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Anesthesia for Liver Transplantation

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Abstract

Liver transplantation is a high-risk surgery performed on a high-risk patient and is the only treatment for end-stage liver disease. Ever since the first successful liver transplant performed, patient survival increased due to improvement of surgical technique and anaesthetic management as well as the emergence of new generations of immunosuppressants. The pre-anaesthetic evaluation is mandatory and plays an important role in patient inclusion on the transplant list. Liver transplantation is performed under general anaesthesia, and the anaesthetic monitoring is very important for a successful liver transplantation as it can expose problems before irreversible damage occurs. Haemodynamic instability is common during surgery, requiring complex invasive haemodynamic monitoring. Continuous assessment of the patient's volemic status and the amount of perfused fluids represent the key to a successful liver transplantation. Inadequate fluid therapy can lead to pulmonary oedema, abnormal gas exchange, congestion, decrease in perfusion and oedema of the graft. Liver reperfusion takes place in the neohepatic phase and is the most unstable period during liver transplantation, representing a real challenge for the anaesthetist. It can have severe consequences due to a decrease in cardiovascular function with haemodynamic instability, abnormal acid base balance and metabolic abnormalities.

Keywords: liver transplant, cirrhotic cardiomyopathy, postreperfusion syndrome

1. Introduction

Liver transplantation is the only treatment for end-stage liver disease regardless of its aetiology as well as for other categories of liver failure. The procedure is performed on a high-risk patient with impairment of cardiovascular, pulmonary, renal and coagulation systems. Due to increasingly good results, transplant candidates are older and frequently have co-morbidities.

Since the first transplant interventions in the 1960s, postintervention morbidity rate decreased and patient survival increased. This is due to the improvement of surgical technique and anaesthetic management as well as the emergence of new generations of immunosuppressants. Medical care of pre-transplant patients has also experienced a favourable evolution.

The outcome of patients undergoing liver transplantation depends on the perioperative management. Dedicated and specialized teams for liver transplantation have a major role on the outcome of these patients.

2. Preoperative assessment

Liver transplantation is a high-risk surgery performed on a high-risk patient, the cirrhotic patient with end-stage liver disease. The pre-anaesthetic evaluation is mandatory and plays an important role in accepting the inclusion of the patient on the transplant list. Today, patients eligible for transplant are older and often associate co-morbidities.

2.1. Cardiac evaluation

2.1.1. Coronary artery disease (CAD)

The cirrhotic patient has long been considered to be protected from coronary artery disease (CAD) due to his/her haemodynamic profile associated to a low serum cholesterol level. However, recent studies show that CAD has the same prevalence in this group compared to the general population. Patients frequently associate risk factors for CAD such as obesity, diabetes and hypertension.

The incidence of CAD does not seem to be influenced by the aetiology of cirrhosis except for non-alcoholic steatohepatitis (NASH), in which case it is twice as high, NASH associating with the metabolic syndrome [1]. The importance of CAD detection is due to the haemodynamic high stress during liver transplant leading to exacerbation of the cardiac suffering during surgery or generating postoperative cardiac complications [2, 3]. Recognizing CAD is very important, but the best therapeutic approach in case of significant coronary stenosis is not well defined.

Coronary angioplasty may be recommended, but due to the need for heavy anti-aggregation, this may increase the risk of bleeding in the cirrhotic patient. When required, bare metal stents are preferred to pharmacologically active ones because of a shorter period of anti-aggregation. Surgical intervention for myocardial revascularization is not recommended due to a very high mortality risk in the cirrhotic patient [2, 4].

2.1.2. Cirrhotic cardiomyopathy

Cirrhotic patients have myocardial dysfunction secondary to hepatic impairment [5].

Regardless of the aetiology of cirrhosis, cardiomyopathy is characterized by

- increased cardiac output at baseline,
- impaired contractile reserve in response to stress; this is due to a lower density of beta adrenergic receptors as well as to the negative inotropic effect of excess nitric oxide production,

- diastolic dysfunction; it is more pronounced in patients with ascites,
- electrophysiological alterations like prolongation of the QT interval [3, 6].

The prolonged QT interval is associated with the severity of liver disease and the degree of portal hypertension as well as mortality [2]. A QTc interval of >440 ms correlates with an increased risk of ventricular arrhythmias [7].

