Review Article

Cardiac Complications in Chronic Liver Diseases

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Chronic liver diseases can occur due to various etiologies and each type is associated with specific cardiovascular manifestations. Hyperdynamic syndrome and cirrhotic cardiomyopathy are commonly associated with liver cirrhosis. These are manifested by systolic, diastolic and electrophysiological changes in the heart. However recent studies have revealed cardiovascular abnormalities in NAFLD, Chronic hepatitis C infection, Primary Biliary Cirrhosis and Hepatocellular Carcinoma. Recipients of orthotopic liver transplantation have also reported cardiac dysfunction which necessitates a proper evaluation of their cardiac status.This review discusses cardiac complications in chronic liver diseases, bringing in light over the pathophysiologic and clinical implications.

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Key words **: Chronic liver disease, Hyperdynamic syndrome, Cirrhotic cardiomyopathy, Cardiac dysfunction, Liver transplantation.**

Ancient Germans had termed the liver as “lifere” (meaning life), underscoring the relation of this organ to heath and existence. The importance of liver lie in its functional diversity.It is related to other organs in health and disease. A systemic disease can involve both liver and heart. However a cardiac disease can affect the liver and also vice versa can happen. Each category of these mutually manifest diseased conditions have their own clinical implications therapeutic strategies. Cardiac complications in a patient with chronic liver disease have brought in increased mortality and morbidity[1]. Hepatic dysfunction can lead to various haematological, metabolic and multiple other systemic anomalies which in turn can cause cardiac dysfunction, even in the absence of previous cardiac anomalies. But specific cardiovascular pathology in these patients is now well established.

Chronic Liver Disease (CLD)comprises of hepatic injury, inflammation and/ or fibrosis occurring in the liver for more than 6 months[2]. The etiology of CLD is diverse and each of them is now acknowledged to be associated with specific cardiac manifestations. A vasodilatatorystate, hyperdynamic circulation, cirrhotic cardiomyopathy and electrophysiological abnormalities in heart are common and characteristic cardiovascular manifestations of cirrhosis of liver[3]. Hepatopulmonary syndrome and porto-pulmonary hypertension are other elements of cirrhosis of liver. Non Alcoholic Fatty Liver Disease (NAFLD), due to its association with other metabolic disorders such as diabetes, dyslipidemia, hypertension and obesity is a known risk factor for cardiovascular disease. Moreover, cirrhotics are prone to especially nocturnal hypoglycaemia for a variety of reasons (poor appetite, low hepatic glycogen reserve) that can lead to sudden cardiac death too. Most recent studies have shown echocardiographic features of early LV diastolic dysfunction and impaired LV energy metabolism even in patients of NAFLD without ailments like hypertension or diabetes mellitus. Infections like chronic Hepatitis C can lead to chronic inflammation of the myocardium which can later cause dilated cardiomyopathy. Moreover, approximately 30% of liver transplant recipients have a CVD complication (myocardial infarction, heart failure, cardiac arrest, atrial fibrillation, pulmonary embolism, or stroke) within 1 year of Liver Transplantation which is a major cause of mortality[5,6]. It also causes perioperative mortality and graft loss even in donor liver transplant recipients.[7] For these reasons, research is being focussed on these pathologies, to study the potential reversibility of these cardiovascular alterations, early diagnosis and effective treatment.

Editor's Comment :

- Chronic liver diseases have profound effects on the cardiovascular system.
- This substantiates the importance of an elaborate cardiovascular evaluation in these patients.
- Newer therapeutic measures to reverse these changes can increase the longetivity and improve the quality of life of these patients.

Cirrhosis of Liver :

Cirrhosis of liver leads to Hyperdynamic Syndrome which is a major cardiovascular manifestation. There is high heart rate and cardiac output on one hand ,and reduced systemic vascular resistance and arterial blood pressure on the other hand which result in this

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syndrome. Apart from this, these patients have cardiac contractile impairment to stress and exhibit diastolic dysfunction. In addition, they have ECG abnormalities in the absence of known cardiac disease[8,9]. It has been termed as Cirrhotic cardiomyopathy. Some studies have suggested the Association of Cardiac Dysfunction with Hepatorenal Syndrome[10,11]. QT prolongation is the commonest ECG abnormality seen in about 50% of the cirrhotic patients[12].

