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STATE-OF-THE-ART PAPER

Cardiohepatic Interactions in Heart Failure

An Overview and Clinical Implications

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Heart failure (HF) is a major public health problem leading to frequent hospitalizations, impaired quality of life, and shortened life expectancy. Heart failure leads to a chronic inability to meet metabolic requirements of end organs or skeletal muscle. Current literature lacks comprehensive descriptions of HF effects on hepatic function. In this review paper, we summarize the literature that is available in hopes of highlighting the key differences in clinical presentation, histological findings, and biochemical profiles of patients who present with both acute and chronic liver injury secondary to HF. We further discuss the use of liver function tests as prognostic markers in patients with HF, as well as the implications of liver injury on drug metabolism in this patient population. Finally, we provide recommendations regarding the management of both types of liver injury in HF patients. (J Am Coll Cardiol 2013;61:2397–405) © 2013 by the American College of Cardiology Foundation

Heart failure (HF) is a major public health problem, with frequent hospitalizations, impaired quality of life, and shortened life expectancy (1). As HF advances, it is often characterized by an increasing inability to meet the metabolic requirements of end organs or skeletal muscle. While much attention has been directed toward the intersection of HF and renal function, the impact of HF on hepatic function has been poorly described.

Similar to the now widely described "cardiorenal" syndromes, more attention is needed in describing "cardiohepatic" interactions. Over the last several years, a number of studies have described poor outcomes associated with the development of cardiorenal syndromes, as well as potential solutions to mitigate further renal injury while treating HF (2). In contrast, much less is known about impaired liver function in patients with HF. Furthermore, HF patients may present with liver-related symptoms including abdominal distention, intermittent right upper quadrant discomfort, nausea, early satiety, or anorexia. The presence of these symptoms may direct a primary gastrointestinal evaluation rather than consideration of primary cardiac pathology, thereby creating a delay in the initiation of life-prolonging interventions.

Abnormalities in liver function tests (LFTs) are not an uncommon finding in patients with HF. These abnormalities are a result of impaired perfusion or elevated right-sided cardiac pressures, or are secondary to drug toxicity. Attempts at describing the features of chronic liver damage secondary to HF have been ongoing since the early 20th century (3,4). Nevertheless, neither the pathophysiologic basis underlying these findings nor the clinical impact of impaired liver function on HF outcomes have been clearly delineated. In this paper, we review the contemporary data characterizing histopathological findings and biochemical profiles of various types of hepatic dysfunction occurring in acute and chronic HF. We explore the prognostic significance of liver injury markers in the various stages of HF. Finally, we discuss potential strategies to effectively investigate, manage, and treat liver dysfunction in HF patients, as well as future research efforts that may further improve our understanding of cardiohepatic interactions in HF.

Liver Dysfunction in HF Patients: Presentation, Histology, and Biochemical Profiling in Acute HF

Acute cardiogenic liver injury. PRESENTATION AND PATHOPHYSIOLOGY. Acute cardiogenic liver injury (ACLI), historically called "ischemic hepatitis," is often described in patients with HF who have progressed to critical cardiogenic

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Abbreviations and Acronyms

ACLI = acute cardiogenic liver injury
ALT = alanine aminotransferase
GGT = gamma-glutamyl transpeptidase
HF = heart failure
LDH = lactate dehydrogenase
LFT = liver function test
LVAD = left ventricular assist device
MELD = model for end-stage liver disease
modMELD = modified model for end-stage liver disease
NYHA = New York Heart Association
TR = tricuspid regurgitation

shock, in which cardiac output is no longer sufficient to meet the metabolic demands of hepatic cells (5). However, review of the literature suggests that an acute change in hepatic blood flow is not the sole incident responsible for the development of ACLI (6). In a retrospective analysis of patients with clinical and biochemical evidence of ACLI, Seeto et al. (7) found that hypotension alone did not induce acute liver injury. Patients with ACLI were compared with a control group comprising trauma victims who had evidence of prolonged hypotension (7). No patients in the control group had findings consistent with ACLI. Conversely, nearly all patients with a clinical diagnosis of ACLI had evidence of cardiac disease, with 29 of these 31 subjects demonstrating evidence of elevated right-sided or venous filling pressures (7). Similarly, Henrion et al. (8) examined ACLI in patients admitted to the coronary intensive care unit with evidence of low cardiac output. Patients with biochemical evidence of cardiogenic injury had significantly higher central venous pressures compared to patients who had low cardiac output but no ACLI (8).

