World Journal of Hepatology

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DOI: 10.4254/wjh.v7.i4.662

World J Hepatol 2015 April 8; 7(4): 662-672
ISSN 1948-5182 (online)

REVIEW

Arrhythmia risk in liver cirrhosis

Ioana Mozos

Ioana Mozos, Department of Functional Sciences, "Victor Babes" University of Medicine and Pharmacy, 300173 Timisoara, Romania

Author contributions: Mozos I reviewed the literature and wrote the manuscript.

Conflict-of-interest: No potential conflicts of interest relevant to this article were reported.

Correspondence to: Ioana Mozos, MD, PhD, Associate Professor, Department of Functional Sciences, "Victor Babes" University of Medicine and Pharmacy, T. Vladimirescu Street 14, 300173 Timisoara, Romania. ioanamozos@yahoo.de
Telephone: +40-745-610004
Fax: +40-256-490626

Received: August 23, 2014
Peer-review started: August 24, 2014
First decision: October 14, 2014
Revised: December 4, 2014
Accepted: January 15, 2015
Article in press: January 19, 2015
Published online: April 8, 2015

Abstract

Interactions between the functioning of the heart and the liver have been described, with heart diseases affecting the liver, liver diseases affecting the heart, and conditions that simultaneously affect both. The heart is one of the most adversely affected organs in patients with liver cirrhosis. For example, arrhythmias and electrocardiographic changes are observed in patients with liver cirrhosis. The risk for arrhythmia is influenced by factors such as cirrhotic cardiomyopathy, cardiac ion channel remodeling, electrolyte imbalances, impaired autonomic function, hepatorenal syndrome, metabolic abnormalities, advanced age, inflammatory syndrome, stressful events, impaired drug metabolism and comorbidities. Close monitoring of cirrhotic patients is needed for arrhythmias, particularly when QT interval-prolonging drugs are given, or if electrolyte imbalances or hepatorenal syndrome appear. Arrhythmia risk may persist after liver transplantation due to possible QT interval prolongation, persistence of the parasympathetic impairment, post-transplant reperfusion and chronic immunosuppression, as well as consideration of the fact that the transplant itself is a stressful event for the cardiovascular system. The aims of the present article were to provide a review of the most important data regarding the epidemiology, pathophysiology, and biomarkers of arrhythmia risk in patients with liver cirrhosis, to elucidate the association with long-term outcome, and to propose future research directions.

Key words: Arrhythmia; Atrial fibrillation; Cirrhotic cardiomyopathy; Electrocardiography; Liver cirrhosis; Liver transplantation; Sudden cardiac death; T_{peak}-T_{end} interval; Ventricular tachycardia; Long-QT syndrome

Core tip: Arrhythmias and electrocardiographic changes occur in several non-cardiac diseases, including liver cirrhosis. Supraventricular and ventricular arrhythmias, including atrial fibrillation and flutter, and premature atrial and ventricular contractions, have been reported in cirrhotic patients. It is questionable whether the prevalence of atrial fibrillation and flutter is high in patients with liver cirrhosis, or if liver cirrhosis protects against supraventricular arrhythmias.

Mozos I. Arrhythmia risk in liver cirrhosis. *World J Hepatol* 2015; 7(4): 662-672 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i4/662.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i4.662

INTRODUCTION

Interactions between the functioning of the heart and the liver have been described, with heart diseases affecting the liver, liver diseases affecting the heart, and conditions that simultaneously affect both[1,2]. Thus, it is important for both hepatologists and cardiologists to understand the relationship between the liver and the heart. Indeed, involvement of the cardiovascular system in end-stage liver disease is well recognized, and there are reports of cardiovascular symptoms in patients with liver cirrhosis, including chronotropic incompetence, cardiomyopathy, prolonged QT intervals, hyperdynamic circulation with an increased cardiac output and decreased peripheral vascular resistance, and impaired ventricular contractility in response to physiologic and pharmacologic stimuli[3,4].

