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HEART FAILURE AND LIVER DISEASE: CARDIOHEPATIC INTERACTIONS

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Summary

Heart failure (HF) is a complex clinical syndrome that affects multiple organ systems, including the liver. The interplay between the heart and liver is bidirectional and often underrecognized, with hepatic congestion and hypoperfusion significantly contributing to patient morbidity and mortality. Understanding this interaction is critical to improving diagnostic accuracy and therapeutic strategies. The aim of the research was to investigate the underlying pathophysiological mechanisms, clinical significance, and diagnostic complexities associated with hepatic involvement in heart failure. A comprehensive literature review was conducted to explore the interrelationship between heart failure and liver disease, with a particular focus on congestive hepatopathy, ischemic hepatitis, and overall cardiohepatic interactions. Elevated central venous pressure in right-sided HF leads to hepatic congestion, sinusoidal dilatation, hepatocellular atrophy, and ultimately fibrosis—known as congestive hepatopathy. In severe cases, cardiac cirrhosis develops. Acute reductions in cardiac output, particularly in the setting of decompensated heart failure, can lead to ischemic hepatitis—also known as acute hypoxic hepatitis—characterized by significant elevations in liver enzymes and associated with adverse clinical outcomes. Neurohormonal imbalances, such as RAAS and SNS overactivation, further aggravate hepatic injury and promote systemic inflammation. Additionally, gut involvement through intestinal edema and dysbiosis forms a gut-liver-heart axis, exacerbating cachexia and disease progression. Cardiohepatic interactions significantly influence the clinical course of HF. Early recognition of liver dysfunction, including subclinical forms, is essential for comprehensive care. A multidisciplinary approach targeting hemodynamic stability, congestion relief, and gut-liver support holds promise in improving prognosis and reducing complications in HF patients.

Keywords: *heart failure, congestive hepatopathy, ischemic hepatitis, cardiohepatic syndrom*

Rezumat

Insuficiența cardiacă și boala hepatică: interacțiuni cardiohepatice

Insuficiența cardiacă (IC) este un sindrom clinic complex ce afectează mai multe organe, inclusiv ficatul. Relația inimă-ficat este bidirecțională și adesea subevaluată, congestia hepatică și hipoperfuzia contribuind semnificativ la morbiditate și mortalitate. Înțelegerea acestor interacțiuni este crucială pentru diagnostic și tratament. Scopul cercetării a fost de a investiga mecanismele fiziopatologice subiacente, semnificația clinică și complexitățile diagnostice asociate cu implicarea hepatică în insuficiența cardiacă. A fost efectuată o revizuire sistematică a literaturii privind legătura dintre IC și afectarea hepatică, cu accent pe hepatopatia congestivă, hepatita ischemică și interacțiunile cardio-hepatice. Presiunea venoasă centrală crescută în IC dreaptă provoacă congestie hepatică, dilatare sinusoidală, atrofie hepatocitară și fibroză (hepatopatie congestivă). În forme severe, poate apărea ciroza cardiacă. Reducerea bruscă a debitului cardiac, mai ales în IC decompensată, poate duce la hepatită ischemică (sau hipoxică acută), cu creșteri marcate ale enzimelor hepatice și prognostic nefavorabil. Activarea RAAS și SNS agravează afectarea hepatică și inflamația sistemică. Edemul intestinal și disbioza amplifică axa intestin-ficat-inimă, contribuind la cașexie și progresia bolii. Interacțiunile cardiohepatice influențează semnificativ evoluția IC. Recunoașterea precoce a disfuncției hepatice este esențială, iar o abordare multidisciplinară poate îmbunătăți prognosticul și reduce complicațiile.

Cuvinte-cheie: *insuficiență cardiacă, hepatopatie congestivă, hepatită ischemică, sindrom cardiohepatic*

Резюме

Сердечная недостаточность и заболевания печени: кардиогепатические взаимодействия

Сердечная недостаточность (СН) — это сложный клинический синдром, затрагивающий различные органы, включая печень. Взаимосвязь между сердцем и печенью является двусторонней и часто недооценивается; при этом венозный застой и гипоперфузия печени существенно способствуют увеличению заболеваемости и смертности. Понимание этих взаимодействий имеет решающее значение для диагностики и лечения. Целью исследования было изучение основных патофизиологических механизмов, клинического значения и диагностических сложностей, связанных с поражением печени при сердечной недостаточности. Был проведён систематический обзор научной литературы, посвящённой взаимосвязи между сердечной недостаточностью и поражением печени, с особым вниманием к застойной гепатопатии, ишемическому (гипоксическому) гепатиту и общим кардиогепатическим взаимодействиям. Повышенное центральное венозное давление при правожелудочковой СН вызывает застой в печени, расширение синусоидов, атрофию гепатоцитов и фиброз (застойная гепатопатия). В тяжёлых случаях может развиться кардиоцирроз. Резкое снижение сердечного выброса, особенно при декомпенсированной СН, может привести к ишемическому (гипоксическому) гепатиту, сопровождающемуся значительным повышением уровня печеночных ферментов и неблагоприятным прогнозом. Активация ренин-ангиотензин-альдостероновой

системы (РААС) и симпатической нервной системы (СНС) усугубляет поражение печени и системное воспаление. Отёк кишечника и дисбиоз усиливают ось кишечник–печень–сердце, способствуя развитию кахексии и прогрессированию заболевания. Кардиогепатические взаимодействия существенно влияют на течение сердечной недостаточности. Раннее выявление печеночной дисфункции имеет ключевое значение, а мультидисциплинарный подход может улучшить прогноз и снизить частоту осложнений.