Several larger studies characterizing the etiology of ACLI have shown that the majority of cases of ACLI are related to acute HF, respiratory failure, and septic shock. However, these same studies have also shown that between 39% and 70% of patients with ACLI have the underlying diagnosis of chronic HF (6,9,10). These findings suggest that ACLI does not result from a single hemodynamic insult, but rather, ACLI is linked to the combination of hepatic congestion from elevated hepatic venous pressure coupled with impaired perfusion (Fig. 1) (8). Venous congestion may ultimately increase the susceptibility of the liver to injury caused by reduced perfusion. The notion that a "second hit" is required for acute liver injury is not captured in the nomenclature commonly used to describe this process, such as "ischemic hepatitis" or "shock liver." Therefore, we believe that "ACLI" is a more accurate diagnostic term (5), encapsulating the underlying pathophysiological process.

Although the pathophysiological process is not clearly defined, the injury pattern of ACLI represents the release of hepatic proteins in response to tissue hypoxia and cell death (6). After hemodynamic recovery, symptoms related to the liver injury can present after a latency period of 2 to 24 h (5). These symptoms may include weakness, apathy, and (in a minority of cases) persistent mental confusion, tremor, hepatic coma, and jaundice (11). A bleeding diathesis from acquired coagulopathy may also develop due to impaired production of coagulation factors (11). These abnormalities peak at 1 to 3 days after onset of symptoms and, in patients who survive, return to normal within 5 to 10 days after onset (5,12,13).

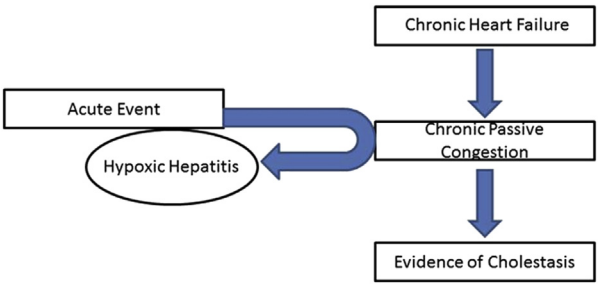

Figure 1 **Mechanisms Leading to 2 Types of Cardiogenic Liver Injury**

Chronic heart failure (HF) leading to chronic passive congestion of the liver leads to a liver function panel consistent with cholestasis. Patients with chronic HF who experience an acute decompensation show evidence of hypoxic hepatitis.

HISTOPATHOLOGY. The histologic hallmark of ACLI is necrosis surrounding the central vein where oxygenation is poor (zone 3) (4). Depending on the duration of ischemia, a variable degree of architectural collapse around the central veins can occur (4,14). Necrosis can extend to the mid-zonal hepatocytes with prolonged ischemia; however, necrosis rarely occurs predominantly in the middle zones (Fig. 2) (4,14). Although clinical and laboratory diagnostic data are usually sufficient for the diagnosis, a liver biopsy may be useful when it is necessary to clarify the underlying etiology of an acute rise in aminotransferase levels (15).

BIOCHEMICAL PROFILE. The typical pattern in laboratory studies consists of a substantial and rapid elevation in aminotransferase and lactate dehydrogenase (LDH) levels to 10 to 20 times normal, typically between 1 and 3 days after hemodynamic insult, and without evidence of another etiology such as cholecystitis or viral hepatitis (8,11). With correction of hemodynamics, these levels will return to normal within 7 to 10 days (5). Early and rapid increase in serum LDH is a distinguishing feature of ACLI, and a ratio of serum alanine aminotransferase (ALT) to LDH <1.5 early in the course of liver injury is characteristic of cardiogenic injury as opposed to other etiologies of hepatitis (16). Laboratory abnormalities may also include sharp increases in serum ALT and aspartate aminotransferase (AST; typically 10 times normal values), increased serum bilirubin, and prolongation of the prothrombin time (5). In fact, 2 studies have shown as much as a 50% decrease in prothrombin activity in 79.5% and 84% of ACLI patients, which is thought to be unusual in the case of viral hepatitis (6).

Although there are few data regarding LFT alterations among patients with acute HF, a recently published analysis

