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STATE-OF-THE-ART REVIEW

Relationship of Nonalcoholic Fatty Liver Disease and Heart Failure With Preserved Ejection Fraction

Husam M. Salah, MD,[a] Ambarish Pandey, MD,[b] Anzhela Soloveva, MD, PhD,[c] Manal F. Abdelmalek, MD,[d] Anna Mae Diehl, MD,[d] Cynthia A. Moylan, MD, MHS,[d] Kara Wegermann, MD,[d] Vishal N. Rao, MD, MPH,[e,f] Adrian F. Hernandez, MD, MHS,[e,f] Ryan J. Tedford, MD,[g] Kishan S. Parikh, MD,[e] Robert J. Mentz, MD,[e,f] Robert W. McGarrah, MD,[e] Marat Fudim, MD, MHS[e,f]

HIGHLIGHTS

- **There is a bidirectional relationship between HF and liver disease.**
- **NAFLD may drive some HFpEF phenotypes.**
- **This review proposes 3 HFpEF phenotypes: obstructive HFpEF, metabolic HFpEF/NAFLD, and advanced liver disease/cirrhosis HFpEF.**
- **Additional studies are required to explore the pathophysiology and hemodynamic parameters of these phenotypes and investigate potential treatments.**

ABSTRACT

Although there is an established bidirectional relationship between heart failure with reduced ejection fraction and liver disease, the association between heart failure with preserved ejection fraction (HFpEF) and liver diseases, such as nonalcoholic fatty liver disease (NAFLD), has not been well explored. In this paper, the authors provide an in-depth review of the relationship between HFpEF and NAFLD and propose 3 NAFLD-related HFpEF phenotypes (obstructive HFpEF, metabolic HFpEF, and advanced liver fibrosis HFpEF). The authors also discuss diagnostic challenges related to the concurrent presence of NAFLD and HFpEF and offer several treatment options for NAFLD-related HFpEF phenotypes. The authors propose that NAFLD-related HFpEF should be recognized as a distinct HFpEF phenotype.
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From the [a]Department of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA; [b]Division of Cardiology, Department of Medicine, University of Texas Southwestern, and Parkland Health and Hospital System, Dallas, Texas, USA; [c]Department of Cardiology, Almazov National Medical Research Centre, Saint Petersburg, Russian Federation; [d]Division of Gastroenterology and Hepatology, Duke University, Durham, North Carolina, USA; [e]Division of Cardiology, Department of Medicine, Duke University, Durham, North Carolina, USA; [f]Duke Clinical Research Institute, Durham, North Carolina, USA; [g]Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina, USA.
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Heart failure (HF) and liver disease are among the most common causes of morbidity and mortality worldwide (1,2). The bidirectional relationship between HF and liver disease can occur in 2 forms: liver complications of HF (eg, congestive hepatopathy) and cardiac complications of liver disease with resultant HF (eg, cirrhotic cardiomyopathy). The prevalence of this bidirectional relationship can reach up to 65% (3). Although the relationship between HF and liver disease is generally well recognized, the association between HF with preserved ejection fraction (HFpEF), in particular, and liver disease has not been well studied or defined. In this review, we highlight the relationship between HFpEF and nonalcoholic fatty liver disease (NAFLD), and we propose that some phenotypes of HFpEF are cardiac manifestations of NAFLD rather than 2 independent disease forms. We also discuss challenges related to diagnosing NAFLD-related HFpEF phenotypes and diagnosing either entity in the presence of the other. We also propose several treatments for NAFLD-related phenotypes on the basis of plausible mechanism of actions.

METHODS

We conducted a search of the MEDLINE database for publications using the search terms "heart failure and liver," "heart failure and nonalcoholic fatty liver disease," "heart failure with preserved ejection fraction and liver," "diastolic dysfunction and liver," "diastolic dysfunction and nonalcoholic fatty liver disease," "diastolic dysfunction and NAFLD," "heart failure with preserved ejection fraction and nonalcoholic fatty liver disease," "HFpEF and liver," "HFpEF and nonalcoholic fatty liver disease," and "HFpEF and NAFLD" from inception till June 1, 2021. No language restrictions were applied. We also searched the reference lists of review papers for relevant publications. A total of 121 studies were included in this review.

NONALCOHOLIC FATTY LIVER DISEASE

NAFLD is the hepatic manifestation of metabolic syndrome (ie, insulin resistance, obesity, and dyslipidemia) that defines a spectrum of conditions ranging from simple hepatic steatosis (≥5% liver fat content) to nonalcoholic steatohepatitis (NASH) and is characterized by necroinflammatory injury with or without hepatic fibrosis (4,5). NASH, the more severe form of NAFLD, more often progresses to advanced hepatic fibrosis or cirrhosis and its associated negative clinical outcomes (6). NAFLD is the most common cause of chronic liver disease worldwide and is prevalent in up to 30% of the population in developed countries. NAFLD and NASH are more common in patients with type 2 diabetes mellitus, in whom prevalence may reach up to 59% (7). Patients with NAFLD may be asymptomatic or present with nonspecific symptoms. Fatigue and shortness of breath are among the most predominant symptoms among patients with NAFLD (4).

The pathophysiology of NAFLD involves a complex interplay among inflammatory, hormonal, nutritional, and genetic factors that results in insulin resistance, exaggerated lipogenesis, abnormal adipokine levels, increased circulating triglyceride levels, and elevated systemic proinflammatory mediators (5).

NAFLD AND CARDIOVASCULAR DISEASE.

Several studies have shown a close association between NAFLD and cardiovascular disease, which is the leading cause of death among patients with NAFLD (8). In addition to the well-defined association between NAFLD and atherosclerotic cardiovascular disease (eg, coronary artery disease) (9), a less defined association between NAFLD and HF exists. Several studies have shown impaired left ventricular (LV) systolic and diastolic function associated with NAFLD. For example, Fotbolcu et al (10) showed that compared with control subjects, nondiabetic, normotensive patients with NAFLD (diagnosed by ultrasonography) have lower early diastolic relaxation (e′) velocity and lower systolic velocity (s′) on tissue Doppler echocardiography, suggesting impaired LV systolic and diastolic function in patients with NAFLD. Additionally, patients with NAFLD have lower values of LV global longitudinal strain and strain rate in systole compared with healthy individuals (11). In an analysis of the CARDIA (Coronary Artery Risk Development in Young Adults) study, patients with NAFLD had lower e′ velocity, higher LV filling pressure, and worse absolute global longitudinal strain than patients without NAFLD (12); also, NAFLD was associated with myocardial remodeling and dysfunction (12). In a retrospective cohort of bariatric surgery patients, Simon et al (13) demonstrated that NASH is associated with increased left atrial volume index, LV concentric remodeling, and impaired diastolic function perioperatively. In a study by Zhang et al (14), NAFLD was independently associated with LV mass index and LV fibrosis size in patients with HF with reduced ejection fraction (HFrEF) (14). In patients with chronic HF (regardless