Liver cirrhosis is a fatal condition, and is most often caused by harmful alcohol consumption, metabolic syndrome related to being overweight or obese, or hepatitis B or C virus infection[5,6]. Arrhythmias and electrocardiographic changes can occur with liver cirrhosis, for which cases of atrial fibrillation and flutter, premature atrial and ventricular contractions, and ventricular arrhythmias have been reported[7]. The most important risk factors for arrhythmias in patients with cirrhosis include cirrhotic cardiomyopathy, cardiac ion channel remodeling, electrolyte imbalances, impaired autonomic function, hepatorenal syndrome, metabolic abnormalities, advanced age, inflammatory syndrome, and comorbidities. The aims of the present article were to provide a review of the most important data regarding the epidemiology, pathophysiology and biomarkers of arrhythmia risk in patients with liver cirrhosis, to elucidate the association with long-term outcome, and to propose future research directions.

CIRRHOTIC CARDIOMYOPATHY

The heart is one of the most adversely affected organs in patients with liver cirrhosis[8]. Cirrhotic cardiomyopathy can appear in all forms of cirrhosis due to physical or pharmacologic stress, and includes increased cardiac output, decreased response to physiologic and pharmacologic stimuli, systolic and diastolic dysfunction, and electrophysiologic abnormalities in the absence of any known cardiac disease[1,9-11]. Cirrhotic cardiomyopathy involves changes affecting the cardiomyocyte plasma membrane, attenuated stimulatory pathways, and increased activities of inhibitory systems[3]. In order to differentiate between cardiomyopathy resulting from cirrhosis with cardiomyopathy due to the underlying cause of cirrhosis, Zaky *et al*[8] prefer the term "cirrhosis-associated cardiomyopathy".

Diastolic dysfunction at rest is present in most cirrhotic patients, is more prevalent in those with ascites[12], and precedes the development of systolic dysfunction[9]. Although severe heart failure due to cirrhotic cardiomyopathy is rare, its prevalence is unknown, considering that the disease is latent, and becomes apparent when the patient is subjected to a stressful event, including exercise, drugs, hemorrhage, infections, and surgery[9,13]. At least one feature of cardiomyopathy is present in the majority of patients with severe or moderate liver failure, though the association between liver disease severity and cardiac dysfunction is controversial[9,12]. Cirrhotic cardiomyopathy is reversible after liver transplantation[14] and may contribute to the pathogenesis of hepatorenal syndrome[9].

Structural and histologic changes in cardiac chambers and subsequent structural myocardial heterogeneity may contribute to electrical instability. Increased left ventricular wall thickness was described as a supportive criterion in patients with cirrhotic cardiomyopathy[15], and it is known to impair myocardial oxygen demand. Myocardial hypertrophy (left ventricular hypertrophy and increased interventricular septum) and fibrosis cause diastolic dysfunction and contribute to structural heterogeneity and arrhythmia risk[2]. Autopsy studies have described subendocardial and myocyte edema and patchy fibrosis, in addition to myocardial hypertrophy[16]. However, further studies are needed to confirm the relationship between cardiac structural heterogeneity and arrhythmic events in cirrhotic patients.

VENTRICULAR ABNORMALITIES IN LIVER CIRRHOSIS

Multiple electrophysiologic abnormalities have been described in liver cirrhosis, including prolonged QT intervals, increased QT dispersion, chronotropic incompetence, and electromechanical uncoupling. These signs occur in the absence of known cardiovascular disease, and are related to autonomic dysfunction, severe portal hypertension, liver dysfunction, cytokines and endotoxins, and are independent of the cause of cirrhosis[1,7,17-19].

The QT interval varies from daytime to nighttime due to the diurnal variations in autonomic tone, circulatory status and oxygen demands[18,20]; the minimum value of the corrected QT (QTc), rather than the maximum value, shows a significant diurnal variation[20]. The Bazett formula incompletely corrects the QT interval for heart rate, and the Fridericia method is therefore suggested to be the most reliable and valid[7]. Chronotropic incompetence refers to lack of heart rate response to physiologic and pharmacologic demands, including exercise, head tilt, inotropes, and increased norepinephrine concentrations[8], which limits exercise capacity. Electromechanical uncoupling leads to the dyssynchrony between electrical and mechanical systole[8].

