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Nonischemic Cardiomyopathy in Liver Transplant Recipients

Alexander A. Vitin, Dana Tomescu and Leonard Azamfirei

Abstract

Nonischemic cardiomyopathy is a collective term, encompassing a spectrum of cardiac comorbidities, accompanying the progressing end-stage liver disease. Alcoholic and cirrhotic cardiomyopathies are the most researched, well-known clinical entities in the list of nonischemic cardiac disorders that bear the most substantial impact on the clinical course, management, and outcomes of liver transplantation in ESLD patients. In this chapter, morphology, pathophysiology, diagnostic criteria, clinical manifestations, and management options of nonischemic cardiomyopathy in liver transplant candidates and recipients, the patients with end-stage liver disease due to advanced stages of cirrhosis, are discussed.

Keywords: nonischemic cardiomyopathy, cirrhosis, liver transplantation, morphology, physiology, management

1. Introduction

The trend of performing liver transplants on an ever-increasing number of sicker patients with more severe cardio-vascular comorbidities, once considered as posing insurmountably high risk, prohibitive for surgery, is quickly becoming an everyday reality. Among other comorbidities, cardiomyopathies are considered as very common conditions that significantly alter the course of the liver disease and candidacy for liver transplant and contributes substantially to perioperative hemodynamic profile and management and, eventually, to immediate and long-term outcome. While coronary artery disease-related morbidity remains the most serious concern in respect to liver transplant recipient well-being and outcomes, the groups of nonischemic cardiac conditions, that are increasingly common, oftentimes go underappreciated, underdiagnosed, and simply overlooked. The recent trends, however, demonstrate an increasing awareness and deeper understanding of these conditions.

Limited data is available about the actual prevalence of cardiomyopathy and its impact on the liver transplantation outcome. According to recent studies, it has been estimated that as many as 50% of patients undergoing liver transplantation developed at least some signs of cardiac dysfunction [1], and overall mortality from overt heart failure in the post liver transplantation period was estimated at about 7–21% [2].

In this review, we will focus on physiological and clinical aspects of nonischemic cardiomyopathy, which accompany practically every liver disease in the advanced stages.

Nowadays, the majority of transplant subspecialty physicians consider cardiomyopathy mostly as either “cirrhotic” or “alcoholic,” with disregard to differences in physiology, clinical course and, for liver transplant recipients, even to outcome impact.

We suggest considering a “cardiomyopathy” as a collective term that refers to the spectrum of myocardial pathology, with a variety of etiological factors, ways and timing of development, similar, albeit not exactly identical, clinical manifestations, and degrees of contribution to hemodynamic profile of the liver transplant recipient. Furthermore, based on clinical features, cardiac morbidities, encountered in liver transplant candidates/recipients that qualify for nonischemic cardiomyopathy, may be divided into chronic forms (such as cirrhotic, alcoholic, etc.) and acute (stress-induced and Takotsubo).

In this review, we will focus on etiology, morphology, pathophysiology, diagnostic criteria, and clinical manifestations of chronic nonischemic cardiomyopathies in liver transplant candidates. Acute nonischemic stress-induced cardiomyopathy discussion is beyond this chapter’s scope.

2. Etiology-related morphology

Etiologically different forms of cardiomyopathy have generally similar pathological morphology and histopathology, with minimal, sometimes imperceptible, differences in microscopic details. In majority of cases, a histomorphological picture of nonischemic cardiomyopathy may be identified as having common features with chronic myocarditis, resulting in myocardial fibrosis, hypertrophic, dilated cardiomyopathy, or their combination.

As it has been demonstrated (using endomyocardial biopsy), a distinction between idiopathic, chronic inflammatory, and alcoholic cardiomyopathy is virtually impossible. Common features such as fibrosis, cardiac myocyte hypertrophy, and nuclear alterations have been observed in the alcoholic cardiomyopathy [3] or the World Heart Federation/International Society and Federation of Cardiomyopathy (WHF/ISFC) definition of myocarditis [4, 5]. Alcohol consumption is considered to be the major contributory factor of secondary nonischemic dilated cardiomyopathy in up to 33% of all cases of dilated cardiomyopathy [6, 7]. In alcoholic cardiomyopathy, dilation and impaired contraction of the left or both ventricles are observed [8]. Left ventricular end-diastolic diameters are increased compared to age- and weight-matched controls, the left ventricular mass index is increased, and the left ventricular ejection fraction is well below normal (<45%) [9].

