**Hepatic Hypoperfusion in Complex Cardiac Pathology: A Case of Ischemic Hepatitis Secondary to Congenital Heart Disease with HFpEF and Atrial Fibrillation**

**ABSTRACT**

Ischemic hepatitis (IH) is an acute liver injury caused by hepatic hypoperfusion, typically occurring in shock states. We present a 77-year-old woman with congenital heart disease (CHD), heart failure with preserved ejection fraction (HFpEF), and atrial fibrillation who developed IH without overt hypotension. She presented with dyspnea, weakness, and oliguria, accompanied by severe transaminitis (Aspartate Aminotransferase - AST 6602 U/L, Alanine Aminotransferase - ALT 3886 U/L), coagulopathy (International Normalized Ratio - INR 7.35), and lactic acidosis (lactate 6.8 mmol/L). Echocardiography revealed atrial fibrillation with rapid ventricular response, pulmonary hypertension, and valvular abnormalities. Management included rate control, diuresis, and hepatic support. Liver enzymes improved by day 4, confirming recovery. This case demonstrates that IH can occur in HFpEF patients with CHD and arrhythmia, even in the absence of profound hypotension. Early recognition and hemodynamic optimization are critical to prevent irreversible liver damage. This case report underscores IH as a potential complication in high-risk cardiac patients, necessitating vigilant monitoring and prompt intervention.

**KEYWORDS:** Ischemic hepatitis, HFpEF, congenital heart disease, atrial fibrillation, cardiogenic liver injury

**INTRODUCTION**

Ischemic hepatitis (IH), also known as shock liver or hypoxic hepatitis, is a diffuse liver injury caused by acute hypoperfusion. It typically follows episodes of hemodynamic instability or hypoxia, such as hemorrhage, sepsis, pulmonary embolism, heart failure, arrhythmias, acute myocardial infarction or severe respiratory distress. The condition is marked by a transient yet significant elevation of serum hepatic transaminases and is associated with centrilobular hepatic necrosis. Serum hepatic transaminase levels typically rise to 10–300 times the upper limit of normal and usually return to baseline within 5–25 days.1 In patients with chronic heart failure, severe Aspartate Aminotransferase/Alanine Aminotransferase (ALT/AST) elevation is less common unless accompanied by a low-output state. Ischemic hepatitis can occur in cardiogenic shock, typically in the setting of significantly reduced ejection fraction.2 Cardiogenic ischemic hepatitis, can develop after a severe hypotensive episode in patients with acute heart failure.3 In heart failure patients, liver damage may manifest as chronic congestive hepatopathy or ischemic hepatopathy, also known as acute cardiogenic liver injury (ACLI).4 Ischemic hepatitis can develop from diminished hepatic blood flow due to low cardiac output, even without overt shock.5 Several studies have pointed out that the hemodynamic changes in heart failure with preserved ejection fraction (HFpEF) were different from HFrEF. This case report highlights an occurrence of ischemic hepatitis in a patient with congenital heart disease, HFpEF and atrial fibrillation.

**CASE DESCRIPTION**

A 77-year-old female patient was admitted to ICU in the department of Cardiology with complaints of generalized weakness, acute dyspnea and oliguria. Her past medical history included hypothyroidism, Type 2 Diabetes Mellitus (T2DM), systemic arterial hypertension, dyslipidemia, persistent atrial fibrillation, congenital heart disease (CHD) and heart failure with preserved ejection fraction (HFpEF). Patient has no prior history of liver and pulmonary disease. The patient had been on multiple medications, including Tab Levothyroxine 150 mcg once daily, Tab Metoprolol succinate 50 mg twice daily, Tab Cilnidipine 10 mg once daily, Tab Atorvastatin 10 mg once daily, Tab Torsemide/Spironolactone 10/25 mg once daily, Tab Apixaban 5 mg twice daily, Tab Metformin 500 mg once daily and Tab fenofibrate 160 mg once daily.

