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Review

How to interpret liver function tests in heart failure patients?

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ABSTRACT

Cardiac hepatopathy has generally been used to describe any liver damage caused by cardiac disorders in the absence of other possible causes of liver damage. Although there is no consensus on the terminology used, cardiac hepatopathy can be examined as congestive hepatopathy (CH) and acute cardiogenic liver injury (ACLI). CH is caused by passive venous congestion of the liver that generally occurs in the setting of chronic cardiac conditions such as chronic HF, constrictive pericarditis, tricuspid regurgitation, or right-sided heart failure (HF) of any cause, and ACLI is most commonly associated with acute cardiocirculatory failure resulting from acute myocardial infarction, acute decompensated HF, or myocarditis. Histologically, CH is characterized by sinusoidal dilation, replacement of hepatocytes with red blood cells extravasating from the sinusoids, and necrosis/apoptosis of zone 3 of the Rappaport acinus, and it could progress to cirrhosis in advanced cases. In ACLI, however, massive necrosis of zone 3 is the main histological finding. Primary laboratory findings of CH are elevated serum cholestasis markers including bilirubin, alkaline phosphatase, and γ-glutamyl-transpeptidase levels, whereas those of ACLI are a striking elevation in transaminase and lactate dehydrogenase levels. Both CH and ACLI have a prognostic value for identifying cardiovascular events and mortality and have some special implications in the management of patients undergoing ventricular assist device implantation or cardiac transplantation. There is no specific treatment for CH or ACLI other than treatment of the underlying cardiac disorder.

Keywords: Cardiac hepatopathy, congestive hepatopathy, acute cardiogenic liver injury

INTRODUCTION

Heart failure (HF) is a systemic clinical syndrome with typical symptoms and signs (dyspnea, leg swelling, paroxysmal nocturnal dyspnea, and orthopnea) that result from any structural or functional impairment of ventricular filling or ejection of blood (1,2). HF is a major health problem with significant personal and public implications. In the United States, approximately 5.1 million people have HF, and approximately 50% of these people die within 5 years of diagnosis, despite survival having improved during the recent years with some advances in medical and device therapies (1,3).

Heart failure may result from congenital or acquired disorders of the pericardium, myocardium, endocardium, heart valves, great vessels, heart rhythm, or conduction or from certain metabolic abnormalities; however, disorders of the left ventricular myocardium impairing the ability of the left ventricle (LV) to fill with or eject blood is the underlying cause in the most of HF patients (1). Therefore, HF is generally described using the measurement of LV ejection fraction (EF, the end-diastolic volume minus the end-systolic volume divided by the end-diastolic volume). HF with reduced EF (HFrEF) is described as the clinical syndrome of HF with LVEF≤40%. It is also referred to as systolic HF because the basic pathology is reduced cardiac contractility. HF with preserved EF (HFpEF) is defined as the clinical syndrome of HF with LVEF≥50%. It is also referred to as diastolic HF, in which the objective evidence of LV dia-

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stolic dysfunction and/or relevant structural changes supported by echocardiography or cardiac catheterization should be established in addition to preserved LVEF and symptoms and signs of HF. HFpEF is predominantly a disease affecting older women with hypertension. Several studies suggest that in clinical HF patients, the prevalence of HFpEF is approximately 50% with morbidity and mortality rates comparable with those of HFrEF (4).

In HF, the heart cannot deliver oxygen at a rate proportionate to the demands of the metabolizing tissues that may result in damage to other organ systems such as the kidney, bone marrow, or liver (5-8). In literature, a spectrum of liver damages from mild liver function test (LFT) abnormalities to cardiac cirrhosis has been reported in both chronic and acute HF patients (9-11). Recently, more systematic evaluations have been performed in large patient cohorts to assess the prognostic value of LFT abnormalities in HF patients (5,12). Here, we aim to review the current available literature on the significance of the liver abnormalities in HF patients.

Pathophysiology of liver damage

Although there is no consensus on terminology, "cardiac hepatopathy" has generally been used to describe any liver damage caused by cardiac disorders in the absence of other possible causes of liver damage (13-16). In cardiac hepatopathy, the primary pathophysiology is either passive venous congestion that results in "congestive hepatopathy (CH)" or low cardiac output and arterial hypoperfusion that results in "acute cardiogenic liver injury (ACLI)" (14,15,17,18). In literature, ischemic hepatitis, shock liver, or hypoxic hepatopathy have also been used instead of ACLI, however, we propose that ACLI provides more details about the underlying pathophysiological process (18,19). CH generally occurs in the setting of chronic cardiac conditions that may increase systemic venous pressure such as chronic HF, constrictive pericarditis, mitral stenosis, tricuspid regurgitation, cor pulmonale, severe pulmonary arterial hypertension, long-standing Fontan procedure, or right-sided HF of any cause. Acute cardiogenic liver injury, however, is most commonly associated with acute cardiocirculatory failure resulting from acute myocardial infarction, acute decompensated HF (ADHF), myocarditis, or massive pulmonary embolism (17,18). In fact, passive congestion secondary to right-sided HF and reduced arterial perfusion and oxygenation due to left-sided HF often coexist and potentiate the deleterious effects of each other on the liver (11,14,19,20).