Long QT intervals

A prolonged QT interval, found incidentally by Kowalski *et al*[21], is the electrophysiologic hallmark of cirrhotic cardiomyopathy. It represents the most common

Table 1 Factors associated with QT prolongation in liver cirrhosis

Factor	Example
Autonomic neuropathy	Plasma norepinephrine, diurnal variations
Liver dysfunction	Child-Pugh class, portal hypertension, pediatric end-stage liver disease score
Serum markers	Electrolytes, serum uric acid, serum bile salts, creatinine, plasma renin activity, aldosterone, atrial natriuretic factor, gonadal hormones, norepinephrine
Volume overload	Left ventricular end diastolic dimensions
Coronary heart disease	Risk factors: older age, male gender, smoking, arterial hypertension, diabetes mellitus
Left ventricular hypertrophy	-
Stressful events	Acute gastrointestinal bleeding
Drugs: excessive accumulation, impaired metabolization, distribution, or excretion	Erythromycin, fluoroquinolones, telipressin, sevoflurane

electrocardiographic finding in patients with liver cirrhosis, appearing in half of cirrhotic patients[4,10,22,23], with a higher incidence than in patients with mild chronic active hepatitis[24]. Prolongation of the QT interval predisposes the patients to a potentially fatal polymorphic ventricular tachycardia called torsade de pointes, which can degenerate into ventricular fibrillation and cause sudden cardiac death[25]. Delayed repolarization of cardiomyocytes due to potassium channel abnormalities and sympathoadrenergic hyperactivity may contribute to QT interval prolongation[17,18,26]. The main factors associated with QT interval prolongation in cirrhotic patients are reviewed in Table 1. Gender difference in the QTc interval is abolished in cirrhosis, which is not influenced by gonadal hormones nor restored after liver transplantation[27].

QT prolongation in liver pathology was first described in alcoholic liver diseases[28], and has since been associated with alcoholic etiology in patients with liver cirrhosis[10,19,29]. Chronic, heavy alcohol consumption affects both the heart and the liver, increases the mass and impairs the function of the left ventricle[1,30], and causes subclinical heart muscle injury, patchy delays in conduction and cardiac arrhythmias[31]. Delays in intraventricular conduction and nonuniform myocardial involvement have been described in alcoholic cardiomyopathy[30], and life-threatening ventricular arrhythmias are found in alcoholics without heart disease[32]. Alcohol alters the resting membrane potential due to inhibition of sodium-potassium-ATPase, delays calcium binding and transport by the cardiac sarcoplasmic reticulum, and impairs calcium channels[33]. Acute alcoholic states, including binge drinking and the "holiday heart syndrome," are also associated with an increased prevalence of cardiac arrhythmias and sudden cardiac death[34]. The amount and duration of alcohol intake is related to life-threatening arrhythmias, though small quantities can be significant in susceptible individuals[35]. On the other hand, a protective effect of moderate alcohol consumption against sudden cardiac death has also been demonstrated[36,37], likely related to polyphenols, increased concentrations of high-density lipoprotein cholesterol, fibrinolysis, and polyunsaturated fatty acids, decreased platelet aggregation and coagulation factors, with beneficial effects on endothelial function and inflammation[38]. Arrhythmogenesis may be attributed to the hyperadrenergic state of drinking and withdrawal, electrolyte imbalances, impaired vagal heart rate control, repolarization abnormalities with prolonged QT intervals, worsening of myocardial ischemia, or sleep apnea[31].

Prolonged QT intervals have been reported in patients with primary biliary cirrhosis and other chronic non-alcoholic liver diseases, and were shown to be associated with the severity of autonomic neuropathy and increased cardiovascular risk[39], as well as with the pathophysiology of cirrhosis and liver dysfunction[17,40,41]. A prolonged QT interval is common in children with chronic liver disease[42], where it is related to the pediatric end-stage liver disease score, portal hypertension, and high mortality[43]. QT interval prolongation is proportional to the Child-Pugh class[10,17,16], and is related to the presence of portal hypertension, including mild portal hypertension[18,22,44,43], liver dysfunction[44], hepatic venous pressure gradient[22], and markers of hyperdynamic circulation[40]. Furthermore, plasma calcium level[22], serum uric acid[10], serum bile salts, electrolytes, creatinine, plasma renin activity, aldosterone, atrial natriuretic factor, and gonadal hormones are associated with prolonged QT intervals in patients with liver cirrhosis[17,45]. QT interval is also related to cardiac serum markers, but not to vasodilator (endothelin-3, calcitonin gene-related peptide) or vasoconstrictor (endothelin-1) markers[46]. A multivariate analysis showed that plasma norepinephrine was independently correlated with QTc duration, demonstrating that sympathoadrenergic hyperactivity is a risk factor for QT prolongation[17,47]. Disturbances of excitation-contraction coupling have been reported in cirrhotic patients with QT interval prolongation, attributable to defective potassium channel function in ventricular cardiomyocytes[18,40]. Moaref *et al*[13] showed a positive correlation between QT prolongation and left ventricular end diastolic dimensions in cirrhotic patients, indicating a direct relationship between electrophysiologic changes and the severity of volume overload. Volume overload is related to the progression of liver cirrhosis and prolongation of the repolarization time by the stretching of myofibers, and