Recent studies have demonstrated that Hepatitis C virus (HCV) also possesses tropism trait for other than liver tissues, such as lymphatic system and myocardial cell membranes. However, precise mechanisms of the myocardial damage have not yet been elucidated. Development of HCV-associated cardiomyopathy is considered as a result of multiple factors, such as viral, immunologic, and apoptotic-related in genetically susceptible patients [10]. Recent studies have demonstrated hepatitis C virus (HCV) involvement in the development of dilated cardiomyopathy, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy in addition to myocarditis and myocardial fibrosis [11].

Cirrhotic cardiomyopathy is defined as “cardiac dysfunction in patients with cirrhosis, characterized by impaired contractile responsiveness to stress, diastolic dysfunction, and electrophysiological abnormalities in the absence of known cardiac disease” [12]. There is only very limited information about epidemiology, as well as actual prevalence of this condition at present time. Its diagnosis is difficult, because the majority of liver transplant candidates demonstrate nearly normal (for

cirrhotic patient) cardiac function at rest, and only during ESLD decompensation phases, they present with diastolic and/or high cardiac output heart failure [13]. However, QT interval prolongation in cirrhotic patients (25% in cirrhosis Child Pugh class A, 51% in Child Pugh class B, and 60% in Child Pugh class C) may be considered the earliest sign of cirrhotic cardiomyopathy; some information of prevalence might be derived from these data [14–16]. In earlier studies, cirrhotic cardiomyopathy has been considered to be related to both portal hypertension and cirrhosis itself, and is characterized by intrinsic alterations in myocardial function [17]. In its advanced stages, the morphology of cirrhotic cardiomyopathy may be described as, essentially, a combination of both dilated and hypertrophic cardiomyopathy, with various degrees of fibrosis development. Oftentimes, right- or bilateral atrial enlargement, along with right ventricle distension may be seen using TTE.

Hemochromatosis, due to iron deposition in myocardial cells, predisposes to either dilated or restrictive cardiomyopathy. If left untreated, hemochromatosis eventually progresses to end-stage heart and liver disease, with heart-liver transplantation as the best treatment option [18]. Early electrocardiographic abnormalities are frequent in patients with cirrhosis due to hemochromatosis. However, overt CHF is unusual [19]. Morphology of hemochromatosis-related cardiomyopathy in cirrhotic patients includes increased left ventricular mass, end-diastolic and end-systolic diameters of the left ventricle, and left atrium diameters, as well as significant changes of systolic function indices [20].

Nonalcoholic fat liver disease is becoming highly prevalent in the adult population (15–30%), with increase to 70–90% in obesity and type 2 diabetes, representing one of the most common causes of chronic liver disease among LT candidates [21, 22]. The correlation between almost two-fold increased cardiovascular mortality and nonalcoholic steatohepatitis (NASH) has been clearly demonstrated [23]. Increased amounts of liver fat are associated with the presence of markers of inflammation and risk factors of coronary vascular disease, independent of BMI. Steatosis has been found to be the strongest independent risk predictor of vascular damage and also involved in pathogenesis of coronary vascular disease in liver transplant candidates. In a recent study, severe early LV diastolic and systolic dysfunctions were observed in NASH patients [24–26]. In a retrospective study, comparing patients with nonalcoholic steatohepatitis (NASH) and alcoholic cirrhosis, NASH was more frequently associated with cardiovascular events after liver transplant in comparison with that in the alcoholic cirrhotic patients [27, 28]. Although coronary artery disease and related ischemic cardiomyopathy is beyond the scope of this review, it seems worth mentioning the involvement of such common etiology of ESLD, such as NASH cirrhosis, in cardiomyopathy development.