The liver is enlarged, tender, and firm in CH. The main histological finding in a congestive liver is hemorrhage and necrosis of zone 3 of the Rappaport acinus with normal or mildly steatotic areas in zones 1 and 2 (9,11,13,21). Because obesity, hyperlipidemia, and diabetes are common risk factors for both HF and hepatosteatosis, non-alcoholic hepatosteatosis is frequently observed in CH patients (9,14,22). The changes in zone 3, however, largely depend on the transmission of elevated systemic venous pressure to hepatic sinusoids through hepatic vessels that result in sinusoidal dilation, replacement of hepatocytes with red blood cells extravasating from the sinusoids, and centrilobular tissue destruction (21,23-26). A small study evaluating the pattern of hepatocyte cell death in cardiac hepatopathy suggests that apoptosis is the major process of cell death in chronic HF patients, whereas necrotic cell death is prominent in acute HF (25). In CH, increased venous pressure also promotes ascites formation, which is present in up to 60% of cardiac hepatopathy patients (13), bile duct damage (27), and thrombi formation in sinusoids, hepatic venules, and portal tracts (28). If congestion remains for a longer duration, these changes are followed by the deposition of collagen to forming fibrous septa and bridges between adjacent central veins that ultimately results in cardiac cirrhosis (29). To date, cardiac cirrhosis, in general, is rare, but it is still important in special patient groups such as Fontan survivors (30), overlooked constrictive pericarditis cases (31), and untreated severe tricuspid regurgitation (29). In contrast to primary liver disease-related cirrhosis, cardiac cirrhosis shows a reverse lobulated pattern, in which damage is more prominent in zone 3 than in zone 1 (20). Another distinct feature of cardiac cirrhosis is the presence of a matched distribution pattern between liver fibrosis and the fibrous obliteration of hepatic and portal veins caused by organized thrombi. The fibroblast activating effect of focal thrombi has been suggested to explain this finding (28). Vascular congestion caused by HF can induce a transient increase in liver stiffness assessed by elastography, which can mislead the diagnosis of liver cirrhosis (32). In HF patients, the diagnosis of cardiac cirrhosis should be based on clinical, biochemical, and radiographic findings.

Because the liver has a high metabolic activity and perfusion rate, acute circulatory changes such as cardiogenic shock or ADHF may result in ACLI when the liver's compensatory mechanism of increasing oxygen extraction from the blood (up to 95%) is being insufficient in the setting of persistent circulatory failure (11,12,33,34). Hepatic blood flow declines by approximately 10% for every 10 mmHg drop in arterial pressure; however, with this excellent compensatory mechanism, previously healthy individuals with shock do not appear to frequently develop liver damage frequently (11). A retrospective analysis of 31 patients with ischemic hepatitis indicated that all patients had a severe underlying cardiac disorder with passive congestion of the liver. Thus, they suggested that a baseline hepatic congestion is required to predispose the liver to damage induced by a hypotensive event (10). Other larger studies also supported the hypothesis that ACLI results from an acute impairment of liver perfusion that is superimposed on a pre-existing hepatic congestion caused by elevated hepatic venous pressure (18,35,36). Histologically, ACLI is characterized by necrosis of pericentral zone 3 hepatocytes, which receive poorly oxygenated blood compared to periportal zone 1 and 2 hepatocytes (11,29).

Clinical findings and implications of the laboratory changes

Congestive hepatopathy is generally asymptomatic, but a mild discomfort in the right upper quadrant caused by liver cap-

sule stretching, early satiety, nausea, and anorexia is reported by some patients (17,37). Jaundice, tender hepatomegaly, hepatojugular reflux, ascites, and pulsatile liver are the main findings on physical examination (17,38). In a retrospective analysis of 661 patients referred to a "jaundice hotline" service, a primary cardiac cause is identified in eight patients (1.2%) as an underlying cause for jaundice (39). The hepatojugular reflux is defined as a sustained rise of more than 3 cm in the jugular venous pressure elucidated by the application of firm and consistent pressure to the right upper quadrant. It is a very useful maneuver for predicting heart failure. Pulsatile liver is generally caused by tricuspid regurgitation, tricuspid stenosis, constrictive pericarditis, restrictive cardiomyopathy, or pulmonary hypertension (17). Splenomegaly is present in a minority of chronic HF patients, but esophageal varices are rare because of a normal hepatic venous pressure gradient in majority of patients (13,20).

