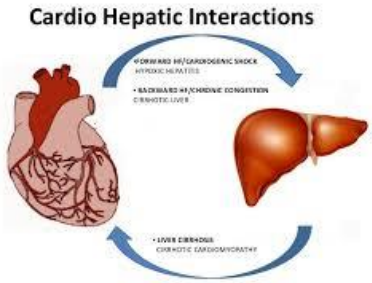
Cardio-Hepatic Interaction



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- Heart Heart failure (HF) is a major public health problem, with frequent hospitalizations, impaired quality of life, and shortened life expectancy.
- As HF advances, it is often characterized by an increasing inability to meet the metabolic requirements of end organs. (Liver, Kidney, Brain ,…etc)
- While much attention has been directed toward the intersection of HF and renal function, the impact of HF on hepatic function has been poorly described.

- Similar to the now widely described "cardiorenal" syndromes, more attention is needed in describing

… "Cardiohepatic-Syndrome"…..

- In contrast, much less is known about impaired liver function in patients with HF. Furthermore,HF patients may present with liver-related symptoms including abdominal distention, right hypochondrial discomfort, nausea, early satiety, or anorexia.
- The presence of these symptoms may direct the physician to a primary GIT rather than consideration of primary cardiac pathology.

Cardiac-Hepatic Interactions in Heart Failure

Impaired perfusion

Elevated Rt. Sided pressure

Drug Toxicity

(A)

Impaired Perfusion

Acute cardiogenic liver injury

- Acute cardiogenic liver injury (ACLI), historically called "Ischemic hepatitis,"
- It is often described in patients with HF who have progressed to critical cardiogenic shock, in which cardiac output is no longer sufficient to meet the metabolic demands of hepatic cells.

However,

Recent literatures confirm that, Acute change in hepatic blood flow is not the sole incident responsible for ACLI

- **Prolonged hypotension and liver hypoperfusion alone doesn't cause Acute Liver Injury …..How ??**

- Seeto et al. in 2000, Studied the effect of prolonged hypotension on acute liver injury. In trauma victims who had evidence of prolonged hypotension compared to the control normal individuals group.

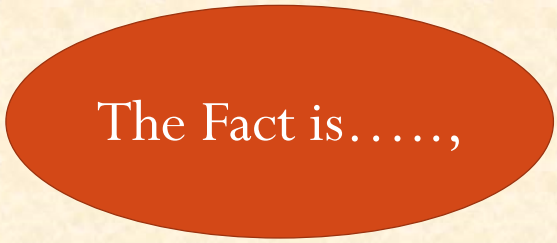
- He found that, nearly all patients with a clinical diagnosis of ACLI had evidence of cardiac disease, with 29 of these 31 subjects demonstrating evidence of elevated right-sided or venous filling pressures

- Similarly, Henrion et al. , examined ACLI in patients admitted to the coronary intensive care unit with evidence of low cardiac output.

- Patients with biochemical evidence of cardiogenic injury had significantly higher central venous pressures compared to patients who had low cardiac output but no Liver congestion.

- Several larger studies characterizing the etiology of ACLI have shown that the majority of cases of ACLI are related to acute HF, respiratory failure, and septic shock.

- However, these same studies have also shown that between 40% and 70% of patients with ACLI have the underlying diagnosis of chronic HF.



- These findings suggest that ACLI does not result from a single hemodynamic insult, but must be linked to hepatic congestion from elevated hepatic venous pressure PLUS impaired perfusion ……..

- Venous congestion may ultimately increase the susceptibility of the liver to injury caused by reduced perfusion.

- The notion that a "second hit" is required for acute liver injury is not captured in the nomenclature

"ischemic hepatitis" or "shock liver."

- Therefore, we believe that "ACLI" is a more accurate diagnostic term , encapsulating the underlying pathophysiological process.

Then, what's the scenario if Isolated Prolonged Acute Hypotension

Yes, there's injury pattern of the liver represents the release of hepatic proteins in response to tissue hypoxia and cell death ….'**Hepatolysis'**

These symptoms may include weakness, apathy and (in a minority of cases) persistent mental confusion, tremor, hepatic coma, and jaundice

A bleeding diathesis from acquired coagulopathy may also develop due to impaired production of coagulation factors

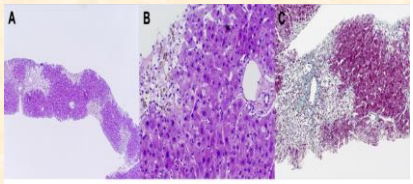
But, . . .

