REVIEW

QT Interval Prolongation in Cirrhotic Cardiomyopathy

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Abstract: The liver and the heart are related to each other in many aspects. So liver diseases affect the heart, and heart disease affects the liver. Hyperdynamic circulation, the inability of ventricular contractility, hypertrophy of the heart, and electrophysiological alteration of the heart (prolongation QT interval) are some complications of cirrhosis. The most known complication of cirrhosis in the heart is cirrhotic cardiomyopathy. The original definition of cirrhotic cardiomyopathy was stated at the World Congress of Gastroenterology (2015). It is characterized by cardiac alteration (both in structure and function) in patients with cirrhosis without previously known cardiac problems. The pathological mechanism of cirrhotic cardiomyopathy includes physiological and chemical changes in cardiac muscle cells and increased inhibition of cardiomyocytes. Beta-adrenergic receptors defect and desensitization, endogenous cannabinoids, and cardiomyocyte depressants (NO and inflammatory cytokines) decrease cardiac contractility. Forty to fifty percent of the patients with cirrhosis had QT interval prolongation. QT interval prolongation is the most known electrophysiological abnormality in cirrhotic cardiomyopathy. The main cause of QT interval prolongation is a receptor and ion channel defect and a change in membrane fluidity.

Keywords: QT interval, cirrhosis, cirrhotic cardiomyopathy

Introduction

There are cardiovascular changes like general cardiac dysfunction, hyperdynamic circulation, and cardiac electrophysiological abnormalities in cirrhosis patients. The final result of circulatory and humoral changes in the heart in cirrhosis is called cirrhotic cardiomyopathy. Cirrhotic cardiomyopathy has a prevalence of 60%.[1,2] In cirrhosis patients, the impaired response by cardiomyocytes to physical, exercise, and medical or pharmacological stimuli is common. This impaired response to any stimuli is not due to the direct effect of alcohol toxicity. It has been confirmed that nonalcoholic cirrhosis patients have these manifestations.[3–5]

Generally, cirrhosis can be caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), and hepatocellular carcinoma (HCC).[57] The commonest causes of cirrhosis are chronic infection with hepatitis B (HBV) or C (HCV), alcohol misuse, and non-alcoholic fatty liver disease (NAFLD).[58]

The definition of cirrhotic cardiomyopathy should include some important components or manifestations (decreased cardiac contractility, electrophysiological abnormalities). These manifestations will happen without previously known cardiac disease.[6–8] Cirrhotic cardiomyopathy uses systolic and diastolic dysfunction and cardiac electrophysiological abnormalities as diagnostic criteria.[6] To know whether the patients developed cirrhotic cardiomyopathy or not, they should be exposed to any stress. As the disease is silent, the correct prevalence of the disease (cirrhotic cardiomyopathy) is not well known, but it is estimated that it is 60%.

Cirrhotic patients can be classified as Child class A, B, and C by their CTP or MELD scores, which shows the stages or severity of the disease. When the severity of cirrhosis is increased from Child–Pugh A to Child–Pugh C, cardiac complications are increased. These include systolic and diastolic dysfunction and cardiac electrophysiological

abnormalities. QT interval prolongation is the most common cardiac electrophysiological abnormality in cirrhosis. These manifestations developed due to the development of cirrhotic cardiomyopathy in cirrhotic patients.[9–11]