Both diastolic and systolic dysfunction can be causes of postoperative pulmonary oedema. Right heart dysfunction, when present, has a higher predictive value for postoperative cardiac complications.

2.1.3. Other causes for cardiac impairment

Chronic consumption of ethanol may cause dilated cardiomyopathy; it is characterized by left ventricular dilatation with altered systolic function. In the initial stages of heart disease, abstinence from alcohol can significantly improve the symptoms.

In the case of haemochromatosis, excess iron will be deposited in the myocardium, leading to restrictive cardiomyopathy [2].

2.1.4. Steps of cardiac evaluation

Investigating a patient will begin with the existence of a history of heart disease as well as symptoms suggestive of cardiovascular events such as rhythm disorders or angina. Because of their low exercise capacity due to cirrhosis, the incidence of angina is low and frequently coronary heart disease can be underestimated.

The baseline assessment includes an electrocardiographic (ECG) recording at rest and an echocardiography.

The echocardiography evaluates the following [8]:

- measurements of cardiac chambers
- valvular characteristics and function
- evaluation of systolic function of the left ventricle (LV) expressed as ejection fraction; we must not forget that these values are obtained under the conditions of low blood pressure due to the vasodilatation of the cirrhotic patient, so they can underestimate the real ejection fraction
- evaluation of diastolic function of the left ventricle by measuring early and late diastolic velocities through the mitral valve to determine the E/A ratio (ventricular filling phases = initial E vs. tardive A); $E/A < 1$ reflects a diastolic dysfunction; diastolic dysfunction is more pronounced in patients with ascites [6]

If electrocardiogram and echocardiography are two mandatory pre-transplant investigations, the question is what other methods should be used in those patients who require additional methods.

According to AASLD (American Association for the Study of Liver Disease), AHA (American Heart Association) and ACCF (American College of Cardiology Foundation), additional

investigations should be undertaken for patients who have three or more associated risk factors of the following: diabetes, left ventricular hypertrophy, history of CAD, age > 60 years, smoking, hypertension, dyslipidaemia and obesity [4, 9].

Several types of investigations have been proposed:

- stress echocardiography using dobutamine, adenosine or dipyridamole,
- myocardial perfusion scintigraphy,
- computerized cardiac tomography which allows calculating the calcium score; this is a rapid and non-invasive way to measure calcium deposits in the coronary vessel wall as an expression of coronary stenosis; results are measured in Ca scores: a Ca of >100 score carries a moderate risk of cardiac events and a score of >400 a high risk [10].

Valvular dysfunctions in the cirrhotic patient on the transplant list are poorly studied. The evaluation of such a patient should include the severity of the valve dysfunction, either stenosis or regurgitation, the degree of alteration of myocardial contractility and the clinical presence of signs of insufficient cardiac output. Several cases of simultaneous liver transplantation and aortic valve replacement for tight aortic stenosis were reported in the cirrhotic patient [6].

2.2. Pulmonary system

Chronic liver disease can affect both the pleural space and the pulmonary parenchyma. The two pulmonary conditions characteristic of the cirrhotic patient are hepatopulmonary syndrome and pulmonary hypertension. The two syndromes exclude each other, and their pathophysiology depends on predominant vasodilator or vasoconstrictor elements resulting from liver dysfunction.

Portopulmonary hypertension is a pulmonary hypertension syndrome with vascular obstruction, coexisting with portal hypertension. The portopulmonary syndrome has important haemodynamic consequences with minor changes in blood gases.

All patients proposed for transplantation should be screened for portopulmonary hypertension as the postoperative evolution depends on it. It might be suspected in the case of a right branch block on ECG. Echocardiography can detect pulmonary hypertension and can evaluate it, but correct values are obtained by right heart catheterization. Depending on the mean pressure in the pulmonary artery (PAPm), hypertension is classified in mild (PAPm 25–34 mmHg), moderate (PAPm 35–44 mmHg) and severe (PAPm >45 mmHg).

Severe pulmonary hypertension excludes the patient from liver transplantation; moderate form may benefit from vasodilator drug treatment in pre-transplant [4]. Decision to perform liver transplant in this case depends on the response to therapy and is taken by the transplant team on an individual basis.