Ключевые слова: *сердечная недостаточность, застойная гепатопатия, ишемический гепатит, кардиогепатический синдром*

Introduction

Heart failure (HF) and liver disease frequently coexist due to complex cardiohepatic interactions as well as shared systemic conditions such as alcohol use disorder, drug toxicity, inflammation, autoimmune diseases, and infections. Consequently, patients with both acute and chronic HF often exhibit hepatic dysfunction. Liver dysfunction resulting from heart failure significantly worsens prognosis and poses additional challenges in the clinical management of heart failure.

The interdependence between the cardiac and hepatic systems creates a vicious cycle: cardiac dysfunction contributes to hepatic injury, while liver pathology promotes systemic inflammation, metabolic dysregulation, and coagulopathy, all of which further compromise cardiovascular function. This bidirectional relationship poses significant therapeutic challenges. Liver impairment can alter drug metabolism, limit therapeutic options, and increase the risk of complications such as fluid overload, thrombosis, and arrhythmias [1].

Moreover, hepatic dysfunction in the context of HF is associated with adverse clinical outcomes, including increased hospitalizations, a higher risk of multi-organ failure, and significantly elevated mortality. Despite its prognostic importance, hepatic involvement in HF is frequently underrecognized and undertreated—largely due to its nonspecific clinical presentation and the absence of standardized diagnostic criteria. The low sensitivity of existing screening tools often leads to delayed diagnosis and treatment, further worsening prognosis.

A clear understanding of the mechanisms through which hepatic dysfunction contributes to HF progression is essential for developing effective therapeutic strategies and improving patient outcomes. As the global burden of HF continues to rise, there is an urgent need for an integrated, multidisciplinary approach that combines cardiovascular and hepatological care to optimize prognosis and reduce complications [1, 2].

The aim of the research was to investigate the underlying pathophysiological mechanisms, clinical significance, and diagnostic complexities associated with hepatic involvement in heart failure.

Material and Methods

A structured and comprehensive literature review was conducted to explore the interrelationship between heart failure (HF) and liver disease, with a particular focus on congestive hepatopathy, ischemic hepatitis, and overall cardiohepatic interactions. The databases PubMed, Scopus, and Web of Science were systematically searched for relevant literature published between 2018 and 2025.

The following keywords and Medical Subject Headings were used in various combinations: *"heart failure," "congestive hepatopathy," "ischemic hepatitis", "cardiohepatic syndrome," "cardiohepatic interaction", "liver dysfunction.*

Results

The liver is particularly vulnerable to reductions in blood flow, as it receives up to 25% of the cardiac output. Cardiac hepatopathy typically occurs in the setting of acute or chronic heart failure. However, a clear-cut distinction between acute and chronic forms is not always possible, as clinical and pathophysiological features of both may coexist. Since liver dysfunction can significantly influence the prognosis and clinical course of cardiac disease—and is reversible only through interventions that improve cardiac function—early detection and accurate diagnosis of cardiac hepatopathy are essential [3].

Hepatic congestion may be caused by any cause of right heart failure (RHF), i.e., cardiomyopathy, mitral stenosis, tricuspid regurgitation (TR), and constrictive pericarditis. The two main mechanisms of cardiac hepatopathy are passive congestion secondary to increased systemic venous pressure and arterial perfusion decrease, both with harmful effects enhanced by associated hypoxia. Acute heart failure leading to hypoxic hepatitis is mainly due to arterial hypo perfusion, while congestive hepatopathy (CH) due to chronic heart failure is mainly due to passive congestion (Figure 1). Focal liver cell necrosis can spread peripherally in case of persistence and exacerbation of heart failure. This is followed by deposition and connective tissue development between the two major veins, which subsequently results in cirrhosis[4].

