Ethiopian International Journal of Multidisciplinary Research

pISSN:2349-5707 Volume:12,Issue 12,December-2025 eISSN:2349-5715

THE DIAGNOSTIC PRINCIPLES FOR CIRRHOTIC CARDIOMYOPATHY.

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Abstract: Cirrhotic cardiomyopathy (CCM) is a specific form of cardiac dysfunction that develops in patients with liver cirrhosis and significantly affects clinical outcomes. Despite preserved or increased cardiac output at rest, patients demonstrate impaired systolic and diastolic responses to stress, as well as characteristic electrophysiological abnormalities. The condition remains underdiagnosed due to its latent clinical course, yet it plays a crucial role in perioperative morbidity and mortality, particularly in candidates for liver transplantation. This article provides a comprehensive review of current management strategies for cirrhotic cardiomyopathy, including pathophysiological mechanisms, diagnostic approaches, conservative and pharmacological treatment options, and perioperative considerations.

Key words: cirrhotic cardiomyopathy, liver cirrhosis, cardiac dysfunction, management strategies, prognosis

Liver cirrhosis is a progressive chronic disease associated with significant structural and functional alterations in multiple organ systems. Among extrahepatic complications, cardiovascular dysfunction occupies a central position due to its impact on survival and treatment outcomes. Cirrhotic cardiomyopathy represents a distinct clinical entity characterized by impaired myocardial contractility under stress conditions, diastolic dysfunction, and electrophysiological abnormalities in the absence of underlying structural heart disease.The concept of cirrhotic cardiomyopathy was formally introduced in 2005; however, its clinical relevance has become increasingly apparent with the growing number of patients undergoing invasive procedures such as transjugular intrahepatic portosystemic shunt (TIPS) placement and liver transplantation[4,5]. The absence of specific symptoms in early stages contributes to delayed diagnosis and underestimation of disease prevalence.

The pathogenesis of CCM is complex and multifactorial. One of the central mechanisms involves dysregulation of β-adrenergic signaling pathways. In patients with cirrhosis, downregulation and desensitization of β-adrenergic receptors lead to a reduced myocardial response to catecholamines, thereby impairing contractile reserve. The progression from chronic liver disease to cirrhosis involves a series of maladaptive responses to chronic liver injury: inflammation, activation of hepatic stellate cells, and subsequent fibrogenesis and angiogenesis, alongside parenchymal extinction lesions resulting from microthrombi and vascular occlusion [1]. This sequence of events leads to significant microvascular changes in the liver, marked by sinusoidal remodeling, which includes extracellular matrix deposition from proliferating activated hepatic stellate cells, resulting in the loss of fenestrae, leading to the capillarization of hepatic sinusoids[2,3]. Moreover, this process promotes the formation of intrahepatic shunts, nodules of fibrosis, and hepatic endothelial dysfunction.

These histological abnormalities associated with cirrhosis disrupt the hepatic angioarchitecture, resulting in increased resistance to portal blood flow, which is a primum movens in the development of portal hypertension[6]. Moreover, disruption in the balance between intrahepatic vasoconstrictors and vasodilators results in predominant vasoconstriction, contributing to a dynamic, functional component of hepatic resistance that may lead to rapid changes in portal pressure [7,8]Nitric oxide is the most extensively studied vasoactive agent in the context of hepatic endothelial dysfunction. In cirrhotic livers, sinusoidal endothelial cells exhibit impaired nitric oxide production, primarily due to decreased activity of endothelial nitric oxide synthase. This reduction is attributed to insufficient protein kinase B-dependent phosphorylation, a lack of

pISSN:2349-5707 Volume:12,Issue 12,December-2025 eISSN:2349-5715

essential cofactors, elevated oxidative stress leading to increased nitric oxide scavenging, and elevated levels of endogenous nitric oxide inhibitors . Acute events, such as infections, may further suppress nitric oxide levels. This reduction in nitric oxide exacerbates hepatic resistance, thereby contributing to elevated portal pressure. Concomitantly, the production of vasoconstrictors—primarily driven by androgenic stimulation and thromboxane A2—is elevated, alongside activation of the renin–angiotensin system, antidiuretic hormone, and endothelin-1, all of which contribute to a further restriction of sinusoidal blood flow.