Hepatopulmonary syndrome is characterized by hypoxemia secondary to intrapulmonary shunt due to vascular dilation. In contrast with pulmonary hypertension that may be

aggravated by surgery for liver transplant, the hepatopulmonary syndrome's evolution is extremely favourable post transplantation with net amelioration or even complete resolution.

The cirrhotic patient might develop **pleural effusions**. The hydrothorax appears most frequently on the right side and generally accompanies ascites. It is due to an anatomical defect in the right hemidiaphragm. Sometimes, it might need drainage prior to surgery [11–13].

The cirrhotic patient may suffer from any other pulmonary disease not related to the chronic liver failure. Chronic obstructive pulmonary disease may be associated with cirrhosis, especially in smoker patients, resulting in obstructive respiratory insufficiency, which together with restrictive ascites dysfunction may greatly compromise respiratory function. Patients will be evaluated by a pneumologist for treatment and encouraged to quit smoking.

Since the necessary immunosuppression after transplantation may lead to reactivation of a dormant latent tuberculosis, it is mandatory to test transplant candidates for latent tuberculosis. This is done either with the tuberculin skin test or with the quantiferon TB test, a cell immune response assay using a *Mycobacterium tuberculosis*-like protein substrate.

Depending on the lung's status, investigations will be limited to a chest X-ray or will go further to pulmonary ultrasound or computed tomography (CT) scan of the thorax [14, 15].

2.3. Evaluation of renal function

Renal dysfunction in the cirrhotic patient is due to a decreased blood volume due to vasodilation, with a decrease in glomerular filtration. It may not be reflected correctly in serum creatinine levels; the end-stage liver disease patient often has a less muscle mass and a low creatinine production. Higher sensitivity tests are cystatin C or NGAL (neutrophil gelatinase-associated lipocalin).

Two types of kidney dysfunction are related to cirrhosis: hepatorenal syndrome is type 1 with rapid deterioration in renal function (doubling serum creatinine or increasing it to >2.5 mg/dl in less than 2 weeks) and a type 2 with slower evolution.

The occurrence of renal dysfunction can be precipitated by haemorrhage and infection [4, 16]. Preoperative renal dysfunction increases the risk of adverse development of postoperative complications.

2.4. Coagulation status

Coagulation abnormalities are caused by reduced concentrations of vitamin K-dependent factors and an imbalance between procoagulant and anticoagulant factors. Standard coagulation tests do not reflect rebalanced haemostasis and must not be used to predict the risk of bleeding. Procoagulant factors must not be administered unless signs of bleeding are present [17].

The Guidelines of the European Society of Anaesthesia regarding cirrhotic patients do not recommend routine preoperative correction of international normalized ratio (INR) (1.5–5) using fresh-frozen plasma but advise correction through point of care tests: rotational thromboelastometry or thromboelastography [18].

3. Conduct of anaesthesia

Despite recent advances, liver transplantation remains a major challenge to the anaesthetist due to the important cardiovascular changes throughout surgery: important changes in pre-load, afterload, arrhythmias, hypotension and hyperkalaemic events. All these increase the chances of severe cardiac dysfunction.

Liver transplantation is characterized by haemodynamic instability and various complications that can arise throughout the three important surgical phases: preanhepatic, anhepatic and neohepatic.

- **Preanhepatic:** dissection and liver mobilization takes place; usually massive bleeding can occur that can lead to hypovolaemia and haemorrhagic shock.
- **Anhepatic:** between clamping hepatic inflow and before graft reperfusion; consists of clamping of the inferior vena cava (IVC); significant decrease in cardiac output (CO) occurs.
- **Neohepatic:** characterized by liver reperfusion, reappearance of flow in the vena cava and vena porta, blood volume goes back to normal; can be complicated by reperfusion syndrome or bleeding from vascular anastomosis (hepatic artery, portal vein).

3.1. Patient monitoring during liver transplantation

Liver transplantation is performed under general anaesthesia, and the anaesthetic monitoring plays an important part in a successful liver transplantation as it can expose problems before irreversible damage occurs.

Haemodynamic instability is common during liver transplantation, and that is why the anaesthetic monitoring is complex, being divided into standard monitoring, haemodynamic (invasive and non-invasive), neurologic and neuromuscular monitoring.