Hyperdynamic Syndrome :

Kowalski and Abelmann were the first to describe this syndrome about 60 years back[13]. Increased heart rate and cardiac output and reduced systemic vascular resistance , as mentioned above are the chief features of this syndrome. The resultant hypotension leads to peripheral and splanchnic vasodilatation and ultimately portal hypertension in cirrhosis. However, sepsis and hypovolemia are common etiologies of new onset or worsening hypotension in these patients and thus should be promptly recognized and treated. In this situation, a mean arterial blood pressure of 60-65 mm Hg will ensure organ perfusion.Important clinical signs owing to systemic vasodilatation are palmar erythema, bounding pulse, reddish skin etc[14].

Pathogenesis :

Chemicals such as Nitric Oxide (NO) is depleted in intrahepatic circulation while over produced in splanchnic circulation. This leads to splanchnic vasodilation. There is an imbalance between mediators of vasodilatation like adrenomedullin, cytokines, endothelins, natriuretic peptides and vasoconstriction like angiotensinII in peripheral circulation. Vasoconstrictors are predominantly present in hepatic microcirculation. This ultimately results in resistance in hepatic circulation and peripheral vasodilatation including splanchnic vasodilatation[16]. Moreover, cirrhotics are prone to infections. Endotoxins and cytokines such as tumor necrosis factor-á further lead to increased NO production[17]. Endocannabinoid are lipid like substances and are also stimulated by bacterial endotoxins. Apart from these chemical mediators, renin angiotensin system plays a role in mesenteric vasodilatation. Here angiotensin 1-7activate the G-protein coupled Mas receptor (MasR) resulting in vascular hypocontractility and hence might serve as a potential therapeutic target for portal hypertension[18]. Also, studies have found a marker protein in brain (CNS Fos), which has been found to be associated with hyperdynamic circulation in rat models[19]. The reduction in peripheral resistance is compensated by increased cardiac output which leads to hyperdynamic syndrome. The evolution of cardiomyopathy in cirrhosis is a complex interaction among cellular, neuronal and humoral signaling pathways in the systemic scenario rather than happening locally in the heart.

Cirrhotic Cardiomyopathy :

Cirrhotic cardiomyopathy was defined by World Congress of Gastroenterology 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"[20]. The *Diagnostic criteria* were

(a) Systolic dysfunction:

- Blunted increase in cardiac output with exercise, volume challenge or pharmacological stimuli
- Resting Ejection Fraction < 55%

(b) Diastolic dysfunction:

- E/A ratio (early diastolic/atrial filling) < 1.0 (age-corrected)
- Prolonged deceleration time (> 200 ms)
- Prolonged isovolumetric relaxation time (> 80 ms)

(c) Supportive criteria:

- Electrophysiological abnormalities
- Abnormal chronotropic response
- Electromechanical uncoupling/dyssynchrony
- Prolonged QTc interval
- Enlarged left atrium
- Increased myocardial mass
- Increased Brain Natriuretic Peptide (BNP) and pro-BNP
- Increased troponin level

The classical features of even established cardiomyopathy may be difficult to recognized, unless precipitated by stress factors.

Systolic Dysfunction :

Inability of the heart to generate adequate blood pressure and cardiac output signifies systolic dysfunction. Cirrhotics have a normal Left Ventricular Ejection Fraction (LVEF) at rest. However systolic dysfunction occurs with exercise[21,22]. This dysfunction gets unmasked due a blunted heart rate response to stress, reduced myocardial reserve and impaired ability to extract oxygen by the cardiac muscles. Moreover ,administration of vasoconstrictors like terlipressin increases the Systemic Vascular Resistance and thereby the left ventricular afterload unveiling a latent left ventricular dysfunction in cirrhosis. Hence these agents should be cautiously used.

