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Chapter

Hepatic and Endocrine Aspects of Heart Transplantation

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Abstract

End-organ dysfunction is a progression that can often develop in patients with end-stage heart failure. Hepatic abnormalities in advanced systolic heart failure may affect several aspects of the liver function. Hepatic function is dependent on age, nutrition, previous hepatic diseases, and drugs. The hepatic dysfunction can have metabolic, synthetic, and vascular consequences, which strongly influence the short- and long-term results of the transplantation. In this chapter, the diagnostic and treatment modalities of the transplanted patient will be discussed. On the other hand, endocrine abnormalities, particularly thyroid dysfunction, are also frequently detected in patients on the waiting list. Endocrine supplementation during donor management after brain death is crucial. Inappropriate management of central diabetes insipidus, hyperglycemia, or adrenal insufficiency can lead to circulatory failure and graft dysfunction during procurement. Thyroid dysfunction in donors and recipients is conversely discussed.

Keywords: hepatic dysfunction, heart transplant, MELD score, thyroid function, donor management, endocrine dysfunction

1. Introduction

The increased need for transplantation cannot be met because of the shortage of the available grafts. In the last decades, the number of heart transplantation has not increased. As a consequence, the patients will be longer on the waiting list, becoming older and having more severe end organ dysfunction, or even they lose their candidacy for transplantation because of the irreversible hepatic or liver failure. Bridging techniques, such as temporary extracorporeal circulation or implantable mechanical assist devices, may improve and reverse the end-organ failure and transplantation can be done. The physician of the transplantation team must be familiar with the diagnosis and possible treatment of these organ dysfunctions. Recently, recognition and extended investigation of the end-stage heart-failure-related hepatic failure have been highlighted, since the liver dysfunction can worsen in the posttransplantation period through hypoxic hepatitis or by the immunsuppressive medications, which should be taken lifelong.

Besides the liver, another important system, the endocrine hormones, must be strictly followed in the perioperative period. End-stage heart failure can cause thyroid dysfunction, and it can lead to circulatory failure or hemodynamic instability.

Amiodarone, a frequently applied antiarrhythmic drug, can cause severe hypo- or hyperthyreosis. In the postoperative period, the physicians must distinguish the nonthyroidal illness syndrome from the chronic illness-related thyroid dysfunction. Endocrine replacement must be also initiated during the donor procurement to decrease the graft loss or the graft dysfunction in the posttransplant period.

In this chapter, we aimed to describe briefly the basic liver function, the diagnostic modalities in the preoperative evaluation, and the special considerations related to transplantation care. The endocrine part will overview the thyroid dysfunction, the treatment of central diabetes insipidus, and the posttransplantation endocrine management.

2. Hepatic aspects of heart transplantation

2.1 Basic anatomy and physiology of the liver

The human liver is wedge-shaped with two lobes, and it weighs cca 1.5 kg [1, 2]. The hepatic artery via the celiac trunk and the portal vein are the main blood supply of the liver. The liver receives approximately one-fourth of the cardiac output, which secures one-third of the blood supply, and the rest will be supplied by the portal system. These blood vessels divide into small capillaries, called hepatic sinusoids, which then build the lobules. Lobules are the functional units of the liver. Each lobule is made up of hepatocytes. The lobules are held together by fibroelastic connective tissue that extends from a fibrous capsule covering the entire liver [3]. The function of the liver is very complex and diversified. Liver has excretion function, including synthesis and excretion of biliary acids. Furthermore, liver also plays a key role in endocrine homeostasis in the metabolism of various hormones. To understand the potential perioperative issues, it is necessary to review the complex role of the liver in the human body. Oxidative capacity decreases with the age and congestive disorders, which may cause delayed drug metabolism [4].

2.2 Congestive heart-failure-related hepatic dysfunction

Heart failure with reduced ejection fraction can alter many pathways in the liver. As a forward failure due to (the) low cardiac output syndrome, reduced systolic function leads to hypoperfusion, while backward failure caused by biventricular or isolated right ventricular dysfunction will result in venous congestion. As a response for the constantly elevated high pressure in the inferior caval and hepatic veins, the perivenular space of the lobule will be dilated, and fibrotic transformation will be initiated. As the congestive state persists, perivenular-perivenular bridging develops, which has less effect on centrally located portal tracks. This pattern is the reverse lobulation. As the circulatory failure progresses, the portal part also undergoes fibrotic transformation and complete congestive hepatopathy may develop. The collagen is deposited in the subendothelial region and in the Disse space. The elevated right ventricular pressure can now affect the portal circulation, causing cirrhotic portal hypertension. The well-known symptoms of cirrhosis, such as ascites and development of the varices of esophageal veins, are often present. Laboratory parameters remain unchanged or minimally elevated in the early phase of the congestion. Only elevation of aspartate aminotransferase (AST) and alanine transaminase (ALT) may be abnormal, an increase in bilirubin or obstructive enzyme

(alkaline phosphatase, ALP) levels is frequently seen. Highly elevated transaminase levels and increased bilirubin levels are more common in advanced or end-stage liver failure, usually associated with acute on chronic heart failure.

2.3 Preoperative evaluation algorithms

Routine laboratory tests, including hepatic function tests, are good but rough indicators of hepatic dysfunction in the pre-transplant period. It should be stressed that normal transaminase and serum bilirubin levels are not suitable for early detection of hepatic problems. As shown in the scores presented, elevated serum bilirubin levels and spontaneous prolonged coagulation are strong predictors of a negative outcome. Nonalcoholic fatty liver disease is a sign that the congestion has reached a distinct stage caused by heart failure with or without reduced ejection fraction. Transient elastography is a good and reliable method to measure fibrotic transformation of the liver. In the decompensated period of advanced heart failure, fibroelastography shows higher than real fibrotic results.

Liver biopsy is the most accurate way to assess fibrotic transformation of liver tissue. In some advanced cases, a liver biopsy can be used to rule out candidates for a heart transplantation or to determine the need for combined heart and liver transplantation [4]. Existing gallstone should be removed before surgery as it is potential infectious focus.

2.4 Laboratory tests

The classic laboratory tests for estimating hepatic function are serum bilirubin, transaminases (ALT, AST), alkaline phosphatase, lactate dehydrogenase, total serum protein and albumin, serum bilirubin, and coagulation parameters, especially prothrombin time. Most patients with advanced heart failure were found to have moderately elevated levels of transaminase in random blood samples. Chronic anticoagulation can influence the prothrombin levels and must be considered in the calculation of model for end-stage liver disease (MELD) scores.