Rappaport's key contribution to the understanding of hepatic microarchitecture was the introduction of the acinar model. In this model, each hexagonal hepatic lobule contains six acinar units arranged around a central portal tract, which

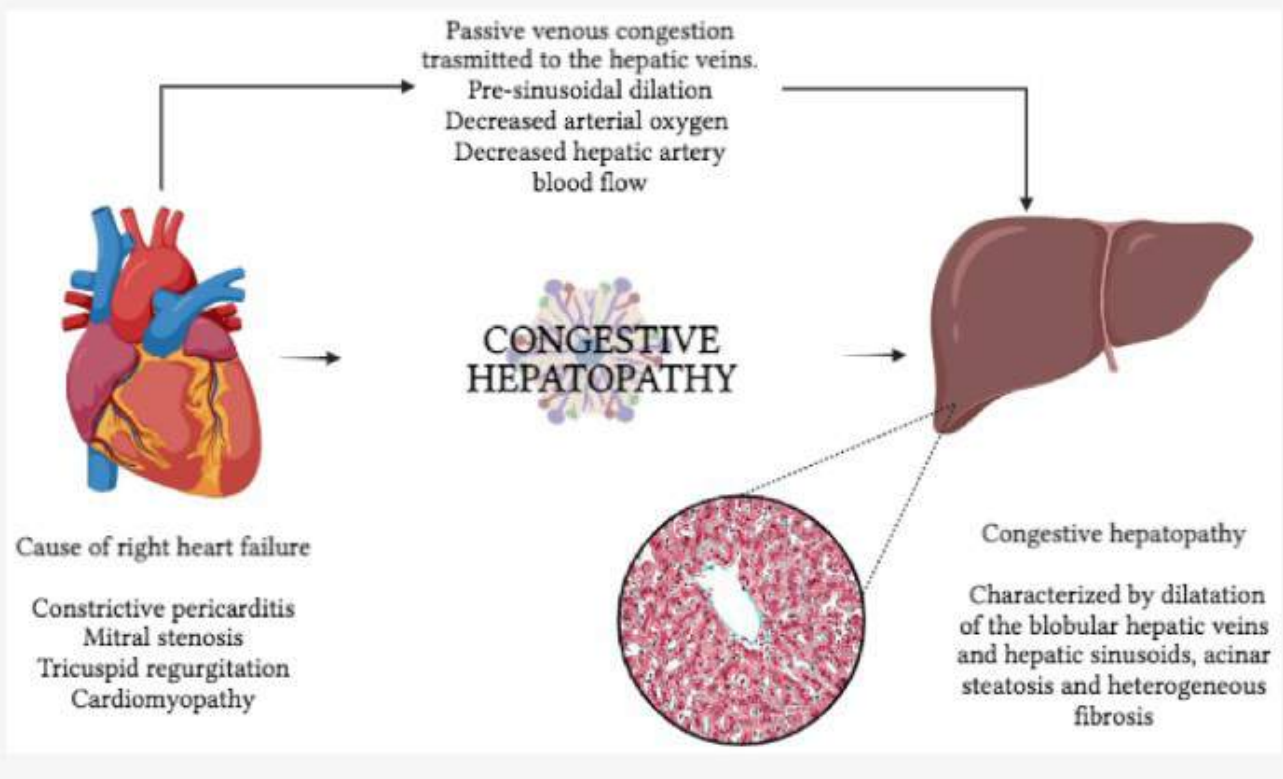

Figure 1: *Pathophysiology of hepatic congestion in Heart Failure [6]*

includes branches of the portal vein (PV), hepatic artery (HA), and bile duct (BD). Hepatocytes closest to the portal tract—known as zone 1—receive the most oxygenated blood. Oxygen levels gradually decline through zone 2 and reach their lowest in zone 3, near the terminal hepatic venules (THVs), reflecting a gradient that also corresponds to shifts in metabolic activity [5].

A noteworthy aspect of this model is the identification of watershed regions, which Rappaport named the "nodal points of Mall," in recognition of Franklin Mall's earlier work on hepatic structure. These regions represent the junctions where opposing portal and hepatic circulations merge into capillary networks [7].

Visualizing portal tract-centered zonation remains challenging, particularly given the long-standing dominance of Kiernan's classic hepatic lobule model, which is centered around the hepatic vein. To further refine this model, a modern conceptual framework known as the "Hepatology Snapshot" integrates the idea of zonation not only in terms of oxygen distribution but also in relation to specific metabolic functions—such as glycolysis, bile acid synthesis, xenobiotic clearance, gluconeogenesis, and protein secretion—as well as the roles of non-parenchymal cells, including endothelial, stellate, and Kupffer cells. This zonal approach also helps to explain patterns of damage observed in various liver diseases [8].

Congestive hepatopathy (CH) is a common complication in patients with chronic heart failure (CHF), with studies reporting that approximately 20–30% of individuals with CHF progress to CH [8]. This significant association underscores the clinical relevance of hepatic involvement in the context of heart failure and highlights the need for early recognition and timely intervention. Despite its impact on patient outcomes, CH is frequently underdiagnosed, largely due to its often subclinical presentation, which may obscure its contribution to disease progression.

CHF initiates a cascade of hemodynamic disturbances that gradually impair hepatic perfusion, ultimately resulting in hepatocellular injury and functional hepatic impairment. Key pathophysiological factors contributing to the development of CH include elevated central venous pressure, sinusoidal congestion, hepatocellular damage and inflammation, as well as activation of hepatic stellate cells. This cellular activation promotes fibrogenesis, leading to progressive hepatic fibrosis and further decline in liver function [9]stemming from compromised hepatic venous flow or heightened intrahepatic pressure, represents a significant consequence of cardiovascular conditions like congestive heart failure (CHF.

