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 (HFP EF) 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-
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 cholesta-sis 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 regurgita-tion (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 proteinuria) 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 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
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 HFpEF 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).

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

<table>
<thead>
<tr>
<th>Pharmacologic agent</th>
<th>Hepatic interaction</th>
<th>Suggestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme (ACE) inhibitors</td>
<td>Most of them are pro-drugs and require hepatic metabolism for activation. ACE inhibitors can cause cholestasis, acute hepatocellular injury, and mixed hepatitis</td>
<td>Usual dose with frequent monitoring</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>Losartan has extensive 1st pass hepatic metabolism and can cause acute hepatocellular injury.</td>
<td>Lower initial doses for losartan, not for valsartan or irbesartan</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Route of elimination is hepatic for carvedilol and metoprolol, and hepatic and renal for bisoprolol.</td>
<td>Carvedilol not recommended in hepatic impairement. Lower initial doses for metoprolol and bisoprolol.</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Renal elimination</td>
<td>For cirrhosis, furosemide is best initiated in the hospital. No dose adjustment needed.</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Renal elimination, can cause jaundice</td>
<td>Usual dose</td>
</tr>
<tr>
<td>Statins</td>
<td>Statins can cause acute hepatocellular injury and autoimmune hepatitis.</td>
<td>Contraindicated in active liver disease or unexplained ALT&gt;3 times the upper normal limit</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Primarily eliminated by hepatic metabolism and can cause mild degree of chronic steatohepatitis or cholestasis.</td>
<td>If liver enzymes increase to &gt;3 times normal or double in a patient with elevated baseline stop or reduce dosage.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Eliminated by hepatic metabolism. Intrinsic coagulation factor production is already impaired in hepatic congestion.</td>
<td>Lower initial doses with frequent INR monitoring.</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Renal elimination. Administration to patients with moderate hepatic impairment (Child-Pugh class B) showed a large intersubject variability.</td>
<td>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.</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Eliminated by multiple pathways. No dosage adjustment necessary in mild hepatic impairment. Not recommended in moderate-severe hepatic impairement.</td>
<td>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.</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Renal and hepatic elimination. Significant increases in exposure and pharmacodynamic effects in moderate hepatic impairement (Child-Pugh class No data in severe hepatic impairement.</td>
<td>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.</td>
</tr>
</tbody>
</table>

ALT: alanine transaminase; INR: international normalized ratio; HF: heart failure.
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 m². 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 HFrEF, 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 HFrEF 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). Verbeek 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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