3. Pathophysiology and mechanisms of nonischemic cardiomyopathy

3.1 Contractility impairment, systolic dysfunction, and diastolic dysfunction

Overall myocardial dysfunction physiology in cirrhotic patients is exceedingly complex, multicomponent, and still not entirely understood. Two main components should be considered: myocardial contractility impairment and contribution of high cardiac output & low afterload hemodynamic profile (typical for ESLD patient hyperdynamic circulation), with secondary hemodynamic derangements, such as portopulmonary hypertension and related syndromes.

In their comprehensive review, Møller and Hendriksen [12] listed a number of potential mechanisms involved in the impairment of contractile function of the cardiomyocyte in cirrhotic cardiomyopathy on the receptor level. These include:

downregulation of β -adrenergic receptors with decreased content of G-protein, causing inotropic incompetency, and upregulation of cannabinoid 1-receptor stimulation; increased inhibitory effects of cardiodepressant substances such as hemoxygenase, carbon monoxide (CO), nitric oxide synthase (NOS)-induced nitric oxide (NO) release, and tumor necrosis factor- α (TNF- α). Many postreceptor effects are mediated by adenylyl cyclase inhibition or stimulation. Altered function and reduced conductance of potassium channels, inhibition of L-type calcium channels, and increased fluidity of the plasma membrane (increased cholesterol/phospholipid ratio) also contribute to reduced calcium release and contractility.

It has been demonstrated that the reduced β -adrenergic-dependent inotropic effect could be attributed to an overexpression of inhibitory G-protein and regulators of G-protein signaling, which inhibit the adenylyl cyclase, and those that accelerate degradation of cAMP such as phosphodiesterase [29]. The endogenous and exogenous cannabinoids exert mostly a vasodilatory effect. The ability of endocannabinoids to induce apoptosis of hepatic stellate cells, promoting the development of portal hypertension and hyperdynamic circulation, amplifies by vasodilation [30]. Increased local endocannabinoid production in cirrhosis and activation of CB1 receptors by endogenous anandamide contributes to the reduced cardiac contractility in cirrhosis [31].

Experimental evidence suggests that nitric oxide (NO) plays a significant role in the decreased vascular responsiveness to vasoconstrictors [32]. NO has been shown to cause significant impairment of the contractility in cirrhotic rats. Results of experimental studies have indicated that the cytokine-NO pathway occurs in cirrhotic rat hearts with enhanced expression of the NO synthase, and that inhibition of the NO synthesis by the NO inhibitor L-NAME reverses the impaired cardiac contractility [33–35].

Abnormalities in the properties of the plasma membrane determine the magnitude of the ion channel dysfunction. A decreased density of potassium currents in ventricular myocytes, which may contribute to prolong the QT interval, has been found on an experimental model. Also, a reduced expression and density of L-type Ca^{++} channels and inward cellular calcium current have been found as well, which may contribute to reduced contractility and also cause changes in excitation-contraction coupling and prolonged QT interval, with arrhythmogenic effect ensued [36–38].

B-type natriuretic peptide (BNP) and its prohormone, pro-BNP, are sensitive markers of even mild myocardial injury. Both compounds have been found elevated in patients with compensated and decompensated cirrhosis and seemingly correlate with the severity of cardiac dysfunction and myocardial hypertrophy [39, 40].

All aforementioned mechanisms of contractility impairment contribute to systolic dysfunction development. In majority of liver transplant candidates, the left ventricular ejection fraction (LVEF), which serves as relatively integral index of systolic function assessment, has been found normal (EF of 50–60%) or increased (EF > 70%) at rest in patients with cirrhosis [41, 42]. Some attenuation of LVEF has been shown after exercise, sodium load, or erect posture [43]. Blunted heart rate response to stress, reduced myocardial reserve, and impaired muscular oxygen extraction are among reasons that potentially contribute to the systolic dysfunction in cirrhotic patients [44].