In acute hypoxic hepatitis, transaminases (AST, ALT) can rise more than 100-fold above normal ranges. This increase reflects the severity of centrolobular hepatic necrosis. Peak transaminase is usually expected within 12–24 hours, and normalization take 2 weeks with treatment. Abnormalities in alkaline phosphates and serum bilirubin levels are less common. Prolonged prothrombin time has important prognostic value. Thrombocytopenia, if present, occurs simultaneously with prolonged prothrombin time. Renal failure is often associated with global hypoperfusion.

2.5 Hepatic vein flow Doppler measurement

Nowadays, hepatic vein flow measurement using duplex Doppler technic is an arising increasingly common method of assessing changes caused in heart failure. It may also be useful and feasible for noninvasive hemodynamic monitoring in acute conditions. Accurate interpretation of spectral Doppler tracing from hepatic veins is valuable, because they reflect important cardiac and hepatic physiology. There are usually four phases: A, S, V, and D; the S and D waves indicate the antegrade flow toward the heart. In hepatic and cardiac disease, these normal waves may be absent, indicating non-physiological flow in the hepatic circulation. In addition, transient patient factors, such as phase of the respiratory cycle, may can affect the appearance

of the spectral trace. Knowledge of the normal and abnormal spectral Doppler waveforms of the hepatic veins and the corresponding physiology and pathophysiology provide valuable insights. Systematic analysis of the direction, regularity, and phasing of the spectral trace and the ratio of S- and D-wave amplitudes allows in most cases a correct differential diagnosis [5].

Under abnormal conditions, the normal triphasic pattern is altered, and the original waves may not exist or be distinguishable. The biphasic pattern may indicate severe tricuspid valve regurgitation and/or acute right ventricular overload. Normally, the hepatic vein spectrum shows the normal S-wave to D-wave ratio, where the S-wave is larger than the D-wave. According to Scheinfeld, there are three types of right-sided heart failure. (According to its classification, in mild tricuspid regurgitation, the relationship between the S-wave and the D-wave changes, with the S-wave being smaller than the D-wave.) Type 1 tricuspid regurgitation is classified as a change in the relationship between the S-wave and the D-wave, with the S-wave being smaller than the D-wave. However, there is still antegrade flow during the ventricular systole. In type 2 tricuspid regurgitation, there is no systolic flow during the ventricular systole. In type 3 tricuspid regurgitation, there is retrograde flow during the ventricular systole [5].

In the early state of fibrotic hepatic transformation or nonalcoholic fatty liver disease (NAFLD). the hepatic vein waveform may be remarkably damped due to stiffness of hepatic tissue and vessel walls. Flow pattern changes, such as monophasicity or blunt waveform, are also often observed in these conditions. Hepatic vein flow patterns also suitable for follow-up of the right ventricular function, the severity of tricuspidal regurgitation, and the venous congestion during the perioperative period. On the pictures 1 and 2, hepatic vein flow patterns are shown (**Figure 1**).

2.6 Transient elastography

Transient elastography (TE) is a noninvasive, simple, fast, and highly accurate clinical examination method. During TE, a special probe is used to measure the liver stiffness, which correlates well with the fibrotic hepatic remodeling [6]. However, the test has high reliability and may overestimate the level of liver fibrosis depending on the severity of decompensation. Thus, the examination should be planned in an elective setting with relatively well-compensated patient [7, 8].

In the literature reports could be seen with examination of the relationship between chronic coronary syndrome and nonalcoholic fatty liver disease (NAFLD). Reports have appeared in the literature examining the association between chronic coronary syndrome and nonalcoholic fatty liver disease (NAFLD). These findings are noteworthy because the liver structure transformation begins before the presence of a notable reduction in global cardiac function or congestive right heart failure [9].

2.7 Risk stratification system

Precise multidisciplinary risk assessment in the pre-transplant period is a key factor. The possible contraindicating coexisting diseases and states should be ruled out. The risk estimation can be helpful in planning, preparing, and managing the intraoperative and postoperative period. For preoperative hepatic dysfunction, two scores are mostly used. The Child-Pugh score is a traditional risk estimation method.

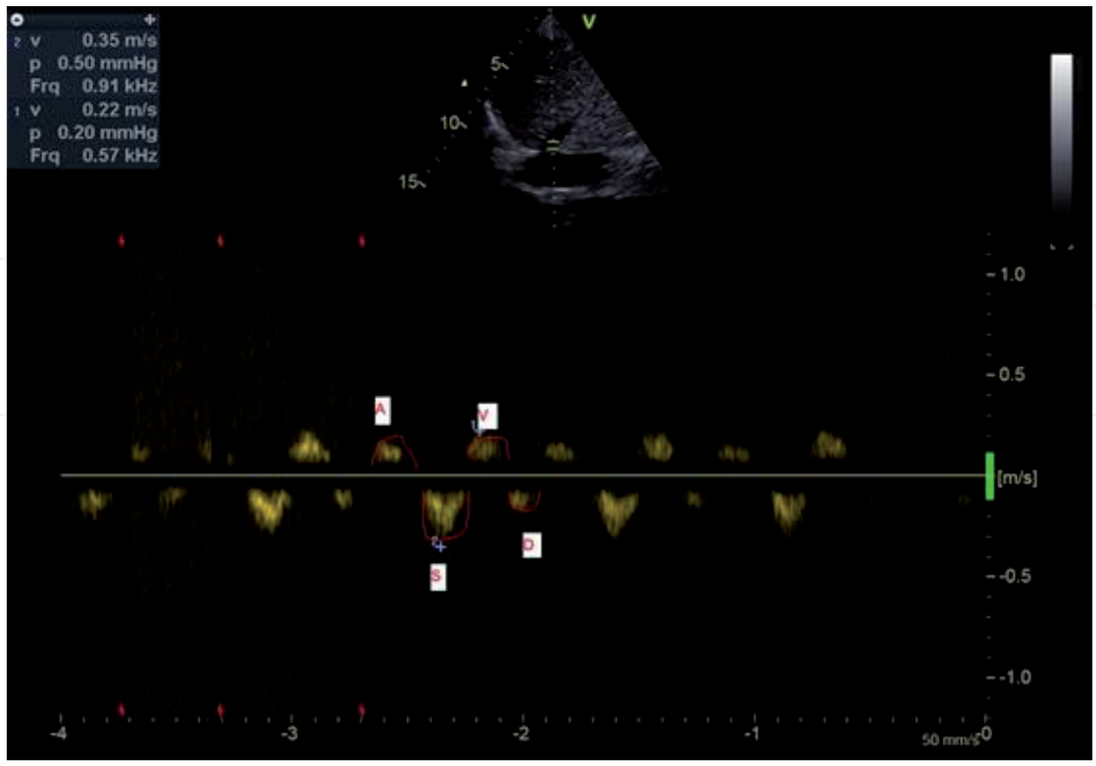

Figure 1.
Hepativ vein flow pattern.