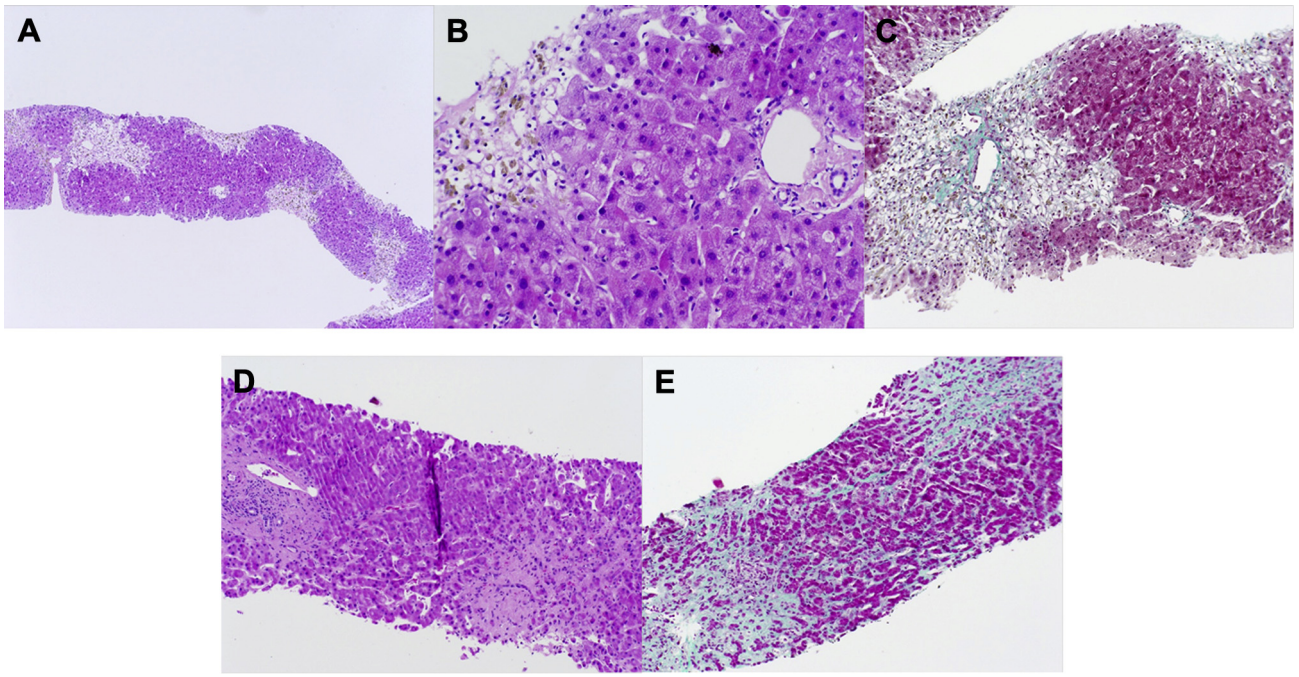

Figure 2 **Photomicrographs**

Histology slides showing acute hepatic passive congestion in a patient with heart failure (HF). Changes consistent with acute cardiogenic liver injury: **(A)** hematoxylin and eosin, original magnification ×4; and **(B)** hematoxylin and eosin, original magnification ×20. The pattern of hepatocyte loss is consistent with ischemia. The hepatocytes have completely disappeared, leaving only a loose reticular framework. There is no regenerative activity or collagen fibrosis—**(C)** Masson trichrome stain, original magnification ×10—thereby suggesting a fairly recent event. The presence of mild ductular changes including ductular proliferation, occasional neutrophils associated with ductules, and ductular bile stasis are likely secondary to the ischemic event. **(D)** Changes consistent with chronic hepatic passive congestion, in a patient with chronic HF (hematoxylin and eosin, original magnification ×10). There is minimal inflammation in the portal areas, and no interface activity is evident. Only 1 focus of canalicular cholestasis is seen. Extensive spidery and dense perivenular fibrosis exists; this extends into the lobule and bridges (stage 3) with other central, and focally, portal areas. **(E)** Masson trichrome stain (original magnification ×10) highlights the extensive nature of zone 3 (central) fibrosis. Some of the perisinusoidal hepatic plates are atrophic and attenuated.

of the SURVIVE (Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support) trial (17) helps understand explain how LFTs can be altered in patients presenting with acutely decompensated HF. Baseline LFTs were abnormal in 46% of the 1,134 patients enrolled in the SURVIVE study; of these, 11% had an isolated abnormality in alkaline phosphatase levels, 26% had isolated transaminase abnormalities, and 9% had abnormal alkaline phosphatase and transaminases (18). Interestingly, abnormal alkaline phosphatase was associated with marked signs of congestion and elevated right-sided filling pressures, as well as increased 180-day mortality. Abnormal transaminases were associated with clinical signs of hypoperfusion and increased 31- and 180-day mortality (Table 1) (19–28).

Chronic passive congestion. Since the original description of the "nutmeg liver," there has been an interest in understanding the biochemical and histological changes associated with transmission of elevated right-sided filling pressures to the hepatic venous system. While the term "congestive hepatopathy" has become synonymous with this clinical syndrome, the incidence of passive congestion, histological changes in the liver, and the impact on physiology and prognosis have not been clearly delineated.

PRESENTATION AND PATHOPHYSIOLOGY. Patients with chronic passive congestion or congestive hepatopathy from long-standing elevation of right-sided filling pressures may present at various stages along a continuum (3). In severe cases associated with end-stage biventricular failure, severe tricuspid regurgitation (TR), or restrictive/constrictive cardiomyopathy, affected patients may be indistinguishable from patients with chronic liver disease or cirrhosis (4). In other HF syndromes, the clinical presentation may be more subtle, with intermittent right upper quadrant discomfort, nausea, early satiety, or anorexia (29). Symptoms are difficult to distinguish from primary hepatobiliary or gastrointestinal conditions such as cholelithiasis, peptic ulcer disease, or even ischemic colitis (30). Careful evaluation of the jugular venous pressure provides critical information in the assessment of these symptoms (29). Importantly, these findings may occur in the absence of overt ascites or lower extremity edema (particularly in younger patients), and a high degree of suspicion should be maintained for HF even in the absence of the typical signs or symptoms.

