diameter of the optic nerve sheath. These techniques are currently not accurate enough to replace traditional ICP monitoring in high risk patients, however they are able to distinguish between normal and increased ICP. (43)

As the liver plays a central role in glucose metabolism, and glucose control tends to worsen during LT, frequent plasma glucose monitoring is important during anesthesia.. Dyselectrolytemias and acid-base disturbances are frequent in liver disease, and should also be monitored and corrected. Continuous temperature monitoring and maintenance of normothermia is important, as hypothermia has negative effects on wound healing and coagulation. (44)

7.2 Induction of anesthesia

Benzodiazepine premedication appears to be safe, although it should be avoided in patients with hepatic encephalopathy. (45) A routine rapid sequence induction with cricoid pressure should be performed in order to prevent aspiration. Following preoxygenation, induction can be performed using intravenous anesthetic drug. (13) Anesthesia is maintained using a volatile agent, such as isoflurane, desflurane or sevoflurane. (46) Another suggested technique is propofol and remifentanil, followed by maintenance with desflurane inhalation and remifentanil infusion. (47) Midazolam is also useful due to its amnestic properties and small effects on hemodynamics. (13) Nitrous oxide should be avoided because of its cardiodepressive effects, and tendency for bubble formation. The main objective in induction is to maintain cardiovascular stability. (45) Liver failure is frequently associated with renal failure and hypokalemia, therefore use of succinylcholine should be avoided. Cis-atracurium and atracurium are preferred neuromuscular blocking drugs because of their organ independent elimination. However, other neuromuscular blocking drugs, such as vecuronium, pancuronium and rocuronium can be used safely. Caution should be used with these drugs as they rely on hepatic metabolism. (13) (46)

7.3 Preanhepatic stage

The preanhepatic stage begins with surgical incision and ends with cross clamping of the portal vein and the suprahepatic and infrahepatic inferior vena cava (IVC). (48) During this stage, the liver is mobilized and dissected. Drainage of massive amounts of ascitic fluid, as well as blood loss may lead to hemodynamic instability. (13) The risk of bleeding is higher in patients with severe portal hypertension with abundant portosystemic shunting in the abdominal wall. The greatest concern at this stage is surgical bleeding, and the main goal is to maintain volume status. (29) Hypovolemia should be treated withcristaloids, colloids and blood derivates. (48) Fluid rescuscitation results in a decreased concentration of coagulation factors, therefore packed red cells and fresh frozen plasma should be prepared. Monitoring of coagulation parameters differs between centers, but most centers monitor INR, PTT, fibrinogen and platelet count, with some centers also using thromboelastography and activated clotting time. (13) In order to prevent blood loss, CVP can be maintained at a low level (5 cm H2O). This has been shown to decrease bleeding by 80%, although this practice is controversial. (49) In patients with severe portal hypertension, octreotide infusion may be used to decrease portal pressure. (29) Preoperative autologous blood donation, erythropoietin administration, intraoperative hemodilution, blood salvage and maintenance of normothermia in order to prevent worsening of coagulopathy are other techniques used to minimize blood loss. Blood transfusions are associated with complications and worse outcomes and therefore its use should be kept to a minimum. In case of sudden decrease in expired CO2 in the prescence of hemodynamic instability, an air embolism from manipulation of the vena cava should be suspected. (13) During the first and second stage of LT surgery, aggressive management of potassium levels should be initiated in anticipation of hyperkalemia during the reperfusion stage. Methods include insulin and glucose, treatment of metabolic acidosis with bicarbonate and maintenance of diuresis. (29)