ABBREVIATIONS AND ACRONYMS

ALT = alanine aminotransferase

AST = aspartate aminotransferase

AV = arteriovenous

BCAA = branched-chain amino acid

GLP = glucagon-like peptide

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

IL = interleukin

LV = left ventricular

LVEF = left ventricular ejection fraction

NAFLD = nonalcoholic fatty liver disease

NASH = nonalcoholic steatohepatitis

NT-proBNP = N terminal pro-B-type natriuretic peptide

RAAS = renin-angiotensin aldosterone system

SGLT2 = sodium-glucose cotransporter 2

SPSS = spontaneous portosystemic shunt(s)

TNF = tumor necrosis factor

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of ejection fraction), NAFLD fibrosis score was significantly higher in patients who had cardiovascular events, and a higher score was associated with a higher risk for cardiovascular events, advancing New York Heart Association functional class, and higher serum brain natriuretic peptide levels (15).

The prevalence of NAFLD is higher in patients with HFpEF than in those with HFrEF, reaching up to 50% (16). In a post hoc analysis of patients with HFpEF from the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) trial, Peters et al (17) showed that advanced liver fibrosis may be present in up to 37.5% of patients. The presence of fibrosis in patients with HFpEF carries a negative prognostic value; the degree of fibrosis on the basis of fibrosis-4 is independently associated with hospitalization for HF (17). Also, in a prospective observational study, NAFLD fibrosis score was an independent predictor of all-cause mortality in patients with HFpEF (18).

NAFLD: A CAUSE OF HFpEF? HFpEF is a heterogeneous clinical syndrome characterized by diastolic and systolic reserve abnormalities, atrial dysfunction, inappropriate chronotropic reserve, pulmonary hypertension, endothelial dysfunction, and preload reserve failure (19). Although HFpEF was initially studied as one unified syndrome, it is evident that there are distinct phenotypes of HFpEF with different underlying causes.

NAFLD is associated with structural and functional cardiac abnormalities that are commonly seen in patients with HFpEF. In a population-based, longitudinal study, NAFLD was independently associated with incident LV hypertrophy, abnormal LV geometry, and increased LV strain (20). In a study that included 171 patients with morbid obesity and no known cardiac disease, 66% of the patients had either NASH or isolated steatosis on liver biopsy (21). Furthermore, patients with NASH demonstrated LV concentric remodeling and had hyperdynamic circulation (21). The concept of phenomapping, which is a clustering analysis using dense phenotypic data to identify phenotypically distinct HFpEF classification, has recently emerged (22). A metabolic phenotype of HFpEF was identified during phenomapping that is characterized by a high prevalence of obesity, diabetes, and obstructive sleep apnea. This phenotype, compared with other phenotypes of HFpEF, has the worst LV relaxation, highest pulmonary vascular resistance, and highest pulmonary capillary wedge pressures (22). In another phenomapping analysis of the TOPCAT study, a phenogroup of patients with HFpEF demonstrated a high prevalence of obesity, diabetes, chronic kidney disease, elevated renin level, and high proinflammatory biomarkers (eg, tumor necrosis factor-alpha [TNF-α]), concentric LV hypertrophy, and liver fibrosis (23). These findings support the concept of a pathophysiological continuum between NAFLD and HFpEF. This continuum likely relates to multiple shared pathophysiological mechanisms.

We propose that NAFLD may drive 3 major HFpEF phenotypes, which may represent a continuum from mild to severe disease with variable progression patterns among different patients (**Table 1, Central Illustration**).

OBSTRUCTIVE HFpEF PHENOTYPE. Preload reserve failure was recently proposed as a mechanism by which NAFLD may lead to HFpEF (19). Preload reserve is the ability of the cardiovascular system to increase preload in times of stress such as physical activity. Almost one quarter of circulating blood volume must pass the liver via the portal vein and hepatic artery to return back to the heart (19). As the driving pressures between the splanchnic compartment and the central venous compartment are normally low, any increase in the resistance across hepatic sinusoids, such that occurs in NAFLD, can significantly impair venous return to the heart, thus limiting preload reserve (**Figure 1**) (19). Transhepatic blood flow obstruction caused by increased resistance in the sinusoidal area begins in early stages of NAFLD (24). As hepatic fibrosis increases, the hepatic venous pressure gradient can significantly increase and significantly decrease hepatic blood flow in response to exercises, with subsequent underfilling of the right ventricle (25). Through these mechanisms, limitations in preload reserve likely explain some of the impaired peak oxygen consumption observed in patients with NAFLD (26).

Features typifying this phenotype include: 1) high-normal LV ejection fraction (LVEF) at rest and exercise; 2) high-normal cardiac output at rest but impaired cardiac output augmentation with activity; and 3) low levels of natriuretic peptides. All 3 of these features are commonly encountered in patients with HFpEF and support a possible contribution of NAFLD to the observed limitation in cardiac output augmentation. 1) Patients with this phenotype typically exhibit high-normal LVEF. Right ventricular and LV underfilling through an outflow block of blood from the splanchnic compartment results in a reduced end-diastolic volume. Paired with an inotropic function of a sympathetically overactive system, the result is a high-normal LVEF. Sympathetic hyperactivation with subsequent increase in stroke volume is likely driven in part by the

TABLE 1 HFpEF Phenotypes Associated With Nonalcoholic Fatty Liver Disease

HFpEF Phenotype	Pathophysiology	Characteristics	Proposed Treatment
Obstructive HFpEF phenotype	Increase in the resistance across hepatic sinusoids leading to impairment venous return to the heart, thus limiting preload reserve	• High-normal cardiac output state at rest • Impaired cardiac output augmentation with activity • Low natriuretic peptides levels	• Weight loss • SGLT2 inhibitors • GLP-1 receptor agonists • RAAS inhibitors • ARNIs • Loop diuretic agents
Metabolic HFpEF phenotype	Chronic low-grade inflammatory process	• Metabolic syndrome • Excess visceral adipose tissue	• Weight loss • SGLT2 inhibitors • GLP-1 receptor agonists • RAAS inhibitors • ARNIs • Loop diuretic agents
Advanced liver disease/ cirrhosis HFpEF phenotype	Formation of spontaneous portosystemic and arteriovenous shunts	• Increased arterial blood flow and decreased systemic vascular resistance resulting in high cardiac output at rest • Impaired cardiac output augmentation with activity	• Loop diuretic agents