Diastolic dysfunction is characterized by abnormal left ventricular relaxation, impeding blood flow through the ventricle, increasing left ventricular end-diastolic pressure, and increasing atrial contribution to late ventricular filling [45]. Diastolic dysfunction may be a consequence of either hypertrophic or dilated cardiomyopathy, myocardial patchy fibrosis, and subendothelial edema [46]. The histopathology of diastolic dysfunction showed cardiomyocyte hypertrophy, altered pigmentation, interstitial fibrosis, and myofiber vacuolization [47]. Diastolic dysfunction,

manifesting in impaired passive and active filling of the left ventricle during diastole, causes an inability to adequately increase stroke volume in response to stress and other stimuli. Diastolic dysfunction may precede systolic dysfunction in cirrhosis [48]. The clinical significance of diastolic dysfunction has been best demonstrated in cases of rapidly developing heart failure after transjugular intrahepatic portosystemic shunts (TIPS) [49]. It has been found that after TIPS, there is an increase in the left atrial diameter, the pulmonary capillary wedge pressure, and total pulmonary resistance [50].

3.2 Role of the hyperdynamic circulation

As it has been shown in numerous studies, peripheral and splanchnic vasodilation appears to be the leading cause of hyperdynamic circulation in advanced stages of ESLD [51]. Initially, a reduction in systemic vascular resistance is compensated by an increase in cardiac output (almost to 200% of baseline), and effective circulating blood volume satisfies the requirements for adequate peripheral perfusion. In advanced stages of cirrhosis, a further reduction in systemic vascular resistance cannot be compensated by a further increase in cardiac output, which leads to relative “hypovolemia” that manifests in hemodynamic instability and poor stress (e.g. blood loss) tolerance. At this stage, other mechanisms, such as activation of the renin-angiotensin system, sympathetic nervous system, and antidiuretic hormone overproduction, are employed to maintain effective circulating blood volume and perfusion pressure. Activation of these same compensatory systems is the leading cause of sodium and water retention and, ultimately, ascites formation [52, 53].

Though overt heart failure in even advanced stages of ESLD is a rare occurrence, the compensation mechanisms eventually are becoming overwhelmed, and, in a view of very limited myocardial reserve, already impaired contractility, systolic and diastolic dysfunctions, and myocardial performance are starting to decline substantially.

3.3 Role of portopulmonary hypertension

Portopulmonary hypertension is defined as pulmonary hypertension, associated with portal hypertension with or without accompanying liver cirrhosis. The correlation between development of portopulmonary hypertension and the severity of liver disease has not been found. Approximately 20% of candidates for liver transplantation will have elevated pulmonary artery pressures, but have a normal pulmonary vascular resistance (PVR). Such PA pressure increase may be the result of volume overload, cardiac failure, and high output circulation. True portopulmonary hypertension has a prevalence of 5–6% among liver transplant candidates and is the result of pathological changes in the pulmonary vasculature [54].

In the assessment of a liver transplant candidate, presenting with portopulmonary hypertension, a right heart catheterization, a transthoracic echocardiography, and a test-challenge with volume bolus and dobutamine test are instrumental in determining the limits of patient's tolerance for potential liver transplantation procedure [55].

The most important component of the porto-pulmonary syndrome physiology is, actually, not so much the degree of pulmonary hypertension, expressed in pulmonary artery pressure figures, but rather right ventricle (RV) dysfunction, namely significant shape (i.e. RV dilation) and systolic function alterations. In the group of patients with more rapid increase in PAP (as opposed to the slow, gradual pulmonary hypertension development), early RV dilation and more significant pulmonary regurgitation, leading to various degrees of right ventricular failure and decompensation, have been found [56].

Portopulmonary hypertension has an enormous impact on liver transplantation outcome. A mean pulmonary artery pressure (MPAP) of 50 mm Hg or greater has been found to be associated with a 100% post-OLT mortality rate, and a MPAP of 35 to <50 mm Hg is associated with a 50% post-OLT mortality rate [57]. For the time being, severe portopulmonary hypertension is considered to be an absolute contra-indication to liver transplant. Patients with moderate severity should be considered for pulmonary vasodilator therapy, and their candidacy for liver transplantation depends on their hemodynamic response [58].

Liver transplantation may not reverse the portopulmonary hypertension. Long-term vasodilator therapy may be necessary after the surgery, and, nevertheless, the syndrome may persist for years [59, 60].