The Pathophysiological Mechanism of Cirrhotic Cardiomyopathy

Cirrhosis causes intrahepatic vascular resistance, which intern leads to portal hypertension. Portal hypertension leads to peripheral vasodilation, especially splanchnic vasodilation due to released vasodilator mediators like nitric oxide and carbon monoxide, endocannabinoids, tumor necrosis factor-alpha, and haem oxygenase.[12–14] These vasodilator mediators dilate arteries to decrease systemic vascular resistance. But the vasodilators decrease central blood flow. Decreased central blood flow deactivates baroreceptors to compensate for reduced blood flow in arteries. This intern increases cardiac output and heart rate by activating the sympathetic nervous system causes adrenergic hyperactivity, activates angiotensin II and aldosterone, causes myocyte hypertrophy, increases cardiomyocyte permeability, causes cardiac fibrosis development, QTc prolongation, causing decreased arterial pressure and general vascular resistance. So hyper-dynamic circulation is the initial response to vasodilation related to cirrhosis.[15,16] Cardiomyocytes are directly injured in patients with cirrhotic cardiomyopathy. Pro-inflammatory cytokines, vasoactive peptides, and reduced response to sympathetic stimulation cause cardiomyocyte injury.[17]

QT interval prolongation in cirrhotic cardiomyopathy causes fatal arrhythmia such as polymorphic ventricular tachy-cardia and torsades de Pointes which is the leading cause of sudden cardiac death. Fatal arrhythmias and sudden cardiac death are major public health problems worldwide. The risk of developing torsades de pointes is three times higher in patients with QT intervals greater than 500 ms. For every 10 ms increase in QT interval duration, there is an approximate 5–7% increase in the risk of developing ventricular arrhythmias, which increases hospital stay and mortality.[59–61]

Generally, the cardiac electrophysiological abnormality is the manifestation of cirrhotic cardiomyopathy. The most common cardiac electrophysiological abnormality is QT interval prolongation. Altered cardiac functioning in cirrhotic cardiomyopathy involves many pathogenic mechanisms (change in cardiomyocyte receptors, membrane permeability, ion channel and exchanger function, and vasodilator mediators).

The Role of Cardiomyocyte Receptors: A Beta-Adrenergic Receptor of Ventricles

Beta-adrenergic receptors become decreased both in function and density in cirrhotic cardiomyopathy. A decrease in function and density of the receptor impairs response to any stimuli, which sometimes causes defective beta-adrenergic receptor function.[18,19]

Cardiomyocyte Plasma Membrane Change

Patients with cirrhotic cardiomyopathy will have decreased plasma membrane fluidity. This is because of different molecular mechanisms. One of the reasons is that cirrhosis, which causes cirrhotic cardiomyopathy, causes high cholesterol adulation than phospholipids. A decrease in membrane fluidity, because of increased cholesterol, will decrease beta-adrenergic response which intern uncouples G-coupled stimulatory protein of the receptor, decrease cyclic adenosine monophosphate (cAMP) production which deactivates cascades of reaction for cardiac muscle fiber contrac-tion. Second, bile acid also decreases the plasma fluidity of cardiomyocytes.[19–21]

Muscarinic Receptors in the Ventricle

There are five types of muscarinic receptors from M1 through M5.[21] Among these muscarinic receptors, only M2 and M3 are found in cardiomyocytes, especially on the T tubule of cardiac muscle fibers.[22] Even if these receptors are distributed in all parts of the heart, they are found more in the endocardium and atria than the ventricles and epicardium.[23] They are also found in non-contractile cells of the heart such as SA and AV nodes.[24] Patients with cirrhotic cardiomyopathy will have a decreased response of muscarinic receptor type 2, and then a defective response to cyclic AMP.[25,26]

Potassium Ion Channel in Ventricles

The potassium channel controls the relaxation of cardiomyocytes by facilitating repolarization. Thus, activation of this channel will cause early and total repolarization of cardiomyocytes. However, there are both activators and inhibitors of

the channel. Calcitonin and adenosines are activators of the channel. Norepinephrine, 5-hydroxytryptamine, neuropeptide-Y, angiotensin II, endothelin-1. The activators cause hyperpolarization and then relaxation, whereas inhibitors cause depolarization and then contraction. Patients with cirrhotic cardiomyopathy have less density potassium ion channels. This causes prolonged contractility of the heart due to prolonged action potential generation in cardiomyocytes which intern leads to QTc prolongation, a common electrophysiological abnormality in cirrhosis.[10]