ARNI = angiotensin receptor-neprilysin inhibitors; GLP-1 = glucagon-like peptide 1; HFpEF = heart failure with preserved ejection fraction; RAAS = renin-angiotensin-aldosterone system; SGLT2 = sodium-glucose cotransporter 2.

congestion of the splanchnic vascular compartment (27). 2) As portal hypertension progresses, formation of intrahepatic and extrahepatic shunts (eg, portosystemic shunts, intrapulmonary arteriovenous [AV] shunts) occurs. These shunts may explain the high-normal cardiac output state at rest independent of the mechanism described previously. In NAFLD (but also applicable to HFpEF), the augmentation of the high-normal baseline cardiac output state is impaired through a combination of impaired inotropy, impaired chronotropy, and preload recruitment via shunting of vasodilatory substances, such as nitric oxide and endocannabinoids (26). 3) Natriuretic peptides: as the resistance in hepatic sinusoids increases in NAFLD, a decreased preload would be expected and thus lower intracardiac pressure with subsequent low levels of N terminal pro-B-type natriuretic peptide (NT-proBNP). As NAFLD progresses and more venous return impedance occurs, NT-proBNP levels would be expected to decrease even more. Furthermore, low intracardiac filling pressures would be expected in this phenotype. In a cross-sectional study of the MESA (Multi-Ethnic Study of Atherosclerosis) that included 4,529 subjects, low levels of NT-proBNP were associated with higher prevalence of NAFLD (28). In another cross-sectional study that included patients with biopsy-proven NAFLD and no history of cardiovascular disease, lower plasma levels of NT-proBNP were strongly associated with a greater prevalence of NASH (29). These findings may relate to a state of decreased preload associated with NAFLD (caused by a preload reserve failure).

METABOLIC HFpEF/NAFLD PHENOTYPE. Metabolic syndrome is a cluster of metabolic and inflammatory abnormalities with key features of insulin resistance, visceral adiposity, endothelial dysfunction, and atherogenic dyslipidemia (30). An overlap between NAFLD and metabolic syndrome is well described, and both entities carry a similar risk profile (eg, both metabolic syndrome and NAFLD can predict type 2 diabetes and cardiovascular disease) (31). Although both NAFLD and HFpEF share a close metabolic relationship, a direct causal relationship is not commonly recognized. We propose that along the spectrum of NAFLD and the metabolic syndrome lies a metabolic phenotype of HFpEF.

The common basis for the metabolic HFpEF/NAFLD phenotype is inflammation (**Figure 2**). A growing body of evidence suggests that a chronic low-grade inflammatory process may be a key factor in the pathogenesis of metabolic syndrome and is closely associated with its pathophysiological consequences (30). As NAFLD progresses from simple steatosis to NASH, increased systemic proinflammatory markers, such as interleukin (IL)-1β, IL-6, C-reactive protein, TNF-α, and chemokine (C-C motif) ligand 3, are produced (32). Increased systemic inflammation further contributes to endothelial dysfunction, which is also associated with HFpEF. Systemic inflammation in NAFLD is also associated with diastolic dysfunction. In rats with collagen-induced arthritis, inflammation was associated with LV diastolic dysfunction and myocardial deformation (33). In a family-based population study, Kloch et al (34) showed a significant correlation between IL-6 levels and E/A ratio early

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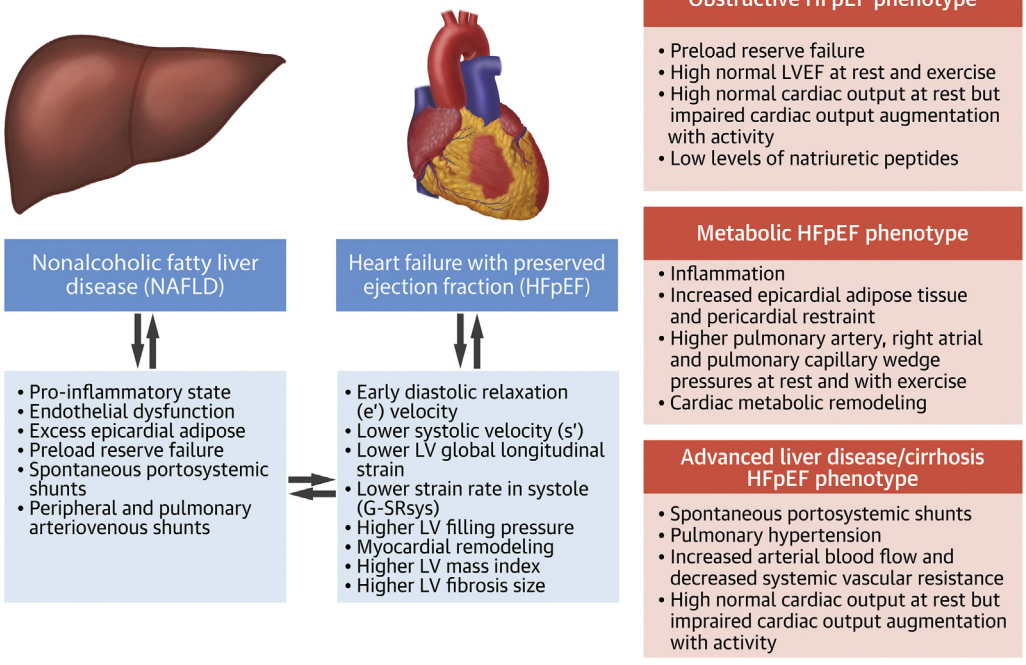
CENTRAL ILLUSTRATION The Association Between Nonalcoholic Fatty Liver Disease and Heart Failure With Preserved Ejection Fraction