The Child-Pugh score was based on serum bilirubin and albumin levels, international normalized ratio (INR), and the presence of ascites and encephalopathy. While the Child-Pugh score is useful for risk stratification in the clinical practice, MELD score(s) are more feasible for patients admitted to intensive care unit (ICU) due to their better prognostic value and lower negative likelihood ratio [10].

2.7.1 Model for end-stage liver disease (MELD) score

MELD score was originally developed to predict mortality in patients with hepatopathy and/or cirrhosis after porto-jugular shunt placement. The baseline MELD score gives an estimate of 3-month mortality as a function of the need for dialysis, INR, serum bilirubin, and creatinine (**Table 1**) [11].

$$MELD\ score\ calculation = \left(0.957 \times \ln\left(seCreat\right) + 0.378 \times \ln\left(seBilirubin\right) + 1.120 \times \ln\left(INR\right) + 0.643\right) \times 10 \quad (1)$$

The MELD score has several modifications according to the patients' comorbidities. MELD XI score excludes INR from the equation. MELD XI is promoted for use in patients receiving anticoagulant therapy. Frequent anticoagulant therapy in end-stage heart failure emphasizes the INR-independent MELD score.

Since UNOS (United Network for Organ Sharing) started using the MELD score, its importance for estimating the risk of liver complications and mortality before heart transplantation is unquestioned. Use of Na-corrected or XI (INR excluded) MELD scores in patients with end-stage heart failure in the pre-transplant period is the basics for liver failure risk estimation [12].

Parameter, factor	Range
Dialysis twice at the last week (or continuous veno-venosus hemodialysis ≥24 hours at last week)	yes/no
Creatinine	normal range: 62–115 μmol/L (0.7–1.3 mg/dL)
Bilirubin	normal range: 5.13–32.49 μmol/L
INR	0.8–1.2
Sodium	normal range: 136–145 μmol/L (mEq/L)

Table 1.
The components of updated MELD score (used for 12 years and older patients after 2016).

3. Perioperative considerations

3.1 Synthetic dysfunctions in perioperative period

Decreased serum albumin levels are present in 30–50% of patients, but the serum level is usually not less than 25 g/L. Low albumin levels do not correlate with hepatic injury, but are associated with nutritional impairment and protein wasting. The serum albumin level is an independent risk factor for mortality after heart transplantation [13]. Multiple studies suggest that serum albumin level under 35 g/L is related with worse mortality. Intravenous albumin substitution was not proven useful in the perioperative period.

Mild increase of the prothrombin time (PT) indicates a secondary impairment of the coagulation factor synthesis. In case of portal hypertension, the protein content of the ascites is usually more than 25 g/L and the ratio higher than 1:1 (serum albumin to ascites albumin). Some studies have reported a significant relationship between central venous pressure, low cardiac index, and elevated total bilirubin, AST, or ALT levels [14]. Increased transaminase levels correlate with the severity of hepatocellular injury caused by hypoperfusion. Increased direct bilirubin and ALP with ALT/ALP levels are markers of cholestatic injury and increased venous congestion. Increased bilirubin levels have been reported to be associated with high inotropic requirement, low cardiac output states, early readmission, in patients with advanced heart failure [15].

3.2 Hepatic dysfunction in patients during mechanical circulatory support (MCS)

End-stage heart failure patients with significantly impaired end-organ dysfunction often need a bridging method to become candidates for heart transplantation. For these patients, more frequent use of various mechanical circulatory supports may be a solution. However, even short to medium periods of support for planned pathophysiological changes caused by devices should be of concern. Short-term devices (veno-arterial extracorporeal membrane oxygenation, VA-ECMO) and various mid-term ventricular assist devices, such as left ventricular assist device (LVAD) or biventrular assist devices (BIVAD), also have a major impact on complex physiological processes. In case of LVAD implantation—similar than in heart transplantation cases—the low serum albumin level (≤35 g/L) is related to worse survival (**Figures 2** and **3**) [16].

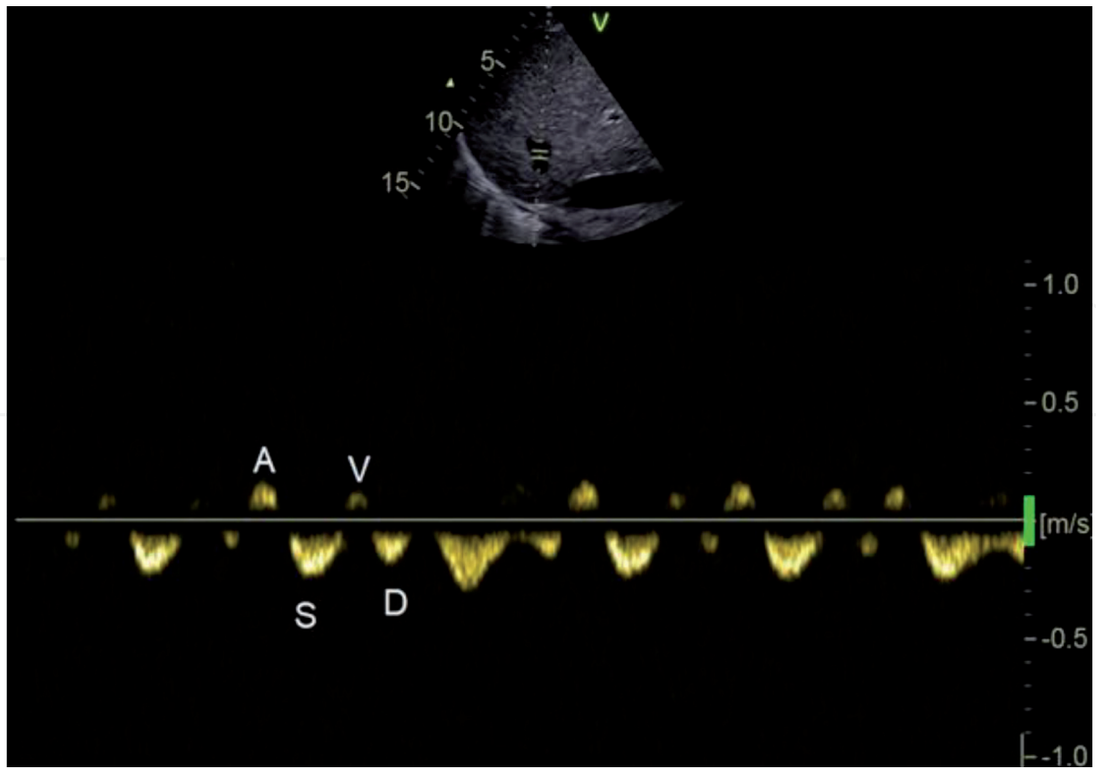

Figure 2.
Normalization of hepatic vein flow pattern in a patient with end-stage heart failure on BiVAD treatment for 85 days. The flow pattern is normal with minimal retrograde flow in venticular systole.