volume control is recommended in cirrhotic patients to prevent decompensation[13].

Prolonged QTc is related to an increased mortality rate in patients with chronic liver diseases[48]. Among these, patients with a QTc longer than 440 ms have a significantly lower survival rate than those with normal QTc[17]. The clinical significance of QT prolongation in liver cirrhosis is unclear, considering that sudden cardiac death and torsade de pointes are rare[9]. However, acute gastrointestinal bleeding further prolongs QTc in patients with liver cirrhosis, which predicts bleeding-induced mortality[49]. QT prolongation and electromechanical dyssynchrony have not been observed in septic cardiodepression, the inflammatory phenotype of cardiac dysfunction that is mediated through cytokines[15].

Drug-induced QT prolongation

Child-Pugh and model for end-stage liver disease scores correlate with drug clearance[50]. As a result, patients with liver disease often require dosage adjustments in order to prevent adverse effects caused by excessive drug or metabolite accumulation[51]. Accumulation results from altered activity of drug-metabolizing enzymes and drug distribution, as well as from impaired renal excretion. For example, the activity of cytochrome P450 3A, the most abundant hepatic drug-metabolizing enzyme, is reduced in liver cirrhosis[51,52]. The activity of this enzyme varies according to the etiology and severity of liver disease[51,53]. Patients with transjugular intrahepatic portosystemic shunts are at increased risk for abnormal QT prolongation when exposed to oral cytochrome P450 substrates with QT-prolonging effects[54].

Drugs affecting the QT interval should be avoided in patients with liver cirrhosis, or used with caution under close ECG monitoring[2]. For example, the use of fluoroquinolones as secondary prophylaxis for spontaneous bacterial peritonitis in cirrhotic patients can predict QT prolongation[19]. Drug administration should be critically reviewed, with consideration of indications, interactions and adverse reactions, to prevent drug-induced torsade de pointes[55] and QT prolongation, particularly in patients with hepatic failure[56,57]. Werner *et al*[55] described a case of secondary torsade de pointes tachycardia in a 50-year-old patient with alcoholic liver cirrhosis who was admitted for hematemesis and melena after administration of QT-active drugs. Chung *et al*[58] reported a case of torsade de pointes after induction of anesthesia for liver transplantation with QT prolonging drugs: sevoflurane (to maintain anesthesia) and palonosetron (for postoperative nausea and vomiting). Faigel *et al*[45] also reported prolonged QT intervals and torsade de pointes in three cirrhotic patients with bleeding esophageal varices who received endoscopic sclerotherapy, vasopressin and neuroleptics. Lehmann *et al*[59] presented a patient with newly diagnosed cirrhosis and kidney failure who underwent cardiopulmonary resuscitation twice after terlipressin, an analogue of vasopressin.

Ventricular repolarization

The T_{pe} corresponds to the transmural dispersion of repolarization, and is a predictor of ventricular arrhythmias and sudden cardiac death[60-62]. The T_{pe}/QT ratio is also used as an index of ventricular arrhythmogenesis[63]. A prolonged T_{pe} interval and T_{pe}/QT interval ratio have been reported in patients with chronic hepatitis B infection, indicating an increased ventricular repolarization heterogeneity[64]. Liver cirrhosis affects ventricular repolarization *via* electrolyte imbalances, impaired autonomic function, subclinical cardiomyopathy, reduced β-adrenergic receptor function, post-receptor pathway defects, altered physical properties of myocyte plasma membranes, elevated levels of cardiotoxins, ion channel remodeling, portosystemic shunting, and systemic circulatory disturbances[10,16,22,44,65,66].