In CH, primary laboratory findings are elevated serum cholestasis markers including bilirubin, alkaline phosphatase (AP), and γ-glutamyl-transpeptidase (GGT) (12,40-43). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels generally show mild elevations up to 2-3 times the normal reference level (20). A mild decrease in albumin (approximately in 25% patients) levels and a slight increase in prothrombin time are also frequent in CH patients (5,29,44). Increase in liver function tests are more strongly correlated with decreased cardiac index, increased filling pressures, and severe tricuspid regurgitation (41,44). In a study of 1087 ambulatory HF patients, the prevalence of elevated GGT was reported to be 43% in men and 48% in women and that of total bilirubin was reported to be 17% in men and 8% in women. Both GGT and total bilirubin levels were found to be associated with disease severity, but only GGT level is independently associated with adverse outcomes in that study (45). The analysis of liver function tests in 2679 (candesartan in heart failure: assessment of reduction in mortality and morbidity) patients revealed that total bilirubin is above the upper limit of normal levels in 13% of patients. After adjustment for other variables, only total bilirubin level was found to be independently associated with morbidity and mortality in the CHARM program (5). Another prospective study of 552 chronic HF patients suggested that all abnormal LFTs are markedly associated with mortality, but AST and total bilirubin levels show the highest association (46). Poelzl et al. (47) found that AP (HR 1.52) and GGT (HR 1.22) are independent predictors of death from any cause and heart transplantation in a group of 1032 ambulatory HF patients. They also reported that total bilirubin, AP, and GGT levels independently correlate with functional class and clinical signs of HF including jugular venous distention, tricuspid regurgitation, and peripheral edema. In recent studies evaluating patients undergoing left ventricular assist device (LVAD) implantation, total total bilirubin level was found to be an independent marker for right ventricular failure after LVAD implantation (48). Today, total bilirubin level is a component of risk models for adverse outcomes after LVAD implantation or cardiac transplantation (48,49). Hypoalbuminemia, mainly caused by HF-associated systemic inflammation, is another prognostic marker in acute and chronic HF (18). Hypoalbuminemia has a prognostic value in LVAD patients and is a component of risk models (50). The ascites associated with chronic HF also has distinct features that may aid in making the differential diagnosis. Cardiac ascites has high protein content (usually≥2.5g/dL) and high serum ascites albumin gradient (>1.1g/dL) due to preserved synthetic function of the liver (11). Red blood cell counts and lactate dehydrogenase (LDH) levels are also higher in cardiac ascites than in cirrhotic ascites of other causes due to the extravasation of red blood cells into the ascites with resultant lysis (11). In the differential diagnosis, another useful marker is serum or ascites NT-proBNP levels. Sheer et al. (51) reported that both serum and ascites NT-proBNP levels have high sensitivity and specificity in predicting HF as the cause of ascites. Both the American College of Cardiology and European Society of Cardiology Heart Failure Guidelines recommend the inclusion of LFTs in the diagnostic workup of all patients presenting with HF (1,2).

Acute cardiogenic liver injury is generally asymptomatic, but nausea, vomiting, weakness, right upper quadrant pain, and apathy may be present after a latent period of 2–24 h after the acute event (11). In minority of cases, mental confusion, jaundice, flapping tremor, or hepatic coma might develop; however, in a patient with acute cardiocirculatory failure, mental confusion and coma generally represent cerebral hypoxia rather than hepatic encephalopathy (11,15,24,33). Fulminant hepatic failure has also been reported in rare cases of HF (52). Retrospective analysis of 1147 acute liver failure patients from the Acute Liver Failure Study Group revealed that 4.4% of patients had ischemic hepatitis. Only 31% of these patients had knowledge regarding their cardiac disease before presentation, but a cardiopulmonary precipitant of hepatic ischemia was identified in 69% (53). In that analysis, hepatic encephalopathy was found to be associated with short-term mortality, but long-term prognosis was largely determined by the underlying cardiac disorder. In another study comprising 202 acute liver failure patients, cardiogenic shock was found in 13 patients. The mortality rate was 54% in these 13 patients, and only the cardiac index was different between survivors and non-survivors (54). In some patients with acute liver failure, underlying cardiogenic cause may not be so obvious at first. An abnormal electrocardiogram associated with cardiac murmurs should warrant an echocardiographic examination for diagnosis in patients with acute liver failure of unknown etiology (14).