The onset of congestive hepatopathy arises from hemodynamic disturbances secondary to CHF, primarily characterized by elevated central venous

pressure due to reduced cardiac output and systemic venous congestion. This increased pressure is transmitted through the hepatic venous system, impairing the liver's normal venous drainage. As a result, sinusoidal congestion develops, leading to blood stasis within the hepatic sinusoids, hepatocellular hypoxia, and subsequent metabolic dysfunction.

The ongoing dilation of hepatic sinusoids, along with microvascular congestion, exacerbates hepatic perfusion deficits. This significantly impairs the delivery of oxygen and essential nutrients to hepatocytes, contributing to progressive hepatocellular injury and functional deterioration [10].

Chronic hepatic congestion contributes to progressive hepatocellular dysfunction, impairing essential liver functions such as protein synthesis, detoxification, and metabolic homeostasis. Blood flow stasis and resulting hypoxia trigger the upregulation of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and transforming growth factor-beta (TGF-β). These cytokines play a central role in promoting oxidative stress and initiating signaling cascades that exacerbate hepatocellular injury and stimulate hepatic fibrogenesis. Sustained inflammation perpetuates liver damage and is a key contributor to the pathogenesis of chronic liver disease, including chronic hepatitis [9,11]stemming from compromised hepatic venous flow or heightened intrahepatic pressure, represents a significant consequence of cardiovascular conditions like congestive heart failure (CHF.

Fibrogenesis and Structural Modulation

Chronic liver injury leads to the activation of hepatic stellate cells (HSCs), which transdifferentiate into myofibroblasts. These cells contribute to the excessive deposition of collagen and other extracellular matrix components, driving the process of fibrogenesis. As a result, the liver's architectural framework is progressively altered, intrahepatic vascular resistance increases, and portal hypertension develops. Portal hypertension has numerous consequences, including the formation of ascites and varices, as well as worsening hepatic congestion. Additionally, chronic injury induces sinusoidal capillarization, characterized by the loss of fenestrations in the liver sinusoids. This transformation imparts a continuous, capillary-like morphology to the sinusoids, further impairing hepatic microcirculation and hepatocyte metabolic function[12, 13]stemming from compromised hepatic venous flow or heightened intrahepatic pressure, represents a significant consequence of cardiovascular conditions like congestive heart failure (CHF.

In the advanced stages of congestive heart failure (CHF), the combined effects of chronic hepatic congestion and reduced perfusion lead to hepatocellular injury and ischemic necrosis. This further impairs liver function and, in the terminal phase of the disease, may culminate in acute liver failure, thereby complicating the clinical course of CHF [14] stemming from compromised hepatic venous flow or heightened intrahepatic pressure, represents a significant consequence of cardiovascular conditions like congestive heart failure (CHF.

The Relationship Between Hepatic and Systemic Dysfunction

The pathological processes of CHF are intricately linked with both cardiac and systemic dysfunction. Reduced cardiac output leads to systemic hypoperfusion, exacerbating hepatic ischemic injury. Additionally, chronic inflammation and oxidative stress inherent to CHF contribute to hepatocellular damage and promote the progression of hepatic fibrosis. This interplay between progressive cardiac and hepatic dysfunction establishes a vicious cycle, underscoring the importance of early detection and timely therapeutic intervention [15]stemming from compromised hepatic venous flow or heightened intrahepatic pressure, represents a significant consequence of cardiovascular conditions like congestive heart failure (CHF.

Liver congestion is characterized by an increase in liver size, a purplish or reddish discoloration, and prominent radiating hepatic veins observable on physical examination. Morphological changes within the liver parenchyma are readily apparent. The hepatic arteries within the lobules are initially affected by the elevated hepatic venous pressure, which leads to the dilation of the surrounding fenestrated sinusoidal structure. Chronic perivenular congestion leads to localized steatotic changes and atrophy or necrosis of the centrilobular hepatic parenchyma. Over time, chronic congestion with progressive accumulation of collagen within the sinusoids results in the expansion of fibrous septa that connect neighboring central veins. This characteristic pattern of fibrosis produces a histopathological appearance referred to as 'reverse lobulation' of the liver. Pathologically, the term Nutmeg liver refers to the speckled appearance of the cut liver in chronic venous congestion, due to dilated and congested red central veins surrounded by paler, unaffected liver tissue (resembling a grated nutmeg kernel). Nutmeg liver is most commonly associated with right-sided heart failure. This diagnosis can be supported by additional imaging features such as retrograde opacification of the hepatic veins, hepatomegaly, enlarged cardiomegaly, pleural effusions, ascites, and periportal edema [15,16]. In cases of pericardial disease, find-

ings may include pericardial effusion, thickening, or calcification. Nutmeg liver is also typically observed in the subacute or chronic stages of Budd-Chiari syndrome. In these cases, it may be accompanied by absent or narrowed hepatic veins and intrahepatic inferior vena cava, hypertrophy of the caudate lobe, atrophy of the peripheral liver parenchyma, and the presence of intrahepatic collateral vessels [17].