Calcium Ion Channel in Ventricles

Calcium ion both from the extracellular fluid and sarcoplasmic reticulum is the determinant ion for the contraction of cardiomyocytes. Depolarization of cardiomyocytes opens L-type voltage-gated calcium ion channels. Action potential propagates to the sarcoplasmic reticulum of cardiomyocytes through ryanodine receptors.[27] As a result, additional calcium ion is released from the sarcoplasmic reticulum. Calcium ions enter the interior of the cell from extracellular fluid, and calcium released from the sarcoplasmic reticulum causes contraction of cardiac muscle fibers. Cardiac muscle fibers become relaxed by the reuptake of calcium in the sarcoplasmic reticulum and expulsion of calcium from the cytosol into the extracellular space by adenosine triphosphate-driven calcium pumps and ion gradient-dependent Na/Ca exchangers.[28] Calcium entry from the extracellular fluid to the interior of the cell and calcium release from the sarcoplasmic reticulum to the cytosol is decreased in cirrhotic cardiomyopathy.[29]

Sodium–Potassium Counter Transporter

This is called a sodium–potassium exchanger. It is found on the extracellular part of cardiomyocytes, which transports three sodium ions to the interior of the cells and one calcium ion to the exterior of the cells to maintain calcium ion balance between the intra and extracellular fluids.[30] Na^+/Ca^{2+} exchanger abnormality is common in patients with cirrhotic cardiomyopathy. The exchanger abnormalities may lead to more flow of calcium ions to the interior of the cell (cardiomyocytes). This intern causes repeated contraction of the heart which finally causes the development of cirrhotic cardiomyopathy.[31]

Causes of Cirrhotic Cardiomyopathy

Carbon Monoxide

The production of carbon monoxide is carried out by sympathetic stimulation, norepinephrine secretion, or increased cytokine in patients with cirrhosis by introducing bacteria and endotoxin through the portal vein. Carbon monoxide has to do two things to decrease the contractility of ventricular cardiac muscle fibers in cirrhosis: 1) it increases cGMP and 2) it decreases calcium influx. The whole purpose of this is to bring about splanchnic arterial vasodilation by carbon monoxide.[32]

Endogenous cannabinoids

The molecule cannabinoids have their own receptors on different cells of the body. There are different types of cannabinoid receptors. Type one cannabinoid receptor is found in the heart. The binding of cannabinoids on this receptor causes splanchnic arterial vasodilation and decreases ventricular contractility. The adrenergic receptor of the heart became deactivated by endogenous cannabinoids. This decreases the response of cardiomyocytes to any stimuli, and this is called cirrhotic cardiomyopathy.[33,34] Generally, increased release of cannabinoids and increased activation of its receptor (CB1) impairs cardiac muscle contractility. Cannabinoids inhibit L-calcium channels and also reduce the function of cAMP to impair cardiac muscle contractility.[35]

Nitric Oxide

Cardiomyocytes, as well as endothelial cells of the vasculature, produce nitric oxide. Its production is facilitated by the enzyme nitric oxide synthase. It converts L-arginine to L-citrulline. Endothelial nitric oxide synthase initiates cardiac tissue perfusion and inhibits apoptosis of cardiomyocytes. So endothelial NOS has a cardioprotective effect. Whereas inducible nitric oxide synthase (iNOS) impairs cardiac muscle contractility and induces apoptosis.[36] In patients with cirrhosis, there is overproduction of NO which leads to hyperdynamic circulation and splanchnic arterial

vasodilation.[37,38] In cirrhotic patients, tumor necrosis factor-alpha and interleukin-1 beta are high inducers of iNOS which intern increases NO production. Overproduction of NO stimulates the production of soluble guanylyl cyclase which intern increases cGMP. Overproduction of NO also impairs RyR2 function. This process impairs 1) calcium influx into cardiomyocytes through calcium channels and 2) impairs calcium release from the sarcoplasmic reticulum which intern decreases contractility of the heart. When NO reacts with superoxide, reactive oxygen species will result. Reactive oxygen species inhibit cardiac function by the process called nitration of cardiac contractile proteins like actin. This is another mechanism of how NO causes the development of cirrhotic cardiomyopathy.[39–42]