Hepatopathy secondary to chronic congestive HF is attributed to 3 main processes: increased hepatic venous pressure, decreased hepatic blood flow, and decreased arterial

Table 1 Studies Demonstrating Association Between Liver Function Test Abnormality and Mortality in Heart Failure Patients and Descriptions of Study Cohort, Number of Subjects, and Laboratory Marker of Interest

First Author (Ref. #), Year	Patient Population	n	Lab	Summary of Findings
Horwich (19), 2008	NYHA class III/IV chronic HF	1,726	Alb	Hypoalbuminemia associated with significantly increased 1- and 5-yr all-cause mortality, progressive HF death, and increased risk of urgent cardiac transplantation.
Uthamalingam (20), 2010	ADHF	438	Alb	Hypoalbuminemia independently associated with increased 1-yr mortality in patients with ADHF admitted to hospital.
Kinugasa (21), 2009	ADHF	349	Alb	In elderly ADHF patients, serum albumin associated with in-hospital mortality, even after adjustment for other known prognostic factors.
Kato (22), 2012	Consecutive patients with LVAD implanted at CUMC	307	Alb	Pre- and post-operative measures of serum albumin predicted neurologic complications after LVAD implantation.
Nikolaou (18), 2012	ADHF	1,134	AP, AST, ALT	Of patients with ADHF, 46% presented with altered LFTs. Abnormal AP was associated with marked signs of congestion, elevated right-sided filling pressures, and increased 180-day mortality. Abnormal transaminases were associated with clinical signs of hypoperfusion and increased 31- and 180-day mortality.
Poelzl (23), 2012	Unselected stable HF patients, with primarily LV dysfunction	1,032	AP, GGT	AP, Tbili, and GGT levels inversely associated with survival. In multivariate analysis, only AP and GGT maintained independent predictive capacity for transplant-free survival.
Poelzl (24), 2009	Unselected outpatients with HF	998	GGT	Serum GGT can provide prognostic information independent of established clinical and biochemical markers including age and NT-proBNP. Predictive GGT value is greater in NYHA class I–II HF (HR: 2.9) compared to NYHA class III–IV HF (HR: 1.2).
Ruttman (25), 2005	Healthy adult outpatients	163,944	GGT	GGT found to be a prognostic indicator of fatal events in apparently healthy subjects.
Szygula-Jurkiewicz (26), 2007	NYHA class II/III HF secondary to hypertension	124	Tbili	Elevated bilirubin levels associated with higher incidence of death in patients with hypertension-related chronic HF.
Allen et al. (27), 2009	Chronic HF	2,679	Tbili	Tbili was a strong independent predictor for worsening HF, cardiovascular death, and all-cause mortality.
Matthews (28), 2008	Advanced HF patients with LVAD implanted at UM	197	Tbili, AST	Tbili and AST identified as independent markers for development of right ventricular failure after LVAD implantation.
Fuhrman (9), 2009	Patients admitted to ICU with "hypoxic hepatitis"	117	INR	Peak INR >2 identified as an independent predictor of overall mortality in patients with "hypoxic hepatitis."
Raurichh (10), 2011	Patients admitted to ICU with "hypoxic hepatitis"	182	INR	INR was found to be an independent predictor of in-hospital mortality in patients with hypoxic hepatitis.

ADHF = acutely decompensated heart failure; Alb = albumin; AP = alkaline phosphatase; AST = aspartate aminotransferase; CUMC = Columbia University Medical Center; EF = ejection fraction; GGT = gamma-glutamyl transpeptidase; HF = heart failure; HR = hazard ratio; ICU = intensive care unit; INR = international normalized ratio; LFT = liver function test; Lab = laboratory (marker of interest); LVAD = left ventricular assist device; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; Tbili = total bilirubin; UM = University of Michigan.

oxygen saturation (14). Elevated central venous pressures are transmitted through the hepatic veins and into the small hepatic venules. The effect of this transmitted pressure is passive congestion of the liver with resulting elevated hepatic venous pressure, which can impair delivery of oxygen and nutrients to hepatocytes, leading to sinusoidal fenestrae enlargement (14). Consequently, hepatocyte necrosis and leakage of protein-rich fluid into the space of Disse occurs (3,14). Although these histological processes can be subclinical, abdominal symptoms are primarily attributed to stretching of the liver capsule resulting in abdominal discomfort (29).