On admission, cardiovascular examination revealed pansystolic murmurs, blood pressure 140/90 mmHg and a pulse rate of 112 bpm. ECG showed atrial fibrillation with fast ventricular response (AF with FVR). An echocardiography assessment showed congenital heart disease, subpulmonic ventricular septal defect with left-to-right shunt, interventricular gradient of 56 mmHg, dilated right atrium, left atrium and right ventricle, with an ejection fraction of 60%. Other findings included anterior mitral leaflet prolapse, grade 3 mitral regurgitation, mild aortic regurgitation, grade 3 tricuspid regurgitation, moderate pulmonary arterial hypertension, right ventricular systolic pressure of 54+ right atrial pressure mmHg, and a thin rim of pericardial effusion.

Pulmonary examination revealed air entry bilaterally equal, dyspnea on exertion, grade 2-3 dyspnoea, bilateral basal crepitations. Examination revealed dyspnoea secondary to cardiac illness. Chest X-ray revealed bronchovascular markings and cardiomegaly.

On admission, laboratory investigations as shown in Table 1 revealed markedly elevated liver function test (LFT) parameters, with aspartate aminotransferase (AST) at 353 U/L, alanine aminotransferase (ALT) at 224 U/L and alkaline phosphatase (ALP) at 60 U/L. Serum total bilirubin was 2.3 mg/dL, with direct bilirubin at 1.4 mg/dL. Electrolyte levels showed sodium at 131 mEq/L and potassium at 4.9mEq/L. Arterial blood gas (ABG) shows pH 7.29, pCO2 38 mmHg and lactate levels at 6.8 mmol/L. Hematology investigations showed total counts were elevated at 13020 cells/ul and Erythrocyte sedimentation rate (ESR) of 15 mmhr. C- reactive protein (CRP) was elevated to 13.5 mg/dl. Trop I levels showed elevation to 0.02 ng/ml and BNP was elevated to 876 pg/ml. Blood glucose values were elevated, with random blood sugar (GRBS) of 172 mg/dL. Urinalysis showed significant proteinuria (+++), RBCs (10-12/HPF), and a mild increase in pus cells (2-4/HPF), suggestive of possible renal involvement. Dengue IgM, leptoIgM, HBsAg, anti HCV, HIV, Anti HEV IgM and Hepatitis B were found to be negative.

On Day 2, prothrombin time (PT) and INR revealed highly elevated values of 89.1 and 7.35, Serum sodium remained at 134 mEq/L, while potassium was highly elevated to 6 mEq/L, after further management it was dropped further to 3.2 mEq/L. Blood glucose remained elevated, with fasting blood sugar (FBS) at 169 mg/dL and GRBS at 152 mg/d. Procalcitonin was elevated to 0.1 mcg/l.

By Day 3, repeat LFT showed hepatic enzyme elevation, with AST at 6602 U/L, ALT at 3886 U/L and ALP of 75 U/L. Total bilirubin levels were at 2.4 mg/dL with direct bilirubin at 1.4 mg/dL. LDH was elevated to 3342 U/L, GGT elevated to 59 U/L and S. CK to 229 U/L.

On day 4, LFT parameters showed a slight improvement, with AST decreasing to 2747 U/L, ALT to 2746 U/L and ALP 76U/L. Total bilirubin levels were at 2.6 mg/dL with direct bilirubin at 1.6 mg/dL. Electrolytes showed stabilization, with sodium and potassium were improved following supplementation and treatment.

During stay in the hospital, Tab Fenofibrate 160 mg was stopped in view of elevated LFT. The patient received Inj Calcium Gluconate 1 ampule stat and Neb Salbutamol 4 respules stat for hyperkalemia, Inj Meropenem 1 g three times daily for 5 days for infection and was switched to oral Ofloxacin 200 mg once daily, Inj Pantoprazole 40mg once daily, Tab Metoprolol succinate 50 mg twice daily for rate control in atrial fibrillation, Tab Apixaban 5 mg twice daily was given for atrial fibrillation and was temporarily stopped from second day of admission due to elevated INR and was restarted when INR reduced to 2.5 during discharge, Tab torsemide/spironolactone 10/25 mg once daily was stopped temporarily and started Inj Furosemide 20mg twice daily was given for a day and then changed dose to 10 mg twice daily in view of decreased urine output and mild volume overload and was stopped after 2 days, Tab Sildenafil 20 mg twice daily was given in view of pulmonary hypertension, Tab Ursodeoxycholic acid 300 mg twice daily, Syp lactulose 30 ml twice daily for hepatic dysfunction, Tab Sodium bicarbonate 500 mg three times daily, and her past medications were continued.