Late ventricular potentials

Chronic alcoholics exhibit late ventricular potentials, low-amplitude and high-frequency waveforms appearing in the terminal part of the ECG QRS complex, which are predictors of re-entry ventricular tachycardia and sudden cardiac death[35,67]. Late ventricular potentials are associated with histologically significant fatty liver caused by chronic alcohol intake, revealing preclinical myocardial lesions and identifying alcoholic patients at risk of lethal arrhythmias[68].

Ion channel remodeling

Cardiac ion channel remodeling, particularly of potassium channels, occurs in patients with liver cirrhosis[26]. Moreover, reduced transient outward and delayed rectifier potassium currents have been detected in ventricular myocytes from cirrhotic animals[26], which prolong the action potential and the QT interval[7]. Ionic channels, as well β-adrenergic receptors and G proteins, are altered by endotoxins and increased biliary acids in patients with cholestasis[16].

AUTONOMIC FUNCTION

Patients with liver cirrhosis show impaired autonomic cardiovascular reflexes, with the parasympathetic system more commonly affected than the sympathetic system[7]. The escape of systemic and intestinal vasodilators from degraded, diseased liver and the formation of new blood vessels in the gut explain arteriolar vasodilation of the systemic and splanchnic circulations[8]. The reduction in circulating blood volume and hyperdynamic circulation enhances the activities of the sympathetic nervous and renin-angiotensin-aldosterone systems. The resulting increased cardiac output and reduced systemic vascular resistance may induce myocardial remodeling and left ventricular hypertrophy, causing systolic and diastolic dysfunction and cardiomyopathy[7,8]. Sympathetic overactivity is

associated with an increase in inflammatory cytokines, such as interleukin-1b, -6 and -8, tumor necrosis factor (TNF)-α, and transforming growth factor-β[8], which is a profibrogenic and proapoptotic stimulant[18]. Cardiovascular autonomic dysfunction has also been described in chronic alcoholic liver disease and chronic hepatitis B and C virus infections[64].

CARDIAC MANIFESTATIONS WITH HEPATITIS

Palpitations, dyspnea, angina chest discomfort, electrocardiographic changes, tachycardia and bradycardia have all been described in patients with viral hepatitis[69], myocarditis, acute pericarditis and cardiomyopathy[70-72]. Sinus tachycardia occurs in most patients and is related to the febrile response[72]. Myocarditis may be a serious extrahepatic complication, and hepatitis B virus antigens have been detected in small intramyocardial vessels[71]. The cardiac abnormalities may be caused by viral infection, hyperbilirubinemia, hemorrhage in the myocardium and pericardium, or by immune mechanisms[69,71]. Chronic hepatitis B infection triggers autoimmune disorders and several extrahepatic disorders may appear, including of the ganglia and the heart[73]. Endothelial progenitor cells may serve as a virus carrier, enabling transinfection in injured endothelial cells to cause hepatitis B virus-associated myocarditis[73]. Hayashi *et al*[69] reported a case of fulminant hepatitis complicated with myocarditis, with myocardial infarction-like electrocardiographic changes. Hepatitis C virus infection has been detected often in patients with dilated and hypertrophic cardiomyopathy, and may be an important causal agent in the pathogenesis of the disease and cause arrhythmias[72,74]. Interferon, successfully used to treat patients with chronic hepatitis C infections, may induce several cardiovascular complications, such as tachycardia, myocardial infarction and congestive heart failure[75].

MARKERS OF CARDIAC DYSFUNCTION

Cell death is a central mechanism involved in liver damage, for which several promising noninvasive biomarkers have been associated with QT prolongation, including soluble cytokeratin 18, TNF and TNF-related apoptosis-inducing ligand receptors and their ligands, various isoforms of high mobility group box-1, small non-coding RNAs (microRNAs) and microparticles (extracellular vesicles)[76]. These biomarkers could be utilized in future studies to assess arrhythmia risk in liver cirrhosis. Fibrosis serum markers, such as hyaluronic acid and laminin[77], may also be indicators of electrophysiologic abnormalities in cirrhotic patients.

