

Decompensated HF Management in Patients with Liver Cirrhosis

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Introduction

- Severe congestive heart failure is associated with two distinct forms of liver dysfunction called “**cardiac hepatopathy**”. The two entities include:
- Jaundice related to passive congestion (**congestive hepatopathy (Cardiac Cirrhosis)** from backward cardiac failure) and acute hepatocellular necrosis caused by impaired hepatic perfusion (**hypoxic hepatitis** from forward cardiac failure).
- HYPOXIC HEPATITIS
- Hypoxic hepatitis is defined as an acute and reversible significant elevation of serum AST and ALT levels to more than 20 times the upper limit of normal in the absence of known acute hepatitis or hepatocellular injury and with an appropriate clinical picture specifically involving acute circulatory, cardiac, or respiratory failure.
- More recent literature has proposed hypoxic hepatitis as a more appropriate name than “shock liver”.

- Liver cirrhosis is associated with severe hemodynamic changes which include hyperdynamic circulation with increased cardiac output, heart rate and reduced systemic vascular resistance.
- The term **cirrhotic cardiomyopathy** is defined as the presence of chronic cardiac dysfunction, characterized by blunted contractile responsiveness to stress and altered diastolic relaxation with ECG abnormalities (QT interval prolongation), all occurring in the absence of any other cardiac disease.
- The key role in diagnosis is played by 2-dimensional echocardiography, electrocardiography and various serum markers (natriuretic peptides).

- How is primary liver disease differentiated from CHF-associated liver Disease?

There are a number of clinical characteristics as well as laboratory tests that help distinguish CHF-related liver Disease from primary liver disease. For example, patients with CHF-associated liver disease rarely have evidence of portosystemic shunts, such as esophageal varices .

- The ascites associated with CHF compared with that seen in primary liver disease tends to be associated with higher lactate dehydrogenase levels, higher protein levels in the ascites (>2.5 g/dL), and higher red blood cell counts (RBCs).
- These parameters are seen in cardiac ascites as opposed to ascites of primary liver disease due to hepatic congestion and leaking of RBCs into the ascites via lymph tissue, with resulting lysis in the setting of preserved synthetic function (Cosmas C. Giallourakis, MD Gastroenterology and Hepatology; 2013).
- Jaundice is relatively uncommon in CHF-related liver disease. Only about 5% of patients with hepatic disease and CHF will have clinically overt jaundice but up to 70% of patients may have a mild increase in unconjugated bilirubinemia (<3 g/dL total bilirubin).



Figure 1: Cut surface of the congested liver reminiscent of the classic "nutmeg appearance" which is caused by chronic passive congestion of the central veins with hemorrhage and necrosis in zone 3. Red cells pool and distend the sinusoids around the central vein. These regions develop a darker red-violet color, in contrast to the surrounding tan liver parenchyma.

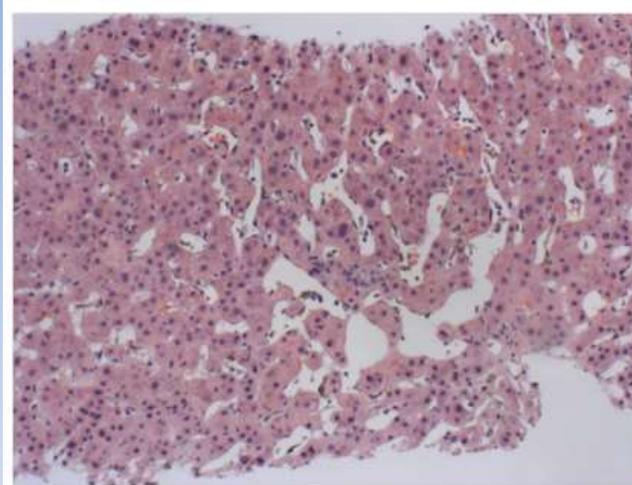


Figure 2: H/E section of liver (10x magnification) with sinusoidal dilation in zone 3. As the severity of the lesion increases, the sinusoids around the central vein become distended with extravasated red cells and there is adjacent hepatocyte plate atrophy.

- If a question persists about the etiology of the liver disease, a liver biopsy may be revealing.
- Fibrosis in chronic CHF-associated liver disease manifests as a reverse lobulated pattern characteristic of cardiac cirrhosis with relative sparing of the portal regions and radiating from the central vein, whereas damage is focused in zone 1 in most primary liver diseases (Shailja C. Shah¹ and David A. Sass; 2015).