Additionally, chronic intrahepatic venous stasis may increase the risk of intrahepatic thrombi, which can hasten fibrosis and ultimately result in cirrhosis. Protein-rich fluid may also exude into the Disse space as a result of sinusoidal congestion. Excess fluid in the Disse gap is generally drained into hepatic lymphatics. However, if the lymphatic capacity is exceeded, high-protein fluid may flow from the liver's surface and drain into the peritoneal cavity. This mechanism separates cardiac ascites from other forms of ascites and results in high-protein-concentration ascites, usually >2.5 g/dL. The relatively high protein concentration in cardiac ascites may be explained by the comparatively mild elevation in portal pressure seen in these patients, as well as by the better preserved hepatic synthetic function, in contrast to the lower protein levels typically found in patients with intrinsic cirrhosis, where synthetic capacity is more severely impaired. It's interesting to note that hepatic steatosis, which is common in patients with cardiac hepatopathy due to concomitant diseases such diabetes, obesity, and hyperlipidemia, makes the liver more vulnerable to ischemia renal damage [17,18].

Cardiogenic ischemic hepatitis

Cardiogenic ischemic hepatitis, also referred to as acute cardiogenic liver injury, is a clinical and pathological condition marked by a sudden and temporary elevation in serum transaminases. This occurs as a result of an acute decrease in cardiac output, which significantly reduces hepatic perfusion. According to estimates, 20–30% of patients with acute heart failure develop cardiogenic ischemic hepatitis [19]. The pathophysiology of this acute liver injury is primarily driven by alterations in hepatic blood flow. Under normal conditions, approximately 20% of the cardiac output is directed to the liver, supplied through both the hepatic artery and the portal vein. A reduction in cardiac output results in decreased portal venous flow, triggering an increase in adenosine production by hepatocytes and Kupffer cells. Elevated adenosine levels promote dilation of the hepatic artery through an autoregulatory mechanism known as the hepatic arterial buffer response, which appears to serve a protective role [20].

Acute cardiogenic liver injury commonly occurs in the context of acute coronary syndromes, arrhythmias, or severe but transient hypotensive episodes. Retrospective studies suggest that hepatic venous congestion due to acute right-sided heart failure increases susceptibility to ischemic liver damage during hypotensive events. Hepatic oxygenation is further impaired in cardiogenic shock, where reduced systemic vascular resistance and elevated mean pulmonary capillary wedge pressure lead to diminished hepatic perfusion [21,22]. Clinical investigations have highlighted that the combination of passive hepatic congestion and reduced arterial perfusion are key contributors to the development of this condition. These findings underscore the pivotal role of right-sided heart failure and systemic hypoperfusion in the pathophysiology of ischemic hepatitis [23].

Cirrhotic Cardiomyopathy

Cirrhotic cardiomyopathy (CCM) is recognized in cirrhotic patients as a syndrome featuring reduced myocardial contractile reserve under stress, diastolic impairment, and electrophysiological abnormalities—all in the absence of any primary heart disease. Although frequently overlooked or diagnosed late, CCM may be present in as many as half of individuals with cirrhosis [24].

In patients with cirrhosis, ventricular ejection fraction during exertion is notably reduced compared to non-cirrhotic individuals. This attenuated response is primarily attributed to impaired chronotropic competence and diminished myocardial contractility under stress conditions [25].

Altered β-adrenergic receptor function at the cardiomyocyte membrane has been implicated in the reduced myocardial responsiveness observed in patients with cirrhosis. Prolonged exposure to elevated levels of noradrenaline—commonly seen in cirrhosis due to heightened sympathetic activity leads to internalization, sequestration, and downregulation of β-adrenergic receptors on the cell surface competence and diminished myocardial contractility under stress conditions [26,27].

Diastolic dysfunction is regarded as an early indicator of cirrhotic cardiomyopathy, often preceding the onset of systolic impairment. It is defined by a reduction in both the rate and extent of left ventricular relaxation, accompanied by elevated end-diastolic filling pressures. In contrast to systolic dysfunction, which typically becomes apparent under stress, diastolic abnormalities can be detected on echocardiography even at rest [26, 28].

It has been proposed that disruptions in the cardiac β-adrenergic signaling pathway lead to reduced activity of protein kinase A (PKA), which in

turn may impair the phosphorylation of titin, resulting in increased passive stiffness of the left ventricle. Furthermore, diminished PKA levels can decrease the phosphorylation of cardiac troponin I (cTnI), a process essential for facilitating calcium dissociation from cardiac troponin C (cTnC), thereby potentially slowing myocardial relaxation.

Liver cirrhosis has been linked to altered expression of collagen isoforms in ventricular myocardium, a change that correlates with the development of diastolic dysfunction. Studies in cirrhotic rat models have demonstrated an increased presence of type I collagen in ventricular tissue compared to controls, which significantly contributes to diastolic impairment by enhancing passive myocardial stiffness[25].