At discharge, the patient was prescribed with a structured medication regimen, including anti-hypertensives, metformin, thyroxine and supportive therapies. She was advised to follow up in the cardiology outpatient department after five days with repeat laboratory investigations, including a complete blood count (CBC), renal function tests (RFT), serum sodium (Na) and potassium (K) levels, international normalized ratio (INR) and liver function tests (LFT).

Table 1. Trends in Laboratory Investigations from Admission to Discharge

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Lab Investigations** | **Normal Values** | **Day 1** | **Day 2** | **Day 3** | **Day 4** |
| Total Bilirubin | <1.0mg/dl | 2.3 |  | 2.4 | 2.6 |
| Direct Bilirubin | <0.3mg/dl | 1.4 |  | 1.4 | 1.6 |
| SAP- Serum Alkaline Phosphatase | 35-147 U/L | 60 |  | 75 | 76 |
| ALT-Alanine Aminotransferase | Up to 40 U/L | 224 |  | 3886 | 2746 |
| AST- Aspartate Aminotransferase | Up to 40 U/L | 353 |  | 6602 | 2747 |
| PT- Prothrombin Time | 13.8 |  | 89.1 |  |  |
| INR- International Normalised Ratio | 1 |  | 7.35 |  | 2.6 |
| LDH- Lactate Dehydrogenase | 140-280u/l |  | 3342 |  |  |
| GGT- Gamma Glutaryltransferase | 5-40u/l |  |  | 59 |  |
| S. CK- Serum Creatinine kinase | 30-170u/l |  |  | 229 |  |
| CRP- C reactive protein | < 0.3 mg/dl | 13.5 |  |  | 13.9 |
| BNP- B Natriuretic peptide | <100pg/ml | 876 |  |  |  |
| Sodium | 135-145mmol/L | 131 | 134 | 137 | 134 |
| Potassium | 3.4-5.5mmol/L | 4.9 | 6/3.2 | 3.2 | 3.5 |
| Magnesium | 1.8-2.8mg/dl | 1.6 | 1.8 |  |  |

**DISCUSSION**

The pathophysiology of ischemic hepatitis remains incompletely understood, several mechanisms have been proposed. Initially, severe systemic hypotension, typically occurring during shock, was considered the primary cause. More recently, low cardiac output and reduced hepatic blood flow ("forward failure") have been recognized as potential contributors, even in the absence of shock. A clear understanding of hypoxic hepatitis requires knowledge of the liver’s blood supply and the consequences of its disruption. The liver receives approximately 25% of cardiac output, with about two-thirds supplied by the portal vein and one-third by the hepatic artery. Blood is drained from the liver via the right, left, and middle hepatic veins into the inferior vena cava, which then empties into the right atrium. To safeguard against ischemia, the hepatic circulation relies on multiple compensatory mechanisms to maintain blood flow during acute and chronic conditions. These include the passive expulsion of blood from the hepatic reservoir into the central venous system, the hepatic artery buffer response, and the hepatorenal reflex.1

Congenital heart disease (CHD) is often associated with liver dysfunction due to factors such as hepatic congestion, hypoxemia, or reduced cardiac output. While cardiac outcomes are generally favourable for a long term, non-cardiac complications like hepatic impairment warrant careful attention. Effective management requires a multidisciplinary approach tailored to this vulnerable population.14