Natriuretic peptides are produced by the cardiac atrial and ventricular myocytes[78], and are higher in myocardial ischemia, heart failure and left ventricular tachycardia, as well as in liver cirrhosis and renal failure[79]. Plasma levels of N-terminal pro-brain natriuretic peptide (BNP) are useful markers of increased cardiovascular risk, cardiac subclinical dysfunction, atrial volume, and early decompensation of cirrhosis, and are increased proportionate to the stage of chronic liver disease[78]. Elevated levels of BNP are related to interventricular septal thickness and the impairment of diastolic function in asymptomatic patients with cirrhosis, and may be a marker of the presence of cirrhotic cardiomyopathy[80]. Henriksen *et al*[81] also reported that circulating pro-BNP and BNP are related to severity of liver disease (Child-Pugh score, serum albumin, coagulation factors and hepatic venous pressure gradient) and markers of cardiac dysfunction (QT interval, heart rate and plasma volume), but not to indicators of hyperdynamic circulation.

RELATED COMPLICATIONS AND CONDITIONS

Cirrhotic patients also have an increased risk and prevalence of coronary heart disease, which is also a cause of QT prolongation[1,82,83]. Risk factors for coronary heart disease, such as older age, male gender, smoking and arterial hypertension[82,84], are independent predictors of several electrocardiographic abnormalities in cirrhotic patients[19]. Moreover, liver disease severity is associated with many electrocardiographic features of coronary heart disease[19]. Considering low serum cholesterol, low blood pressure values and higher levels of circulating estrogens, cirrhosis should protect against coronary atherosclerosis[82]. However, recent reports have demonstrated an increased prevalence of major risk factors for atherosclerosis and cardiovascular disease in liver cirrhosis, especially in nonalcoholic steatohepatitis-cirrhosis[19,85]. Hypercholesterolemia in patients with primary biliary cirrhosis should be considered a cardiovascular risk factor, and further studies are needed to confirm if arrhythmias are related to it.

Arrhythmias are also associated with hypoxia and orthodeoxia due to hepatopulmonary syndrome. Hepatorenal syndrome may be another important contributor, influenced by systolic dysfunction and insufficient ventricular contractile reserve[2,86]. Ventricular arrhythmia risk and sudden cardiac death are increased in patients with renal failure, and even mild reductions in kidney function can alter the electrophysiologic properties of the myocardium[87]. Arrhythmia risk is related not only to renal function, but also to electrolyte imbalances, sympathetic activity, and levels of parathyroid hormone, hemoglobin, hematocrit and inflammatory markers[87].

Accumulation of bile acids in the liver due to obstructed ducts results in high circulating concentrations[88], with immunosuppressive effects[89]. In addition to the concentration, the composition of bile acids is important for arrhythmogenesis[90]. Taurocholic acid, a conjugated primary bile acid, has a negative inotropic effect and reduces the duration of the action potentials in the ventricular myocytes by reducing inward sodium and

calcium and increasing outward potassium currents[88]. The increased level of non-ursodeoxycholic acids in patients with arrhythmias suggests that ursodeoxycholic acids provide cardioprotective and hepatoprotective effects[90]. Although the exact intracellular effects of bile salts are not clear, they may act on muscarinic or cell-surface bile acid receptors involved in the regulation of macrophage functions[89] or directly damage cardiac calcium channels due to the detergent-like properties[91].

SUPRAVENTRICULAR ARRHYTHMIAS AND CONDUCTION DISORDERS IN LIVER CIRRHOSIS

Atrial fibrillation and flutter are arrhythmias that are more frequently diagnosed in cirrhotic patients, and are significantly associated with arteriosclerosis, hypercholesterolemia and diabetes mellitus[92]. Atrial fibrillation after septic shock and sinus bradycardia with cardiac arrest were reported after living-donor liver transplantation in a 58-year-old man diagnosed with hepatocellular carcinoma and liver cirrhosis, which required resuscitation and temporary pacing[93]. Josefsson *et al*[19] reported several supraventricular arrhythmias in cirrhotic patients, such as atrial and junctional premature beats, atrial flutter or fibrillation, sinus tachycardia or bradycardia. Pre-transplant evaluation of cirrhotic patients also revealed atrioventricular-conduction defects, such as complete or incomplete right or left bundle branch block and intraventricular blocks.