Diagnostic Approach

Given the often-subclinical nature of cirrhotic cardiomyopathy, diagnosis requires an integrated approach that includes clinical evaluation, laboratory testing, electrocardiography, and cardiac imaging. Electrocardiographic findings may reveal QT interval prolongation and arrhythmias in affected individuals. Echocardiographic assessment of left ventricular systolic function may demonstrate a reduced ejection fraction either at rest or in response to catecholamine stimulation, indicating latent systolic dysfunction. Diastolic dysfunction is typically characterized by diminished early ventricular filling (E wave), increased atrial filling (A wave), resulting in an E/A ratio of less than 1.0, along with a prolonged deceleration time (greater than 200 ms) and extended isovolumetric relaxation time (IVRT exceeding 80 ms).

Cardiac biomarkers such as cardiac troponin I (cTnI), B-type natriuretic peptide (BNP), and N-terminal pro-BNP may be elevated in the early stages of CCM and are often reflective of the underlying severity of liver disease [29,30].

Discussions

In the context of heart failure, the impact on hepatic function is increasingly recognized as clinically significant. The bidirectional relationship between cardiac dysfunction and hepatic congestion contributes to a pathophysiological feedback loop that exacerbates disease severity and complicates patient management. Reduced cardiac output, along with elevated central venous pressure—particularly in right-sided HF—results in hepatic venous congestion, which in turn promotes hepatocellular injury and impairs liver function **[**31]**.** This cardiohepatic interaction not only accelerates the progression of both cardiac and hepatic dysfunction**,** but also contributes to increased morbidity and a poorer overall prognosis. Timely recognition of hepatic involvement in HF is essential for comprehensive management and may lead to the development of more targeted therapeutic strategies. As venous congestion worsens, it leads to hepatomegaly and ascites, gradually impairing liver function. Clinically, this manifests as abnormal liver function tests, jaundice, and coagulopathy. Prolonged hepatic congestion can ultimately result in congestive hepatopathy, hepatic fibrosis, and, in advanced cases, cardiac cirrhosis and liver failure [32].

In parallel, reduced hepatic perfusion, particularly during episodes of systemic hypotension or cardiogenic shock, can cause ischemic hepatitis (or "shock liver"), characterized by hepatocellular injury and necrosis due to inadequate oxygen delivery. Furthermore, HF has a detrimental impact on the gastrointestinal system. Systemic venous congestion and hypoperfusion contribute to intestinal edema, which increases bowel wall thickness, impairs motility, and disrupts digestion. This leads to malabsorption of key nutrients, including fats, proteins, and vitamins [33].

The mechanisms linking heart failure (HF) to liver dysfunction are multifactorial and involve a complex interplay of hemodynamic alterations, neurohormonal activation, and systemic inflammation [34]. One of the principal contributors is elevated central venous pressure, particularly in the setting of right-sided HF, which leads to hepatic and intestinal congestion. The liver, being highly sensitive to venous pressure, undergoes sinusoidal dilation, hepatocellular hypoxia, and progressive fibrosis, culminating in congestive hepatopathy and, in advanced stages, cardiac cirrhosis [35].

Neurohormonal activation also plays a central role in the development of liver dysfunction in HF. Persistent stimulation of the renin-angiotensin-aldosterone system (RAAS), a compensatory response to preserve blood pressure and organ perfusion, has deleterious consequences. Elevated levels of aldosterone and angiotensin II promote sodium and water retention, aggravating systemic and splanchnic congestion. This worsens hepatic venous pressure, intestinal edema, and nutrient malabsorption. Moreover, angiotensin II, a potent vasoconstrictor, reduces hepatic and splanchnic perfusion, contributing to hepatocellular ischemia. Beyond their hemodynamic effects, both aldosterone and angiotensin II exert pro-fibrotic and pro-inflammatory actions, stimulating extracellular matrix deposition in the liver and gut. This promotes hepatic fibrosis, increased intestinal permeability, and further bacterial translocation [36].

Excessive activation of the sympathetic nervous system (SNS) in heart failure further contributes to splanchnic vasoconstriction, thereby exacerbating the

reduction in hepatic and intestinal perfusion. Chronic splanchnic hypoperfusion can result in intestinal ischemia, delayed gastric emptying, and impaired nutrient absorption, which collectively contribute to malnutrition and the development of cardiac cachexia—both recognized as adverse prognostic indicators in patients with HF. Moreover, sustained SNS overactivity has been implicated in alterations of the gut microbiota, leading to a state of dysbiosis characterized by an imbalance between beneficial and pathogenic microbial populations [37].

Over time, these changes may culminate in cardiac cirrhosis, characterized by pericentral fibrosis and impaired hepatic function. Clinically, this is reflected by elevated liver enzymes particularly alkaline phosphatase and gamma-glutamyl transferase—alongside hyperbilirubinemia and jaundice due to disrupted bilirubin metabolism. The liver's synthetic function is also compromised, resulting in coagulopathy from reduced clotting factor production and hypoalbuminemia, which in turn contributes to worsened fluid overload, ascites, and systemic congestion. These derangements establish a self-perpetuating cycle that exacerbates HF symptoms and complicates overall disease management.