3.1.1. Standard monitoring

According to the American Society of Anaesthesia (ASA) protocols, standard monitoring applies to all patients during all types of anaesthesia with the aim of increasing patients' quality of care. Trained personnel must be present in the operating room during the entire surgery, while continuous monitoring of the oxygenation, ventilation, circulation and temperature is mandatory [19].

Oxygenation: gas monitoring as the level of inspired oxygen (FiO_2) and the level of expired CO_2 (ETCO_2 capnography) and blood oxygenation in a continuous form as peripheral capillary oxygen saturation (SpO_2 pulseoxymetry).

Ventilation: chest movements and lung auscultation but also the volume of expired gas and capnography.

Circulation: continuous electrocardiogram (ECG) for rhythm, frequency, signs of ischaemia (ST segment), QT interval and measurement of blood pressure in a non-invasive way before induction of anaesthesia.

Temperature: central temperature is the blood temperature which bathes the vital organs (heart and brain). Important sites of measurement are the following: tympanic membrane, nasopharynx, distal oesophagus, blood, urinary bladder and rectum [20].

3.1.2. Haemodynamic monitoring

Patients with chronic liver disease usually present many other systemic complications including portal hypertension, ascites, coagulopathy, hyperdynamic circulatory syndrome (high cardiac index and low systemic vascular resistance) and cirrhotic cardiomyopathy. Due to all these changes, advanced haemodynamic monitoring is necessary. Monitoring parameters and normal values are shown in **Table 1** [21].

3.1.2.1. Invasive blood pressure

Invasive arterial pressure monitoring represents standard practice during liver transplantation. The arterial catheter is usually inserted in the radial artery and is being used for continuous pressure monitoring, blood gas analysis and other blood tests. Due to variations of radial artery pressure which may sometimes underestimate aortic pressure in hypotensive states, when high dose vasopressors are used and after reperfusion of the liver, some anaesthetists prefer using the femoral artery. Despite all these, the mean central and peripheral arterial pressures are usually the same [22]. An important problem when deciding the sites for catheter insertion is the cirrhotic coagulopathy which can lead to important puncture site bleeding. The number and sites of line insertion vary according to the transplant centre and experience.

3.1.2.2. Central venous pressure

Central venous pressure (CVP) monitoring is essential during liver transplantation. Central venous pressure is measured via a central catheter inserted in the superior vena cava system. Maintaining a low CVP in a normovolaemic patient can reduce the risk of bleeding but can increase the risk of vital organ hypoperfusion in case of a hypovolaemic patient or a massive bleeding [23].

3.1.2.3. Cardiac output and pulmonary artery pressures

Since its discovery, the pulmonary artery flotation catheter (Swan Ganz) has been considered the gold standard for cardiac output measurement. Swan Ganz catheters are still used routinely in some transplant centres around the world. A pulmonary artery catheter is mandatory if pulmonary hypertension is diagnosed or suspected.

Pulmonary artery pressures, cardiac output measurements and mixed venous oxygen saturation help in the diagnosis and management of haemodynamic instability during surgery. The new modified Swan Ganz catheters help anaesthetists with continuous cardiac output measurements and right ventricular end-diastolic volume as a more accurate parameter of preload.

Despite the massive use in the last 40 years, its high cost and patient safety have led to question its utility [24].