QT Interval Prolongation

Different types of cardiac electrophysiological abnormalities are diagnosed among cirrhotic patients. Cirrhotic cardiomyopathy is common in cirrhosis. Cardiac electrophysiological abnormality is related to cirrhotic cardiomyopathy. Alteration of cardiac electrical activity is related to autonomic dysfunction.[10,11]

QT interval prolongation is the most common and well-known electrophysiological abnormality among others, and it is the most important indicator or sign to diagnose cirrhotic patients who are at risk of cirrhotic cardiomyopathy.[43] QT interval is said to be prolonged when it is greater than 0.44 s (>0.45 for men and >0.47 for women).[11,26] QT interval prolongation is caused by prolonged repolarization of the heart muscle fibers. Delayed repolarization is caused by potassium ion channel alterations and sympatho-adrenergic over activation.[44]

As aforementioned earlier, a decrease in the fluidity of the plasma membrane as well as the receptor and ion channel abnormalities are the main causes of cardiac electrophysiological abnormalities in cirrhotic cardiomyopathy. Beta-adrenoreceptor density and CAMP production are suppressed by the above causes and sometimes by bile acid itself.[20,21] When the plasma membrane fluidity is changed because of different causes, this change in plasma membrane disturbs ion channels which intern causes action potential prolongation and so is QT interval. The prolonged repolarization phase is caused by reduced potassium ion flow to the exterior of the cells. This causes a prolonged action potential of cardiac muscle fibers. This intern causes QT interval prolongation in cirrhotic cardiomyopathy.[44] In another way, a reduced influx of calcium to the intracellular fluid and the reduced release of calcium from the sarcoplasmic reticulum into cytosol causes prolonged cardiac contraction and impaired relaxation in cirrhotic cardiomyopathy.[47,48]

Sympathetic over-activation causes QT prolongation.[16] Sympathetic over-activation is caused by baroreceptor-mediators, hypotension, and hypovolemia related to cirrhosis.[49–51] Repeated and enhanced activation of the sympathetic nerve causes cardiomyocyte injury and reduced density and desensitization of the beta-adrenergic receptor and post-receptor (cardiac G protein) of the heart.[52–54] Troponin I secretion is increased in cirrhosis. This causes injury to cardiomyocytes.[55] The response of cardiomyocytes to any stimuli is decreased. This is because of the defective beta-adrenergic function and reduced function and expression of the cardiac G coupled proteins. Beta-adrenergic signal transduction is impaired, which intern decreases cardiac excitation-contraction coupling. This will bring about prolonged QT.[56] QT should be calculated in cirrhotic patients because it is affected by the rate.[45] QT interval increases when the severity of cirrhosis advances.[46]

Conclusion

It has been known for a long period that the heart and liver are interrelated. So liver disease affects the heart and heart disease affects the liver. One of the complications of liver disease is cirrhotic cardiomyopathy. In cirrhotic cardiomyopathy, contractility of the heart is decreased, and cardiac electrophysiology is disturbed. The most common electrophysiological abnormality in cirrhotic cardiomyopathy is QT interval prolongation. QT interval prolongation is caused by cardiomyocyte injury, defects in beta-adrenergic receptors of the heart and defects in the second messenger system (G coupled protein-adrenergic cyclase cascades of reaction), and reduced cardiac excitation-contraction coupling.