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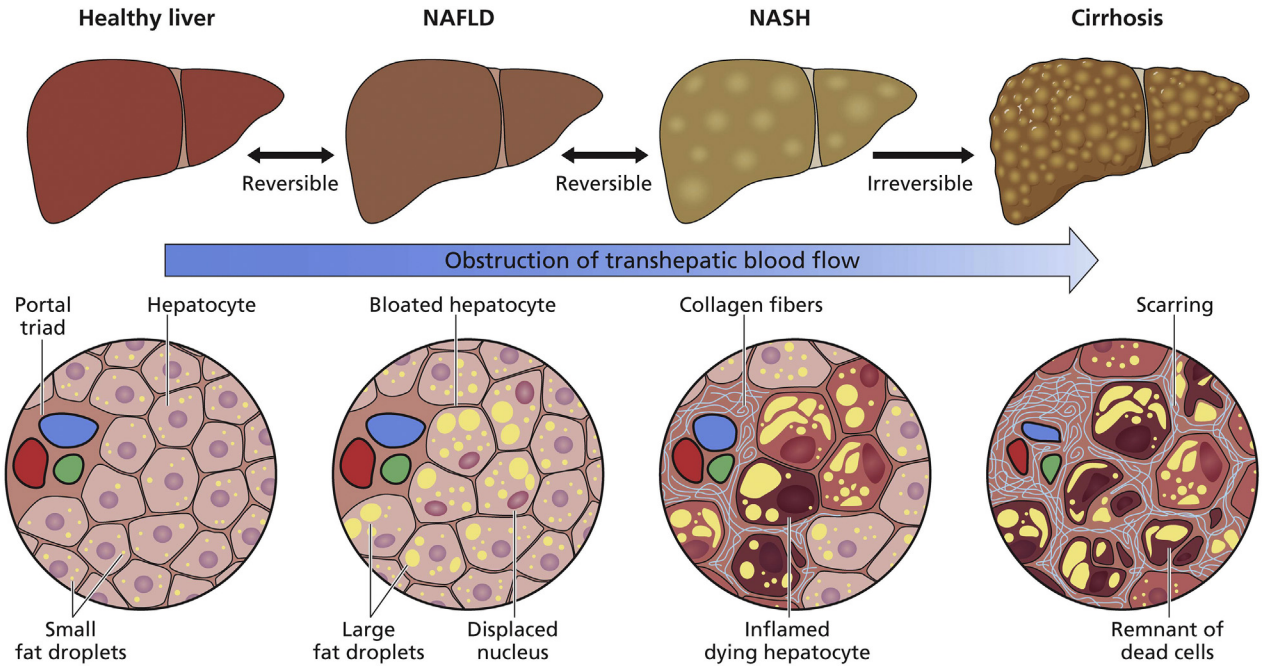
diastolic peak velocities of the mitral annulus displacement (E′) values among the general population. Also, IL-6 and C-reactive protein levels were associated with pulmonary vein systolic-to-diastolic velocity ratio, suggesting that systemic inflammation is strongly associated with LV diastolic dysfunction.

Osteopontin, a member of the matricellular protein family, plays an important role in inflammation, extracellular matrix deposition, and fibrosis (35). Circulatory levels of osteopontin are increased in NAFLD (36) and are positively correlated with the degree of fibrosis (37). The increased levels of osteopontin may directly or indirectly be related to the development and progression of HFpEF, as circulatory levels of osteopontin are increased in patients with diastolic HF and are positively correlated with the severity of HF symptoms (38). NAFLD is also characterized by increased secretion of asymmetrical dimethyl arginine (32,39), which is an endogenous antagonist of nitric oxide synthase. Increased secretion of asymmetrical dimethyl arginine can contribute to endothelial dysfunction. Also, NAFLD can cause alteration of methionine metabolism and thus disturbs the metabolism of homocysteine in the liver, resulting in increased serum homocysteine levels (40). Hyperhomocysteinemia is typically associated with increased vascular resistance in the liver, impairing nitric oxide formation (41). It also increases oxidative stress and enhances platelet activation (41).

Visceral obesity is an abnormally high level of visceral adipose tissue deposition (42). Visceral adipose tissue is hormonally active and possesses biochemical characteristics that play a key role in several physiological and pathological processes, including the metabolic syndrome (42). For example, visceral adipose tissue secretes several adipose-specific cytokines (ie, adipokines), such as leptin, which elicit local and systemic responses (43). Visceral obesity is a driver of both NAFLD and HFpEF (44); it is associated with the development and progression of NAFLD (45), and it is closely related to excess epicardial adipose tissue, which can contribute to the development of HFpEF (46). In a study that involved 60 healthy subjects, visceral fat accumulation had a strong correlation with epicardial adipose tissue thickness on the basis of transthoracic echocardiographic and cardiac magnetic resonance studies (47). Furthermore, epicardial adipose tissue is a source of inflammatory mediators, such as IL-1β, IL-

FIGURE 1 **Obstructive HFpEF Phenotype and Preload Reserve Failure**



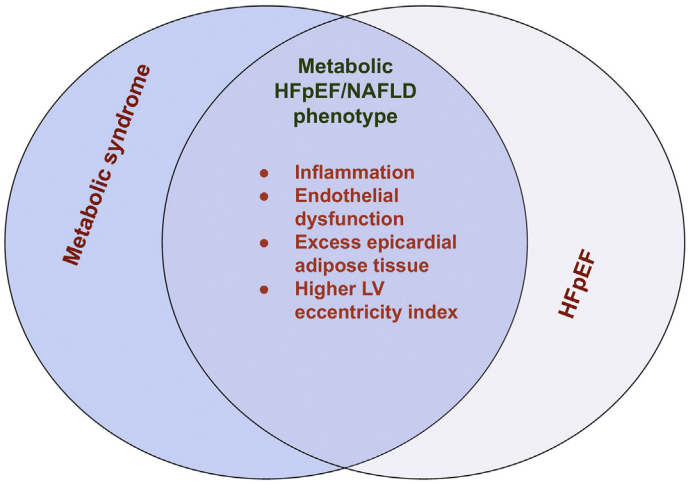
As liver fibrosis advances, resistance across hepatic sinusoids increases, resulting in increasing obstruction of the transhepatic blood flow. This obstruction leads to impairment of venous return to the heart, Thus limiting preload reserve. NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis.

6, monocyte chemotactic protein-1, and TNF-α (48). Epicardial adipose tissue is also associated with adverse hemodynamic changes in patients with HFpEF. In a study by Koepp et al (49) that included 169 patients with HFpEF and obesity, increased epicardial adipose tissue was associated with a higher LV eccentricity index, suggesting an increase in pericardial restraint. Excess epicardial adipose tissue was associated with a higher pulmonary artery, right atrial, and pulmonary capillary wedge pressures at rest and with exercise. Furthermore, patients with HFpEF and excess epicardial adipose had peak oxygen consumption that was 20% lower ($P < 0.01$) compared with those with HFpEF and no excess epicardial adipose tissue.

In addition to the association of NAFLD with cardiac structural remodeling in HFpEF, NAFLD is also associated with cardiac metabolic remodeling, which may precede and drive some of the structural changes that have been observed. For instance, in a study of 55 individuals with type 2 diabetes and coronary artery disease, liver fat content as measured by nuclear magnetic resonance was the most strongly correlated clinical variable with myocardial insulin resistance as indicated by decreased insulin-stimulated glucose uptake on cardiac positron emission tomography (50). Similarly, hepatic triglyceride content was associated with decreased cardiac adenosine triphosphate production in 61 individuals with type 2 diabetes (51). Changes in cardiac metabolism have also been seen in individuals with NAFLD without diabetes. In a study of young men without diabetes matched for anthropometric features with (n = 21) or without (n = 21) hepatic steatosis, epicardial fat was increased and cardiac adenosine triphosphate content was decreased in those with hepatic steatosis (52). Notably, cardiac structure and function were not different between groups, suggesting that cardiac metabolic remodeling may precede the structural remodeling observed in more advanced NAFLD (52).