It remains unclear, to which exact degree portopulmonary hypertension contributes to worsening of preexisting cardiomyopathy. However, its role in the development of right ventricle dilation and ultimate right heart failure appears to be more significant than commonly recognized.

4. Diagnostic criteria

A proposal for diagnostic and supportive criteria for cirrhotic cardiomyopathy agreed upon at the 2005 World Congress of Gastroenterology in Montreal published in 2008, a working definition of cirrhotic cardiomyopathy is formulated as follows: “A cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac diseases.” The diagnostic criteria are summarized in **Table 1**.

While systolic dysfunction ECO-diagnosis is more or less straightforward, diastolic dysfunction sometimes presents a certain challenge. TTE/TEE diagnostic criteria of diastolic dysfunction include decreased ratio of early to late atrial phases of ventricular filling (E/A ratio, less than 1). The decreased E/A ratio is a relatively common finding in cirrhotic patients [43, 61]. Measurement of the mitral annular E

Systolic dysfunction
1. Blunted increase in cardiac output on exercise, volume challenge, or pharmacological stimuli
2. Resting ejection fraction, 55%
Diastolic dysfunction
1. E/A ratio, 1.0 (age-corrected)
2. Prolonged deceleration time (0.200 ms)
Supportive criteria
1. Electrophysiological abnormalities:
• Abnormal chronotropic response
• Electromechanical uncoupling/dyssynchrony
• Prolonged Q-Tc interval
2. Enlarged left atrium
3. Increased myocardial mass
4. Increased BNP and pro-BNP
5. Increased troponin I

BNP, brain natriuretic peptide; E/A ratio, ratio of early to late (atrial) phases of ventricular filling (from: 46, with modifications).

Table 1.
Diagnostic criteria of cirrhotic cardiomyopathy.

wave (E') is considered a more accurate marker for evaluation of diastolic dysfunction, due to its decreased dependency on the preload in the presence of diastolic dysfunction. With worsening of the diastolic dysfunction, the E' decreases, which reflects the increased stiffness of the ventricle. The $E:E'$ ratio has been found to reflect left ventricular filling pressure, and this ratio increases as diastolic function worsens [62–65].

5. Clinical manifestations and reversibility

The clinical manifestations of cirrhosis-related myocardial dysfunction are becoming evident during liver transplantation surgery, when the hemodynamics are affected by numerous factors that include blood loss and fluid shifts with substantial third space formation, mechanical ventilation, large vessel clamping (specifically portal vein and IVC), and effects of anesthesia. In severe cases, heart failure manifests in significant reduction in the cardiac output [66, 67]. The problem is that, considering the baseline abnormally increased CO (up to 10–12 L/min), a gradual decrease to 4–5 L/min may not be immediately perceived as such and interpreted as a sign of ongoing myocardial decompensation. In the clinical study on 209 liver transplant recipients, abnormal cardiac response was observed in 47 (22.5%) patients after reperfusion. The authors suggested that the abnormal cardiac response observed during liver transplantation is a manifestation of occult cirrhotic cardiomyopathy [68].

A number of factors affect myocardial performance in the immediate postoperative period. Persisting metabolic disturbances, specifically lactic acidosis, hypothermia, and electrolyte disturbances (hyperkalemia and hypocalcemia) can further compromise cardiac performance. Among multiple causes of postoperative hemodynamic instability (such as underestimated hypovolemia due to ongoing or occult hemorrhage, third space formation/losses), a preexisting dilated cardiomyopathy should not be overlooked.

The rapid improvement of systemic vasodilatation, especially in combination with use of vasoactive agents, can result in a sudden increase in the afterload, which is another possible cause of excessive myocardial stress, leading to potential development or worsening of the existing heart failure. It has been found that after liver transplantation, almost 25% of liver transplant recipients have cardiovascular complications and an increased risk for postoperative pulmonary edema [16]. Postoperative pulmonary edema is quite common occurrence, and at least 50% of edema episodes develop within the first 24 h after surgery [69].