Heart failure is classified based on left ventricular ejection fraction (LVEF) into two main categories: heart failure with preserved ejection fraction (HFpEF), defined as LVEF ≥ 50%, and heart failure with reduced ejection fraction (HFrEF), characterized by LVEF < 40%.4 Atrial fibrillation (AF) is a common comorbidity in HFpEF, affecting 62% of patients either before or after diagnosis. It is linked to an 11% increase in all-cause mortality and serves as an independent predictor of cardiovascular death and stroke in HFpEF. AF and HFpEF share not only similar risk factors but also overlapping pathophysiological mechanisms that contribute to the development of AF.7 In patients with HFpEF and progressively worsening atrial fibrillation, cardiac output declines, leading to elevated filling pressures. This results in pulmonary vascular disease and ultimately right heart failure. The passive congestion from increased filling pressures can cause mild elevations in transaminases, which may become significantly elevated in cases of hypotension and hepatic ischemia.2

The role of systemic hypotension as a key pathogenic factor was recognized over four decades ago, giving rise to the clinical term shock liver. Among patients studied, cardiogenic causes such as acute myocardial infarction, arrhythmias, cardiac tamponade, and acute pulmonary embolism were the predominant triggers of hypotension, accounting for 77% (24 out of 31) of cases.5

In patients with hypoxic hepatitis, several biochemical abnormalities may be observed. An early rise in lactate dehydrogenase (LDH) typically occurs within 12–48 hours after the triggering event, often accompanied by an Alanine Aminotransferase ALT/LDH ratio of less than 1.5. Serum creatinine levels frequently increase alongside liver enzymes, while international normalized ratio (INR) and bilirubin may also be elevated. However, serum alkaline phosphatase (AP) levels rarely exceed twice the upper normal limit. In acute congestive liver injury (ACLI), a marked elevation in aminotransferases (10–20 times the normal range) and LDH is commonly seen within 1–3 days following acute heart failure decompensation. If hemodynamics improve, these levels typically normalize within 7–10 days. A rapid increase in LDH and aminotransferases, followed by a decline in ALT within 72 hours, is a useful marker for differentiating ACLI from viral, alcoholic, or drug-induced hepatitis. Mild elevations in serum bilirubin, AP, and prothrombin time are also observed. Among liver enzymes, aspartate aminotransferase (AST) tends to rise more significantly than ALT in these patients. Although LDH levels are not routinely assessed in all cases, its initial elevation is often substantial. In contrast, AP levels typically show only minor increases. At the time of diagnosis, bilirubin and prothrombin time abnormalities are usually mild, with prolonged prothrombin time noted in 9 out of 11 cases. Additionally, renal dysfunction, reflected by elevated serum creatinine levels, is a common finding in these patients.1,4,5

This prospective, observational cohort analysis conducted by Dalos D et al. represents the first time that serum gamma-GT levels have been identified as an independent predictor of clinical outcomes in a well-defined HFpEF patient cohort, alongside hemoglobin and NT-proBNP. Although they observed a significant correlation between serum gamma-GT levels and the extent of left ventricular diastolic function as well as blood pressures in the right atrium, the precise underlying pathophysiological mechanisms remain unclear. It is challenging to determine whether the alterations in gamma-GT in HFpEF patients are driven by liver congestion resulting from increased filling pressures on both the left and right sides of the heart, by systemic low-grade inflammation leading to cardiac stiffness and elevated pressures, or by a combination of these factors. Nonetheless, there is a scarcity of evidence regarding liver enzymes and liver function tests in patients with heart failure and preserved ejection fraction.8

The simultaneous presence of factors like reduced blood flow, low oxygen levels, or exposure to endotoxins may trigger ischemic hepatitis (IH). In individuals with ongoing respiratory failure, liver congestion due to passive mechanisms also leads to an increased risk of hypoxic hepatitis. The key differential diagnoses to evaluate in individuals with significantly elevated serum hepatic transaminase levels (greater than 20 times the normal limit) include viral hepatitis, hepatitis induced by drugs or toxins, and ischemic hepatitis.1 In our patient, alongside negative serological tests for Dengue IgM, lepto IgM, HBsAg, anti-HCV, HIV, Anti HEV IgM, and Hepatitis B, several factors strongly indicate IH: first, the patient had a history of HFpEF and congenital heart disease and has no history of ingestion of hepatotoxins; second, there was a swift increase in serum aminotransferase levels while ALP levels remained normal; third, there was an early and significant rise in the serum LDH level.