The initial elevation in portal pressure, driven by increased intrahepatic vascular resistance, leads to circulatory disturbances, most notably the development of splanchnic arterial vasodilation . In contrast to what happens in hepatic circulation, the production of nitric oxide by endothelial cells is amplified in splanchnic circulation as a result of vascular shear stress initially and later by disease exacerbation caused by bacterial translocation and sustained inflammatory response typical for advanced cirrhosis[9] Vasodilation within the splanchnic capillaries and arterioles increases portal venous inflow. When combined with elevated intrahepatic vascular resistance, this leads to a rise in portal pressure, culminating in the development of portal hypertension. Since the splanchnic vascular bed comprises about 25% of the total systemic vascular resistance, persistent splanchnic vasodilation decreases the effective arterial blood volume, leading to systemic hypotension and arterial underfilling. This, in turn, triggers the activation of neurohumoral vasoconstrictor systems, including the renin–angiotensin–aldosterone system, the sympathetic nervous system, and non-osmotic vasopressin secretion. These systems aim to counteract vasodilation, leading to sodium and water retention and an increase in plasma volume, predisposing patients to ascites, hyponatremia, kidney injury, infection, or hemorrhages[9]. Some of this excess plasma volume accumulates in the peritoneal cavity as ascites due to portal hypertension. Increased sinusoidal pressure induces ascites from increased lymph production, which extravasates into the peritoneum when the lymphatic drainage capacity is exceeded. As cirrhosis progresses, vasodilation intensifies, and systemic blood pressure continues to decline, with a maximal activation of vasoconstrictors. This cascade leads to marked vasoconstriction within the renal circulation, which can progress to hepatorenal syndrome, a form of acute kidney injury.

Systemic vasodilation can also contribute to pulmonary ventilation/perfusion mismatch, which, in severe cases, may result in hepatopulmonary syndrome (HPS) with arterial hypoxemia or portopulmonary hypertension due to increased pulmonary vasoconstriction. The expansion of plasma volume increases cardiac output, contributing to a hyperdynamic circulatory state[10]. This, combined with splanchnic vasodilation, augments portal venous inflow and exacerbates portal hypertension. The elevated portal pressure leads to a reversal in blood flow and, subsequently, the dilation of existing collateral channels at anatomical sites where the systemic and portal circulations intersect, such as the gastro-esophageal junction, and activates angiogenesis, which facilitates the formation of new collateral vessels, for which vascular endothelial growth factor (VEGF)-driven angiogenesis plays an important role.The most clinically relevant portosystemic collaterals are gastroesophageal varices. Variceal bleeding occurs when the intravariceal pressure surpasses the elastic capacity of the vessel wall. The risk of variceal bleeding is directly related to increased wall tension, which is influenced by portal pressure, variceal diameter, and the thinness of the variceal wall. Dilatation of the gastric mucosal vessels contributes to the development of portal hypertensive gastropathy. Moreover, the presence of portosystemic shunts, in conjunction with progressive hepatic dysfunction, plays a central role in the pathogenesis of HE by declining the first-pass metabolism of orally administered drugs, impairing endothelial function, and reducing the hepatic clearance of gut-derived ammonia. While the mechanisms are not fully understood, the presence of hepatic fibrosis alongside liver injury from inflammation contributes to genetic and epigenetic alterations that can lead to a progression into malignancy and the development of HCC.

pISSN:2349-5707 Volume:12,Issue 12,December-2025 eISSN:2349-5715

Pathophysiological evidence has long delineated portal hypertension with splanchnic and systemic vasodilation and a hyperdynamic circulatory state, as a central mechanism in the development of AD. Portal hypertension (PH) is defined as increased pressure within the portal vein. It is due to a rise in the hepatic venous pressure gradient (HVPG) due to increased intrahepatic vascular resistance and impaired hepatic sinusoidal circulation. PH, most frequently arising from CLD, is an important determinant of its disease course and prognosis. Clinically significant portal hypertension (CSPH) is a major milestone in the natural history of CLD. It is defined as an increase in HVPG to ≥10 mmHg. Above this threshold, the complications of portal hypertension might emerge .

Recent findings have integrated the concept of systemic inflammation—evidenced by the translocation of gut microbiota components, elevated oxidative stress levels, and increased circulating pro-inflammatory cytokines and chemokines—into the classical paradigms of AD .The bidirectional interaction between the gut and liver highlights the critical role of the gastrointestinal microbiome in the pathogenesis and progression of chronic liver disease, as well as in triggering decompensation events. Bile acids and liver-derived antimicrobial peptides play a critical role in regulating and shaping the composition and function of the gastrointestinal microbiota. Conversely, the portal vein serves as the primary conduit for the transport of gut-derived metabolites and microbial products to the liver. Among the principal etiological factors of chronic liver disease, alcohol consumption and dietary patterns not only induce direct local hepatic injury, triggering the release of damage-associated molecular patterns (DAMPs), but also contribute to the gut's microbial dysbiosis and increased gut permeability. This disruption facilitates the translocation of pathogen-associated molecular patterns (PAMPs) into the portal venous circulation, further perpetuating hepatic inflammation. In end-stage liver disease, these factors are often exacerbated by increased bacterial translocation and a diminished hepatic capacity to clear microbial products Bacterial translocation is facilitated by delayed intestinal transit, bacterial overgrowth, and increased gut permeability in the context of altered gut microbiota function and composition[11].