Reversibility of cardiomyopathy after liver transplant, albeit previously presumed very likely, appears to be not all that assured, let alone guaranteed, according to recent clinical studies. In the retrospective study on 243 liver transplant recipients, the diastolic dysfunction and QT interval changes have been investigated in postoperative period. The results revealed that the grade of diastolic dysfunction significantly worsened on echo performed after transplantation. Diastolic function worsened in up to 40% of the patients. Furthermore, longer QT was independently associated with adverse outcomes after OLT. Although QT significantly decreased after OLT, prolonged QT continued to be prevalent among patients after OLT. However, as study demonstrated that despite being associated with a longer hospital stay, the presence of diastolic dysfunction was not independently associated with long-term adverse outcomes after OLT. The authors concluded that some parameters, representing cirrhotic cardiomyopathy, such as diastolic dysfunction and prolongation of QT, continued to worsen or, at least persist in patients for many years after OLT [70].

6. Management: possible treatment options

Universally accepted treatment for clinically significant cardiomyopathy is yet to be established. Pharmacological interventions should be directed at the most important components of the syndrome, such as systolic and diastolic dysfunction, electrophysiological abnormalities, and impaired contractility. Liver transplant remains an ultimate cure for cirrhosis and for its major complications; it is also likely to cure the cirrhotic cardiomyopathy. However, neither time frame nor the extent of myocardial functional and structural recovery is known yet.

Nonselective β -blockers have been shown to improve the prolonged QT interval; β -blockers-induced cardiac output modification/reduction might play a positive role in the reduction of the hyperdynamic load [71, 72].

The common principles of the congestive heart failure treatment are completely applicable and should be followed, once heart failure manifests in liver transplant recipient. Depending on renal function (or lack thereof, in cases of severe hepatorenal syndrome or acute kidney injury), the treatment of CHF in cirrhotic patient will, most likely, include diuretics. It is likely, that patients with manifesting heart failure also exhibit a diuretic-resistant ascites. Even in these cases, aldosterone antagonists, such as spironolactone, might be beneficial in reducing left ventricular hypertrophy and dilatation, potentially improving diastolic dysfunction [73]. The known effects of aldosterone, such as myocardial fibrosis development, and baroreceptor dysfunction, provide a rationale for using an aldosterone antagonist, to counteract these effects [74].

The most significant hemodynamic instability, occurring during liver transplantation surgery, may be partially attributed, among other well-recognized factors (such as inherently low Systemic Vascular Resistance (SVR), to the manifestation or exacerbation of myocardial dysfunction due to preexisting cardiomyopathy.

At the start of the anhepatic stage, the portal cross clamp causes a variable (20–30% of baseline) degree of venous return decrease. IVC complete cross-clamp oftentimes leads to a more substantial and poorer tolerated (approximately 50%) decrease of venous return, whereas IVC partial clamp causes a variable, about 25–50%, decrease of venous return [75]. This rapid decrease in preload may be tolerated poorly by patients with ESLD. These patients have notoriously very limited ability, if any, to compensate for the rapid decrease in venous return with systemic vasoconstriction, due to inherent low SVR.

The possible solution to compensate, at least temporarily, for the decreased venous return (thus drop in cardiac output, which becomes substantially more pronounced in patients with both systolic and diastolic dysfunctions) is a venovenous bypass (VVB). It has been suggested that hypotension (30% decrease in MAP) or a decrease in cardiac index (50%) during a 5-min test period of hepatic vascular occlusion can be used to identify the group of patients, who require VVB. Other indications to the VVB include the presence of pulmonary hypertension, impaired ventricular function from previous myocardial infarction, ischemic heart disease, and cardiomyopathy [76, 77].

In patients with pulmonary hypertension (either idiopathic or due to portopulmonary syndrome), excessive fluid loading to compensate for hypovolemia-related hemodynamic instability may result in acute right ventricular dysfunction. Patients with preexisting cardiomyopathy, mostly impaired left ventricular function, express a limited ability to generate an adequate CO. These patients, too, may benefit from the ameliorative effect of the preload, associated with VVB, throughout the whole of liver transplant surgery, but particularly during anhepatic and postreperfusion stages [67].