Inflammation may promote cardiac and arrhythmogenic complications in non-alcoholic fatty liver disease[94]. Patients with liver fibrosis have elevated plasma levels of inflammatory markers, and several studies have indicated that inflammation plays a significant role in the generation, maintenance, and perpetuation of atrial fibrillation[95]. However, Zamirian *et al*[96] suggested that liver cirrhosis has a protective effect against atrial fibrillation, despite significant metabolic abnormalities, inflammatory syndrome and enlarged left atria. The low prevalence of atrial fibrillation observed in their study may be the result of the accumulation of anti-arrhythmic or anti-inflammatory substances that are normally metabolized by an intact functioning liver; this would explain the development of atrial fibrillation after liver transplantation[96]. However, no data concerning the influence of inflammation in the relationship of arrhythmias and liver cirrhosis have been reported, which should be the aim of future studies.

The low prevalence atrial fibrillation in cirrhotic patients reported by Zamirian *et al*[96] may also have been related to the low prevalence of systemic hypertension in their patients or the administration of medications (spironolactone and beta-blockers) that reduce atrial excitability. Spironolactone reduces myocardial fibrosis of dilated atria and P-wave duration, producing an antifibrotic effect in the ventricles and reducing QT interval duration[97,98]. Beta-blockers are given as prophylaxis for variceal bleeding, such as for large esophageal varices, resulting in vasoconstriction in the splanchnic compartment, which increases preload and improves diastolic function[78]. Beta-blocker therapy may also prevent bleeding from portal hypertensive gastropathy and the development of spontaneous bacterial peritonitis. However, recent studies have warned about their use in decompensated cirrhosis, as they are associated with poor survival[99,100]. Beta-blockers decrease chronotropy and depress atrioventricular conduction, resulting in bradycardia or high-grade heart block[100].

Myocardial fibrosis is dysrhythmogenic[98], and atrial interstitial fibrosis is associated with changes in the electrical properties of the atria, including depressed excitability, increased refractoriness and conduction slowing or block[96,101]. Angiotensin-converting enzyme (ACE) inhibitors protect against myocardial fibrosis and prevent cardiac remodeling[102] and atrial fibrillation[103]. Drugs that interfere with the renin-angiotensin system, such as angiotensin Ⅱ-receptor blockers, also prevent atrial remodeling[103]. However, ACE inhibitors and other afterload-reducing drugs should be used with caution considering the risk for aggravating the vasodilatory state[2].

Statins are known for their pleiotropic and anti-hypertrophic effects, suppressing arrhythmogenesis and improving endothelial function[104]. Desensitization of cardiac myocytes to catecholamines due to down-regulation of beta-adrenergic receptors in the myocardium of cirrhotic patients could also be a protective mechanism against occurrence of tachyarrhythmia and atrial fibrillation[96].

The main mechanisms explaining the influence of cirrhosis on the higher prevalence or the protection against atrial fibrillation are reviewed in Table 2.

THERAPY

No specific therapy can be recommended for cirrhotic patients with heart conditions, but it should be supportive and directed against heart failure and pulmonary stasis[1,15]. Surgical stress, including transjugular intrahepatic portosystemic shunt insertion, surgical portosystemic shunting and liver transplantation can facilitate heart failure[15,103]. However, severe heart failure can be prevented by vasodilated peripheral circulation, which unloads the heart, and a compensatory decrease of some negatively inotropic regulatory mechanisms[15]. Aldosterone antagonists may reduce left ventricular dilatation and wall thickness, and improve diastolic function[15]. QT interval prolongation may be improved by beta-blockers, which also lower portal pressure and reduce the hyperdynamic load, but their effect on contractile dysfunction and mortality should be the focus of further studies[15,105].