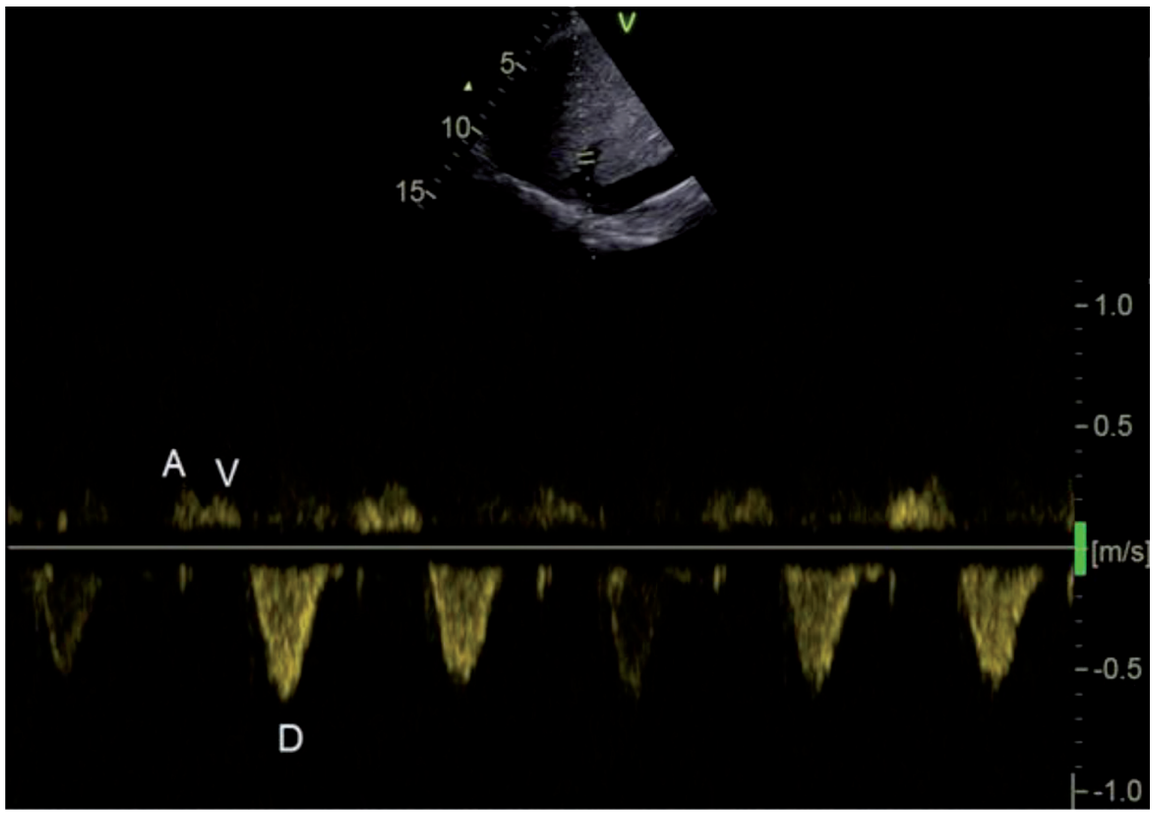

Figure 3.
Hepatic vein flow in a patient with end-stage heart failure treated with implantable LVAD for 22 days. Regarding grade 3 tricuspidal regurgitation, prominent V wave could be seen. Often the A, S, and V waves are fusional and indicate severe retrograde flow during the global systole.

3.3 Lactic acidosis, decreased lactate clearance

The liver is 60% responsible for the elimination of lactate via the Cori cycle, (lactate is therefore a glycogen precursor molecule). Renal lactate excretion is meaningful as serum lactate levels above 6–8 mM. In cirrhosis patients, lactate clearance is decreased, which can lead to type B lactic acidosis caused by reduced activity of lactate dehydrogenase. A parallel problem is the dysregulated carbohydrate balance. Without a well-functioning hepatic enzyme system, accumulated substrate levels slowly return to normal.

3.4 Coagulation disorders

In intraoperative settings, hepatic impairment is often associated with hemostatic disorders. The liver plays a crucial role in hemostasis through the synthesis of procoagulants, anticoagulants, and components of the fibrinolytic system, as well as the clearance of activated clotting factors. In hepatic dysfunction, these synthetic functions are insufficient, and hemostatic changes within and between procoagulant, anticoagulant, and fibrinolytic systems result in a new balance, defined as a rebalanced hemostatic state. This conception is defined as a) dysfunction in thrombin generation/disturbance in thrombus production and b) instability in the face of relatively small disturbances that commonly lead to a disruption of the balance between bleeding or thrombotic events [17].

The most sensitive laboratory parameters are prothrombin time (PT) and partial thromboplastin time (PTT), which are sensitive to reduced levels of procoagulants but not to anticoagulants; this has led to the erroneous assumption in the past that patients with liver disease are auto-anticoagulated and are protected against thrombosis. Nevertheless, PT and INR are not reliable risk factors for bleeding after surgery or invasive procedures [17, 18].

Under VA-ECMO support, patients with preexisting hepatic dysfunction have increased morbidity and mortality, with obviously serious implications for the planning and further bridging [19]. According to the current recommendations for the implantable LVAD devices, the candidacy for implantation must fulfill strong criteria in their hepatic function. Mid-term and especially long-term LVADs are associated with serious side effects by altering the molecular mass spectrum of von Willebrand factor (vWf). A kind of degradation (more precisely multimerization into smaller molecules) of von Willebrand factor caused by shear stress associated with mechanical circulatory devices can lead to device specific coagulopathy and unexpected and defective angiogenesis—smaller multimers of vWf may act as vascular endothelial growth factor. The clinical context is often driven by unexplained bleeding from interstitial angiodysplasias. The acquired von Willebrand factor dysfunction type of hemostatic dysfunction is diagnosed mostly by viscoelastic tests [20].

Furthermore, coagulopathy based on hepatic dysfunction is often accompanied by thrombocytopenia. Platelet function seems to be normal in patients with cirrhosis, but intrinsic dysfunction has not yet been confirmed [21].

4. Immunosuppressive therapy and the liver

A major function of the liver is drug metabolism. Drugs given in the perioperative period, lifelong immunosuppressive therapy often interact with the liver. In the

perioperative period, special attention should be paid to hepatic function problems caused by immunosuppressive therapy. The impaired liver condition before surgery makes these interactions more complex and difficult.

In heart transplant patients, the drugs that induce immunosuppression are mostly antithymocyte globulin (ATG). ATG is safe to use in liver failure; however, some case reports have reported extremely elevated transaminase levels within a few hours of infusion. Liver damage associated with ATG therapy is usually mild and asymptomatic, self-limited [22].