HISTOPATHOLOGY. Boland and Willius (3) first demonstrated that nearly 50% of patients with severe HF had pathologic changes consistent with chronic passive liver congestion. Atrophy, necrosis, or both were present and most pronounced in the central third of the hepatic lobule. Generally, these findings were most prominent immediately adjacent to the central vein, with decreasing degeneration towards the lobule periphery (3). Results were later confirmed by the work of Sherlock (4), which described microscopic sinusoidal engorgement and degeneration. Centrilobular hepatic necrosis was almost always present, with worsening HF resulting in peripheral spread of necrosis and healing of the lesion being associated with decreasing right atrial pressure. Also noted were variable degrees of cholestasis, occasionally with bile thrombi in the canaliculi (Fig. 2) (4).

BIOCHEMICAL PROFILES. Recent studies have attempted to characterize the biochemical profiles observed in peripheral blood associated with cardiogenic liver injury. Kubo et al. (31) examined the incidence of liver disease among 133 patients with chronic systolic HF secondary to dilated cardiomyopathy. Abnormalities in LFTs were common, but generally of small magnitude and primarily limited to patients with a cardiac index <1.5 l/min/m^2. As cardiac output decreased and intracardiac filling pressures increased, elevations in transaminases, LDH, and total bilirubin were statistically different but did not correlate with hepatomegaly (31). In a retrospective analysis of patients with more severe HF, LFT abnormalities more characteristic of cholestasis (i.e., increased alkaline

phosphatase, gamma-glutamyl transpeptidase [GGT], total bilirubin, and hypoalbuminemia) were noted and correlated with the severity of TR (32).

The impact of HF on LFT abnormalities in a more contemporary and larger patient cohort was recently described in the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Program) trial (27). In addition to the previously described cholestatic LFT pattern associated with chronic stable HF, the investigators observed significantly elevated total bilirubin levels in patients with evidence of volume overload compared with those in patients who were clinically euvolemic (27). Poelzl et al. (23) also described a cholestatic pattern of LFTs in patients with stable HF and showed a positive correlation between elevations in cholestatic LFTs and disease severity as assessed by the New York Heart Association (NYHA) functional classification. Specifically, total bilirubin, alkaline phosphatase, and GGT independently correlated with signs of right HF, including the presence of jugular venous distention, peripheral edema, and TR (23). These data, in conjunction with the relationship between LFTs and TR (32), suggest that elevated right-sided filling pressures may contribute more to LFT elevation in stable HF than reduced cardiac output.

Liver Function Tests as Prognostic Markers

Bilirubin and GGT. As the biochemical profiles of liver dysfunction are more clearly delineated, there is a growing interest to use these tests to predict prognosis in HF patients. Single-center studies have described higher rates of death, cardiac transplantation, and HF rehospitalizations in patients with increased plasma bilirubin (23,26). These results have been confirmed in larger cohorts such as in the CHARM substudy, which demonstrated that total bilirubin was a strong independent predictor for worsening HF, cardiovascular death, and all-cause mortality (27). A more recent study (n = 1,032) showed that in an unselected cohort of patients with stable HF, alkaline phosphatase, total bilirubin, and GGT levels, all of these factors are inversely associated with survival. In multivariate analysis, only alkaline phosphatase and GGT maintained independent predictive capacity for transplant-free survival in this cohort in which 339 events were recorded with a median follow-up of 36 months (23). Poelzl et al. (24) showed that serum GGT can provide prognostic information independently of established clinical and biochemical markers including age, body mass index, ischemic etiology, NYHA functional class, and N-terminal pro–B-type natriuretic peptide. In patients with mild HF symptoms defined as NYHA class I/II, the predictive value of GGT is greater (hazard ratio: 2.9) compared with that in patients with NYHA class III/IV failure (hazard ratio: 1.2) (24). Furthermore, there are data suggesting that a multiple-marker approach combining GGT and N-terminal pro–B-type natriuretic peptide improves the ability to predict 3-year event rates, suggesting that GGT may reflect aspects of disease severity that cannot be provided by clinical judgment alone (24). The predictive impact of GGT in the earlier stages of HF has been examined in subjects without evidence of structural heart disease or symptoms (American Heart Association stage A and B HF). In a large epidemiologic study by Ruttmann et al. (25), GGT was found to be a prognostic indicator of fatal events. Interestingly, in this study of >160,000 subjects, GGT was associated with all-cause mortality, coronary artery disease, and incident HF, indicating that GGT shows promise as a marker for subclinical or early stage disease.

Total bilirubin also has important utility as a marker for worse outcomes, especially after left ventricular assist device (LVAD) implantation. This finding was highlighted in a recent study in which total bilirubin was an independent marker for development of right ventricular failure after LVAD implantation, likely representing impaired right ventricular function prior to the operative procedure and a greater degree of hepatic congestion (28). Total bilirubin has subsequently been incorporated into a validated risk score predicting right ventricular failure after LVAD surgery (28) and, even more recently, is a component of a risk model for adverse outcomes after cardiac transplantation (33).