Abbreviations

AMP, adenosine monophosphate; AV, atrioventricular; Ca^{2+}, calcium ion; cAMP, cyclic adenosine monophosphate; CB1, type 1 cannabinoid receptor; cGMP, cyclic guanosine monophosphate; CTP; iNOS, inducible nitric oxide synthase; M1, type 1 muscarinic receptor; M2, type 2 muscarinic receptor; M3, type 3 muscarinic receptor; M4, type 4 muscarinic

receptor; M5, type 15 muscarinic receptor; Na$^+$, sodium ion; No, nitric oxide; NOS, nitric oxide synthase; QTc, corrected QT; SA, sinoatrial.

Ethics Statement

The study was conducted following the Declaration of Helsinki.

Disclosure

The author reports no conflicts of interest in this work.

References

1. Razpotnik M, Bota S, Wimmer P, et al. The prevalence of cirrhotic cardiomyopathy according to different diagnostic criteria. *Liver Int*. 2020;41:1058–1069.
2. Kowalski H, Abelmann WH. The cardiac output at rest in Laennec's cirrhosis. *J Clin Invest*. 1953;32:1025–1033. doi:10.1172/JCI102813
3. Grose RD, Nolan J, Dillon JF, et al. Exercise-induced left ventricular dysfunction in alcoholic and non-alcoholic cirrhosis. *J Hepatol*. 1995;22:326–332. doi:10.1016/0168-8278(95)80286-X
4. Torregrosa M, Aguade S, Dos L, et al. Cardiac alterations in cirrhosis: reversibility after liver transplantation. *J Hepatol*. 2005;42:68–74. doi:10.1016/j.jhep.2004.09.008
5. Mohamed R, Forsey PR, Davies MK, Neuberger JM. Effect of liver transplantation on QT interval prolongation and autonomic dysfunction in end-stage liver disease. *Hepatology*. 1996;23(5):1128–1134. doi:10.1002/hep.510230529
6. Moller S, Henriksen JH. Cardiovascular complications of cirrhosis. *Gut*. 2008;57:268–278. doi:10.1136/gut.2006.112177
7. Moller S, Henriksen JH. Cirrhotic cardiomyopathy. *J Hepatol*. 2010;53(1):179–190. doi:10.1016/j.jhep.2010.02.023
8. Timoh T, Protano MA, Wagman G, Bloom M, Vittorio TJ. A perspective on cirrhotic cardiomyopathy. *Transplant Proc*. 2011;43(5):1649–1653. doi:10.1016/j.transproceed.2011.01.188
9. Baik SK, Fouad TR, Lee SS. Cirrhotic cardiomyopathy. *Orphanet J Rare Dis*. 2007;2(1):15. doi:10.1186/1750-1172-2-15
10. Bernardi M, Calandra S, Colantoni A, et al. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. *Hepatology*. 1998;27(1):28–34. doi:10.1002/hep.510270106
11. Hendrickse MT, Trigger DR. Vagal dysfunction and impaired urinary sodium and water excretion in cirrhosis. *Am J Gastroenterol*. 1994;89:750–757.
12. Cahill PA, Redmond EM, Rodges R, Zhang S, Sitzmann JV. Increased endothelial nitric oxide synthase activity in the hyperemic vessels of portal hypertensive rats. *J Hepatol*. 1996;25:370–378. doi:10.1016/S0168-8278(96)80124-3
13. Morita T, Perella MA, Lee ME, Kourembanas S. Smooth muscle cell-derived carbon monoxide is a regulator of vascular cGMP. *Proc Natl Acad Sci USA*. 1995;92:1475–1479. doi:10.1073/pnas.92.5.1475
14. Goldberg DS, Fallon MB. Lung and heart disease secondary to liver disease. *Clin Gastroenterol Hepatol*. 2015;13:2118–2127. doi:10.1016/j.cgh.2015.04.024