Calcineurin inhibitors are metabolized by the liver's P450 enzyme system (CYP 3A4). The most commonly used calcineurin inhibitors are cyclosporin and tacrolimus. Initiation of cyclosporine therapy may sometimes be associated with a slight increase in serum bilirubin levels, often without a considerable increase in serum ALT or alkaline phosphatase. Tacrolimus therapy is associated with a mild to moderate increase in serum aminotransferase levels in 5–10% of patients. Rises in serum aminotransferase levels are usually mild, asymptomatic, and self-limiting, but occasionally persistent and may require a dose modification. Tacrolimus has also been implicated in the development of cholestatic hepatitis, but clinically apparent liver damage is rare [22].

Corticosteroids are the basis of the immunosuppressive therapy, particularly in the early period and in case of rejection. Corticosteroids also have major effects on the liver, particularly when given in long term and in higher doses. Glucocorticoid usage may result in liver enlargement, steatosis, or glycogenosis. Hepatomegaly and moderate elevation of serum aminotransferase levels are common in glycogenosis. There is little or no change in alkaline phosphatase and serum bilirubin levels. Furthermore, steroids can aggravate nonalcoholic fatty liver disease. Long-term therapy can also worsen chronic viral hepatitis. Thus, hepatic complications of corticosteroids are mostly associated with high intravenous dosing and usually represent the worsening or triggering of an underlying liver disease, and rarely are the result of drug

Modality	Information	Pathology	Optimal timing
Laboratory tests	Transaminase levels	Hepatocellular injury caused by congestion Excessively increased levels often seen in hypoperfusion NB: viral hepatitis, medical therapy	Routinely preoperative examination and heart failure care (monthly)
	Serum bilirubin level	Indicator of severe hepatic (conjugation) function loss	
	Albumin, Total protein	Related to the hepatic synthetic function and nutritional state (NB: adsorption problems, protein loss in enteropathy)	
	INR, PT	Indicator of hemostatic disorders regarding synthesis of coagulation system factors	
Transient elastography		Classification of hepatic fibrotic transformation	Before transplantation in well compensated state
Biopsy	Microscopic structure of liver tissue	Classification of fibrotic transformation/cirrhosis	Before transplantation in case of serious indication

Table 2.
The preoperative examination modalities, their focus and optimal timing before the heart transplantation.

hepatotoxicity. High doses of intravenous corticosteroids, such as those used in anti-rejection shot therapy, are rarely associated with fatal acute liver injury [22].

Among antiproliferative agents, azathioprine and mycophenolate-mofetil (MMF) are commonly used in heart transplant patients. Azathioprine has a worse side effect profile, including severe hepatic problems, so MMF is usually preferred. In mild cases, azathioprine has been associated with a transient and asymptomatic rise in serum aminotransferase levels, which is associated with acute cholestatic damage in the first year after initiation of therapy. Chronic damage to the liver characterized by peliosis hepatis, veno-occlusive disease or nodular regeneration is typical with long-term use. Hepatocellular carcinomas have also been reported with long-term azathioprine use. In contrast, MMF use is safe, with side effects mostly nausea and digestive problems that respond well to dose reduction (**Table 2**) [22].

5. Thyroid function and transplantation

Nonthyroidal illness (NTI) is a syndrome that is observed in critically ill patients. As the name suggests, it is not a primary endocrine disease, but a result of severe systemic stress. Many conditions can lead to a generalized stress, such as severe infection, sepsis, prolonged starvation, bone marrow transplantation, extensive myocardial infarction, end-stage heart failure, heart transplantation, or any potentially life-threatening condition [23]. As for the changes in hormone levels, plasma T3 levels decrease, followed by a decrease in plasma T4 levels, while rT3 levels show an increasing trend. This is due to both altered protein binding and altered deiodinase enzyme activity. However, in the vast majority of cases, plasma TSH levels remain unchanged or decrease slightly [24]. In the international literature, several synonyms for nonthyroidal illness are common, such as euthyroid sick syndrome or low T3 syndrome (**Table 3**) [23].

The course of nonthyroidal illness can be divided into two basic phases, an acute phase and a chronic phase. The first acute phase is observed during a sudden change in critical condition. The main laboratory parameters in the acute phase are characterized by decreased peripheral free T3 levels and elevated rT3 concentrations. This is due to mechanisms such as reduced binding of plasma proteins to thyroid hormones and altered activity of certain deiodinase enzymes (D1, D3). In fact, the acute phase of NTI is an adaptive response to a reduced nutrient supply to the body due to a critical condition. Consequently, this phase of NTI, whose primary purpose is to reduce the catabolism of the body, has a positive effect on the body [24]. Other research has also observed that during starvation, the catabolism of peripheral skeletal muscle slows down as T3 levels decrease, while thyroid hormone administration increases its breakdown again [25, 26]. However, some research is in stark contrast to this view, as there is no correlation between a decrease in T3 levels during starvation and a concomitant decrease in peripheral skeletal muscle breakdown [27].

In the event that the acute phase is prolonged, the adaptive response that initially seems beneficial is replaced by a phase that is already less beneficial to the body. This is the chronic phase of NTI. In terms of thyroid laboratory parameters, not only the T3 but also the T4 levels start to decrease, while the plasma TSH levels fall below the lower limit of the normal range [24]. According to one study, these changes are due to a decrease in hypothalamic TRH secretion for an as yet unknown reason. This is because the research team found an association between TRH gene expression and plasma T3 and TSH levels [28]. During the chronic phase, adaptive mechanisms are developed in the peripherical located tissues to maximize the utilization of reduced thyroid hormones: increased

Nonthyroidal illness syndrome		
	Acute phase	**Chronic phase**
other names	"Low T_3 syndrome"	"Central hypothyroidism"
CAUSE	Starvation, stress, inflammation	Endo–/exogen dopamine, cortisol
T_3	↓	↓↓
T_4	↑	↓
rT_3	↑↑	↑
TSH	↑/normal (no peak)	norm./↓ (no pulsatility)
TRH	Normal	↓
TBG, albumin	↓	↓
D_1 ($T_4 \rightarrow T_3$)	↓	↓
D_3 ($T_4 \rightarrow rT_3$)	↑	↑
D_2 ($T_4 \rightarrow T_3$)	Normal	↑ (feedback)
Receptor sensitivity	Normal	↑
Result	Adaptive, useful	Maladaptive
Hormonal replacement	Not recommended	Considerable

Table 3.
Hormonal changes in NTI.

transcription and activity of the D2 enzyme, increased localization of certain transporters, and increased activity of active isoforms of TRs' expression [24].