Whether the changes in heart function and metabolism observed in NAFLD are related to NAFLD per se or mediated by shared pathogenic mechanisms such as obesity and systemic insulin resistance remains unclear, in part because of the cross-sectional and/or observational nature of many of the human studies conducted to date. For this reason, animal models may provide insight into the mechanisms connecting NAFLD and HFpEF. One area of recent investigation surrounds the role of hepatic branched-

FIGURE 2 Relation Between Metabolic Syndrome and HFpEF

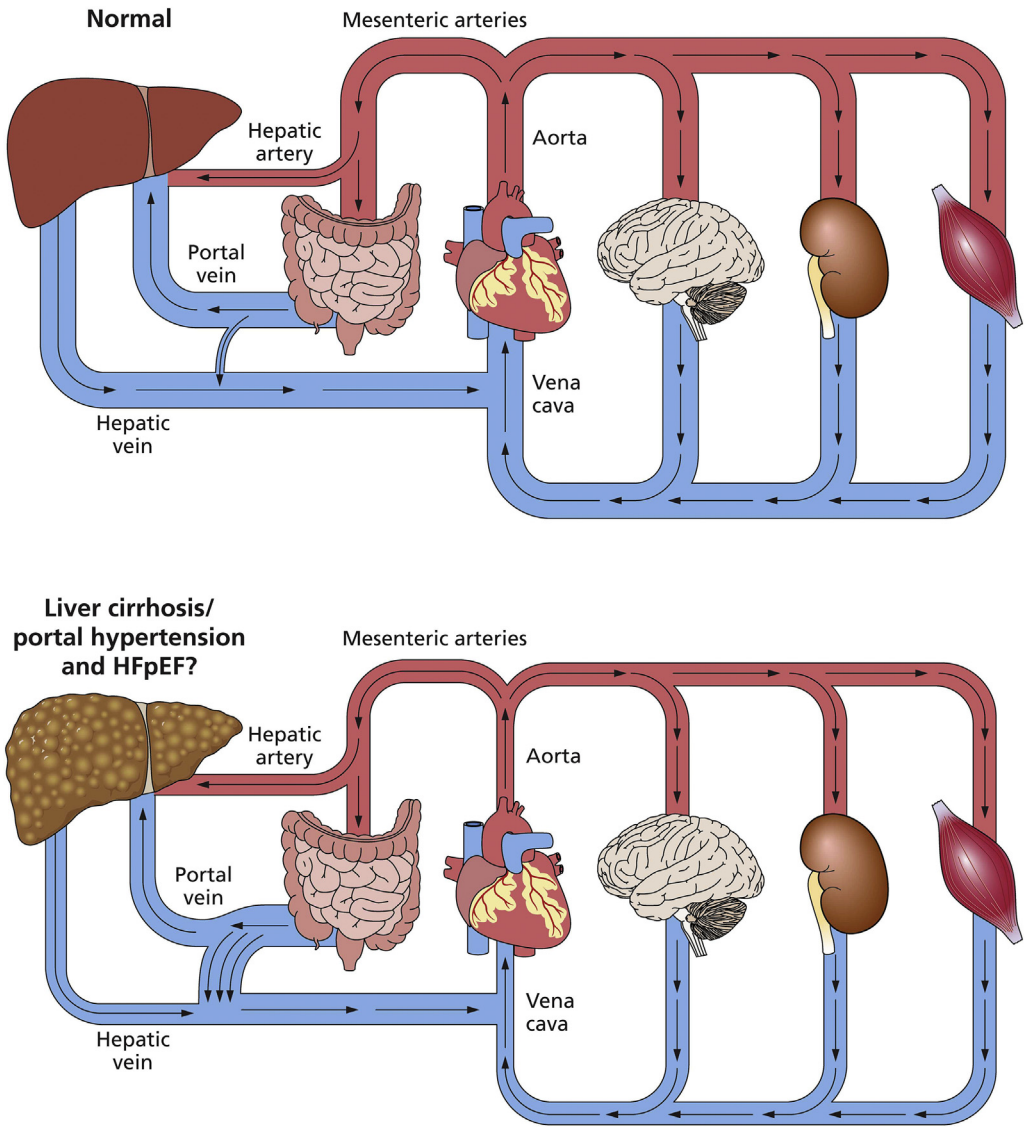


HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; NAFLD = nonalcoholic fatty liver disease.

chain amino acid (BCAA) metabolism in NAFLD and HFpEF. BCAAs—valine, leucine, and isoleucine—are essential amino acids that play important roles in normal cellular growth as metabolic substrates and also via their impact on nutrient signaling pathways. An extensive body of research from both human and animal studies has connected elevated levels of circulating BCAAs and related metabolites from the BCAA metabolic pathway to the pathogenesis of cardiometabolic disorders, including obesity, insulin resistance, diabetes, and HF (53). Circulating BCAAs have also emerged as biomarkers of NAFLD presence and severity (54-57). Changes in gene expression in enzymes of the BCAA metabolic pathway have also been observed in liver tissue from individuals with NAFLD (54,58). In studies using lean healthy rats, liver-specific inhibition of the BCAA pathway is sufficient to raise circulating BCAA levels and induce hepatic steatosis after just 1 week (59). Conversely, in obese Zucker rats (a model of obesity, insulin resistance, and hepatic steatosis that demonstrates elevated plasma BCAAs) activation of the liver BCAA pathway normalizes circulating BCAAs and liver fat after 1 week (59). This interaction between liver BCAA metabolism and hepatic steatosis appears to be driven by shared enzymatic machinery between the BCAA and de novo lipogenesis pathways (59). How might changes in liver BCAA metabolism affect cardiac function? The impaired liver BCAA metabolism seen in patients with NAFLD significantly increases circulating BCAAs and thus delivery of BCAAs to the heart. In obese Zucker rats, restricting dietary BCAAs is sufficient to normalize circulating BCAAs while also enhancing cardiac fatty acid oxidation and decreasing cardiac triglyceride stores to levels of lean rats (60,61). A recent study also showed that exposure of the heart to elevated concentrations of branched-chain ketoacids—metabolites produced by the transamination of BCAAs—that are observed in the circulation of individuals with NAFLD is sufficient to activate cardiac protein synthesis, thus providing a potential mechanistic link to the cardiac structural remodeling seen in NAFLD (62). Additional preclinical studies are needed to further define the liver-heart metabolic crosstalk that occurs in NAFLD.