In addition to chronic hepatic congestion, patients with acute decompensated heart failure particularly susceptible to ischemic hepatitis (shock liver), a condition marked by acute hepatic hypoperfusion due to systemic hypotension and severely reduced cardiac output. Ischemic hepatitis is clinically recognized by a sudden and pronounced elevation in aminotransferases (AST and ALT >1000 IU/L), often accompanied by lactic acidosis, hyperbilirubinemia, and encephalopathy in severe cases. Its presence is an ominous sign of advanced cardiac dysfunction and hemodynamic instability, and if not rapidly corrected, may progress to acute liver failure, significantly increasing mortality [38].

Conclusion

The heart and liver share a close physiological relationship, where dysfunction in one organ can adversely impact the other. The two primary mechanisms linking heart failure to liver injury are hepatic hypoperfusion and venous congestion, both contributing to acute and chronic hepatic damage. Additionally, cirrhotic cardiomyopathy, marked by systolic, diastolic, and electrophysiological abnormalities, exemplifies how liver disease can impair cardiac function.

Emerging evidence highlights the role of altered nuclear receptor signaling (LXR) and the gut–liver axis in the progression of heart failure and its comorbidities. Since the liver is the first organ to encounter gut-derived toxins, the gut–liver–heart connection has become an important area of investigation.

Despite advances, the management of cardiohepatic interactions remains complex, requiring a multidisciplinary and system-based therapeutic approach.

Declarația de conflict de interese

Autorii declară lipsa conflictului de interese.

Bibliography

1. GONZALES DE KOEHNE K. A., LEFKOWITCH J. H. Heart Disease and the Liver: Pathologic Evaluation. In: Gastroenterol. Clin. North Am., vol. 46, no. 2, pp. 421-435, Jun. 2017.
2. HADI El HAMZA, VINCENZO DI A. et al. Relationship between Heart Disease and Liver Disease: A Two-Way Street. In: Cells, 2020, 9(3), 567
3. LOUIE C. Y., PHAM M. X., DAUGHERTY TAMI J. et al. The liver in heart failure: a biopsy and explant series of the histopathologic and laboratory findings with a particular focus on pre-cardiac transplant evaluation. In: Mod. Pathol. 2015; 28(7): 932-43. doi: 10.1038/modpathol.2015.40.
4. POELZL G, ESS M, MUSSNER-SEEBER C. et al. Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance. In: Eur J Clin Investig., 2012; 42:153–63
5. RAPPAPORT, GLISSON, HERING et al. Microscopic and Ultramicroscopic Anatomy of the Liver Into the Modern Age. In: Clin Liver Dis.,2021 Oct 29;18(Suppl 1):76–92
6. ASPROMONTE N., FUMARULO I. et al. The Liver in Heart Failure: From Biomarkers to Clinical Risk. In: Int *J. Mol. Sci., 2023,* Oct 27;24(21):15665.
7. MANCO R, ITZKOVITZ S. Liver zonation. In: *J Hepatol* 2021, Feb;74(2):466-468.
8. LAU C., B KALANTARI B., BATTS K. P. et al. The Voronoi theory of the normal liver lobular architecture and its applicability in hepatic zonation. In: Sci Rep., 2021, 29;11:9343.
9. HADDADIN R, ABOUJAOUDE C., TRAD G. Congestive Hepatopathy: A Review of the Literature. In: Cureus. 2024;16(4):e58766.
10. SESSA A., ALLAIRE M. et al., From congestive hepatopathy to hepatocellular carcinoma, how can we improve patient management? In: JHEP Rep. Innov. Hepatol., 2021, 27;3(2):100249.
11. LOUIE C. Y., PHAM M. X. et al. The liver in heart failure: a biopsy and explant series of the histopathologic and laboratory findings with a particular focus on pre-cardiac transplant evaluation. In: Mod. Pathol. 2015;28(7):932-43. doi: 10.1038/modpathol.2015.40.
12. DAI D.F., SWANSON P. E. et al. Congestive hepatic fibrosis score: a novel histologic assessment of clinical severity. In: Mod. Pathol.,2014. Dec; 27(12):1552-8. doi: 10.1038/modpathol.2014.79.
13. FORTEA J. I. et al., Congestive Hepatopathy. In: Int. J. Mol. Sci., 2020, 10; 21(24): 9420.
14. SUNDARAM V., FANG J. C. Gastrointestinal and Liver Issues in Heart Failure. In: Circulation. 2016, vol. 133, no. 17, pp. 1696–1703.