A clear, definite pathomechanism for the nonthyroidal illness syndrome has not been established. Samples of muscle and liver tissue from several patients who died in intensive care units (ICU) were collected. Biopsies from liver and muscle tissue from died patients were found to be increased in the expression of type 3 deiodinase enzymes and decreased in the expression of type 1 deiodinase enzymes. Blood collected from died patients showed decreased total T3, T4, TSH levels, while rT3 levels were higher than normal. In this study, a correlation was found that the plasma T3/rT3 ratio was positively correlated with the expression of type 1 deiodinase enzyme [29]. rT3 level, T3/rT3 ratio and D3 enzyme expression measured on the very first day of ICU admission may have prognostic value for mortality [30].

In the chronic phase of NTI, decreased TRH gene expression may be strongly influenced by increased D2 enzyme activity mediated by inflammatory mediators, transcription factor NFκB (nuclear factor κB), and corticosterone [31, 32]. Certain drugs, such as dopamine can keep plasma T3, T4, and TSH levels, are low [33]. The role of different drugs in the suppression of the hypothalamic–pituitary-thyroid axis is conversely discussed [34, 35]. This association could not be demonstrated by another study group that used dopexamine and dobutamine simultaneously in high-risk surgical patients (**Figure 4**) [35].

5.1 Amiodarone

Amiodarone is a commonly used antiarrhythmic drug in patients with end-stage heart failure. Moreover, antiarrhythmic treatment of atrial or ventricular arrhythmias with amiodarone is an effective and widely known phenomenon in clinical practice. Amiodarone maintains normal sinus rhythm in patients with atrial fibrillation (AF)

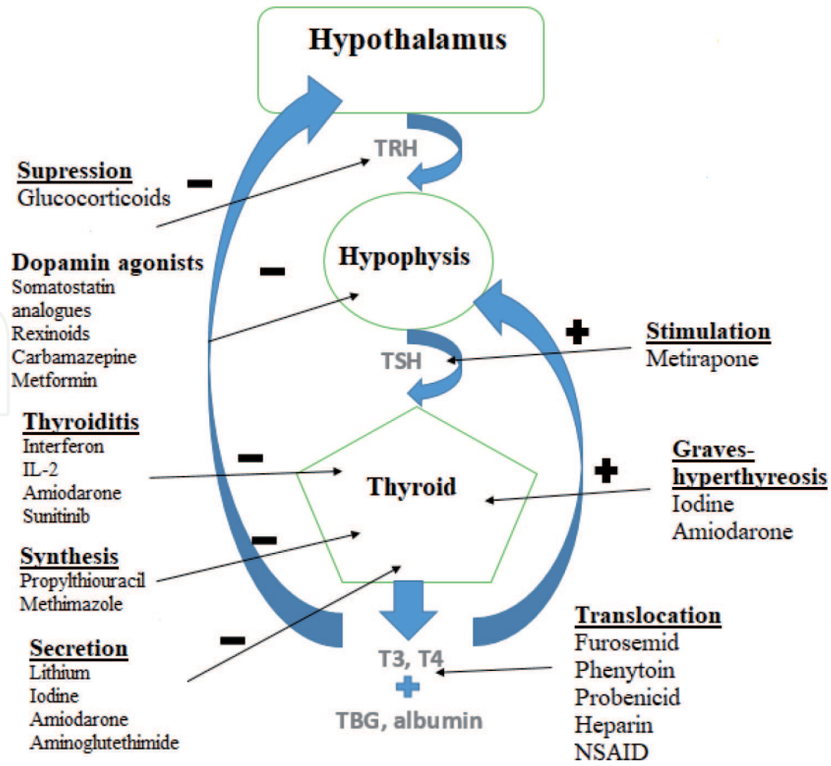

Figure 4.
Regulation of hypothalamic–pituitary-thyroid axis.

and also reduces the recurrence rate of ventricular tachycardia. Amiodarone remains the preferred treatment, particularly for patients awaiting heart transplantation (HTX). Due to its slow distribution in body's tissue, amiodarone may take several months to reach steady-state tissue concentrations and to exert a sufficient antiarrhythmic effect. In addition, the registered half-life of amiodarone is highly variable. Because of this phenomenon, the administration of amiodarone before transplantation has been controversially discussed in the literature, and different results have been reported for morbidity and mortality after heart transplantation [36, 37].

The administration of this antiarrhythmic medication may increase the probability of one-year mortality, graft failure, transplantation, and permanent pacemaker implantation [38]. Amiodarone-induced hypothyroidism (AIH) and amiodarone-induced thyrotoxicosis (AIT) can also occur during chronic administration. In addition, there is a mixed/indefinite form to which both pathogenic mechanisms mentioned above contribute. Type 1 AIT develops in patients with preexisting thyroid disorders, while type 2 AIT occurs in substantially normal thyroid gland. On the one hand, the rate of serious adverse cardiovascular events was three times higher in AIT compared with euthyroid patients [39]. On the other side, several studies demonstrated the safety of amiodarone in end-stage heart failure and in early postoperative atrial fibrillation [36, 37].

6. Donor management

Endocrine dysfunction is common in severe brain injury. Traumatic brain injury is usually associated with increased intracranial pressure, which can be followed by a brainstem herniation, resulting in brainstem infarction [40]. Ischemic lesions can cause dysfunction in the hypothalamic–pituitary axis. One of the most frequent

complications is the posterior pituitary deficiency, characterized by central diabetes insipidus (CDI). Arginine vasopressin (AVP) deficiency can cause inadequate diuresis with hypovolemia, hyperosmolality, and hypernatremia [41]. Anterior pituitary gland dysfunction has also been detected with hypothyroidism and hypocortisolemia. Lack of these hormones may lead to hemodynamic instability, with reduced myocardial function, hypovolemia, inadequate stress response, increased proinflammatory condition. Each of them can impair graft function [42, 43]. Endogenous catecholamine release is enhanced in both neurological death and acute critical illness. Although it causes increased systemic vascular resistance, cardiac output is compromised by myocardial suppression induced by neurological death and by a reduced thyroid hormone release due to pituitary gland deficiency. Therefore, a theoretical advantage exists for exogenous thyroid hormone supplementation [44].