15. Moller S, Henriksen JH. Cirrhotic cardiomyopathy: a pathophysiological review of circulatory dysfunction in liver disease. *Heart*. 2002;87:9–15. doi:10.1136/heart.87.1.9
16. Henriksen JH, Fuglsang S, Bendtsen F, Christensen E, Moller S. Arterial compliance in patients with cirrhosis: stroke volume-pulse pressure ratio as a simplified index. *Am J Physiol Gastrointest Liver Physiol*. 2001;280:G584–G594. doi:10.1152/ajpgi.2001.280.4.G584
17. Glenn TK, Honar H, Liu H, ter Keurs HE, Lee SS. Role of cardiac myofilament proteins titin and collagen in the pathogenesis of diastolic dysfunction in cirrhotic rats. *J Hepatol*. 2011;55:1249–1255. doi:10.1016/j.jhep.2011.02.030
18. Battarbee HD, Farrar GE, Spears RP. Responses to hypotension in conscious rats with chronic portal venous hypertension. *Am J Physiol Gastrointest Liver Physiol*. 1990;259(1):48–55. doi:10.1152/ajpgi.1990.259.1.G48
19. Ma Z, Meddings JB, Lee SS. Membrane physical properties determine cardiac beta-adrenergic receptor function in cirrhotic rats. *Am J Physiol*. 1994;267:87–93.
20. Gazawi H, Ljubuncic P, Cogan U, Hochgraff E, Ben-Shachar D, Bomzon A. The effects of bile acids on beta-adrenoceptors, fluidity, and the extent of lipid peroxidation in rat cardiac membranes. *Biochem Pharmacol*. 2000;59:1623–1628. doi:10.1016/S0006-2952(00)00259-8
21. Ma Z, Lee SS, Meddings JB. Effects of altered cardiac membrane fluidity on beta-adrenergic receptor signaling in rats with cirrhotic cardiomyopathy. *J Hepatol*. 1997;26:904–912. doi:10.1016/S0168-8278(97)80259-0
22. Wang Z, Shi H, Wang H. Functional M3 muscarinic acetylcholine receptors in mammalian hearts. *Br J Pharmacol*. 2004;142:395–408. doi:10.1038/sj.bjp.0705787
23. Brodde OE, Bruck H, Leineweber K, Seyfarth T. Presence, distribution and physiological function of adrenergic and muscarinic receptor subtypes in the human heart. *Basic Res Cardiol*. 2001;96:528–538. doi:10.1007/s003950170003
24. Olshansky B, Sabbah HN, Hauptman PJ, Colucci WS. Parasympathetic nervous system and heart failure: pathophysiology and potential implications for therapy. *Circulation*. 2008;118:863–871. doi:10.1161/CIRCULATIONAHA.107.760405
25. Caulfield MP. Muscarinic receptors-characterization, coupling, and function. *Pharmacol Ther*. 1993;58:319–379. doi:10.1016/0163-7258(93)90027-b
26. Jaue DN, Ma Z, Lee SS. Cardiac muscarinic receptor function in rats with cirrhotic cardiomyopathy. *Hepatology*. 1997;25:1361–1365. doi:10.1002/hep.510250610
27. Ai X, Curran JW, Shannon TR, Bers DM, Pogwizd SM. Ca2/ calmodulin-dependent protein kinase modulates cardiac ryanodine receptor phosphorylation and sarcoplasmic reticulum Ca2 leak in heart failure. *Circ Res*. 2005;97:1314–1322. doi:10.1161/01.RES.0000194329.41863.89
28. Ward CA, Liu H, Lee SS. Altered cellular calcium regulatory systems in a rat model of cirrhotic cardiomyopathy. *Gastroenterology*. 2001;121:1209–1218. doi:10.1053/gast.2001.28653

29. Bernardi M, Fornalè L, Di Marco C, et al. Hyperdynamic circulation of advanced cirrhosis: a re-appraisal based on posture-induced changes in hemodynamics. *J Hepatol*. 1995;22(3):309–318. doi:10.1016/0168-8278(95)80284-3