Albumin. Hypoalbuminemia in HF is common, with recent reports demonstrating a prevalence of approximately 25% (19,27); prevalence grows with increasing age and frailty (34). Historically, hypoalbuminemia in HF has been attributed primarily to inadequate nutrition (35,36), with other contributing etiologies including hemodilution (37) and inflammation (19). Evidence now suggests that systemic inflammation (not nutritional status) may be a primary regulator of hepatic protein metabolism (38,39). Intrinsic liver damage induced through chronic hepatic congestion in the setting of a dynamic systemic inflammatory state present in HF likely contributes more to hypoalbuminemia than previously assumed.

Hypoalbuminemia has also been studied extensively as a prognostic marker in HF and has been shown to be an independent predictor of death in both acute and chronic HF. Horwich et al. (19) demonstrated that hypoalbuminemia is associated with significantly increased 1- and 5-year all-cause mortality, progressive HF death, and increased risk of urgent cardiac transplantation in a cohort of patients with NYHA class III/IV symptoms (19). Low albumin levels also have been found to have prognostic value in patients with acute decompensated HF after adjustment for multiple prognostic variables, including N-terminal pro–B-type natriuretic peptide (20,21).

Hypoalbuminemia has also been identified as an important prognostic variable in the surgical treatment of advanced HF. In patients with advanced HF treated with LVAD therapy, preoperative albumin is an independent predictor of short- and intermediate-term outcomes after implantation (22,40). Indeed, albumin has been incorporated into risk scores that predict outcomes after LVAD implantation (40,41), including a model developed from data with contemporary devices (42).

Impact of Cardiogenic Liver Injury on Drug Metabolism/Effect

Hepatic congestion and hypoperfusion can result in hepatocyte atrophy and impaired oxygen diffusion, leading to impaired hepatocyte metabolism (43,44). Alterations in liver function that would lead to changes in liver drug metabolism include disruption in hepatocyte function (intrinsic function including activity of metabolic enzymes and transporters), changes in liver blood supply, and reductions in the synthesis of plasma protein binding (45–47). These changes can occur alone or in combination where the effect on the pharmacokinetic process is synergistic, not just additive (46). Morgan and McLean (48) suggest that liver disease without cirrhosis usually results in mild alterations in drug pharmacokinetics; however, others have proposed that cardiac cirrhosis resulting from prolonged hemodynamic abnormalities can lead to impaired hepatic function, impaired coagulation, decreased synthesis of albumin, and more prominent alterations in drug metabolism (43,49,50). These proposed alterations in metabolism have been further supported by both human and animal models of metabolism in heart failure (43,49,50).

Hepatic drug clearance is defined as the volume of blood from which a drug is completely removed by the liver per unit of time, and is a function of hepatic blood flow and the hepatic extraction ratio of the drug—a parameter that describes the efficiency of drug removal by the liver (45,47,51). The hepatic clearance of highly extracted drugs is limited by hepatic blood flow; the hepatic clearance of poorly extracted drugs is mainly influenced by changes in blood plasma binding and intrinsic clearance (45,51). Confirmatory studies have demonstrated that impaired drug metabolism in the liver correlates with HF severity, and improves when decompensated HF is treated (43). Thus, whereas there are clear guidelines for the use of specific pharmacotherapies in renal dysfunction, recommendations regarding modification of medication dose, frequency of administration, or use are nonspecific and often difficult to apply in the setting of hepatic impairment. Additionally, anticipation of any potential drug interactions and appropriate dose modifications of coadministered drugs that inhibit or induce hepatic metabolism are clinically challenging in the setting of hepatic impairment. Lastly, the potential for toxicity of certain commonly used drugs (Table 2) has also been incompletely addressed, and to date, has not resulted in a significant change in our own practice (i.e., reduction of statin dose with known hepatic congestion to reduce the potential for hepatitis).

Many of the challenges associated with dose modification in patients with hepatic impairment are related to the poorly understood relationships between LFT abnormalities and hepatic metabolism. No single LFT or group of markers has gained widespread clinical use to allow estimation in a given patient of how hepatic impairment will impact the use of drugs. As a result, the U.S. Food and Drug Administration has developed a guidance document for industry, promoting the completion of pharmacokinetic studies during drug development to identify patients at risk and to establish the need for dosage adjustment if found important (52). This document specifically emphasizes the need for testing if hepatic metabolism and/or excretion accounts for a substantial portion (>20% of absorbed drug) of the parent drug or active metabolite elimination, or if its labeling suggests it has a narrow therapeutic range, even if the drug/metabolite is eliminated to a lesser extent (<20%). The Food and Drug Administration further recommends the use of the Child-Pugh classification as a scale for estimating the degree of hepatic impairment, and suggests a study should be conducted in patients in each of the 3 categories (mild, moderate, and severe), as well as in controls (52–54). Nevertheless, the underlying cause for the liver disease is not specified and it is not clear that cardiac and noncardiac liver injury would result in similar pharmacokinetic derangements. In the absence of recommendations for dosage adjustment in patients with hepatic dysfunction, Verbeeck (51) has suggested considerations for medication management based on the pharmacokinetic features of drugs. These considerations are summarized in Table 3. Commonly used drugs such as beta-blockers, statins, some antiarrhythmic agents, anticoagulants, and antibiotics could potentially accumulate to toxic levels in this patient population, leading to cardiac and noncardiac adverse effects.