6.1 Arginine-vasopressin

Arginine-vasopressin should be considered if hypotension persists despite adequate volume resuscitation or if central diabetes insipidus (CDI) occurs. Damage of the posterior lobe of the pituitary gland, hypothalamic paraventricular nuclei, and supraoptic nuclei results in undetectable or low levels of AVP. The deficiency of AVP can lead to inadequate diuresis and is associated with hyperosmolality, hypovolemia, and hypernatremia, which is consistent with DI. In addition, even in patients who do not meet the criteria for DI, baroreflex-mediated secretion of AVP can be impaired in response to decreased hypotension and decreased circulatory volume. Appropriate therapy with early intervention can restore hemodynamic stability and prevent end-organ damage. A recent analysis of the OPTN database has shown that the administration of AVP in organ donors is independently associated with an increased rate of organ recovery. The study did not recommend indications for AVP use (such as DI and hypotension). Prolonged hypernatremia ($Na^+ > 155$ mmol/L) due to untreated DI has been associated with postoperative graft dysfunction in several retrospective studies and one prospective study; however, this association was not generally reported. Maintaining normal sodium levels remains a reasonable goal of the appropriate treatment. Hypernatremia, excessive diuresis, and volume depletion can occur for reasons other than DI (e.g., osmotic diuresis due to hyperglycemia or mannitol administration) and should be investigated [45]. Treatment of AVP deficiency could be considered if hypotension persists despite adequate resuscitation or in the presence of DI, which is likely to occur if one or more of the following criteria are identified, unless there is another cause of the disorder: polyuria (urinary output>3–4 l/d or 2.5–3.0 ml/kg/h); normal or increased serum motility; inadequately diluted urine (specific gravity <1.005, urinary osmolality <200 mOsm/kg H_2O); hypernatremia ($Na^+ > 145$ mmol/L) [45].

6.2 The use of corticosteroids

The use of corticosteroids can reduce the inflammation caused by brain death and modulating immune functions can improve the quality of donor organs (e.g., lungs) and posttransplant graft function. Corticosteroid administration for brain-dead organ donors is highly recommended for two reasons. The first reason is the treatment of hypothalamic–pituitary–adrenal (HPA) axis failure, which could potentially lead to hemodynamic instability. However, like the axis of the thyroid gland, the HPA axis is generally not deficient after brain death. Additionally, in observational studies,

the donor's hemodynamic instability was not associated with hypocortisolemia or lack of adrenal corticotropin sensitivity. Nevertheless, corticosteroids may improve hemodynamics through their vasopressor effects. The second possible reason for the administration of corticosteroids is reduced inflammation, which can have a negative effect on graft function. Observational studies highlight the increased organ procurement and improved graft and survival of the recipient by administration of corticosteroids. However, good-quality RCT evidence is lacking. With high heterogeneity of the study design and concomitant therapies, as well as poor quality, most RCTs rule out a strong conclusion. Several studies analyzed the effect of high-dose methylprednisolone. Theoretically, corticosteroid-induced hyperglycemia may outweigh all possible benefits. Recently, lower doses of hydrocortisone have been studied. Improved blood glucose was improved by a small observational study control by such strategy without any benefit on patient-centered outcomes. In summary, the indications of corticosteroid use in possible organ donors remain controversial, but can be considered in hemodynamic instability. It is important that it could be administered only after sampling for tissue typing, as it can reduce the expression of human leukocyte antigen [43]. Administration of high-dose corticosteroids (methylprednisone 1000 mg IV, 15 mg/kg IV, or 250 mg IV bolus followed by an infusion at a rate of 100 mg/h) reduces the potential adverse effects of the inflammatory cascade on donor organ function after brain death. Ideally, it should be administered after taking blood for tissue typing as it is able to suppress human leukocyte antigen expression [45].

6.3 The use of thyroid hormone

Changes in the axis of the thyroid are common after brain death, and levels of biologically active T3 are generally low. However, several studies with brain-dead organ donors have shown that the majority of patients have maintained pituitary function with normal or elevated thyroid-stimulating hormone levels due to internal carotid supply. T4 levels generally remain in the normal range and inactive reverse T3 levels are normal or elevated. This constellation points to non-thyroid disease rather than central hypothyroidism in the presence of thyroid gland with increased peripheral inactivation of thyroid hormone, as is the case in patients in the general intensive care unit. Because prolonged and severe hypothyroidism can lead to myocardial dysfunction, low T3 levels are thought to induce hemodynamic instability in the potential donor.

The changes in the neuroendocrine axes have a biphasic manner. During the acute phase of critical illness, it seems to be evolutionarily selective and is likely to be beneficial for survival. Therefore, exogenous intervention may not be required at this stage of critical illness. If these profound changes last longer, a maladaptive phase begins. Although treatment with exogenous active hormones in the chronic phase seems to be a reasonable option, experimental studies have highlighted the difficulties of optimal dosing and posology [46]. In addition, a large study has highlighted the fact that thyroid hormone supplementation may be associated with an increased risk of early graft loss (EGL) and early graft dysfunction (EGD) [47, 48]. However, reliable data have shown that thyroid hormone supplementation in combination with methylprednisolone may reduce the likelihood of developing of primer graft dysfunction (PGD). In addition, thyroxine administration may also have a beneficial effect on long-term survival after HTX [49].

However, it remains unclear whether non-thyroid disease following cerebral death should be treated. An extensive observational study that included data from 63,593 brain-dead organ donors independently linked thyroid hormone replacement to an increased number of procured organs. The apparent benefits of thyroid hormone

replacement were not confirmed by another RCT. However, the relatively low number of patients with hemodynamic stability in RCTs can preclude a conclusion in this subset of patients. Consensus guidelines have suggested that thyroid hormone replacement should be considered in hemodynamically unstable donors. Both T4 and T3 substitutions have been used for this purpose, although T4 is increasingly degraded to inactive reverse T3(46). One commonly utilized protocol is the following: T4 IV administration with a 20 μg bolus, followed by an infusion at 10 μg/h, or administer T3 IV with a 4.0 μg bolus, followed by an infusion at 3 μg/h [45].

Although target glucose levels for intensive insulin therapy in critically ill patients are still a matter of debate, hyperglycemic organ donors should be treated in the same way as other critically ill patients [45].

7. Hormone replacement therapy in recipients during transplantation

Although donor organ replacement therapies are still a matter of debate, there are some reliable data on HRT for cardiac recipients [50]. The use of triiodothyronine (T3) and thyroxine (T4) should be considered in patients with hemodynamic instability or potential cardiac donors with reduced ejection fraction [45]. The perioperative l-thyroxine treatment supplementation of cardiac recipients revealed that thyroid hormone administration initiated preoperatively was associated with a significantly