7.4 Anhepatic stage

The anhepatic stage begins with occlusion of vascular inflow to the liver and ends with reperfusion. (48) At this stage the liver is removed, and whatever function remained in the dysfunctional liver is lost, which leads to striking changes in the patient's physiology. (29) Clamping the IVC and portal vein and dividing hepatic

vascular leads to a loss of venous return. This in turn is a risk for cardiovascular collapse with hypotension and decreased CO. An increase in venous pressure distally increases the risk for bleeding, edema, renal hypoperfusion and intenstinal ischemia. In order to maintain hemodynamic stability and renal perfusion, lessen splanchnic congestion and delay development of metabolic acidosis, veno-venous bypass (VVB) can be used. (13) VVB involves exctracorporeal circulation of blood from the peripheral veins to the central venous circulation. (50) In the piggyback technique, with preservation of flow through the IVC, VVB may not be necessary. (13) Hypotension should be treated with vasopressors rather than large amounts fluids in order to avoid fluid overload. (29) Complications of VVB include air embolism, thromboembolism and inadertent decannulation. (48) During the anhepatic phase, no hepatic clotting factors are produced, leading to worsening coagulopathy. Thrombocytopenia can develop or worsen due to massive blood transfusions and platelet consumption, (45) and in this stage fibrinolysis may occur due to unopposed action of tissue plasminogen activator (tPA). (48) Coagulopathy should not be aggressively corrected as this is a temporary phenomenon and will quickly stabilize after reperfusion. (29) Absence of lactate and citrate metabolism in the liver results in worsening acidosis. Due to citrate accumulation, hypocalcemia may develop, and should be treated with I.V. calcium infusion to prevent worsening of coagulopathy and cardiac depression. (45) During this phase immunosuppressive therapy (corticosteroids) is started.

7.5 Neo-hepatic stage

The neo-hepatic stage begins with reperfusion of the new liver through the portal vein and ends at completion of the procedure. (48, 29) This stage is further subdivided into 5 minutes after reperfusion, and the rest of the procedure, as the first 5 minutes are the most critical in terms of hemodynamic stability. During reperfusion, sequestrated blood in the graft, as well as blood from the lower body if VVB has not been used, return to systemic circulation. (29) Reperfusion is associated with abrupt increase in potassium and hydrogen ion concentrations, increased preload, as well as a decrease in systemic vascular resistance and blood pressure. After reperfusion the graft avidly takes up potassium, and some patients require potassium supplementation. (45) Postreperfusion syndrome is defined as a minimum of 30%

decrease in mean systemic blood pressure for more than 1 minute during the first 5 minutes after reperfusion. (13) This is thought to be caused by cytokines, vasoactive substances released by the liver and complement. (45) Hypotension should be treated with vasopressors and inotropes. (13) On reperfusion there is a return of hyperkalemic, cold, acidotic fluid to the systemic circulation.(45) Calcium chloride and sodium bicarbonate are the drugs of choice for treatment of hyperkalemia in order to prevent arrythmias.(48) Even without treatment, potassium levels fall within minutes of reperfusion, but any EKG changes should be treated promptly. (13) Hypothermia is a marker for the presence of graft flow into the systemic circulation. (48) Coagulation disorders should be corrected at this stage, however using blood products may result in volume overload and a paradoxical increase in blood requirements. Signs of a functional liver graft include decreased calcium requirements, improvement in acidosis, increased urine output, increased core temperature and biliary output from the graft. (13)

8. Postoperative complications

Postoperatively transplanted patients are admitted to intensive care unit.

The main goal is to ensure good perfusion of the graft.

Early extubation is desirable in some patients. In addition to an increased risk of ventilator-associated pneumonia, positive pressure ventilation increases intrathoracic pressure, which reduces venous return and may cause venous congestion in the graft. (51) Spontaneous ventilation reduces intrapleural pressures, improves venous return and hepatic blood flow. Risk factors for prolonged mechanical ventilation include severe hepatic encephalopathy and obesity (body mass index >34). Patients with primary graft dysfunction, renal failure, cardiovascular failure, neurological impairment, who received more than 12 units of blood and have pulmonary edema cannot tolerate early extubation, and must be kept on mechanical ventilation at least 3 hours postoperatively. In case of mechanical ventilation prior to surgery, use of more than 15 units of blood, acute liver failure, retransplantation or severe preservation injury to the graft, the patient needs to be kept on mechanical ventilation for at least 24 hours postoperatively. (13) Difficult weaning from mechanical ventilation can be caused by massive transfusion, pleural effusions, inadequate

clearing of bronchial secretions, pneumonia and adverse effects of immunosuppressive therapy. If prolonged mechanical ventilation is required, ventilatory strategies that minimize insults to both the lung and the liver should be used. Rapid extubation followed by non-invasive ventilation should be considered. (51)