The diagnosis of hypoxic hepatitis typically relies on a combination of hemodynamic disruptions and signs of acute liver damage, and in certain instances, a liver biopsy may be required.9

Patients with HFrEF and/or acute heart failure more commonly exhibited reduced cardiac output and arterial hypoperfusion, which may contribute to elevated ALT and AST levels. However, in the TOPCAT trial, participants had chronic HFpEF, making them less likely to experience low cardiac output or arterial hypoperfusion. In the context of congestive hepatopathy, increased central venous pressure can be transmitted directly to the hepatic veins, leading to hepatic congestion and impaired biliary function.6 Allen et al. discovered that total bilirubin levels were markedly elevated in patients showing signs of volume overload during physical examination.11

The clinical signs of liver injury remained generally in the background of the clinical signs of the underlying condition, while the dramatic but rapidly resolving elevation of serum enzyme activities, the profound fall of prothrombin activity, and the frequent alteration of renal function formed a triad of bio chemical abnormalities that is unusual in cases of viral or drug-induced hepatitis and that strongly suggests the diagnosis of hypoxic hepatitis.10 The presence of liver changes in individuals with heart failure may affect the pharmacokinetics and pharmacodynamics of cardiovascular medications. Drugs frequently prescribed, including beta-blockers, statins, antiarrhythmic agents, anticoagulants, and antibiotics, may accumulate to harmful levels in these patients, resulting in both cardiac and non-cardiac adverse effects. A highly debated topic is the influence of liver dysfunction on patients receiving anticoagulant therapy. The administration of novel anticoagulants such as dabigatran, rivaroxaban, or apixaban is particularly contentious; hence, their use is often restricted in cases of hepatic congestion.4

Ischemic hepatitis may progress to acute liver failure, marked by impaired synthesis of vital proteins and toxin clearance, potentially resulting in jaundice, coagulopathy, encephalopathy, and multiorgan failure. Persistent hepatic injury can also lead to chronic liver disease, including cirrhosis, hepatocellular carcinoma, and portal hypertension, conditions which can significantly compromise prognosis and quality of life. In severe cases, ischemic hepatitis may precipitate sepsis, exacerbating systemic inflammation and organ dysfunction. Another critical complication is hepatic encephalopathy, arising from toxin accumulation due to hepatic insufficiency, manifesting as cognitive impairment, confusion, or coma. Prompt recognition and intervention are essential to prevent progression and improve clinical outcomes.13

There is no designated treatment for IH. However, key components of management include quickly restoring cardiac output and addressing the root cause of the hemodynamic instability. Typically, the prognosis is primarily influenced by the underlying cause rather than the resulting hepatic dysfunction.12

**CONCLUSION**

In summary, when hepatic transaminase levels exceed 1000 IU/L without an identifiable hepatic cause, ischemic hepatitis should be suspected. This case underscores that ischemic hepatitis can develop in patients with heart failure with preserved ejection fraction (HFpEF). It results from impaired diastolic function, leading to reduced cardiac output, increased filling pressures, and/or right-sided congestive heart failure. Our findings highlight the importance of physician awareness of this condition, as it can occur even in patients with normal blood pressure. This case highlights the significance of ischemic hepatitis in the setting of HFpEF and atrial fibrillation. Though IH was the primary diagnosis, concomitant sepsis and prior fenofibrate use may have contributed to the severity of liver injury.The timely discontinuation of fenofibrate was crucial in preventing further hepatic injury. Optimized cardiac and diabetic management contributed to patient recovery. Long-term follow-up is essential to ensure stabilization of liver function and cardiovascular health.

**Consent:**

The authors certify that all necessary patient consent forms have been obtained. In these forms, the patient(s) have granted permission for their images and other clinical information to be published in the journal. The patients are aware that their names and initials will not be disclosed, and every effort will be made to protect their identity, though complete anonymity cannot be guaranteed.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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