ADVANCED LIVER DISEASE/CIRRHOSIS HFpEF PHENOTYPE. With the progression of liver fibrosis and the development of liver cirrhosis, another HFpEF phenotype is likely to occur. Portal hypertension is one of the main complications of advanced liver fibrosis and cirrhosis, and as portal venous system pressures increase, spontaneous portosystemic shunts (SPSS) typically form as an attempt to bypass the liver and decompress the portal venous system (**Figure 3**) (63). The development of SPSS leads to an increase in pulmonary flow and facilitates the transit of vasoactive factors that are produced in the splanchnic circulation with subsequent vasoconstriction and remodeling of the pulmonary vasculature (64). This may result in the development of pulmonary hypertension, which is typically referred to as portopulmonary hypertension (64). Although the development of pulmonary hypertension in patients with HFpEF has generally been associated with LV diastolic dysfunction with subsequent passive pulmonary venous hypertension, followed by reactive increase in pulmonary venous resistance and pulmonary vascular remodeling (65), Lam et al (66) showed in a population-based study a significant contribution of a precapillary component to the development of pulmonary hypertension in HFpEF. It is possible that in patients with SPSS, the increase in the delivery of vasoactive substances to the pulmonary circulation coupled with the increase in pulmonary flow would result in an HFpEF phenotype characterized by pulmonary hypertension. Microshunts may develop early in the disease course, leading to these hemodynamic changes. This phenotype may explain, in part, the dyspnea and fatigue that are commonly seen in patients with advanced liver disease and cirrhosis. In addition to SPSS, patients with cirrhosis have tendency to form AV shunts peripherally and in the pulmonary circulation (67).

FIGURE 3 **Advanced Liver Disease/Cirrhosis HFpEF Phenotype**



With the progression of liver fibrosis and the development of liver cirrhosis, spontaneous portosystemic and arteriovenous shunts form with resultant hemodynamic changes characterized by a state of high cardiac output at rest. A pattern of hepatic flow obstruction also occurs with the progression of liver fibrosis, resulting in preload reserve failure and lack augmentation of cardiac output in response to stress.
HFpEF = heart failure with preserved ejection fraction.

AV shunt formation is typically associated with significant hemodynamic changes, such as increased arterial blood flow and decreased systemic vascular resistance. This can result in a state of high cardiac output. These hemodynamic changes can be associated with changes in cardiac structure, including left atrial and possible right ventricular volumes (68,69). Although HFpEF is thought to be a syndrome of low or normal resting cardiac output, it is becoming more evident that a proportion of patients with HFpEF have a state of high cardiac output at rest (70). These patients typically lack augmentation of their cardiac output in response to exercise, which results from a pattern of hepatic flow obstruction with resultant preload reserve failure, as seen in the obstructive HFpEF phenotype. Combined, these hemodynamic changes may suggest a continuum, in which the obstructive phenotype of HFpEF overlaps with the

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TABLE 2 Criteria for Diagnosing Cirrhotic Cardiomyopathy Based on the Cirrhotic Cardiomyopathy Consortium in 2019

Systolic dysfunction	• LV ejection fraction ≤50% or • Absolute global longitudinal strain <18% or >22%
Diastolic dysfunction	At least 3 of the following: • Septal e′ velocity <7 cm/s • E/e′ ratio ≥15 • Left atrial volume index >34 mL/m^2 • TR velocity >2.8 m/s
Potential additional markers	• Impaired chronotropic and/or inotropic responses • Electrocardiographic changes, such as QTc interval prolongation • Electromechanical uncoupling • Myocardial mass changes • Serum biomarkers, such as BNP and N-terminal prohormone • Chamber enlargement • Cardiac magnetic resonance demonstrating myocardial dysfunction

BNP = brain natriuretic peptide; LV = left ventricular; QTc = corrected QT; TR = tricuspid regurgitation.

advanced liver disease/cirrhosis HFpEF phenotype (Figure 2).

CARDIOHEPATIC DISORDERS RELATED TO HFpEF: CIRRHOTIC CARDIOMYOPATHY. Cirrhotic cardiomyopathy is a clinical syndrome of chronic cardiac dysfunction that occurs in patients with cirrhosis (irrespective of the etiology) with no known cardiac disease and is characterized by high cardiac output at rest and blunted contractility response to stress (whether physiological, pathological, or pharmacologic stress) and/or altered diastolic relaxation with abnormal electrophysiological changes (71). It is estimated that about 60% of patients with cirrhosis have cirrhotic cardiomyopathy (72). Proposed redefined criteria were proposed by the Cirrhotic Cardiomyopathy Consortium in 2019 (Table 2) (73).

The pathophysiological bases for cirrhotic cardiomyopathy relate to LV dysfunction and extracardiac factors, such as autonomic dysfunction and cardiodepressant substances (eg, alcohol) (74). Although systolic function is typically normal or increased in patients with cirrhosis at rest (71), physical or pharmacologic stress typically unmasks underlying systolic dysfunction in such patients (75). The exact mechanism of the increased cardiac output in cirrhosis at rest is not well understood, but it may be related to reduced central and arterial blood volume in patients with cirrhosis (74), which would lead to deactivation of arterial baroreceptors and an increase in the activity of the sympathetic nervous system and thus an increase in heart rate and cardiac output. The reduced cardiac performance in cirrhosis during stress may relate to blunted heart rate response, reduced myocardial contractility, and significant wasting of skeletal muscles (74,76-78). Furthermore, cirrhosis is associated with dysfunctional plasma membrane and ion channels, which predisposes patients with cirrhosis to conduction abnormalities and arrhythmias, which can further exacerbate cardiac dysfunction (74).

CARDIOHEPATIC DISORDERS RELATED TO HFpEF: CONGESTIVE HEPATOPATHY. Congestive hepatopathy is a clinical syndrome that refers to the manifestations of chronic, passive congestion of the liver caused by elevation of the central venous pressure in the setting of HF (HFrEF and HFpEF) or other cardiac disease (eg, tricuspid regurgitation) (79). The incidence of congestive hepatopathy among patients with severe HF ranges from 15% to 65% (80). Any elevation in the pressure of the right heart typically results in an elevation of the central venous pressure and is directly transmitted to the hepatic veins through the inferior vena cava because of their close anatomical relationship. Because of the absence of valves in hepatic veins, the increased pressure in the hepatic veins leads to hepatic congestion, which is characterized mainly by centrilobular congestion and sinusoidal dilation (80). In acute HF, hepatic congestion is typically coupled with arterial hypoperfusion and hypoperfusion-induced hypoxia, which result in hypoxic hepatitis (81). Congestive hepatopathy can result in centrilobular liver cell necrosis (82). This necrotic damage is followed by deposition of connective tissue and fibrosis, ultimately leading to cardiac cirrhosis (82).