Parameter	Abbreviation	Formula	Normal value
Median arterial pressure	MAP	$SBP+(2 \times DBP)/3$	75–105 mmHg
Arterial oxygen concentration	CaO_2	$(0.0138 \times Hb \times SaO_2) + 0.003 \times PaO_2$	16–22 ml/dl
Venous oxygen concentration	CvO_2	$(0.0138 \times Hb \times SvO_2) + 0.003 \times PvO_2$	15 ml/dl
Peripheral capillary oxygen saturation	SpO_2	Measurement	95–100%
Arteriovenous oxygen difference	$C(a-v)O_2$	$CaO_2 - CvO_2$	4–6 ml/dl
Stroke volume	SV	$CO/HR \times 1000$	60–100 ml/beat
Stroke volume index	SVI	$CI/HR \times 1000$	33–47 ml/m ² /beat
Cardiac output	CO	$HR \times SV/1000$	4–8 l/min
Cardiac index	CI	CO/BSA	2.5–4 l/min/m ²
Central venous pressure	CVP	Measurement	2–6 mmHg
Central venous oxygen saturation	$ScvO_2$	Measurement	70–80%
Extravascular lung water	EVLW	$CO \times DSt-0.25GEDV$	
Extravascular lung water index	EVLWI	$EVLW/PBW$	0–7 ml/kgc
Global ejection fraction	GEF	$SV \times 4/GEDV$	>20%
Global end-diastolic volume	GEDV	$CO \times MTt \times f(S1/S2)$	
Global end-diastolic volume index	GEDI	$CI \times MTt \times f(S1/S2)$	650–800 ml/kgc
Intrathoracic blood volume	ITBV	$1.25 \times GEDV$	
Intrathoracic blood volume index	ITBI	$1.25 \times GEDI$	850–1000 ml/m ²
Left ventricular stroke work	LVSW	$SI \times MAP \times 0.0144$	8–10 g/m ² /beat
Left ventricular stroke work index	LVSWI	$SVI \times (MAP-PAOP) \times 0.0136$	50–62 g/m ² /beat
Mean pulmonary artery pressure	MPAP	$PASP+(2 \times PADP)/3$	9–18 mmHg
Oxygen consumption	VO_2	$C(a-v)O_2 \times CO \times 10$	200–250 ml/min
Oxygen delivery	DO_2	$CaO_2 \times CO \times 10$	950–1150 ml/min
Pulmonary artery occlusion pressure	PAOP	Measurement	6–12 mmHg
Pulmonary artery systolic pressure	PASP	Measurement	15–30 mmHg
Pulmonary artery diastolic pressure	PADP	Measurement	8–15 mmHg
Pulmonary vascular resistance	PVR	$80 \times (MPAP-PAOP)/CO$	<250 dynes/s/cm ⁵
Pulmonary vascular resistance index	PVRI	$80 \times (MPAP-PAOP)/CI$	255–285 dynes/s/cm ⁵ /m ²
Stroke volume variation	SVV	$SV_{max}-SV_{min}/SV_{mean} \times 100$	10–15%
Systemic vascular resistance	SVR	$80 \times (MAP-RAP)/CO$	800–1200 dynes/s/cm ⁵
Systemic vascular resistance index	SVRI	$80 \times (MAP-RAP)/CI$	1970–2390 dynes/sec/cm ⁵ /m ²

Table 1. Haemodynamic parameters.

3.1.2.4. Other ways of measuring cardiac output

The pulse contour analysis is useful for continuous monitoring of cardiac output and needs frequent calibration via thermodilution technique:

- PiCCO system (Pulse-induced Contour Cardiac Output): this consists of a thermistor catheter placed in the femoral artery and can estimate stroke volume. A central venous catheter inserted in the superior vena cava circulation is needed for the pulmonary calibration which must be done every 8 h in a haemodynamic stable patient and more frequent for unstable patients [25].
- LiDCO: it uses the same algorithm for stroke volume monitoring. Lithium chloride is used for transpulmonary calibration and can be injected into a peripheral vein.
- Transoesophageal echocardiography gives continuous information on ventricular function and volume status and allows immediate diagnosis of air or thrombus embolization. It also provides information regarding contractility, valvular function, pericardial or pleural effusion. Its main advantage is the ease of continuous use during surgery due to the anaesthetized and intubated patient [26].
- Thoracic bioimpedance: it estimates cardiac output and other haemodynamic parameters based on the electric properties of the thorax produced by blood movements during cardiac cycle; rarely used in liver transplantation.

3.1.3. Neurologic monitoring

- Bispectral index: Fourier analysis of a fronto-parietal electroencephalogram (EEG). It varies between 0 (coma) and 10 (normal cortical activity) with an adequate value between 40 and 60 in an anaesthetized patient [27].
- Transcranial Doppler echography can diagnose vasospasm, intracranial hypertension and cerebral death.
- Oxygen saturation in the jugular bulb (SjvO_2): continuous monitoring of venous oxygen saturation via a central catheter inserted in the internal jugular vein that shows the balance between oxygen intake and consumption. Values below 50% show ischaemia while values above 75% show cerebral hyperaemia.
- Transcerebral cranial oximetry: resembles SjvO_2 .
- Electroencephalogram: rarely used for continuous monitoring during surgery; requires a trained anaesthetist who must differentiate pathological changes from normal changes in a cerebral activity during anaesthesia.

