The liver in Patient with Heart Failure

Introduction

- Known for more than 2 decades "Congested nutmeg liver" (Kiernan 1833) but not fully understand and limited clinical implication.
- With improving HF care, cardiac hepatopathy was less common
- Uniquely supply by 2 circulatory routes: systemic circulation and hepatic portal circulation
- HF pts commonly present with liver related sign and symptoms with abnormal LFT

Heart disease affecting the liver	Liver disease affecting the heart
Acute cardiac liver injury (ACLI) Congestive hepatopathy Cardiac hepatopathy (any liver injury from heart)	Cirrhotic cardiomyopathy

Acute cardiogenic liver injury (ACLI)

- Other names include ischemic hepatitis, shock liver, hypoxic hepatopathy, hepatolysis
- Rare < 1%
- Pathophysiology: Sudden, acute, severe hepatic hypoxia from either from ↓BP or ↓CO.
  - Evidences suggest that hepatic venous congestion, may predispose the liver to hepatic injury (Am J Med. 2000;109:109.).
- Biochemical:
  - ALT, AST 10-20 x ULN
  - ↑Bil, ↑PTT, LDH (ALT/LDH < 1.5)
  - 1-3 days after hemodynamic insult. Return to normal within 7-10 d
- Pathology: Necrosis, imflamation - centrilobular (zone 3)

Congestive hepatopathy

- Passive congestion → fibrosis → cirrhosis (nutmeg liver)
- Frequently silent but may be misdiagnosis with cholelithiasis, PU, ischemic colitis
- Nearly 20% chronic HF, 50% of patient with acute HF have abnormal LFT (Euro Heart J 2013;34:742, Eur J of Heart Fail 2009;11:170.)
- Biochemical:
  - ↑AP, ↑Bil, ↑GGT
  - Correlate with NYHA, RV failure
- Pathology:
  - Chronic or acute on chronic
  - Dilatation, fibrosis - Central third of hepatic lobule

Cirrhotic cardiomyopathy

- Cardiomyopathy in patient with cirrhosis
  - In absence of known cardia disease
  - Exclusion of common heart-liver etiology eg. EtOH, hemochromatosis
- Unknown pathology
  - "High output" – hyperkinetic (↑compliance, ↑ blood volume)
- Clinically Silent
  - Hypertrophy, diastolic dysfunction, long QT
  - Abnormal response to exercise or stress e.g. TIPS, liver transplant Infection.
  - Usually reversible after liver transplant (Journal of Hepatology 42 (2005) 68–74)
  - Other clinical significant include PH (hepatopulmonary vs. portopulmonary) bacterial endotoxin

LFT as a prognosis factor in patient with HF

- Multiple liver parameters are a prognostic marker across HF spectrum
  - Alb, AST, ALT, GGT, Tbil, INR (J Am Coll Cardiol 2013;61:2397)
  - Cardiac cachexia = endstage heart failure
  - Cholesterol
  - MELD score is a strong predictor of mortality in endstage HF
- Likely a maker not a factor
- Not include in HFSS (Heart Failure Survival Score), SHFM (Seattle heart failure model) ESCAPE, EFFECT, ADHERE.

Table 1 Studies Demonstrating Association Between Liver Function Test Abnormality and Mortality in Heart Failure Patients and Descriptions of Study Cohort, Number of Subjects, and Laboratory Marker of Interest

First Author (Ref. #), Year	Patient Population	n	Lab	Summary of Findings
Horwich (19), 2008	NYHA class III/IV chronic HF	1,726	Alb	Hypoalbuminemia associated with significantly increased 1- and 5-yr all-cause mortality, progressive HF death, and increased risk of urgent cardiac transplantation.
Uthamalingam (20), 2010	ADHF	438	Alb	Hypoalbuminemia independently associated with increased 1-yr mortality in patients with ADHF admitted to hospital.
Kinugasa (21), 2009	ADHF	349	Alb	In elderly ADHF patients, serum albumin associated with in-hospital mortality, even after adjustment for other known prognostic factors.
Kato (22), 2012	Consecutive patients with LVAD implanted at CUMC	307	Alb	Pre- and post-operative measures of serum albumin predicted neurologic complications after LVAD implantation.
Nikolaou (18), 2012	ADHF	1,134	AP, AST, ALT	Of patients with ADHF, 46% presented with altered LFTs. Abnormal AP was associated with marked signs of congestion, elevated right-sided filling pressures, and increased 180-day mortality. Abnormal transaminases were associated with clinical signs of hypoperfusion and increased 31- and 180-day mortality.
Poelzl (23), 2012	Unselected stable HF patients, with primarily LV dysfunction	1,032	AP, GGT	AP, Tbil, and GGT levels inversely associated with survival. In multivariate analysis, only AP and GGT maintained independent predictive capacity for transplant-free survival.
Poelzl (24), 2009	Unselected outpatients with HF	938	GGT	Serum GGT can provide prognostic information independent of established clinical and biochemical markers including age and NT-proBNP. Predictive GGT value is greater in NYHA class I–II HF (HR: 2.9) compared to NYHA class III–IV HF (HR: 1.2).
Ruttmann (25), 2005	Healthy adult outpatients	163,944	GGT	GGT found to be a prognostic indicator of fatal events in apparently healthy subjects.
Szyguła-Jurkiewicz (26), 2007	NYHA class II/III HF secondary to hypertension	124	Tbil	Elevated bilirubin levels associated with higher incidence of death in patients with hypertension-related chronic HF.
Allen et al. (27), 2009	Chronic HF	2,679	Tbil	Tbil was a strong independent predictor for worsening HF, cardiovascular death, and all-cause mortality.
Matthews (28), 2008	Advanced HF patients with LVAD implanted at UM	197	Tbil, AST	Tbil and AST identified as independent markers for development of right ventricular failure after LVAD implantation.
Fuhrman (9), 2009	Patients admitted to ICU with "hypoxic hepatitis"	117	INR	Peak INR >2 identified as an independent predictor of overall mortality in patients with "hypoxic hepatitis."
Rauchfh (10), 2011	Patients admitted to ICU with "hypoxic hepatitis"	182	INR	INR was found to be an independent predictor of in-hospital mortality in patients with hypoxic hepatitis.

ADHF = acutely decompensated heart failure; Alb = albumin; AP = alkaline phosphatase; AST = aspartate aminotransferase; CUMC = Columbia University Medical Center; EF = ejection fraction; GGT = gamma-glutamyl transpeptidase; HF = heart failure; HR = hazard ratio; ICU = intensive care unit; INR = international normalized ratio; LFT = liver function test; Lab = laboratory (marker of interest); LVAD = left ventricular assist device; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; Tbil = total bilirubin; UM = University of Michigan.

Other consideration

- Liver as a key player in an inflammation theory of heart failure
  - Translocation of bacterial endotoxin
  - Role of microbiome
- Liver and guts as a key player in cardiac cachexia
- Pulmonary hypertension in hepatopulmonary syndrome and portopulmonary hypertension

Recommended reading

- Cardiohepatic Interactions in Heart Failure An Overview and Clinical Implications. JACC 2013;61:2397.
- Cardiac Hepatopathy: A Review of Liver Dysfunction in Heart Failure. Liver Res Open J. 2015;1:1.