Diastolic Dysfunction :

Increased stiffness of the myocardial wall owing to myocardial hypertrophy, fibrosis, and subendothelia-ledema in cirrhotics leads to diastolic dysfunction. It results in complications and impairs the outcomes of

manoeuvres such as Transjugular Intrahepatic Porto-systemic Shunt (TIPS) insertion which could lead to an increased preload[20].

Electrophysiological Abnormalities :

QT interval prolongation, chronotropic incompetence and electromechanical uncoupling are common in advanced cirrhosis. QT prolongation has a prevalence of over 60% in these patients. Hence drugs prolonging QT should be avoided[12].

Almost all cardiovascular abnormalities have been found to reverse after a few months of liver transplantation[14,20]. The changes can be summed up in Fig 1.

Primary Biliary Cirrhosis :

Hypercholesterolemia occurs in most patients of primary biliary cirrhosis (PBC) which is a cardiovascular risk factor. Ursodeoxycholic acid lowers the circulating levels of cholesterol, thereby decreasing cholestasis. Besides hypercholesterolemia , autonomic dysfunction has been seen in PBC which can also affect the heart and its functions[23].

Hepatopulmonary Syndrome (HPS) :

Advanced liver disease causes increased levels of nitric oxide and vascular endothelial growth factor leading to intrapulmonary vascular dilation. This causes an oxygenation defect[24]. These patients mostly remain asymptomatic during the early stages. However later develop dyspnea. Dyspnea upon standing (platypnea) is an important feature of HPS which is seen in 25% of these patients apart from digital clubbing and cyanosis. Though no established medical therapy has been formulated , it is advisable to prevent chronic hypoxemia by administration of supplemental oxygen. Definitive treatment is liver transplantation.

Non Alcoholic Fatty Liver Disease (NAFLD) :

Main cause of mortality in patients of NAFLD is cardiac complications. NAFLD and NASH are characterised by increased inflammatory biomarkers which may explain the increased association of coronary artery disease in these patients. Dyslipidemia in NAFLD manifested by increased serum triglyceride and low-density lipoprotein cholesterol levels and decreased high-density lipoprotein cholesterol levels, are all key risk factors for cardiovascular disease (CVD)[25]. Moreover CVD risk factors, such as metabolic syndrome, a high Framingham risk score, carotid intima media thickness, and high-sensitivity C-reactive protein (hsCRP) level as well as accelerated atherosclerosis, endothelial dysfunction of the pericardial fat pads, and coronary artery calcification, are significantly elevated in NAFLD patients. Asymptomatic obese children with NAFLD have been

Cardiac morphology	Normal	Hypertrophy (Fibrosis, oedema)	Hypertrophy/ Dilatation
Cardiac function	Normal	Diastolic dysfunction	Systolic dysfunction/ Cardiac failure
Hepatic function	Compensated cirrhosis	Compensated/Mild incompensated cirrhosis Ascites	Decompensated cirrhosis Ascites Renal dysfunction
Systemic circulation	Signs of vasodilatation	Hyperdynamic state	Hyperdynamic state/ Decreasing cardiac output
Cardiac findings	QT ↑	QT↑↑, E/A ↓, DT↑, LVEF ↑	QT↑, Dysynchronised electrical and mechanical systole, LAV and LVEDV↑, LVEF

Fig 1 — Proposal of changes in cardiac output during the course of the liver disease
DT=Deceleration time, LAV=Left atrial volume, LVEDV=Left end-diastolic volume, LVEF=Left ventricular ejection time[20]

shown to have features of early LV diastolic and systolic dysfunction which is more severe in those with Non Alcoholic Steato-Hepatitis (NASH)[26]. Management includes therapeutic lifestyle changes and pharmacotherapy (Statins, fibrates, ezetimibe, omega 3 fatty acids and insulin sensitizing agents).

Chronic Hepatitis C Infection :

Hepatitis C is an infection which causes increased activation of the immune system. It causes chronic inflammation of the myocardium leading to necrosis and loss of myocytes. This later leads to dilated cardiomyopathy. Sometimes it may lead to hypertrophic cardiomyopathy due to virus induced myocyte hypertrophy[27]. Apart from these ,congestive heart failure and presence of metabolic conditions such as type 2 diabetes mellitus and hypertension have also been reported[28].