The typical laboratory finding of ACLI is the presence of a striking elevation in transaminase and LDH levels (generally to 10-20 times the normal values, even up to 2000-fold) (11,54,55). Transaminases and LDH levels reach their peak 1-3 days after the acute event and return to normal limits within 7-10 days if the patient's hemodynamics recover (19,56,57). In ACLI, an early and rapid increase of LDH levels in parallel with transaminase levels, a ratio of ALT to LDH <1.5, and a decrease in ALT levels

Table 1. Dosage modifications of commonly used cardiovascular drugs in patients with heart failure and liver damage

Pharmacologic agent	Hepatic interaction	Suggestion
Angiotensin-converting enzyme (ACE) inhibitors	Most of them are pro-drugs and require hepatic metabolism for activation. ACE inhibitors can cause cholestasis, acute hepatocellular injury, and mixed hepatitis	Usual dose with frequent monitoring
Angiotensin receptor blockers	Losartan has extensive 1st pass hepatic metabolism and can cause acute hepatocellular injury.	Lower initial doses for losartan, not for valsartan or irbesartan
Beta blockers	Route of elimination is hepatic for carvedilol and metoprolol, and hepatic and renal for bisoprolol.	Carvedilol not recommended in hepatic impairement. Lower initial doses for metoprolol and bisoprolol.
Furosemide	Renal elimination	For cirrhosis, furosemide is best initiated in the hospital. No dose adjustment needed.
Hydrochlorothiazide	Renal elimination, can cause jaundice	Usual dose
Statins	Statins can cause acute hepatocellular injury and autoimmune hepatitis.	Contraindicated in active liver disease or unexplained ALT>3 times the upper normal limit
		Non-alcoholic fatty liver disease and stable hepatitis C infection are not absolute contraindications.
Amiodarone	Primarily eliminated by hepatic metabolism and can cause mild degree of chronic steatohepatitis or cholestasis.	If liver enzymes increase to >3 times normal or double in a patient with elevated baseline stop or reduce dosage.
Warfarin	Eliminated by hepatic metabolism. Intrinsic coagulation factor production is already impaired in hepatic congestion.	Lower initial doses with frequent INR monitoring.
Dabigatran	Renal elimination. Administration to patients with moderate hepatic impairment (Child-Pugh class B) showed a large intersubject variability.	The overall benefits of dabigatran relative to warfarin are consistent in patients with and without HF (71) but the degree of anticoagulation cannot be easily monitored.
		The selection of an anticoagulant should be individualized.
Apixaban	Eliminated by multiple pathways. No dosage adjustment necessary in mild hepatic impairment. Not recommended in moderate-severe hepatic impairement.	The overall benefits of apixaban relative to warfarin are consistent in patients with HF (72), but the degree of anticoagulation cannot be easily monitored. The selection of an anticoagulant should be individualized.
Rivaroxaban	Renal and hepatic elimination. Significant increases in exposure and pharmacodynamic effects in moderate hepatic impairment (Child-Pugh class No data in severe hepatic impairment.	The overall benefits of rivaroxaban relative to warfarin are consistent in patients with HF (73), but the degree of anticoagulation cannot be easily monitored. The selection of an anticoagulant should be individualized.

ALT: alanine transaminase; INR: international normalized ratio; HF: heart failure.

by more than 50% within 72 h are characteristic findings that can be useful in the differential diagnosis of acute viral, alcoholic, or drug-induced hepatitis (29,58,59). Other laboratory findings are mild elevations of serum bilirubin and AP levels and prolongation of prothrombin time (11,19,29). Several trials evaluated the prognostic role of LFTs in ADHF patients. A post hoc analysis of 1134 inotropes-treated ADHF patients from the SURVIVE trial indicated that 46% of patients had abnormal LFTs, and among these tests, only abnormal transaminase level were associated with 180-day mortality (12). Another post hoc analysis of the placebo arm of the EVEREST trial that involved hospitalized ADHF patients showed that baseline LFTs abnormalities are common in ADHF patients but that only low albumin and elevated bilirubin levels have a prognostic value for mortality (60). Another acute HF study (Relaxin in Acute Heart Failure, RELAX-AHF study) reported that an increase of ≥20% at early days of acute event in serum ALT levels was associated with 180-day all-cause mortality (61).