30. Bridge JH, Smolley JR, Spitzer KW. The relationship between charge movements associated with ICa and INa-Ca in cardiac myocytes. *Science*. 1990;248:376–378. doi:10.1126/science.2158147

31. Chen X, Zhang X, Kubo H, et al. Ca^{2+} influx-induced sarcoplasmic reticulum Ca^{2+} overload causes mitochondrial-dependent apoptosis in ventricular myocytes. *Circ Res*. 2005;97:1009–1017. doi:10.1161/01.RES.0000189270.72915.D1

32. Liu H, Song D, Lee SS. Role of heme oxygenase-carbon monoxide pathway in the pathogenesis of cirrhotic cardiomyopathy in the rat. *Am J Physiol Gastrointest Liver Physiol*. 2001;280:68–74. doi:10.1152/ajpgi.2001.280.1.G68

33. De Petrocellis L, Cascio MG, Di Marzo V. The endocannabinoid system: a general view and latest additions. *Br J Pharmacol*. 2004;141:765–774. doi:10.1038/sj.bjp.0705666

34. Gaskari SA, Liu H, Moezi L, Baik SK, Lee SS. Role of endocannabinoids in the pathogenesis of cirrhotic cardiomyopathy in bile duct-ligated rats. *Br J Pharmacol*. 2005;146:315–323. doi:10.1038/sj.bjp.0706331

35. Ba´tkai S, Mukhopadhyay P, Harvey-White J, Kechrid R, Pacher P, Kunos G. Endocannabinoids acting at CB1 receptors mediate the cardiac contractile dysfunction in vivo in cirrhotic rats. *Am J Physiol Heart Circ Physiol*. 2007;293:1689–1695. doi:10.1152/ajpheart.00538.2007

36. Kim YM, Bombeck CA, Billiar TR. Nitric oxide is a bifunctional regulator of apoptosis. *Circ Res*. 1999;84:253–256. doi:10.1161/01.RES.84.3.253

37. Ferna´ndez-Muñoz D, Caramelo C, Santos JC, Blanchart A, Hernando L, Lo´pez-Novoa JM. Systemic and splanchnic hemodynamic disturbances in conscious rats with experimental liver cirrhosis without ascites. *Am J Physiol*. 1985;249:316–320.

38. Van der Linden P, Le Moine O, Ghysels M, Ortinez M, Devière J. Pulmonary hypertension after transjugular intrahepatic portosystemic shunt: effects on right ventricular function. *Hepatology*. 1996;23(5):982–987. doi:10.1002/hep.510230507

39. Herring N, Danson EJ, Paterson DJ. Cholinergic control of heart rate by nitric oxide is site-specific. *News Physiol Sci*. 2002;17:202–206. doi:10.1152/nips.01386.2002

40. Seddon M, Shah AM, Casadei B. Cardiomyocytes as effectors of nitric oxide signaling. *Cardiovasc Res*. 2007;75:315–336. doi:10.1016/j.cardiores.2007.04.031

41. Liu H, Ma Z, Lee SS. Contribution of nitric oxide to the pathogenesis of cirrhotic cardiomyopathy in bile duct-ligated rats. *Gastroenterology*. 2000;118:937–944. doi:10.1016/S0016-5085(00)70180-6

42. Gow AJ, Farkouh CR, Munson DA, Posencheg MA, Ischiropoulos H. Biological significance of nitric oxide-mediated protein modifications. *Am J Physiol Lung Cell Mol Physiol*. 2004;287:262–268. doi:10.1152/ajplung.00295.2003

43. Sanyal AJ, Bosch J, Blei A, Arroyo V. Portal hypertension and its complications. *Gastroenterology*. 2008;134(6):1715–1728. doi:10.1053/j.gastro.2008.03.007

44. Ward CA, Ma Z, Lee SS, Giles WR. Potassium currents in atrial and ventricular myocytes from a rat model of cirrhosis. *Am J Physiol*. 1997;273:537–544.