Patients with cirrhosis tend to have impaired cardiac contractility, and in the postoperative period, acidosis, electrolyte disturbances and hypothermia may worsen cardiac contractility, leading to circulatory instability. Hypovolemia and pulmonary edema may impair gas exchange, leading to insufficient perfusion of the graft. Additionally, rapid improvement of pre-existing vasodilatation may cause excessive strain on the heart. Cardiac monitoring needs to be in place in the postoperative period in order to optimize cardiac output and organ perfusion, and to manage fluid and therapy and pharmacologic interventions. After stabilization of postoperative hemodynamics, it is important to promote return of sequestrated fluid in the peripheral circulation in order to prevent pulmonary edema and congestion in the graft. Lowering right ventricular volume and pressure would create pressure gradient between the portal and central circulation that draws blood through the liver. (51)

Primary graft dysfunction (PGD) consists of initial poor function (IPF) and primary non-function (PNF). IPF is reversible in most cases, but once it progresses to PNF it will ultimately progress to graft loss and retransplantation. IPF and PNF represent sequential stages of the same syndrome and therefore signs and symptoms overlap. There are no universal definitions for IPF, it can be assessed by alanine aminotransferase (ALT), aspartate aminotransferase (AST) and prothrombin time. A definition that is widely used is an AST of more than 2000 IU/L, indicating hepatic injury, a prothrombin time more than 16 seconds, indicating reduced synthetic ability, and ammonia above 50 µmol/L between 2 and 7 days postoperatively. In PNF, a progressive rise in AST and ALT is detected in the first 24-48 hours after LT, and is characterized by hepatic encephalopathy, uncorrectable coagulopathy, hypoglycaemia, hyperkalemia, metabolic acidosis, oliguric renal failure, decreased bile production and increased serum bilirubin. This condition requires urgent retransplantation. If patients who received massive blood transfusions during surgery develop metabolic acidosis followed by alkalosis, this is an indication of good graft

function, as transformation of sodium citrate present in transfused blood to sodium bicarbonate is dependent on good hepatocyte function. (52)

Poor graft function, as well as imperfect hemostasis, hypersplenism, hypocalcemia, dilutional coagulopathy and thrombocytopenia may cause bleeding in the postoperative period. Monitoring by thrombelastography may become necessary, but overcorrection of coagulopathy should be avoided due to the risk of hepatic artery or portal vein thrombosis. (51) Hepatic artery thrombosis requires urgent retransplantation.

Renal dysfunction is a common complication after LT, with a incidence between 12-95%, and out of these, 30% are due to acute kidney injury (AKI). The most common cause for AKI post LT is acute tubular necrosis (ATN). Renal dysfunction can also be due to pre-existing AKI, pre-existing chronic kidney disease (CKD) or CKD that develops as a complication of LT. (53)

Because of the necessity of immunosuppression infective complications are the leading cause of morbidity and mortality after LT. More than half of LT patients have at least one infectious complication and half of post LT deaths are due to infections. (54) Potential entry of bacteria from the GI tract during surgery, exposure to pathogens during hospitalization, indwelling urinary and vascular catheters and prolonged mechanical ventilation predispose LT patients to infection within the first month postoperatively. The risk of infection is reduced by prophylactic antibiotics, and although there is no consensus on antibacterial prophylaxis, a third-generation cephalosporin is preferred. Signs and symptoms include fever, leucocytosis, erythema, purulence, drainage and wound dehiscence. (55) Other sources of infection, include the donor organ and transfused blood products, especially viral infections, and reactivation of previous infections. (53) Herpes simplex virus reactivation is common in the immediate postoperative period, but the incidence is decreased by prophylactic acyclovir or ganciclovir. (55) In the intermediate period after LT, from the second to sixth month, infections are most commonly of viral origin, followed by fungal infections. Six months after LT, recipients have the same frequency of bacterial infections as the general population. (53)

Long term complication of LT include chronic rejection, renal failure, arterial hypertension, diabetes mellitus, dyslipidemia, obesity, skeletal complications such as osteopenia, neurologic complications and de novo malignancies. (53)

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11. Biography

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