A growing body of evidence has emerged suggesting that cirrhosis is associated with alterations in gut microbiota composition, most notably marked by a loss of genetic diversity, a decline in autochthonous species, and an overrepresentation of potentially pathogenic and uncommon taxa like *Enterococcus* species[12]. These alterations worsen as cirrhosis progresses. Though mechanisms linking microbiota changes to disease progression are not fully understood, one hypothesis proposes that these alterations may compromise microbiota function, resulting in intestinal inflammation, disruption of the epithelial barrier, and increased intestinal permeability, thereby further aggravating bacterial translocation. The enrichment of pathogenic species may also lead to elevated endotoxemia, causing an increased systemic inflammation. This cascade of events can be attributed to the onset of circulatory dysfunction and directly promotes the progression of multi-organ dysfunction and failure.Altered intracellular calcium handling further contributes to myocardial dysfunction. Reduced calcium influx through sarcolemmal channels and impaired sarcoplasmic reticulum function result in decreased excitation–contraction coupling. In addition, changes in membrane fluidity due to altered lipid composition negatively affect receptor signaling and ion channel activity.Electrophysiological abnormalities, particularly prolongation of the QT interval, are commonly observed in CCM. These changes are attributed to altered potassium channel function, increased nitric oxide production, and inflammatory cytokine activity. Collectively, these mechanisms result in impaired systolic and diastolic function, increased susceptibility to arrhythmias, and reduced cardiovascular adaptability. Cirrhotic cardiomyopathy often remains clinically silent at rest. Symptoms typically emerge during physiological stress, such as exercise, infection, surgery, or volume overload. Patients may present with exertional dyspnea, fatigue, peripheral edema, or hypotension. Advanced stages of CCM are associated with an increased risk of heart failure, arrhythmias, and sudden cardiac death. Importantly, the condition significantly influences outcomes during liver

pISSN:2349-5707 Volume:12,Issue 12,December-2025 eISSN:2349-5715

transplantation, where the inability of the heart to adapt to sudden hemodynamic changes may result in acute cardiac decompensation.

At present, no specific therapy exists for cirrhotic cardiomyopathy. Management is primarily supportive and aimed at minimizing symptoms, preventing complications, and optimizing hemodynamic stability. A multidisciplinary approach involving hepatologists, cardiologists, and anesthesiologists is essential. Non-pharmacological measures include careful control of fluid balance, avoidance of excessive volume loading, sodium restriction, and close monitoring during invasive procedures. Optimization of liver disease management plays a key role in reducing cardiovascular stress. Pharmacological therapy should be individualized due to altered drug metabolism and hemodynamic instability in cirrhosis. Beta-blockers are widely used to reduce portal hypertension but should be prescribed cautiously, as they may further impair cardiac output in advanced CCM. Diuretics may be beneficial for volume control but require careful monitoring of renal function and electrolyte balance. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are generally avoided in advanced cirrhosis due to the risk of hypotension and renal dysfunction. Correction of electrolyte disturbances, particularly potassium and magnesium imbalances, is essential to prevent arrhythmias. Perioperative and Transplant Considerations Patients with cirrhotic cardiomyopathy undergoing liver transplantation are at increased risk of perioperative cardiac complications. Thorough preoperative cardiovascular assessment is mandatory. Intraoperative management should include continuous hemodynamic monitoring, and postoperative care must focus on early detection of cardiac dysfunction.Several studies have demonstrated partial or complete reversibility of cirrhotic cardiomyopathy following successful liver transplantation, emphasizing the functional and potentially reversible nature of the condition.Prognosis Cirrhotic cardiomyopathy adversely affects survival, particularly in patients with decompensated liver disease. Prolonged QT interval, elevated cardiac biomarkers, and impaired stress response are associated with poor outcomes. Early identification and careful management may improve prognosis and quality of life.

Conclusion Cirrhotic cardiomyopathy is a clinically significant but frequently underdiagnosed complication of liver cirrhosis. Early recognition, comprehensive cardiovascular assessment, and individualized management strategies are essential to improve patient outcomes. Further research is required to establish standardized diagnostic criteria and develop targeted therapeutic approaches

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