All these abnormalities peak at 1 to 3 days after onset of symptoms and, in patients who survive, return to normal within 5 to 10 days after onset

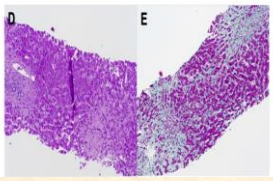
- **How authors confirm this idea :**

Impaired perfusion must be *LINKED* -to- high venous hepatic congestion

A- Histo-pathological Features



The histologic hallmark of ACLI is necrosis surrounding the central vein where the oxygenation is poor . Zone (3)



Depending on the duration of ischemia, … a variable degree of architectural collapse around the central veins can occur

Necrosis can extend to the mid-zonal area with prolonged ischemia; however, necrosis rarely starts in the middle zones Or the periphery…..

B- Bio-chemical Features

- The typical pattern in ACLI consists of :-
  - Sharp and early rise of AST & ALT (10 to 20 times) between 1 and 3 days after hemodynamic insult, and without evidence of another etiology such as cholecystitis or viral hepatitis
  - Early and rapid increase in serum LDH is characteristic
  - Ratio of serum alanine aminotransferase (ALT) to LDH <1.5 early in the course of liver injury is characteristic of cardiogenic injury as opposed to other etiologies of hepatitis
  - Interestingly, abnormal alkaline phosphatase was associated with marked signs of congestion and elevated right-sided filling pressures

- With correction of hemodynamics, these levels will return to normal within 7 to 10 days.
- Although there are few data regarding LFT alterations among patients with acute HF, a recently published analysis of the SURVIVE (Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support) trial Support these explanations.

(B)

Elevated Rt. Sided pressure

"Chronic Passive Congestion"

- Hepatopathy secondary to chronic congestive HF is attributed to 3 main processes:

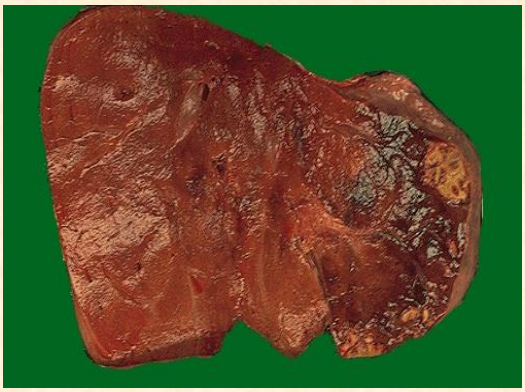
3

- increased hepatic venous pressure,
- decreased hepatic blood flow, and
- decreased arterial oxygen saturation

- Elevated central venous pressures are transmitted through the hepatic veins and into the small hepatic venules. The effect of this transmitted pressure is passive congestion of the liver with resulting elevated hepatic venous pressure, which can impair delivery of oxygen and nutrients to hepatocytes, leading to sinusoidal fenestrae enlargement
- Consequently, hepatocyte necrosis and leakage of protein-rich fluid into the space of Disse occurs with stretching of the liver capsule resulting in abdominal discomfort.

- The Resultant Is ….

….”Nutmeg Liver”…



- **A- Histo-pathological Features**

Necrosis Is Centrilobular

- Boland and Willius first demonstrated that nearly 50% of patients with severe HF had pathologic changes consistent with chronic passive liver congestion.
- Atrophy, necrosis, or both were present and most pronounced in the central third of the hepatic lobule.
- Generally, these findings were most prominent immediately adjacent to the central vein, with decreasing degeneration towards the lobule periphery

- Results were later confirmed by the work of Sherlock , which described microscopic sinusoidal engorgement and degeneration.
- Also important finding is presence of variable degrees of cholestasis, occasionally with bile thrombi in the canaliculi

- **B- Bio-chemical Features**
- As cardiac output decreased and intracardiac filling pressures increased :-
  - Elevations in transaminases, LDH
  - Increased total bilirubin
  - Cholestasis
    - Increased alkaline phosphatase
    - Increased gamma-glutamyl transpeptidase [GGT]
    - Increased total bilirubin, and …
  - Finally, Hypoalbuminemia

All these parameters were found to be correlated with the severity of TR

(C)

"Drug Toxicity"

This item having Two Major Tasks

- Alteration in Drugs-pharmacokinetic process
- Direct Hepato-toxic Effects of Some Cardiac Drugs

- Hepatic congestion and hypoperfusion can result in hepatocyte atrophy and impaired oxygen diffusion, leading to impaired hepatocyte metabolism
- Alterations in liver function that would lead to changes in liver drug metabolism include disruption in hepatocyte function (intrinsic function including activity of metabolic enzymes and transporters)
- Changes in liver blood supply, and reductions in the synthesis of plasma protein binding

These changes may lead to serious effects on Drugs-pharmacokinetic process

- The Final process ends in prolongation of ….