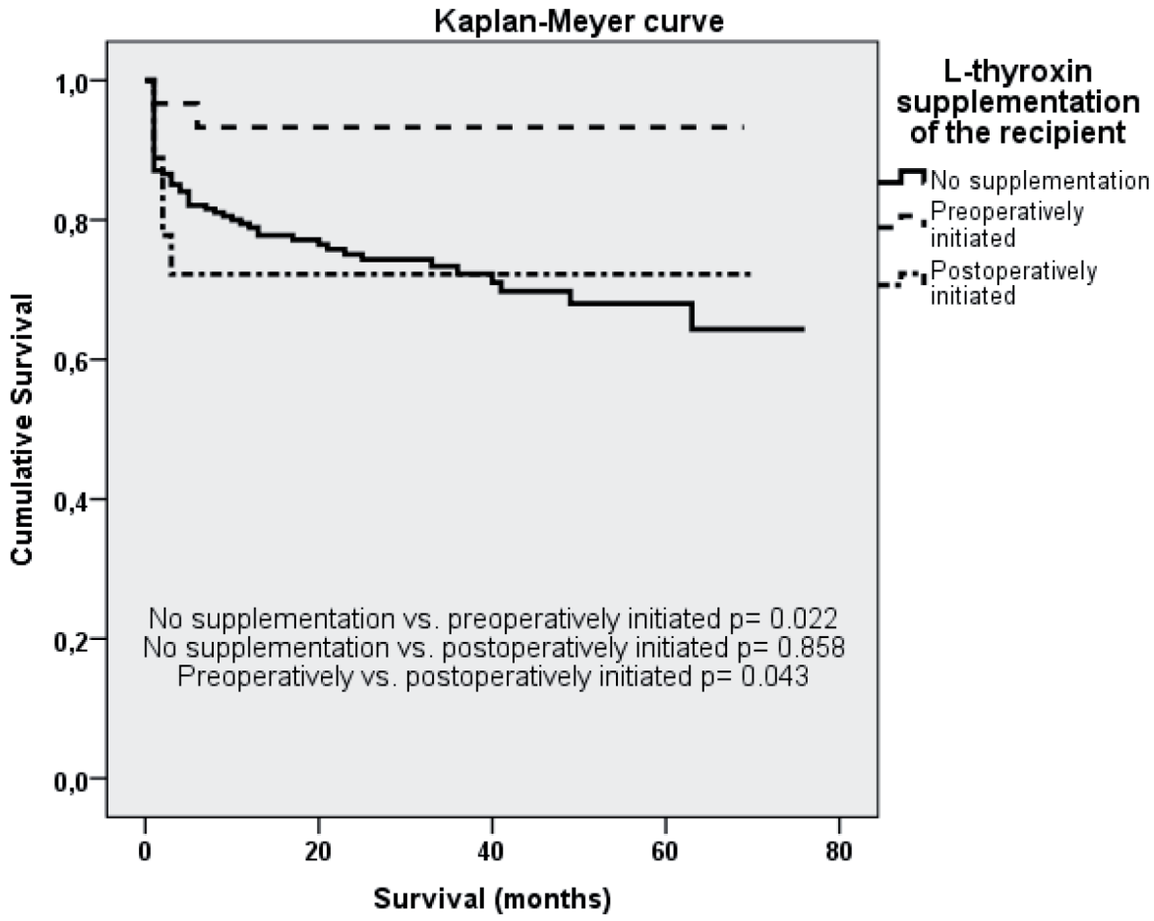

Figure 5.
Kaplan–Meier curve. Survival function according to the initiation of l-thyroxine supplementation in recipients. Preoperatively initiated supplementation was associated with significantly better survival function than no or postoperatively initiated supplementation.

better survival than either no thyroid hormone substitution or postoperative thyroid hormone substitution [50]. According to our institutional practice, thyroid hormone levels should be measured before the transplantation and thereafter weekly. While T3 levels are usually low and considered as a consequence of a natural response for huge stress, T4 levels should be closely monitored and values lower than the normal range must be treated. TSH levels in the perioperative period have also become interest of recent research (**Figure 5**).

8. Conclusions

Detection of hepatic dysfunction during preoperative evaluation, even in subclinical form, is the cornerstone of postoperative mortality estimation. As discussed above, hepatic dysfunction can affect both the intraoperative and postoperative period. In early-stage liver fibrosis, higher transaminase levels after surgery were associated with worse survival [51]. Moderate and elevated MELD XI scores predict increased short- and mid-term mortality after heart transplantation [52]. A remarkable increased MELD XI score is also associated with higher rates of postoperative stroke, need of dialysis, infection, and rejection [53].

Hepatic vein flow patterns are an intensively researched topic. Results suggest that pathological changes in flow patterns, such as damped, reduced, and reversed flow, may be an early predictor of hepatic tissue fibrotic transformation. Therefore, it can be an important marker of adverse outcome after adult heart transplantation. Moreover, hepatic vein congestion signs seem to be not only the marker of the right heart failure but can also estimate the severity of the abdominal venous insufficiency. After a successful heart transplantation [or LVAD implantation], congestive problems no longer exist as they did before the operation. In a manner, hepatic functions may improve. MELD scores are usually improving during the first postoperative year. In the vast majority of cases, normalization occurs within the first two months [54]. However, our findings indicated that a rise in the transaminase levels after transplantation was associated with higher risk of two-year mortality [19]. Hypoxic hepatitis in the early perioperative period must be followed, as it can worsen survival.

Endocrine abnormalities can develop during end-stage heart failure, and it should be monitored to detect early the chronic phase of the maladaptive response, which requires thyroid hormone substitution. Certain hormone replacements during donor procurement, such as treatment of central diabetes insipidus with arginine-vasopressin, are well established. In the current guidelines, use of thyroid hormones has been debated. After transplantation, the steroids can cause impaired glucose tolerance or diabetes. Thyroid hormone levels should be regularly checked.

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Conflict of interest

The authors declare no conflict of interest related to this chapter.

Abbreviations

AF	atrial fibrillation
AIH	amiodarone-induced hypothyroidis
AIT	amiodarone-induced thyrotoxicosis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATG	anti-thymocyte globulin
AVP	arginine vasopressin
BIVAD	biventricular assist device
CDI	central diabetes insipidus
CYP	cytochrome P450 enzymes
D1	type 1 iodothyronine deiodinase
D2	type 2 iodothyronine deiodinase
D3	type 3 iodothyronine deiodinase
EGD	early graft dysfunction
EGL	early graft loss
HRT	hormone replacement therapy
HTX	heart transplantation
ICU	intensive care unit
IL-1	interleukin-1
IL-6	interleukin-6
INR	international normalized ratio
LVAD	left ventricular assist device
MCS	mechanical circulatory support
MELD	model for end-stage liver disease
MMF	mycophenolate-mofetil
NAFLD	nonalcoholic fatty liver disease
NFκB	nuclear factor κB
NTI	nonthyroidal illness
PGD	primer graft dysfunction
PT	prothrombin time
PTT	partial thromboplastin time
RAAS	renin-angiotensin-aldosterone system
rT3	reverse triiodothyronine
SERCA	sarcoplasmic reticulum calcium adenosine triphosphatase
SVR	systemic vascular resistance
T3	triiodothyronine
T4	thyroxine
TE	transient elastography
TNF-α	tumor necrosis factor
TRH	thyrotropin-releasing hormone
TRα1	thyroid hormone receptor alfa-1
TSH	thyroid-stimulating hormone
UNOS	United Network for Organ Sharing
VA-ECMO	veno-arterial extracorporeal membrane oxygenation
vWF	von Willebrand factor

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