3.1.4. Neuromuscular monitoring

Residual neuromuscular block after the use of neuromuscular blockade agents can have a detrimental effect in patients after surgery causing inadequate hypoxic ventilatory response, depressed pharyngeal tone leading to an increased risk of airway obstruction and death.

Peripheral nerve stimulation and depth of block can be assessed using single twitch, train of four, tetanic stimulation and double burst stimulation.

3.1.5. Other parameters monitored during liver transplantation

Other parameters monitored during liver transplantation include the following:

- hourly diuresis,
- haemoglobin and haematocrit,
- electrolytes,
- base excess and lactate,
- coagulation parameters via rotational thromboelastometry (ROTEM).

3.2. Haemodynamic management during the three phases of liver transplantation

3.2.1. Volemic resuscitation

Ever since the first successful liver transplantation in 1960, the surgery has been associated with significant bleeding and an increased amount of blood products transfused [28]. Blood products used during liver transplantation have declined significantly in the last 20 years. Even if bleeding risk has decreased over time, it still can induce a volemic stress.

Clamping of the inferior vena cava during the second phase (anhepatic) of the liver transplantation leads to an important decrease in preload, CO and arterial pressure which need a quick diagnosis and management. Normal response of right ventricle (RV) and left ventricle (LV) to stress does not take place due to all the substances released from the liver in the anhepatic phase.

Continuous assessment of patient's volemic status and the amount of perfused fluids represent the key to a successful liver transplantation. This can be done using dynamic measurements of CVP and pulmonary capillary wedge pressure (PCWP), but these parameters do not correlate with changes in CO [29]. Another way of assessing fluid responsiveness is the use of stroke volume variation (SVV) and global end-diastolic volume index (GEDI). Inadequate fluid therapy can lead to pulmonary oedema, abnormal gas exchange, congestion, a decrease in perfusion and oedema of the graft [30].

This study does not offer an answer for the ideal monitoring system and guiding of fluid therapy [31]. In our clinic, the guidance of fluid management is done with the pulmonary thermodilution technique and pulse contour wave analysis via the PiCCO system.

Using adequate vasoactive substances, which protect the brain, heart and kidney, led to a greater haemodynamic stability, adequate CO and renal perfusion [31]. The CVP can also be correlated with the severity of the post-reperfusion syndrome [32].

Specific fluid management during liver transplantation can be described according to the three surgical phases:

- Preanhepatic phase: cirrhotic patients usually have variate quantities of ascites; the anaesthetist must try and compensate it in order to reach normovolaemia and avoid hypovolaemia during the next phase (anhepatic) when clamping the inferior vena cava. Albumin of 20 or 5% is used for volemic resuscitation.
- Anhepatic phase: fluid restriction is the best solution in this phase while maintaining adequate arterial pressure with the help of vasopressors. The vasopressor of choice is noradrenaline, and the parameters measured with the PiCCO system can guide us to using inotropes such as dobutamine.
- Neohepatic phase: in this stage, the patient needs adequate volemic resuscitation guided by the PiCCO parameters; an important decrease in vasopressors takes place.

Albumin determines the oncotic pressure that keeps fluids in the intravascular space. Cirrhotic patients usually have low albumin levels [32]. Studies have shown that the use of albumin during liver transplantation decreases the amount of intraoperative fluids used and the frequency of pulmonary oedema in cardiac and noncardiac surgery [33]. It has also been proved that albumin decreases mortality in cirrhotic patients, decreases the incidence of post-reperfusion syndrome and the use of vasopressor agents [34].

The use of Hetastarch is not recommended as it affects platelet aggregability and increases the risk of bleeding by decreasing the concentration of coagulation factor 8 [33]. Gelatines can have numerous side effects: anaphylactic reactions, a decrease in thrombin generation and worsening of fibrinolysis which is specific in the anhepatic phase [35].