Hepatocellular Carcinoma :

A significant proportion of cirrhosis complication end up in primary liver cancer, especially in Hepatitis B related cirrhotics. Involvement of the heart in Hepatocellular Carcinoma (HCC) is rare. However right atrial invasion in few cases of HCC have been reported.[29]

Liver Transplantation :

The fact that cardiac manifestations subside or reverse after transplantation of liver shows the association of liver dysfunction with cardiac abnormalities. These features reverse after 6 to 12 months of the procedure. However the immediate post operative period is of importance as it may lead to aggravation of complications. Arrhythmia, acute heart

failure (HF), and myocardial infarctioncan also occur due to reperfusion injury and hence one should be cautious during this period[30]. However, cardiac cirrhosis improves after heart transplant.

Conclusion

Chronic Liver Diseases can affect the heart and blood circulation in many ways. Most commonly LC leads to hyperdynamic syndrome and cirrhotic cardiomyopathy which in turn may facilitate the development of several complications like hepatorenal syndrome and myocyte loss. Liver transplantation causes reversal of almost all cardiovascular abnormalities. However this procedure itself can lead to cardiac death due to causes which have been stated above. Moreover recent studies have shown cardiac complications in patients with NAFLD, hepatitis C, primary biliary cirrhosis as well as hepatocellular carcinoma. Hence a rigorous assessment of cardiac status should be sought for in these patients. Further studies are required to illustrate the pathogenesis and identify therapeutic targets to reverse these changes, as well as to gain insights into the contribution of cardiac dysfunction in the natural history of cirrhosis of liver.