Management of liver damage in the setting of HF

There is no specific treatment of CH other than the treatment of the underlying cardiac disease. In symptomatic HFrEF patients, diuretics are recommended to reduce fluid retention and to improve symptoms (1). It is well known that advanced liver dysfunction may have a negative impact on renal function (hepato-renal syndrome) by way of splanchnic vasodilatation resulting in arterial underfilling and renal vasoconstriction (62). Therefore, in chronic HF patients, liver congestion may directly contribute to impaired natriuresis. Liver congestion, ascites, and jaundice may improve with diuretics therapy, but in refractory cases, combination therapy with diuretics paracentesis, ultrafiltration, or peritoneal dialysis may be needed (18,29,63,64). A small study reported that in volume-overloaded patients admitted with ADHF refractory to intensive medical therapy, paracentesis results in a reduction of elevated intraabdominal pressure with corresponding improvement in renal function (65).

Angiotensin-converting enzyme (ACE) inhibitors [or angiotensin receptor blockers (ARBs) in ACE inhibitor intolerant patients] and beta blockers are recommended in all symptomatic HFrEF patients, unless contraindicated to reduce morbidity and mortality (1,2). Low-dose mineralocorticoid receptor antagonists (MRAs) are also recommended in symptomatic HFrEF patients with an estimated glomerular filtration rate>30 mL/min/1.73 m^2 and potassium<5.0 mEq/L to reduce morbidity and mortality. In HF patients, MRAs are used in low doses (spironolactone up to 50 mg/day); however, in cirrhosis, natriuretic doses of MRAs (spironolactone up to 400 mg) are recommended as the main therapy to produce a negative sodium balance. Future trials should be designed to evaluate additional benefits of higher doses of MRAs over lower doses in HF patients (66). Hydralazine and nitrate combination is recommended in symptomatic African-American patients and patients intolerant to ACE inhibitors and ARBs. In suitable refractory HF patients' cardiac resynchronization therapy, LVAD, or cardiac transplantation are recommended. Cardiac transplantation and LVAD implantation can improve abnormal LFTs (50,67), but if there is a strong suspicion of advanced liver disease, cirrhosis must be ruled out before the cardiac transplantation or combined liver-heart transplantation is performed in suitable cases (68). In HFpEF, no treatment has shown reduction in morbidity and mortality. Diuretics; controlling systolic and diastolic blood pressure, particularly with ACE inhibitors or ARBs; coronary revascularization; and atrial fibrillation management are recommended in suitable HFpEF patients to relieve symptoms (1,2).

In ACLI, restoration of the cardiac output and hemodynamics is the primary goal of therapy. Ventilator support, inotropes/vasopressors, coronary recanalization therapies, and mechanical circulatory support should be used in suitable patients. LFTs should be monitored for recovery (2,18). In the RELAX-AHF study, seralaxin (recombinant human relaxin-2) administration improved LFTs in acute HF patients, which is consistent with more effective prevention organ damage (61).

Cardiac hepatopathy and cardiovascular drugs

The liver, metabolizes many cardiovascular drugs in contrast to the kidney; therefore, there are no rules for the modification of drug dosage in the cases of liver dysfunction. This is partly caused by the fact that none of the LFT abnormalities sufficiently correlate with the degree of alterations in hepatic drug metabolism (17,18). Verbeeck et al. suggested that the individual pharmacokinetic profile of the drug should be considered for the modification of drug dosage (69,70). Suggestions on dosage modification of frequently used cardiovascular drugs in liver dysfunction are summarized in the Table 1.

CONCLUSION

Acute and chronic HF may be complicated with liver damage, which has significant implications on the patient management and underlying heart disease outcomes.