The passive backward hepatic congestion enhances hepatic lymph formation to drain the fluid that accumulates in the interstitial space (83). However, when the production rate of interstitial fluid exceeds the capacity of the lymphatic system, ascites develops (83). Furthermore, increased pressure of hepatic sinusoids disrupts the endothelial cells and the tight junctions between hepatocytes, which separate the extravascular space from the bile canaliculus (84). This disruption results in exposing the bile canaliculus to the sinusoidal blood and thus an increase in the level of serum bilirubin (84).

Congestive hepatopathy typically manifests with jaundice, ascites, edema, hepatomegaly, hepatojugular reflux, pulsatile liver (when associated with tricuspid valve regurgitation) (85), and a cholestatic laboratory pattern (ie, increased serum γ-glutamyl-transpeptidase, alkaline phosphatase, and bilirubin) with normal or mildly increased transaminases (86). The severity of cholestasis typically correlates with the severity of HF and implies significant prognostic values (87); total bilirubin is a strong predictor of adverse outcomes, such as all-cause

mortality, cardiovascular mortality, and HF hospitalization (87).

Treatment of congestive hepatopathy focuses on decongesting the liver (using diuretic agents) and optimizing cardiac output and hemodynamic status (79).

CHALLENGES IN THE DIAGNOSIS OF NAFLD IN HFpEF AND HFpEF IN NAFLD. Because of the close relationship between NAFLD and HFpEF, there are several diagnostic challenges.

First, the presence of nonspecific symptoms such as fatigue and dyspnea could be associated with either HFpEF or NAFLD and make the attribution to either disease complicated. Additionally, it is challenging to identifying which condition came first when NAFLD and HFpEF concurrently exist.

Second, liver aminotransferases are nonspecific markers that can be normal or increased with either entity. In NAFLD, the pattern of elevated aminotransferases is typically consistent with hepatocellular liver injury with alanine aminotransferase (ALT) greater than aspartate aminotransferase (AST). With progression of liver disease, the ALT-to-AST ratio may decrease to <1 and be associated with mild decrease in serum albumin or increase in total bilirubin (88), all of which can also be comparably altered in congestive hepatopathy in the setting of HFpEF (89). The effect of congestive hepatopathy on other serum studies, such as serum fibrosis markers (eg, haptoglobin, alpha-2-macroglobulin, hyaluronic acid) (90), has not been well studied, and therefore their utility in diagnosing NAFLD in the setting of HFpEF is not clear.

Third, ultrasound-based transient elastography and magnetic resonance elastography are 2 imaging modalities that can be used to measure liver stiffness (90). Liver stiffness may be used a surrogate marker for central venous pressure (91), and liver stiffness in patients with acute decompensated HF is associated with increased mortality and HF readmission (92). One of the main disadvantages of both modalities is that liver stiffness measurements may be affected by hepatic congestion, resulting in overestimation of fibrosis; therefore, attention should be paid to the volume status of patients undergoing evaluation with these modalities (90).

Fourth, as discussed previously, natriuretic peptides (eg, NT-proBNP) may be decreased in some phenotypes of NAFLD-related HFpEF (likely because of decreased preload associated with reserve preload failure); therefore, the use of natriuretic peptides in screening for and diagnosing HFpEF in patients with NAFLD may produce misleading findings.

Fifth, HF clinicians rarely perform liver imaging during the initial stages of HF evaluation. Rather, liver imaging is typically performed later in the disease course of HF, and liver fibrosis in these stages is typically attributed to congestive hepatopathy. The preconceived notion of the etiology of liver disease in the setting of HF (ie, HF leading to congestive hepatopathy and liver fibrosis) typically biases clinicians against diagnosing liver disease as a driver for HF.

MANAGEMENT OF NAFLD-RELATED HFpEF PHENOTYPES

No pharmacologic agent has been approved for the treatment of NAFLD. Management of NAFLD focuses mainly on addressing the components of metabolic syndrome (ie, obesity, hypertension, diabetes or insulin resistance, and dyslipidemia). To date, nearly all the clinical trials investigating treatment options for HFpEF have produced neutral findings with respect to clinical benefits. This may be due in part to combining all HFpEF phenotypes into one clinical diagnosis when investigating these treatments.

Besides addressing the metabolic risk factors for NAFLD with lifestyle modification, weight loss, and US Food and Drug Administration–approved therapies to treat patient-specific complications of metabolic syndrome, we propose that the following treatment options may offer benefits in NAFLD-related HFpEF phenotypes on the basis of plausible mechanisms of action in this subset of patients.

SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown significant improvement in cardiovascular outcomes in patients with HFrEF (93-95). Although the effect of SGLT2 inhibitors in patients with HFpEF has not been well established, the cardiovascular benefits of SGLT2 inhibitors were consistent in meta-analyses that included patients with HF regardless of ejection fraction (96,97), and cardiovascular benefits were consistent in a subgroup analysis of the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) trial across the spectrum of LVEF (98). In a meta-analysis of randomized controlled trials, SGLT2 inhibitors reduced liver fat content in patients with NAFLD as estimated by cardiac magnetic resonance proton density fat fraction (99). Furthermore, SGLT2 inhibitors significantly reduced the levels of serum ALT in these patients (99). These results suggest that SGLT2 inhibitors may be a promising treatment in patients with concurrent NAFLD and HFpEF.

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GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS. In a rat model of HFpEF, glucagon-like peptide 1 (GLP-1) agonists improved diastolic function and decreased mortality (100). In a randomized, placebo-controlled trial, 26-week treatment with liraglutide reduced early LV diastolic filling and LV filling pressures in patients with type 2 diabetes mellitus (101). GLP-1 agonists also alleviate NAFLD. In a randomized, double-blind, placebo-controlled phase 2 trial that included 52 patients with NASH, 48-week treatment with liraglutide resulted in resolution of NASH in 39% of the patients (compared with 9% in the placebo group). Liraglutide also prevented the progression of fibrosis in 36% of the patients (compared with 9% in the placebo group) (102). In another randomized, double-blind, placebo-controlled, phase 2 trial that included 320 patients with biopsy-proven NASH and liver fibrosis, semaglutide resulted in a significantly higher percentage of NASH resolution compared with placebo (103). In a randomized, double-blind, placebo-controlled, phase 3 trial that included patients with a body mass index of 30 kg/m^2 or greater, semaglutide resulted in a significant sustained reduction in body mass (104). This finding may suggest particular benefits for GLP-1 agonists in patients with the metabolic HFpEF phenotype.