Manitol can be used in the anhepatic phase before clamping of the IVC (0.5 g/kg) in order to avoid blood congestion in the liver and intraabdominal organ oedema [36].

PiCCO monitoring has a number of advantages: accurate CO calculations and guiding fluid management. ITBV is an accurate parameter of preload even when IVC is clamped [37]. We can also use SVV in order to predict fluid responsiveness [38].

Fluid management is done using PiCCO parameters determined during the three phases of the liver transplantation. This guidance of fluid therapy decreases the post-anaesthesia care unit stay and mortality [39]. The decisional tree regarding fluid management is presented in **Table 2**.

TOE can also be helpful in high-risk patients with various cardiac problems. It has the advantage of direct assessment of cardiac contractility and assesses response to inotropes and volemic status. It can diagnose embolic complications and cardiac tamponade [40].

The use of different monitoring techniques is the key to successful management of haemodynamic instability and fluid guidance during liver transplantation.

3.2.2. Vasoactive substances and inotropes

There are a variety of substances that can be used when haemodynamic instability takes place during liver transplantation. Noradrenaline is most often used, followed by adrenaline and dobutamine. Indications are shown in **Table 3**.

CI < 3 l/min/m ²			
GEDI <700 ml/m ² or ITBI <850 ml/m ²		GEDI >700 ml/m ² or ITBI >850 ml/m ²	
ELWI <10	ELWI >10	ELWI <10	ELWI >10
Administer fluids	Administer fluids (limited) Vasopressor	Vasopressor	Vasopressor Fluid restriction
CI > 3 l/min/m ²			
GEDI <700 ml/m ² or ITBI <850 ml/m ²		GEDI >700 ml/m ² or ITBI >850 ml/m ²	
ELWI <10 ml/m ²	ELWI >10 ml/m ²	ELWI <10 ml/m ²	ELWI >10 ml/m ²
Administer fluids	Administer fluids	No measure	Fluid restriction

Table 2. Fluid therapy decisional tree.

3.2.3. *Postreperfusion syndrome*

Liver reperfusion takes place in the neohepatic phase and is the most unstable period during liver transplantation, representing a real challenge for the anaesthetist. The postreperfusion syndrome is defined as a 30% decrease in the mean arterial pressure that lasts for at least a minute and appears in the first 5 min after the unclamping of the inferior vena cava (IVC) [41].

It can have severe consequences due to a decrease in cardiovascular function with haemodynamic instability, abnormal acid base balance and metabolic abnormalities. Haemodynamic instability is the consequence of severe vasodilation, negative inotropic effects and massive bleeding which may appear during surgery. Graft reperfusion can have fatal consequences such as severe arrhythmias or asystole [42].

The incidence of PRS varies between 5.9 and 60% due to different surgical techniques, haemodynamic intraoperative differences and geographic factors (in some countries, the number of reduced donors led to marginal graft use-expanded criteria donors) [43].

Causes of PRS are not yet clear, but there are several theories. Dyselectrolytemia, cold solutions used for graft preservation and severe vasodilation due to NO release may contribute to PRS. Unclamping of the inferior vena cava leads to vasoactive pro-inflammatory substance released from Kupffer cells and which are the result of the postischaemic graft [44].

Substance	Indications	Dose
Noradrenaline	Arterial hypotension	0.2–1 µg/kgc/min
Adrenaline	Asystole, severe arterial hypotension	0.01–0.5 µg/kgc/min
Dobutamine	Cardiogenic shock	2.5–10 µg/kgc/min
Ephedrine	Arterial hypotension Before unclamping IVC	5–25 mg i.v. bolus every 10 min

Table 3. Main indications of inotropes during liver transplantation.

One of the most important elements released from the graft is potassium as a result of the portal venous congestion. All these substances can contribute to postoperative ischaemia and reperfusion lesions [45]. Another theory is represented by the pro-inflammatory cytokines (IL 1B, IL 2, IL 8, TNF- α) produced by ischaemia and released during the reperfusion of the graft leading to a marked inflammatory response and cellular death. They also have vasodilation and negative inotropic effect. The amount of pro-inflammatory cytokines released does not correlate with the duration of cold ischaemia time (CIT) [46].