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REFERENCES

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62: e147-239. [CrossRef]
2. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; 33: 1787-847. [CrossRef]
3. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics-2013 update: a report from the American Heart Association. Circulation 2013; 127: e6-245. [CrossRef]
4. Heart Failure Society of America, Lindenfeld J, Albert NM, et al. Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail 2010; 16: e1-194. [CrossRef]
5. Allen LA, Felker GM, Pocock S, et al. Liver function abnormalities and outcome in patients with chronic heart failure: data from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Eur J Heart Fail 2009; 11: 170-7. [CrossRef]
6. Felker GM, Allen LA, Pocock SJ, et al. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. J Am Coll Cardiol 2007; 50: 40-7. [CrossRef]
7. de Silva R, Nitikin NP, Witte KK, et al. Incidence of renal dysfunction over 6 months in patients with chronic heart failure due to left ventricular systolic dysfunction: contributing factors and relationship to prognosis. Eur Heart J 2006; 27: 569-81. [CrossRef]
8. Damman K, Navis G, Voors AA, et al. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. J Card Fail 2007; 13: 698-700. [CrossRef]
9. Sherlock S. The liver in heart failure; relation of anatomical, functional, and circulatory changes. Br Heart J 1951; 13: 273-93. [CrossRef]
10. Seeto RK, Fenn B, Rockey DC. Ischemic hepatitis: clinical presentation and pathogenesis. Am J Med 2000; 109: 109-13. [CrossRef]
11. Naschitz JE, Slobodin G, Lewis RJ, Zuckerman E, Yeshurun D. Heart diseases affecting the liver and liver diseases affecting the heart. Am Heart J 2000; 140: 111-20. [CrossRef]
12. Nikolaou M, Parissis J, Yilmaz MB, et al. Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure. Eur Heart J 2013; 34: 742-9. [CrossRef]
13. Myers RP, Cerini R, Sayegh R, et al. Cardiac hepatopathy: clinical, hemodynamic, and histologic characteristics and correlations. Hepatology 2003; 37: 393-400. [CrossRef]
14. Møller S, Bernardi M. Interactions of the heart and the liver. Eur Heart J 2013; 34: 2804-11. [CrossRef]