15. HADI EL H., VINCENZO DI A., VETTOR R. Relationship between Heart Disease and Liver Disease: A Two-Way Street. In: Cells., 2020, 28;9(3):567. doi:10.3390/cells9030567
16. LI YL, LEE KH, CHENG AK, YU ML. Nutmeg liver. In: Abdom Radiol., 2018 May; 43(5):1275-1276.
17. COAKLEY V. FERGUS In: Pearls and Pitfalls in Abdominal Imaging Pseudotumors, Variants and Other Difficult Diagnoses, 2011, pp. 34 – 39
18. CHUNG C., IWAKIRI Y., The lymphatic vascular system in liver diseases: its role in ascites formation. In: Clin Mol Hepatol., 2013 Jun 27;19(2): 99–104.
19. HARJOLA V-P., MULLENS W., BANASZEWSKI M., BAUERSACHS J., ROCCA H., CHIONCEL et al. Organ dysfunction, injury and failure in acute heart failure: From pathophysiology to diagnosis and management. A review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). In: *Eur. J. Heart Fail.,* 2017; 19 (7):821–836.
20. EIPEL C., ABSHAGEN K., VOLLMAR B. Regulation of hepatic blood flow: The hepatic arterial buffer response revisited. In: *World J. Gastroenterol.*,2010;116(48): 6046–6057.
21. SEETO R.K., FENN B., ROCKEY D.C. Ischemic hepatitis: Clinical presentation and pathogenesis. In: *Am. J. Med.,* 2000 Aug 1;109(2):109-13.
22. BIRRER R., TAKUDA Y., TAKARA T. Hypoxic hepatopathy: Pathophysiology and prognosis. In: *Intern. Med.* 2007; 46 (14):1063–1070
23. WIESE S., HOVE J., BENDTSEN F., MØLLER S. Cirrhotic cardiomyopathy: Pathogenesis and clinical relevance. In: *Nat. Rev. Gastroenterol. Hepatol.,* 2014 Mar;11(3):177-86.
24. DÜMCKE C.W., MØLLER S. Autonomic dysfunction in cirrhosis and portal hypertension. In: *Scand. J. Clin. Lab. Investig*., 2008; 68(6):437-47.
25. MØLLER S., DÜMCKE C.W., KRAG A. The heart and the liver. In: *Expert. Rev. Gastroenterol. Hepatol*., 2009, 3(1):51–64.
26. DESHPANDE, D. A., THERIOT, B. S., et al. β-Arrestins specifically constrain β2-adrenergic receptor signaling and function in airway smooth muscle. FASEB J., 2008, 22, 2134–2141
27. SASU D., GAVRILIUC, S., ISTRATI, V. Diabetic cardiomyopathy and diastolic heart failure. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale,* 2019, nr. 2(62), pp. 104-110. ISSN 1857-0011.
28. CHETRUS O., CALIN G, SIRBU O., SASU D., GAVRILIUC S., ISTRATI V. Influence of the cytoprotective drug meldonium on diastolic dysfunction of the myocardium. In: *Mold Med J.* 2022;65(1):24-28.
29. SASU D., POPESCU L., CARAUŞ A. Disfuncţia diastolică şi insuficienţa cardiacă cu fracţia de ejecţie păstrată – generalităţi fiziopatologice şi de tratament. In: *Arta Medica,* 2011, nr. 4(47), pp. 25-28. ISSN 1810-1852.
30. POPESCU L., CARAUŞ A., SASU D. Insuficienta cardiaca cu fracţia de ejecţie preservată: aspecte noi in epidemiologie, fiziopatologie şi tratament. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale,* 2020, nr. 1(65), pp. 128-139. ISSN 1857-0011.
31. WEI H, Wu J, WANG H, HUANG J, Li C, ZHANG Y, et al. Increased circulating phenylacetylglutamine concentration elevates the predictive value of cardiovascular event risk in heart failure patients. In: *J Intern Med.,* 2023;294(4):515-530. doi: 10.1111/joim.13653.
32. ROGLER G., ROSANO G. The heart and the gut. In: *Eur. Heart J.* ,2014, vol. 35, issue 7, pages 426–430.
33. MARTINA E. SPEHLMANN, ASHRAF Y., RANGREZ et al. Heart Failure Severity Closely Correlates with Intestinal Dysbiosis and Subsequent Metabolomic Alterations. In: *Biomedicines.*,2022 Mar 30;10(4):809
34. ZABELL A., TANG W. H., Targeting the Microbiome in *Heart Failure.In: Curr. Treat. Options Cardiovasc. Med.,* 2017 Apr19(4): 27.
35. KUMMEN M, MAYERHOFER C. K., VESTAD B. et al. Gut microbiota signature in heart failure defined from profiling of 2 independent cohorts. In: *J Am Coll Cardiol* 2018; Mar 13;71(10):1184-1186.
36. KITAI T., TANG W. H.W. Gut microbiota in cardio-vascular disease and heart failure. In: *Clin Sci (Lond).*,2018 Jan 11; 132(1):85-91.
37. HARTUPEE J., MANN D. L. Neurohormonal activation in heart failure with reduced ejection fraction. In: *Nat. Rev. Cardiol.* 2017 Jan;14(1):30-38. doi: 10.1038/nrcardio.2016.163.
38. MANOLIS A. A., MANOLIS T. A., MANOLIS A. S. Neurohumoral Activation in Heart Failure. In: *Int. J. Mol. Sci.*, 2023, *24*(20), 15472

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