Factors that may predict PRS are the following:

- donor-related: age, obesity, hypernatraemia (>155 mEq), hepatic steatosis, prolonged intensive care unit (ICU),
- intraoperative factors: duration of the surgery,
- cold ischaemia time exceeding 6 h.

Risk factors include

- patient's volemic status before reperfusion,
- myocardial depression (due to cold solutions released in circulation, abnormal acid base status),
- severity of metabolic acidosis.

Studies have shown that patients who had PRS have a higher risk of postoperative renal dysfunction and 15 days of mortality [43].

Postreperfusion syndrome leads to

- a decrease in arterial pressure and SVR,
- a decrease in CO,
- a moderate increase in PAP,
- frequent malignant arrhythmias.

Therapeutic options include the following:

- optimizing volemic status,
- adequate haemodynamic management,
- adequate graft perfusion; vasodilators are rarely used (calcium channel blockers, prostaglandins),
- liver graft wash with flush fluid of albumin 5% before IVC unclamping,
- correction of hypocalcaemia and hyperkalaemia,
- give ephedrine bolus 5 min before unclamping of the IVC in order to obtain a MAP of 85–100 mmHg [47].

3.3. Coagulation management

Cirrhotic patients have been regarded as having a high risk of bleeding due to standard coagulation test abnormalities caused by cirrhotic coagulopathy. Recent studies have shown that bleeding episodes are caused by vascular abnormalities and portal hypertension [48].

Standard coagulation tests (prothrombin time, INR and activated partial thromboplastin time (aPTT)) reveal the deficit of procoagulant factors without showing the status of the anticoagulant factors.

In order to have an optimal view regarding cirrhotic coagulopathy, global coagulation tests (viscoelastic tests) are recommended [49].

Intraoperative blood transfusion has a negative impact on patient outcome. Intraoperative packed red cells and platelet transfusion are independent predictors of 1 year mortality [50].

There are a few measures that can decrease the need of blood transfusion:

- maintaining a low CVP,
- use of antifibrinolytic agents,
- use of recombinant activated factor 7,
- use of point of care tests for transfusion guidance.

The most important coagulation problems that can appear during the three transplant phases are specific for each phase:

- Preanhepatic phase: bleeding occurs due to extensive dissection, collateral circulation and portal hypertension. Maintaining a normal volemic status may lead to dilutional coagulopathy and thrombocytopaenia [51]. A low CVP must be maintained in this phase. Cell saver can also be used after evacuation of ascites and before biliary anastomosis.
- Anhepatic phase: between clamping hepatic inflow and before graft reperfusion. Usually, minimal bleeding takes place here, but the risk exists. Platelets and coagulation factors are low due to loss and consumption from the previous phase. Synthesis and liver clearance do not exist. An increase in the release of tPA from endothelial cells and the absence of hepatic clearance can lead to hyperfibrinolysis and bleeding. Viscoelastic tests are mandatory for the diagnosis and management of hyperfibrinolysis.
- Neohepatic phase: bleeding can occur due to surgical problems or haemostatic abnormalities. Usually, hypothermia, metabolic acidosis and hypocalcaemia must be corrected before any further decision is taken. Platelets are seized in the liver graft after reperfusion causing important thrombocytopaenia. Some platelets are partially activated in the liver graft and released in the circulation as inefficient.

Hyperfibrinolysis can often appear during liver transplantation, but is self-limited as long as the liver graft is viable.

Antifibrinolytic agents can be used when diffuse bleeding occurs or when point of care tests show hyperfibrinolysis. In case of diffuse bleeding, the anaesthetist must correct hypothermia, acidosis, hypocalcaemia, treat hyperfibrinolysis and then administer fibrinogen 24 mg/kg and platelets.

4. Conclusion

Anaesthesia for liver transplantation is one of the most difficult anaesthesias. This is due to the haemodynamic problems that can occur in the intraoperative, related both to the status of the patient (cardiomyopathy of the cirrhosis, etc.) and to the surgical moments (bleeding and reperfusion syndrome) as well as to the blood coagulation pattern of the patient.

A good understanding of the pathophysiology of the cirrhotic patient is very important for best decision making. Adequate perioperative management is extremely important for a successful liver transplantation with a good outcome.

Conflict of interest

The authors have no conflict of interest to declare.

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