15. Kavoliuniene A, Vaitiekiene A, Cesnaite G. Congestive hepatopathy and hypoxic hepatitis in heart failure: a cardiologist's point of view. Int J Cardiol 2013; 166: 554-8. **[CrossRef]**
16. Weisberg IS, Jacobson IM. Cardiovascular diseases and the liver. Clin Liver Dis 2011; 15: 1-20. **[CrossRef]**
17. Alvarez AM, Mukherjee D. Liver abnormalities in cardiac diseases and heart failure. Int J Angiol 2011; 20: 135-42. **[CrossRef]**
18. Samsky MD, Patel CB, DeWald TA, et al. Cardiohepatic interactions in heart failure: an overview and clinical implications. J Am Coll Cardiol 2013; 61: 2397-405. **[CrossRef]**
19. Henrion J. Hypoxic hepatitis. Liver Int 2012; 32: 1039-52. **[CrossRef]**
20. Giallourakis CC. Liver complications in patients with congestive heart failure. Gastroenterol Hepatol (N Y). 2013; 9: 244-6.
21. Safran AP, Schaffner F. Chronic passive congestion of the liver in man. Electron microscopic study of cell atrophy and intralobular fibrosis. Am J Pathol 1967; 50: 447-63.
22. Myers RP, Lee SS. Cirrhotic cardiomyopathy and liver transplantation. Liver Transpl 2000; 6: S44-52. **[CrossRef]**
23. Dunn GD, Hayes P, Breen KJ, Schenker S. The liver in congestive heart failure: a review. Am J Med Sci 1973; 265: 174-89. **[CrossRef]**
24. Valla D. Cirrhosis of vascular origin. Rev Prat 1991; 41: 1170-3.
25. Herzer K, Kneiseler G, Bechmann LP, et al. Onset of heart failure determines the hepatic cell death pattern. Ann Hepatol 2011; 10: 174-9.
26. Seeto RK, Fenn B, Rockey DC. Ischemic hepatitis: clinical presentation and pathogenesis. Am J Med 2000; 109: 109-13. **[CrossRef]**
27. Cogger VC, Fraser R, Le Couteur DG. Liver dysfunction and heart failure. Am J Cardiol 2003; 91: 1399. **[CrossRef]**
28. Wanless IR, Liu JJ, Butany J. Role of thrombosis in the pathogenesis of congestive hepatic fibrosis (cardiac cirrhosis). Hepatology 1995; 21: 1232-7. **[CrossRef]**
29. Giallourakis CC, Rosenberg PM, Friedman LS. The liver in heart failure. Clin Liver Dis 2002; 6: 947-67. **[CrossRef]**
30. Baek JS, Bae EJ, Ko JS, et al. Late hepatic complications after Fontan operation; non-invasive markers of hepatic fibrosis and risk factors. Heart 2010; 96: 1750-5. **[CrossRef]**
31. Bergman M, Vitrai J, Salman H. Constrictive pericarditis: A reminder of a not so rare disease. Eur J Intern Med 2006; 17: 457-64. **[CrossRef]**
32. Lebray P, Varnous S, Charlotte F, Varaut A, Poynard T, Ratziu V. Liver stiffness is an unreliable marker of liver fibrosis in patients with cardiac insufficiency. Hepatology 2008; 48: 2089. **[CrossRef]**
33. Bacon BR, Joshi SN, Granger DN. Ischemia, congestive heart failure, Budd-Chiari Syndrome and veno-occlusive disease. In: Kaplowitz N, editor. Liver and biliary diease. Baltimore: Williams & Wilkins; 1992. p.421-31.
34. Denis C, De Kerguennec C, Bernuau J, Beauvais F, Cohen Solal A. Acute hypoxic hepatitis ('liver shock'): still a frequently overlooked cardiological diagnosis. Eur J Heart Fail 2004; 6: 561-5. **[CrossRef]**
35. Henrion J, Schapira M, Luwaert R, Colin L, Delannoy A, Heller FR. Hypoxic hepatitis: clinical and hemodynamic study in 142 consecutive cases. Medicine (Baltimore) 2003; 82: 392-406. **[CrossRef]**
36. Raurich JM, Llompart-Pou JA, Ferreruela M, et al. Hypoxic hepatitis in critically ill patients: incidence, etiology and risk factors for mortality. J Anesth 2011; 25: 50-6. **[CrossRef]**
37. Fauci AS, Braunwald E, Hauser SL, Longo DL, Jameson J, Loscalzo J. Harrison's Principles of Internal Medicine. Vol 2. New York, NY: McGraw-Hill Medical, 2008.
38. Kavoliuniene A, Vaitiekiene A, Cesnaite G. Congestive hepatopathy and hypoxic hepatitis in heart failure: a cardiologist's point of view. Int J Cardiol 2013; 166: 554-8. **[CrossRef]**
39. van Lingen R, Warshow U, Dalton HR, Hussaini SH. Jaundice as a presentation of heart failure. J R Soc Med 2005; 98: 357-9. **[CrossRef]**
40. Vasconcelos LA, de Almeida EA, Bachur LF. Clinical evaluation and hepatic laboratory assessment in individuals with congestive heart failure. Arq Bras Cardiol 2007; 88: 590-5. **[CrossRef]**
41. Lau GT, Tan HC, Kritharides L. Type of liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. Am J Cardiol 2002; 90: 1405-9. **[CrossRef]**
42. van Deursen VM, Damman K, Hillege HL, van Beek AP, van Veldhuisen DJ, Voors AA. Abnormal liver function in relation to hemodynamic profile in heart failure patients. J Card Fail 2010; 16: 84-90. **[CrossRef]**
43. Poelzl G, Eberl C, Achrainer H, et al. Prevalence and prognostic significance of elevated gamma-glutamyltransferase in chronic heart failure. Circ Heart Fail 2009; 2: 294-302. **[CrossRef]**
44. Kubo SH, Walter BA, John DH, Clark M, Cody RJ. Liver function abnormalities in chronic heart failure. Influence of systemic hemodynamics. Arch Intern Med 1987; 147: 1227-30. **[CrossRef]**
45. Ess M, Mussner-Seeber C, Mariacher S, et al. γ-Glutamyltransferase rather than total bilirubin predicts outcome in chronic heart failure. J Card Fail 2011; 17: 577-84. **[CrossRef]**
46. Batin P, Wickens M, McEntegart D, Fullwood L, Cowley AJ. The importance of abnormalities of liver function tests in predicting mortality in chronic heart failure. Eur Heart J 1995; 16: 1613-8.
47. Poelzl G, Ess M, Mussner-Seeber C, Pachinger O, Frick M, Ulmer H. Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance. Eur J Clin Invest 2012; 42: 153-63. **[CrossRef]**
48. Matthews JC, Koelling TM, Pagani FD, Aaronson KD. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. J Am Coll Cardiol 2008; 51: 2163-72. **[CrossRef]**
49. Singh TP, Almond CS, Semigran MJ, Piercey G, Gauvreau K. Risk prediction for early in-hospital mortality following heart transplantation in the United States. Circ Heart Fail 2012; 5: 259-66. **[CrossRef]**
50. Chokshi A, Cheema FH, Schaefle KJ, et al. Hepatic dysfunction and survival after orthotopic heart transplantation: application of the MELD scoring system for outcome prediction. J Heart Lung Transplant 2012; 31: 591-600. **[CrossRef]**
51. Sheer TA, Joo E, Runyon BA. Usefulness of serum N-terminal-ProB-NP in distinguishing ascites due to cirrhosis from ascites due to heart failure. J Clin Gastroenterol 2010; 44: e23-6. **[CrossRef]**
52. Kisloff B, Schaffer G. Fulminant hepatic failure secondary to congestive heart failure. Am J Dig Dis 1976; 21: 895-900. **[CrossRef]**
53. Taylor RM, Tujios S, Jinjuvadia K, et al. Short and long-term outcomes in patients with acute liver failure due to ischemic hepatitis. Dig Dis Sci 2012; 57: 777-85. **[CrossRef]**
54. Saner FH, Heuer M, Meyer M, et al. When the heart kills the liver: acute liver failure in congestive heart failure. Eur J Med Res 2009; 14: 541-6.
55. Henrion J, Descamps O, Luwaert R, Schapira M, Parfonry A, Heller F. Hypoxic hepatitis in patients with cardiac failure: incidence in a coronary care unit and measurement of hepatic blood flow. J Hepatol 1994; 21: 696-703. **[CrossRef]**
56. Hickman PE, Potter JM. Mortality associated with ischaemic hepatitis. Aust N Z J Med 1990; 20: 32-4. **[CrossRef]**
57. Naschitz JE, Yeshurun D. Compensated cardiogenic shock: a subset with damage limited to liver and kidneys. The possible salutary effect of low-dose dopamine. Cardiology 1987; 74: 212-8. **[CrossRef]**