RENIN-ANGIOTENSIN ALDOSTERONE SYSTEM INHIBITORS. In an obese Zucker rat model, Toblli et al (105) showed that steatohepatitis is associated with an increase in the expression of angiotensin II in the liver, and renin-angiotensin aldosterone system (RAAS) inhibition with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers results in improvement in insulin sensitivity, reduction in hepatic enzymes, and reduction in the levels of TNF-α, IL-6, and transforming growth factor-beta-1. Although there is paucity of data on the effect of RAAS inhibitors on NAFLD in humans, a recent study suggested that RAAS inhibitors can decrease the risk for NAFLD development and progression in obese patients (106). In a randomized, double-blind, placebo-controlled, phase 2a trial that included 12 children with NASH, losartan improved ALT and AST levels (107). In this context, the RELIEF-NAFLD (Role of Lisinopril in Preventing the Progression of Non-Alcoholic Fatty Liver Disease; NCT04550481) trial is an ongoing study to examine the effect of lisinopril on the prevention and progression of NAFLD. Aldosterone antagonists, such as spironolactone and eplerenone, are also associated with favorable outcomes in patients with NAFLD and HFpEF. In animal studies, both spironolactone and eplerenone reduced steatosis and fibrosis (108,109). In a phenomapping analysis of the TOPCAT trial, the effect of spironolactone on the risk reduction of the primary endpoint of cardiovascular death, hospitalization for HF, or aborted cardiac arrest was most pronounced in the HFpEF phenotype with metabolic syndrome (23). The SPIRRIT (Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction; NCT02901184) study is an ongoing registry-randomized clinical trial that aims to study the effect of spironolactone plus standard of care in patients with HFpEF. Given the significant impact of RAAS inhibitors on mitigating cardiac remodeling (110) and possible counteraction of the pathophysiological mechanisms of NAFLD, RAAS inhibitors may be particularly beneficial in a subset of patients with HFpEF who concurrently have NAFLD.

ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITORS. In the light of recent evidence suggesting possible benefits of the combination of the neprilysin inhibitor prodrug sacubitril and the angiotensin receptor blocker valsartan in patients with HFpEF and low-normal ejection fraction and possible improvement in patients reported outcomes (111,112), the Food and Drug Administration has recently expanded the approved indications of sacubitril/valsartan to include patients with HF regardless of ejection fraction. Data regarding the hepatic effect of sacubitril/valsartan in patients with HFpEF are limited. However, on the basis of current evidence, it is possible that sacubitril/valsartan might be particularly beneficial in patients with NAFLD-related HFpEF phenotypes. In a hyperglycemic rat model, Alqahtani et al (113) showed that sacubitril/valsartan is superior to valsartan alone in improving liver function markers and attenuating inflammation, progression of liver injury, and hepatic fibrosis. In an analysis of the PARADIGM-HF (A Multicenter, Randomized, Double-Blind, Parallel Group, Active-Controlled Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality in Patients With Chronic Heart Failure and Reduced Ejection Fraction) trial, Suzuki et al (114) showed that sacubitril/valsartan improves all conventional measures of liver function in patients with HFrEF compared with enalapril. It is not clear if this effect can be extended to patients with HFpEF, and further studies are needed to examine that.

LOOP DIURETIC AGENTS. Loop diuretic medications (eg, furosemide, bumetanide, torsemide) are the primary agents for reducing the congestion associated with hypervolemia in patients with HFpEF and for optimizing filling pressures in these patients (115). However, because of the significant hemodynamic changes in patients with NAFLD-related HFpEF phenotypes (eg, preload reserve failure with subsequent

right ventricular and LV underfilling), patients with these phenotypes are likely to be highly sensitive to volume changes, with a narrow window between hyper- and hypovolemia. Studies examining the effect of loop diuretic agents in this subset of patients are needed.

WEIGHT LOSS AND BARIATRIC SURGERY. Obesity is a major risk factor for metabolic syndrome and HF (both HFrEF and HFpEF). As discussed earlier, metabolic syndrome may be the driver of a metabolic HFpEF/NAFLD phenotype; therefore, addressing metabolic syndrome may provide a pathway to treat the metabolic HFpEF/NAFLD phenotype. Weight loss (regardless of the approach) is associated with a significant reduction in liver volume, fat content, and fibrosis (116,117). Therefore, encouraging weight loss in patients with NAFLD may prevent the development and progression of NALFD-related HFpEF phenotypes.

Bariatric surgery is associated with reduced symptoms, cardiac structure and function, and reverse cardiac remodeling in obese patients with HFpEF (118). At the same time, bariatric surgery can reverse the pathological liver changes in NAFLD (119). In a prospective study with biopsy-proven NASH, bariatric surgery resulted in resolution of NASH in 84% of patients at 1 year following surgery (120). Furthermore, a meta-analysis showed that bariatric surgery is associated with complete resolution of NAFLD in obese patients (121). This evidence suggests that bariatric surgery should be considered in obese patients with the metabolic HFpEF/NAFLD phenotype.

FUTURE DIRECTIONS

The present review suggests an important association between HFpEF and NAFLD and proposes NAFLD-related HFpEF phenotypes. It also sheds the light on the critical need for more research in this area. There is a need for studies to investigate which subsets of patients with HFpEF should be screened for NAFLD and vice versa and to determine the best tools for such screening. Additionally, it is possible that some of the treatments that were previously investigated in patients with HFpEF and failed to show meaningful clinical benefits (eg, RAAS inhibitors) may provide benefits in patients with NAFLD-related HFpEF phenotypes; therefore, there is a need for more studies and subgroup analyses derived from clinical trials investigating these medications. Last, as the proposed NAFLD-related HFpEF phenotypes are postulated and not proved, there is a need for further research in this area to identify such phenotypes, explore their pathophysiology and hemodynamic parameters, demonstrate their prevalence, and investigate their progression over time.

CONCLUSIONS

In addition to the well-known association between liver disease and HFrEF, liver disease, particularly NAFLD, is closely related to the development and progression of HFpEF. We propose 3 phenotypes of HFpEF that may be driven by NAFLD and that share common pathophysiological bases: 1) obstructive NAFLD/HFpEF, associated primarily with failure of preload reserve; 2) metabolic NAFLD/HFpEF, related to metabolic syndrome with inflammation, endothelial dysfunction, perturbed systemic metabolism, and excess pericardial adipose tissue as a common shared basis; and 3) advanced liver disease/cirrhosis HFpEF, which is characterized by SPSS and AV shunts with resultant decreased systemic resistance and increased cardiac output. In summary, NAFLD-related HFpEF phenotypes should be recognized as a distinct HFpEF phenotype and common cardiovascular and hepatic disorder. Further studies are needed to better characterize this disorder, to develop screening tools, to identify subsets of patients who would benefit from such screening and risk stratification, to determine important clinical outcomes in these patients, and to investigate beneficial treatments.

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ADDRESS FOR CORRESPONDENCE: Dr Marat Fudim, Division of Cardiology, Department of Medicine, Duke University, 2301 Erwin Road, Durham, North Carolina, 27705, USA. E-mail: marat.fudim@duke.edu.

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