In the view of rapid hemodynamic changes, associated with IVC either complete or even partial clamps, large amounts of fluids, along with blood products, are often needed to be administered. In patients with impaired renal function (ranging from acute kidney injury to hepatorenal syndrome and end-stage renal disease, intraoperative dialysis is used, mostly for the purposes of renal function complete replacement or preservation. Hemodialysis is also very efficient means of intravascular volume regulation, specifically in elimination of fluid overload [78]. These properties make hemodialysis and hemofiltration valuable and efficient tools also in decreasing a burden on dysfunctional myocardium, particularly in patients with substantial diastolic dysfunction due to cardiomyopathy. The target is to achieve euvolemia or a zero balance ultrafiltration volume by the use of hemodialysis, which becomes especially beneficial after IVC unclamping, the very intraoperative event, that causes notoriously substantial right ventricle volume overload, with potential to decompensation in cases of advanced cardiomyopathy [79].

Graft reperfusion and postreperfusion syndrome presents the most significant challenge for hemodynamic management, especially in patients with severe cardiomyopathy. Different drug combinations have been tested and recommended for rapid hemodynamic recovery after liver graft reperfusion. Vasopressin in small boluses, 1–2 U, may be highly efficient in opposing the significant and rapid decrease of SVR, and calcium chloride, up to 1000 mg, may enhance inotropic effects of epinephrine [67, 80]. Methylene blue, 2 mg/kg, has been reported as very efficient and “last resort” drug for prolong and profound hypotension, refractory to treatment with other vasoactive drugs [81]. The immediate hemodynamic stabilization (on the face of severely compromised myocardial function, in combination with rapid decrease in SVR, observed during postreperfusion stage), which all these drug combinations provide, should be further maintained with continuous infusion administration of vasoactive agents, such as phenylephrine or vasopressin, targeting primarily reduction of systemic vascular resistance. Compromised myocardial performance due to preexisting dilated cardiomyopathy and especially its worsening after graft reperfusion oftentimes necessitates addition of agents with β -adrenergic activities, such as norepinephrine, and, rarely, epinephrine [82, 83].

To better understand the causes and mechanisms of blunted cardiac response to stress and inotropic incompetence, investigations on the gene expression pattern of the cardiomyocyte adrenergic pathway in animal models of cirrhosis are underway [84]. New gene-targeting pharmacological strategies, based on the findings of these studies, might be the future direction of the cardiomyopathy treatment, and also, of course, a promising new direction of the research.

The normalization of cardiac function after liver transplantation is still a likely and attainable goal in majority of cases, provided all treatment modalities are employed in full and timely manner, and, above all, the liver transplantation procedure is successful.

7. Conclusions

The term “nonischemic cardiomyopathy” represents a spectrum of cardiac comorbidities, encountered in the liver transplant recipient at every stage of the process, namely, in preoperative period, intraoperatively, and during recovery. Alcoholic and cirrhotic cardiomyopathies are the well-known clinical entities. Yet, oftentimes, these conditions remain unrecognized and underdiagnosed in clinical setting.

Morphology of nonischemic cardiomyopathy includes various anatomical derangements, ranging from right and/or left atrial enlargement/distention to severe ventricular dilation and constrictive changes, with correspondent profound

physiological effects that include significant diastolic, followed by systolic, dysfunction and eventually resulting in the frank heart failure. Rhythm disturbances are very common, and serve as an early diagnostic sign of the developing cardiomyopathy.

To date, a consensus on causes, physiological mechanisms, and, most importantly, management and treatment of nonischemic cardiomyopathy is yet to be achieved. The existing management and treatment modalities are directed mostly on hemodynamic optimization at every stage of the transplantation process, and remain extremely complex and challenging intraoperatively, when a clinician faces multilevel surgery-related hemodynamic derangements, exacerbated greatly by the presence of clinically significant cardiomyopathy.

Decades of experience has shown that at least complete hemodynamic recovery, if not a meaningful structural and functional restoration of the myocardium, is an achievable goal in liver transplant recipients, and recent studies in this particular field have achieved promising results.

Further research on physiology, genetics, and treatment options is warranted, and results of multicenter studies, involving large numbers of liver transplant recipients, are much needed to be implemented to ensure successful outcome of liver transplantation in recipients, suffering from nonischemic cardiomyopathy.

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