58. Fuhrmann V, Kneidinger N, Herkner H, et al. Hypoxic hepatitis: underlying conditions and risk factors for mortality in critically ill patients. Intensive Care Med 2009; 35: 1397-405. **[CrossRef]**
59. Cassidy WM, Reynolds TB. Serum lactic dehydrogenase in the differential diagnosis of acute hepatocellular injury. J Clin Gastroenterol 1994; 19: 118-21. **[CrossRef]**
60. Ambrosy AP, Vaduganathan M, Huffman MD, et al. Clinical course and predictive value of liver function tests in patients hospitalized for worsening heart failure with reduced ejection fraction: an analysis of the EVEREST trial. Eur J Heart Fail 2012; 14: 302-11. **[CrossRef]**
61. Metra M, Cotter G, Davison BA, et al. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: correlation with outcomes. J Am Coll Cardiol 2013; 61: 196-206. **[CrossRef]**
62. Hasper D, Jörres A. New insights into the management of hepato-renal syndrome. Liver Int 2011; 31: 27-30. **[CrossRef]**
63. Kisloff B, Schaffer G. Fulminant hepatic failure secondary to congestive heart failure. Am J Dig Dis 1976; 21: 895-900. **[CrossRef]**
64. Verbrugge FH, Dupont M, Steels P, et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J Am Coll Cardiol 2013; 62: 485-95. **[CrossRef]**
65. Mullens W, Abrahams Z, Francis GS, Taylor DO, Starling RC, Tang WH. Prompt reduction in intra-abdominal pressure following large-volume mechanical fluid removal improves renal insufficiency in refractory decompensated heart failure. J Card Fail 2008; 14: 508-14. **[CrossRef]**
66. Bansal S, Lindenfeld J, Schrier RW. Sodium retention in heart failure and cirrhosis: potential role of natriuretic doses of mineralocorticoid antagonist? Circ Heart Fail 2009; 2: 370-6. **[CrossRef]**
67. Russell SD, Rogers JG, Milano CA, et al. Renal and hepatic function improve in advanced heart failure patients during continuous-flow support with the HeartMate II left ventricular assist device. Circulation 2009; 120: 2352-7. **[CrossRef]**
68. Cannon RM, Hughes MG, Jones CM, Eng M, Marvin MR. A review of the United States experience with combined heart-liver transplantation. Transpl Int 2012; 25: 1223-8. **[CrossRef]**
69. Sokol SI, Cheng A, Frishman WH, Kaza CS. Cardiovascular drug therapy in patients with hepatic diseases and patients with congestive heart failure. J Clin Pharmacol 2000; 40: 11-30. **[CrossRef]**
70. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 2008; 64: 1147-61. **[CrossRef]**
71. Ferreira J, Ezekowitz MD, Connolly SJ, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and symptomatic heart failure: a subgroup analysis of the RE-LY trial. Eur J Heart Fail 2013; 15: 1053-61. **[CrossRef]**
72. McMurray JJ, Ezekowitz JA, Lewis BS, et al. Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. Circ Heart Fail 2013; 6: 451-60. **[CrossRef]**
73. van Diepen S, Hellkamp AS, Patel MR, et al. Efficacy and safety of rivaroxaban in patients with heart failure and nonvalvular atrial fibrillation: insights from ROCKET AF. Circ Heart Fail 2013; 6: 740-7. **[CrossRef]**