Liver transplantation is currently the only proven treatment for patients with cirrhotic cardiomyopathy[11]

Table 2 Atrial fibrillation in patients with liver cirrhosis

Higher prevalence due to	Lower prevalence due to
Enlarged left atria (cirrhotic cardiomyopathy)	Accumulation of antiarrhythmic and anti-inflammatory substances
Electrolyte imbalances	Low prevalence of hypertension
Hepatorenal syndrome	Medication: diuretics, beta-blockers, ACE-inhibitors, statins
Serum bile acid concentration	Downregulation of beta-adrenergic receptors in the myocardium
Metabolic abnormalities	
Inflammatory syndrome	
Atrial interstitial fibrosis	

ACE: Angiotensin-converting enzyme.

Table 3 Risk factors for arrhythmias after liver transplantation

Risk factor
Stress of major surgery
Advanced age
Comorbidities: low blood pressure, anemia, limitation of the cardiac reserve
Hydroelectrolytic and acid-base imbalances
Hypothermia
Secondary development of hypertension, diabetes mellitus, obesity

and can improve cardiac hypertrophy, diastolic and systolic function, and autonomic dysfunction[1,2,14,15,29,41,106,107]. The prolonged QT interval reverses in approximately half of the patients after liver transplantation, likely a consequence of diminished portosystemic shunting, but can also be prolonged[27,108]. Total cardiac events after liver transplantation, particularly arrhythmias, and post-transplant mortality are associated with prolonged QTc and the presence of a Q wave[19]. A prolonged QTc interval also predicts post-transplant atrial arrhythmias[19] and peri-transplant heart failure[109]. However, liver transplantation is a stressful event for the cardiovascular system of the patients with advanced liver disease, considering also the advanced age and comorbidities[110]. Furthermore, liver transplantation highlights the limitation of the cardiac reserve, even in patients with no previous history of cardiac disease[15]. Although autonomic dysfunction, measured by heart rate variability, is partially corrected 2-6 years after liver transplantation, parasympathetic impairment is not improved[107].

Considering the high prevalence of cirrhotic cardiomyopathy and coronary heart disease and the high perioperative mortality, a careful cardiac evaluation of patients with liver cirrhosis is required before liver transplantation, including electrocardiography, cardiopulmonary exercise testing, dobutamine stress echocardiography, coronary angiography and myocardial perfusion imaging, and coronary multidetector computed tomography angiography[1,105,111]. Post-transplant reperfusion may result in cardiac death due to arrhythmias, acute heart failure, and myocardial infarction[15,110,112]. Risk factors for arrhythmia occurring during reperfusion of the graft are severe hydroelectrolytic and acid-base imbalances and hypothermia[112]. The most important risk factors for arrhythmias after liver transplantation are included in Table 3. Zaballos *et al*[112] reported the case of a man with severe hemodynamic alterations who developed atrioventricular re-entry tachycardia related to dual nodal conduction during liver transplantation. Kobayashi *et al*[93] reported complete atrioventricular block and cardiac arrest with diffuse myocardial abscesses after liver transplantation in a woman with liver cirrhosis and hepatocellular carcinoma, which required resuscitation and temporary cardiac pacing. Chin *et al*[113] described a case of torsade de pointes and a prolonged QTc after liver transplantation in a 39-year-old male patient with hepatitis B-related cirrhosis, which was due to low hematocrit and a low arterial blood pressure, demonstrating the importance of an optimal coronary perfusion to prevent sudden cardiac death. Cardiovascular disease also contributes to late mortality after transplantation, due to the secondary development of hypertension, hyperlipidemia, diabetes and obesity from chronic immunosuppression[82].

CONCLUSION

The latency of cirrhotic cardiomyopathy requires careful assessment of arrhythmia risk in cirrhotic patients. To evaluate the predictive value of ventricular repolarization indices in liver cirrhosis, further follow-up studies are needed. In particular, future studies should focus on the relationships between arrhythmia risk and structural heterogeneity of the cirrhotic heart, markers of inflammation, fibrosis and immunologic syndromes, and biomarkers of liver cell death and active infection. Close monitoring of cirrhotic patients is needed for arrhythmias, particularly when QT interval-prolonging drugs are given, or if electrolyte imbalances or hepatorenal syndrome appear. Arrhythmia risk may persist after liver transplantation due to possible QT interval prolongation, persistence of the parasympathetic impairment, post-transplant reperfusion and chronic immunosuppression, as well as consideration of the fact that the transplant itself is a stressful event for the cardiovascular system.

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