References

1 Fleming KM, Aithal GP, Card TR, West J — All-cause mortality in people with cirrhosis compared with the general population: a population-based cohort study. *Liver Int* 2012; **32(1):** 79-84.
2 Anstee QM, Jones DEJ — Hepatology. In: Ralston HS, Penman ID, Strachan MWJ, Hobson RP. Davidson's Principles and Practice of Medicine. 23rd Ed. Elsevier; 2018. p856
3 Møller S, Henriksen JH — Cardiopulmonary complications in chronic liver disease. *World journal of gastroenterology: WJG* 2006; **12(4):** 526.
4 Targher G, Day CP, Bonora E — Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *New England Journal of Medicine* 2010; **363(14):** 1341-50.
5 Albeldawi M, Aggarwal A, Madhwal S, Cywinski J, Lopez R, Eghtesad B, *et al* — Cumulative risk of cardiovascular events after orthotopic liver transplantation. *Liver Transpl* 2012; **18:** 370-5.
6 Fussner LA, Heimbach JK, Fan C, Dierkhising R, Coss E, Leise MD, *et al* — Cardiovascular disease after liver transplantation: when, what, and who is at risk. *Liver Transpl* 2015; **21:** 889-96.
7 Raval Z, Harinstein ME, Skaro AI, Erdogan A, DeWolf AM, Shah SJ, *et al* — Cardiovascular risk assessment of the liver transplant candidate.Journal of the American College of Cardiology 2011; **58(3):** 223-31.
8 Caramelo C, Fernandez-Munoz D, Santos JC — Effect of volume expansion on hemodynamics, capillary permeability and renal function in conscious, cirrhotic rats. *Hepatology* 1986; **6:** 129-34.
9 Moller S, Henriksen JH — Cirrhotic cardiomyopathy. *J Hepatol* 2010; **53:** 179-90.
10 Krag A, Bendtsen F, Burroughs AK, Moller S — The cardiorenal link in advanced cirrhosis. *Med Hypotheses* 2012; **79:** 53-5.
11 Ruiz-del-Arbol L, Monescillo A, Arocena C — Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology* 2005; **42:** 439-47.
12 BernardiM,Maggioli C, Dibra V, Zaccherini G — QT interval prolongation in liver cirrhosis: innocent bystander or serious threat? *Expert Rev Gastroenterol Hepatol* 2012; **6:** 57-66.
13 Kowalski H, Abelmann WH. The cardiac output at rest in Laennec's cirrhosis. *J Clin Invest* 1953; **32:** 1025-33.
14 Moller S, Henriksen JH — Cardiovascular complications of cirrhosis. *Gut* 2008; **57:** 268-78.
15 Moller S, Krag A, Bendtsen F — Kidney injury in cirrhosis: pathophysiological and therapeutic aspects of hepatorenal syndromes. *Liver Int* 2014; **34:** 1153-63.
16 Al-Hamoudi WK — Cardiovascular changes in cirrhosis: pathogenesis and clinical implications. *Saudi J Gastroenterol* 2010; **16:** 145-53.
17 Lopez-Talavera JC, Cadelina G, Olchowski J, Merrill W, Groszmann RJ — Thalidomide inhibits tumor necrosis factor alpha, decreases nitric oxide synthesis, and ameliorates the hyperdynamic circulatory syndrome in portal-hypertensive rats. *Hepatology* 1996; **23:** 1616-21.
18 Dharmani M, Mustafa MR, Achike FI, Sim MK — Effects of angiotensin 1-7 on the actions of angiotensin II in the renal and mesenteric vasculature of hypertensive and streptozotocininduced diabetic rats. *Eur J Pharmacol* 2007; **561:** 144-50.
19 Liu H, Schuelert N, McDougall JJ, Lee SS — Central neural activation of hyperdynamic circulation in portal hypertensive rats depends on vagal afferent nerves. *Gut* 2008; **57:** 966-73.
20 Møller S, Bernardi M — Interactions of the heart and the liver. *Eur Heart J* 2013; **12:** 2804-11
21 Kelbaek H, Rabol A, Brynjolf I — Haemodynamic response to exercise in patients with alcoholic liver cirrhosis. *Clin Physiol* 1987; **7:** 35-41.
22 Wong F, Liu P, Lilly L, Bomzon A, Blendis L — Role of cardiac structural and functional abnormalities in the pathogenesis of hyperdynamic circulation and renal sodium retention in cirrhosis. *Clin Sci (Lond)* 1999; **97:** 259-67.
23 Schwartz PJ — The autonomic nervous system and sudden death. *Eur Heart J* 1998; **19 Suppl F:** F72-F80
24 Rodríguez-Roisin R, Krowka MJ, Hervé P, Fallon MB — Pulmonary-Hepatic vascular Disorders (PHD). EurRespir J 2004; **24:** 861-80.
25 Zhang QQ, Lu LG — Nonalcoholic fatty liver disease: dyslipidemia, risk for cardiovascular complications, and treatment strategy. *Journal of clinical and translational hepatology* 2015; **3(1):** 78.
26 Pacifico L, Di Martino M, De Merulis A, Bezzi M, Osborn JF, Catalano C, *et al* — Left ventricular dysfunction in obese . Left ventricular dysfunction in obese children and adolescents with nonalcoholic fatty liver disease. *Hepatology* 2013; Epub ahead of print [PMID: 23843206 DOI: 10.1002/hep.26610]
27 Omura T, Yoshiyama M, Hayashi T, Nishiguchi S, Kaito M, Horiike S, *et al* — Core protein of hepatitis C virus induces cardiomyopathy. *Circ Res* 2005; **96:** 148-50 [PMID: 15618537 DOI: 10.1161/01. RES.0000154263.70223.13]
28 Younossi ZM, Stepanova M, Nader F, Younossi Z, Elsheikh E — Associations of chronic hepatitis C with metabolic and cardiac outcomes. *Aliment Pharmacol Ther* 2013; **37:** 647-52.
29 Agelopoulou P, Kapatais A, Varounis C, Grassos C, Kalkandi E, Kouris N, *et al* — Hepatocellular carcinoma with invasion into the right atrium. Report of two cases and review of the literature. *Hepatogastroenterology* 2007; **54:** 2106-8 [PMID: 18251169]
30 Raval Z, Harinstein ME, Skaro AI, Erdogan A, DeWolf AM, Shah SJ, *et al* — Cardiovascular risk assessment of the liver transplant candidate. *J Am Coll Cardiol* 2011; **58:** 223-31. [PMID: 21737011 DOI: 10.1016/j.jacc.2011.03.026]