Table 2 Hepatotoxic Pharmacologic Agents Commonly Used in Heart Failure Patients

Diagnosis	Pharmacologic Agent
Acute hepatocellular injury	Aspirin, lisinopril, losartan, statins
Chronic steatohepatitis	Amiodarone
Granulomatous hepatitis	Diltiazem, hydralazine, procainamide, quinidine
Cholestasis	ACE inhibitors, clopidogrel, irbesartan, amiodarone
Mixed hepatitis	Captopril, verapamil
Autoimmune hepatitis	Statins

ACE = angiotensin-converting enzyme.

Another theoretical concern unrelated to drug metabolism is the impact of hepatic dysfunction in patients being treated with anticoagulation therapy. Studies have demonstrated decreased prothrombin levels in patients with right- and left-sided HF (43,55,56). Prothrombin concentrations have been found to be reduced in 80% of patients in acute and chronic right HF and could not be corrected with administration of parenteral vitamin K (43,55,56). This is important to note in HF patients who commonly have indications for systemic anticoagulation therapy such as atrial fibrillation, ventricular thrombi, and prior stroke. Impairment of intrinsic coagulation factor production through hepatic congestion may potentiate the anticoagulant effect of vitamin K antagonists such as warfarin, as measured by a prolonged prothrombin time. However, measurement of excessive anticoagulation that results from the use of novel anticoagulants such as dabigatran (57), rivaroxaban (58), or apixaban (59) is more

Table 3 General Considerations for Medication Management in Hepatic Dysfunction* (51)

Drug Characteristic	Expected Change	Possible Management Strategy
High hepatic extraction ratio	Increased oral bioavailability, possible reduced hepatic clearance if hepatic blood flow reduced.	Reduce dose.
Low hepatic extraction and high plasma protein binding (>90%)	Intrinsic drug clearance reduced to degree determined by functional status of liver and specific metabolic pathways involved in elimination. Unbound fraction in blood or plasma may be markedly increased.	Evaluation should be based on unbound blood or plasma concentration and dosage adjustment may be necessary even if total blood and plasma concentrations are within normal range.
Low hepatic extraction and low plasma protein binding (<90%)	Intrinsic clearance reduced to degree determined by liver functional status and specific metabolic pathways involved in elimination. Unbound drug fraction fluctuations in blood/plasma expected to be small and not significantly affect blood/plasma clearance.	May need dose adjustment; goal to achieve normal total (bound plus inbound) plasma concentrations.
Drug is partially excreted in unchanged form by kidneys	Excretion will be impaired; creatinine clearance will over-estimate glomerular filtration rate.	Possible need for dose adjustment.
Drug is hydrophilic	Volume of distribution may be increased in setting of chronic liver disease and edema or ascites.	May need to increase loading doses of candidate drugs for rapid, complete effect. Many hydrophilic drugs eliminated unchanged by kidneys; dose adjustment may be needed if renal function compromised.
Drug has narrow therapeutic index	Increased potential for serious adverse drug effects due to impaired function.	Extreme caution indicated for liver disease or severe liver dysfunction (Child-Pugh class C).

*Assumes drug is mostly eliminated by hepatic mechanisms (metabolism, biliary excretion).

challenging. Consequently, in our own practice, the use of novel anticoagulants has been limited by the development of hepatic congestion and our inability to clearly identify an appropriate degree of anticoagulation in these patients, resulting in continued use of warfarin.

Management Strategies of HF Patients With Secondary Liver Injury

Given the heterogeneity in LFT abnormalities, HF patients presenting with abnormal liver function should first be evaluated for potential biliary tract obstruction and/or primary hepatic pathology before attributing irregularities to cardiac disease. The differential diagnosis should include biliary stasis/cholelithiasis; hemochromatosis; primary biliary cirrhosis; primary sclerosing cholangitis; forms of hepatitis, including viral, alcoholic, and autoimmune; and primary malignancies of the biliary system.

Cardiomyopathies including iron overload and amyloidosis may have direct hepatic involvement and should not be mistaken for chronic and/or acute hepatic injury secondary to HF. Amyloidosis is an infiltrative cardiomyopathy that should be considered in all patients presenting with proteinuria and neuropathy, especially if there are signs and symptoms of restrictive cardiomyopathy or right-side heart failure (60).