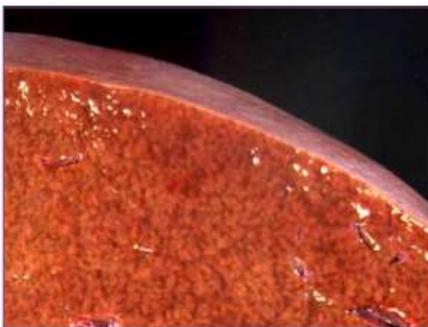


Figure 1. "Nutmeg" liver is characterized by a contrasting combination of reddish hemorrhagic areas, from red blood cells extravasating from the sinusoids, and yellowish portal areas, which represent normal or mild fatty liver. (Image courtesy of James Robert Stone, MD, PhD.)

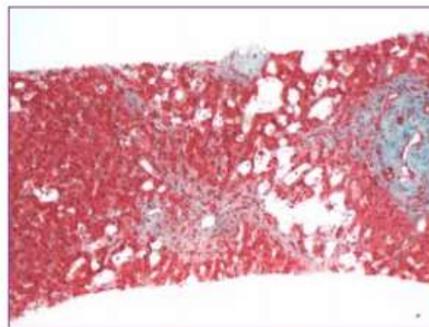


Figure 2. This example of cardiac cirrhosis shows chronic congestion, dilated sinusoids, and reverse lobulation of fibrosis from veins connecting to one another. (Common cirrhosis is portal-linking.) (Hematoxylin and eosin with trichrome stain; image courtesy of Joseph Misdraji, MD.)

Should every cardiologist attack a lesion ?



Management of Liver cirrhosis and CHF

- No accepted pharmacologic treatment for cirrhotic cardiomyopathy exists. To date, there are no clinical studies on the management of cirrhotic cardiomyopathy. Once cardiac failure becomes evident following some forms of stress, management should follow similar guidelines as in noncirrhotic patients.

ACEIs

- Although cardiac afterload reduction will not be well tolerated in patients with advanced cirrhosis who are significantly vasodilated. Vasodilators, like ACE-inhibitors, should be used very carefully because of the risk of further aggravation of the systemic vasodilatory state which aggravates hypotension and tissue hypoperfusion.

B-Blockers

- It has been shown that β -adrenergic blockade can lower portal pressure and potentially reduce the degree of shunting of cardiotoxins from the splanchnic to the systemic circulation. Zambruni and colleagues showed beneficial effect of chronic administration of β -blocker on QT intervals in a cohort of cirrhotic patients with varying degrees of decompensation.

Diuretics

- Patients with cirrhosis and heart failure (HF) share the pathophysiology of decreased effective arterial blood volume because of splanchnic vasodilatation in cirrhosis and decreased cardiac output in HF, with resultant stimulation of the renin-angiotensin-aldosterone system (Shweta Bansa et al;2009).
- Hyperaldosteronism plays a major role in the pathogenesis of ascites and contributes to resistance to loop diuretics. Therefore, the use of high doses of aldosterone antagonist (spironolactone up to 400 mg/day) is the main therapy to produce a negative sodium balance in cirrhotic patients with ascites.
- Treatment with diuretics is indicated in patients with water retention. Aldosterone antagonists may have beneficial effects in the reduction of left ventricular dilatation, wall thickness, and are potentially useful in the improvement of diastolic function.

- Hyperaldosteronism also has increasingly been recognized as a risk factor for myocardial and vascular fibrosis.
- Therefore, low-dose aldosterone antagonists are being used in patients with HF for cardioprotective action. However, the doses (25 to 50 mg/day) at which they are being used in cardiac patients as reported in the Randomized Aldactone Evaluation Study are not natriuretic. It is likely, therefore, that the mortality benefit relates primarily from their effect on cardiac and vascular fibrosis.
- Resistance to commonly used loop diuretics is frequently present in patients with advanced HF. In patients with decompensated HF with volume overload who are loop diuretic resistant, ultrafiltration may be the only available option. This is, however, an invasive procedure.
- The administration of relatively high doses of furosemide (up to 160 mg/day) to nonazotemic cirrhotic patients causes a satisfactory natriuresis in only 50% of patients.
- Overdose of loop diuretics may lead to HCF.
- Thus, patients with marked hyperaldosteronism (CHF and LC) did not respond to furosemide and required high doses of spironolactone (400 to 600 mg/day).