45. Hansen S, Møller S, Bendtsen F, Jensen G, Henriksen JH. Diurnal variation and dispersion in QT interval in cirrhosis: relation to haemodynamic changes. *J Hepatol*. 2007;47(3):373–380. doi:10.1016/j.jhep.2007.03.013

46. Zambruni A, Di Micoli A, Lubisco A, Domenicali M, Trevisani F, Bernardi M. QT interval correction in patients with cirrhosis. *J Cardiovasc Electrophysiol*. 2007;18(1):77–82. doi:10.1111/j.1540-8167.2006.00622.x

47. Bouchard RA, Clark RB, Giles WR. Effects of action potential duration on excitation-contraction coupling in rat ventricular myocytes. Action potential voltage-clamp measurements. *Circ Res*. 1995;76(5):790–801. doi:10.1161/01.RES.76.5.790

48. Zardi EM, Abbate A, Zardi DM, et al. Cirrhotic cardiomyopathy. *J Am Coll Cardiol*. 2010;56(7):539–549. doi:10.1016/j.jacc.2009.12.075

49. Llach J, Ginés P, Arroyo V, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. *Gastroenterology*. 1988;94(2):482–487. doi:10.1016/0016-5085(88)90441-6

50. Henriksen JH, Møller S, Ring-Larsen H, et al. The sympathetic nervous system in liver disease. *J Hepatol*. 1998;29:328–341. doi:10.1016/S0168-8278(98)80022-6

51. Epstein SK, Ciubotaru RL, Zilberberg MD, et al. Analysis of impaired exercise capacity in patients with cirrhosis. *Dig Dis Sci*. 1998;43:1701–1707. doi:10.1023/A:1018867232562

52. Ma Z, Lee SS. Cirrhotic cardiomyopathy: getting to the heart of the matter. *Hepatology*. 1996;24:451–459. doi:10.1002/hep.510240226

53. Opie LH. *The Heart: Physiology, from Cell to Circulation*. 3rd ed. Philadelphia: Lippincott; 1998.

54. Ma Z, Miyamoto A, Lee SS. Role of altered beta-adrenoceptor signal transduction in the pathogenesis of cirrhotic cardiomyopathy in rats. *Gastroenterology*. 1996;110:1191–1198. doi:10.1053/gast.1996.v110.pm8613009

55. Møller S, Hansen EF, Becker U, et al. Central and systemic hemodynamic effects of terlipressin in portal hypertensive patients. *Liver*. 2000;20:51–59. doi:10.1034/j.1600-0676.2000.020001051.x

56. Zavecz JH, Bueno O, Maloney RE, et al. Cardiac excitation-contraction coupling in the portal hypertensive rat. *Am J Physiol Gastrointest Liver Physiol*. 2000;279:G28–G39. doi:10.1152/ajpgi.2000.279.1.G28

57. Wang F-S, Jian-GaoFan ZZ, Gao B, Yang H. The global burden of liver diseases: the major impact of China. *Hepatology*. 2014;60(6):2099–2108. doi:10.1002/hep.27406

58. Mota VG, Filho BM. Review Article Echocardiography in Chronic Liver Disease: systematic Review. *Arq Bras Cardiol*. 2012;100(4):376–385.

59. Kashiwa A, Aiba T. Acquired Long-QT Syndrome: mild but Abnormal? *Intern Med*. 2018;57(6):773–774. doi:10.2169/internalmedicine.9731-17

60. Li M, Ramos LG. Drug-Induced QT Prolongation and Torsades de Pointes. *P T*. 2003;68:483–488.

61. Ramalho D, Freitas J. Drug-induced life-threatening arrhythmias and sudden cardiac death: a clinical perspective of long QT, short QT and Brugada syndrome. *Rev Port Cardiol*. 2018;37:435–446. doi:10.1016/j.repc.2017.07.010