Once primary biliary pathology and systemic conditions that may concomitantly affect the heart and liver have been ruled out, elevated LFTs in conjunction with increased intracardiac filling pressures suggest some component of cardiogenic liver injury. When combined with a normal (<5 mm Hg) gradient between hepatic wedge pressure and right atrial pressure, one can rule out significant portal hypertension secondary to chronic liver disease. If ascites is present, then diagnostic paracentesis should be performed; however, a liver biopsy remains the gold standard for diagnosing liver disease. In the acute setting, biopsies should be reserved for patients whose diagnosis is unclear or the staging of fibrosis is imperative in treatment decisions (i.e., candidacy for isolated cardiac transplantation).

Management of Cardiogenic Liver Injury

In the setting of cardiogenic shock complicated by ACLI, the aim of therapy is to restore cardiac output and simultaneously reduce right-side filling pressures. Monitoring for recovery of liver function should be a priority, with appropriate modification in doses of drugs that undergo hepatic metabolism while function normalizes.

Treatment of the underlying cardiac condition remains the primary approach to restoring normal liver function in congestive hepatopathy. This typically entails aggressive measures to decrease intracardiac filling pressures. Hepatic congestion, ascites, and jaundice may all respond to diuresis, but for patients with severe HF, augmentation of cardiac output may also be required to prevent further deterioration of liver function (61). In truly refractory cases, patients may undergo therapeutic paracentesis to relieve ascites or ultrafiltration to remove edema/ascites that is no longer responsive to diuretic therapy. The impact of these strategies on hepatic function and HF outcomes remains undefined. Furthermore, the physiologic similarities between congestive hepatopathy and intrinsic liver disease may allow translation of proven therapies used in cirrhosis (such as aldosterone antagonism) to play a greater role in the management of patients with severe congestive hepatopathy.

Effects of Advanced Heart Failure Therapies on Liver Function

Data examining the direct effects of advanced HF therapies on end-organ liver damage are limited. Although hepatic

injury, regardless of severity, is not an indication for initiation of advanced HF therapies, recent data suggest that liver function abnormalities improve after orthotopic cardiac transplantation. A small study (n = 56) demonstrated that patients who had chronic cardiac hepatopathy as defined by elevated GGT, alkaline phosphatase, and bilirubin had normalization of these values within 3 months after cardiac transplantation (62). The results of this study were later supported by another larger retrospective study, which showed that in a cohort of 617 patients undergoing heart transplantation, a significant proportion had abnormal LFTs that corrected after the procedure. Specifically, 38% and 68% of patients had pre-transplantation serum levels of alkaline phosphatase and GGT, respectively, that were pathologically elevated (40).

This analysis was also novel in that MELD (Model for End-Stage Liver Disease) and modMELD (modified MELD) scores in these patients were recorded pre-operatively and followed up for 5 years after transplantation. The proportion of patients with elevated MELD scores and intermediate MELD scores (>20 and 14 to 20, respectively) decreased 2 months after transplantation and stabilized by 1 year after transplantation. Similar trends were seen when the modMELD score was used to stratify this cohort (40). While these scores alone have not previously been used to select or disqualify patients for cardiac transplantation, they may provide clues to the presence of advanced liver disease. Patients with biochemical, clinical, or radiographic evidence of advanced disease should be thoroughly evaluated for the presence of cirrhosis. This evaluation typically involves a liver biopsy to identify/stage bridging fibrosis, and in advanced cases, the patient may be excluded from isolated cardiac transplantation due to the negative impact on post-transplantation outcomes (63). Combined heart-liver transplantation may be recommended for select cases of irreversible liver injury.

Conclusions

The impact of HF on hepatic function has been studied for many decades, but there is limited contemporary knowledge on the exact mechanisms underlying liver injury in the setting of HF, response to therapy, and the prognostic impact of LFT abnormalities across the spectrum of clinical HF. Although there is a growing body of literature regarding the prognostic impact of cardiohepatic interactions in the most advanced stages of the disease, there is potential for important avenues of investigation in acute decompensated HF and in the early stages of HF (American Heart Association stages A to C). Finally, the impact of the cardiohepatic axis on drug metabolism and drug effects (particularly for anticoagulant agents) will become increasingly important as more patients have HF and as additional novel therapeutics are introduced.

Heart failure constitutes as a significant source of morbidity and mortality for an aging population. Medical care is becoming more complex as patients live longer with multiple chronic disease processes. Because there are known therapies that have proven mortality benefits, it is imperative that the signs and symptoms of HF are quickly recognized and addressed. Recognizing these signs and symptoms can be challenging, however, due to potential subtle presentations in patients with complex medical histories. In parallel with continued research, we must continue to educate primary care physicians and physician-extenders to recognize and address HF-related cardiohepatic interactions to further reduce unnecessary healthcare spending and to decrease HF-associated morbidity and mortality.

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