- **Aspirin** is prescribed to many cardiac patients as 1ry or 2ry preventive measure against Cardiovasc. or cerebrovasc. Diseases. However, there is an Increased incidence of gastrointestinal bleeding in patients with liver cirrhosis. In general, there is no contraindication to use low dose aspirin on CHF with LC with special attention to a major risk of long-term use of this medications (Benefit-Risk Ratio).
- In a lot of studies suggest that even Low dose aspirin is associated with lower incidence of HCC.

Oral Anti-coagulant:

- Cautious use of anticoagulants is advised because patients have a baseline mild increase in PT/INR and are especially sensitive to warfarin and other related compounds. Oral anticoagulation causes an increased incidence of ICH and GIB in patients with LC and AF.
- LMWH and vit. K antagonists are not contraindicated in Pts with CHF and LC. The risk of thrombosis in pts with CLD is increasingly recognized. As Pts with LC frequently develop indications for anticoagulations (e.g., Venous thromboembolism, Portal Vein Thrombosis, or AF).
- Providers are left to make difficult decisions when selecting OAC in pts with LC in whom already there is coagulation defects (Benefit-Risk Ratio) with special attention to INR (Intagliata et al 2016).
- In a study of Grewal et al (NY, USA) 2014; critical care Medicine; they reported that warfarin with adjusted dose to achieve proper INR doesn't increase the incidence of ICH or GIB in Pts with LC.

Digoxin

- **Hepatic Impairment:** Because only a small percentage (approximately 13%) of a dose of digoxin undergoes metabolism, hepatic impairment would not be expected to significantly alter the pharmacokinetics of digoxin. In a small study, plasma digoxin concentration profiles in patients with acute hepatitis generally fell within the range of profiles in a group of healthy subjects.
- No dosage adjustments are recommended for patients with hepatic impairment; however, serum digoxin concentrations should be used as appropriate to help guide dosing in these patients.
- Digoxin, which is metabolized in the liver and regulates cholesterol levels, has a bidirectional impact; it is metabolized by the liver and can affect the metabolism of other compounds in the liver.

Statin

- Statins are perhaps the most common class of drugs that can cause hepatic toxicity in patients with cardiac disease.
- Cardiovascular disease is one of the leading causes of death among patients with cirrhosis and following liver transplantation. Statins reduce the risk of cardiovascular events, fears about hepatotoxicity have historically led to underuse in patients with liver disease.
- In addition, the pharmacokinetics of statins can be significantly altered in cirrhosis, creating challenges with their use in liver disease. However, emerging data from randomised controlled trials and observational studies suggest that statin therapy appears to be safe and effective in patients with chronic liver disease and compensated cirrhosis.
- The cardiovascular risk benefits as well as the potential pleiotropic benefits of statins warrants strong consideration of use of statin therapy in patients with cirrhosis (Andrew Wright et al;2014).
- Good monitoring of liver enzymes is mandatory.

- The antiarrhythmic amiodarone usually does not cause significant liver abnormalities.
- Paracenteses can relieve symptoms in those with diuretic-refractory tense cardiac ascites, but over time can lead to protein loss and exacerbate the protein malnutrition commonly seen in those with advanced heart failure.
- Transjugular Intrahepatic Portosystemic Shunts (TIPS) or peritoneal-venous shunts are contra-indicated in this population as they can lead to exacerbation of the underlying heart failure.
- In patients refractory to medical therapy who are suitable operative candidates, both LVAD, cardiac resynchronization therapy and cardiac transplantation have been shown to improve the failing heart.
- In select patients combined heart and liver transplant is a feasible option.

New therapeutic approaches are under investigation

- Pozzi et al. demonstrated favorable effect of k-cancreolate (aldosterone antagonist), which was able to reduce circulatory volume and to decrease left ventricular wall thickness.
- Similarly, agonists of farnesoid X receptor (a gene involved in intrahepatic generation of vasodilator hydrogen sulfide) and NCX-1000 (a new compound that releases NO in the liver) are interesting new attempts aimed at correcting the diminished production of endogenous hepatic vasodilators during cirrhosis, but their usefulness is not yet clear in cirrhotic cardiomyopathy.

Conclusion

- Hepatic injury as a consequence of cardiac disease is a relatively common, but often poorly recognized, syndrome.
- The hepatic manifestations of “congestive hepatopathy” and “hypoxic hepatitis” may range from mild liver enzyme abnormalities, compensated cirrhosis to progressive liver injury, rarely, liver failure.
- In general, most cardiovascular drugs—certainly most antihypertensive agents and most diuretics—are well tolerated in the presence of modest liver compromise.
- A team approach characterized by collaboration amongst both cardiologists and hepatologists is critical for optimizing patient care and maximizing positive outcomes.