Hepatic-Drug-Clearance

- As a result …FDA…developed a guidance document for Industry to modify doses of certain drugs in cases of hepatic impairment such as,
  - Beta-blockers
  - Statins
  - Some antiarrhythmic agents
  - Anticoagulants, and antibiotics
- Which could potentially accumulate to toxic levels in this patient population, leading to cardiac and noncardiac adverse effects.

Direct Hepato-toxic Effects of Some Cardiac Drugs

Pharmacologic Agent	Hepato-Toxic Effects
Aspirin, Lisinopril, Losartan,Statin	Acute Hepatocellular Injury
Amiodarone (Cordarone)	Chronic steatohepatitis
Diltiazem, hydralazine, procainamide, quinidine	Granulomatous hepatitis
ACE inhibitors, clopidogrel, irbesartan, amiodarone	Cholestasis
Captopril, verapamil	Mixed hepatitis
Statins	Autoimmune hepatitis

Liver Function Tests

Can Be Used As a Parameter

For HF-Prognosis ?

- Many Trials, including CHARM-trial confirm use of LFTs, as prognostic measures to describe higher rates of death, cardiac transplantation, and HF rehospitalizations in patients with increased plasma bilirubin
- CHARM substudy, which demonstrated that total bilirubin was a strong independent predictor for worsening HF, cardiovascular death, and all-cause mortality .
- A more recent study showed that in an unselected cohort of patients with stable HF, alkaline phosphatase, total bilirubin, and GGT levels, all of these factors are inversely associated with survival.

- In multivariate analysis, only alkaline phosphatase and GGT maintained independent predictive capacity for transplant-free survival in this cohort in which 339 events were recorded with a median follow-up of 36 months.
- Poelzl et al., showed that serum GGT can provide prognostic information independently of established clinical and biochemical markers including age, body mass index, ischemic etiology, NYHA functional class,
- N-terminal pro–B-type natriuretic peptide. In patients with mild HF symptoms defined as NYHA class I/II

- The predictive value of GGT is greater (hazard ratio: 2.9) compared with that in patients with NYHA class III/IV failure (hazard ratio: 1.2)
- In a large epidemiologic study by Ruttmann et al. , GGT was found to be a prognostic indicator of fatal events.
- Total bilirubin has subsequently been incorporated into a validated risk score predicting right ventricular failure after LVAD surgery and, even more recently, is a component of a risk model for adverse outcomes after cardiac transplantation

- Hypoalbuminemia has also been studied extensively as a prognostic marker in HF and has been shown to be an independent predictor of death in both acute and chronic HF.
- Hypoalbuminemia is associated with significantly increased 1- and 5-year all-cause mortality, progressive HF death, and increased risk of urgent cardiac transplantation
- Low albumin levels also has been identified as an important prognostic variable in the surgical treatment of advanced HF.
- In HF-patients treated with LVAD therapy, preoperative albumin is an independent predictor of short and intermediate-term outcomes after implantation

Summary,…

Take Home Messages…….

- Low COP and hypotension Alone doesn't produce permanent liver injury, it needs HF and hepatic congestion as a prerequisite to do that.
- Hypotension such as in trauma or septicemia may produce ACLI but, might be reversible after improving haemodynamic
- The term Shock-liver should be replaced by ACLI
- Chronic HF and congestive hepatopathy termed …"Nutmeg-Liver" …produce atrophy and necrosis of hepatocytes and always in Centri-lobular pattern .

Drug-Toxicity in ACLI appeared in tow features :-

- Prolonged metabolism of drugs due to impaired hepatic drug clearance …
- Direct toxicity of known cardiac drugs
  - Statins and Aspirin
  - Captopril and Lisinopril
  - Irbisartan and Losartan
  - Quinidine & Procainamide
  - Verapamil and Diltizem
  - Hydralazine
  - Amiodarone

- Liver Function Tests (LFTs)…can be used as a prognostic tests for patients with heart-failure
- CHARM and other large Trials confirm sensitivity of :-
  - Total Billirubin
  - GGT 'gamma glutaryl transpeptidase'
  - Alkaline Phosphatase
  - Hypo-albuminemia …and
  - N-terminal pro-B Natriuretic peptide
- As a Marker For…,
  - Worsening of heart failure
  - Recurrent hospitalization
  - Short & Intermediate outcome of LVAD
  - Urgent need for cardiac transplantation
  - Predictive capacity for transplant free survival
  - Cardiovascular & All cause Mortality


Thanks