THE HEART & LUNG IN LIVER DISEASE

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DISCLOSURES

• Consultant: Gilead
OUTLINE

PART I: HEART in Liver Disease
I. Cardiac diseases in the pre-transplant period
II. Relationship between the heart and the liver during liver transplant
III. Relationship between the heart and the liver in the post-transplantation period
IV. Combined Heart-Liver (CHLT) transplant

PART II: LUNG in Liver Disease
I. Portopulmonary Hypertension
II. Hepatopulmonary Syndrome
Part I: Heart in Liver Disease
Pre-Transplant: Cardiac Diseases

• Chronic alcoholism
• Hemochromatosis
• Non-alcoholic fatty liver disease (NAFLD)
• Familial amyloid polyneuropathy
Chronic Alcoholism

- Can lead to cirrhosis and alcoholic cardiomyopathy
  - Main cause of secondary non-ischemic dilated cardiomyopathy in the western world
- Characterized by:
  - Myocardial fibrosis
  - Disruption of the myofibrillary structure
  - Impaired systolic function
  - Left ventricular dilatation
- Abstinence in early stages may lead to improvement
- Alcoholic liver cirrhosis patients have increased risk of CAD.
Hemochromatosis

- Iron overload causes deposition in the myocardium and conduction system
  - Conduction abnormalities
  - Heart Failure

- At early stages of heart involvement, asymptomatic disease may be unmasked by cMRI

- Functional and structural changes can improve with iron removal therapy.

- Patients with hemochromatosis have a 14-fold increase in mortality due to heart disease compared to other age and sex matched population.

- Careful pre-transplant cardiac evaluations is essential.
NAFLD

- Associated with metabolic syndrome
  - Associated with CAD

The NAFLD Spectrum

**NAFL** = Steatosis (Fat > 5% of hepatocytes)

**NASH**: steatohepatitis
1. Steatosis +
2. Inflammation +
3. Hepatocellular

**NASH cirrhosis**
Possible etiology
Cryptogenic cirrhosis:
histological findings are lost by time of biopsy

Liver transplant / Death
Amyloidosis

• Disorder of protein metabolism (autologous protein)
• Acquired or inherited
• Deposition of extracellular, insoluble fibrils in various organs “amyloid”
• Maybe focal, localized, or systemic
  – Visceral involvement involving: kidneys, adrenals, thyroid, heart, eye and intestine.
• Clinical manifestations, prognosis, and therapy vary greatly depending on the specific type of amyloid and structural and functional derangements in the affected organs.
Heart with Amyloid Infiltration

R H Falk Circulation 2005; 112:2047-2060
Amyloidosis

- Familial Amyloidosis:
  - Precursor protein is a mutant form of transthyretin
  - Is transmitted as an autosomal dominant with high penetration (1% of cases of amyloidosis)
  - Presentations occurs from the 3rd decade on, and commonly after the age of 40
  - Deposits predominantly in the peripheral nerves
  - Polyneuropathy and dysautonomy
  - Cardiac amyloid is either absent or limited to the conduction system, most frequently manifesting as sinus node dysfunction.
Amyloidosis

• Familial amyloidosis
  – More than 70 mutations have been described
    • THr-60-Ala: presents with a predominant cardiomyopathy
      – Heart failure
      – Conduction system disturbances
      – Minimal neuropathy
    • Val-122-Iso: mainly cardiac presentation
      – Approximately 4% of the AA population in the US is heterozygous for this mutation
      – Late-onset cardiomyopathy in either sex
      – Progressive congestive heart failure
      – Remarkably consistent features among patients
      – Infiltrative/restrictive cardiomyopathy with predominant signs of right heart failure with ascites and peripheral edema.
<table>
<thead>
<tr>
<th>Type of Amyloidosis</th>
<th>Amyloid Protein Component</th>
<th>Current Therapy</th>
<th>Goal of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL or AH (primary)</td>
<td>Immunoglobulin light chain (AL) or (occasionally) heavy chain (AH)</td>
<td>Melphalan plus dexamethasone; alternative is autologous stem-cell transplantation in selected patients with limited organ involvement who are candidates for the procedure</td>
<td>Eradicate clonal plasma cells that are the source of immunoglobulin protein</td>
</tr>
<tr>
<td>AA (secondary to chronic inflammation or familial Mediterranean fever)</td>
<td>Serum amyloid A protein</td>
<td>Treatment of underlying infection or inflammation; colchicine for familial Mediterranean fever</td>
<td>Reduce level of serum amyloid A protein</td>
</tr>
<tr>
<td>Mutant ATTR (familial)</td>
<td>Mutant form of transthyretin</td>
<td>Liver transplantation</td>
<td>Eliminate source of mutant transthyretin</td>
</tr>
<tr>
<td>Senile systemic amyloidosis</td>
<td>Wild-type form of transthyretin</td>
<td>No therapy</td>
<td></td>
</tr>
<tr>
<td>Other forms of familial amyloidosis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fibrinogen α-chain</td>
<td>Mutant form of fibrinogen α-chain</td>
<td>Hepatorenal transplantation</td>
<td>Eliminate source of fibrinogen α-chain (liver) and replace affected organ (kidney)</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Lysozyme</td>
<td>Undefined</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein</td>
<td>Apolipoproteins A-I and A-II</td>
<td>Renal transplantation</td>
<td>Replace affected organ</td>
</tr>
</tbody>
</table>

Rajkumar and Gertz, NEJM 2007; 356:2413-2415
Familial Amyloid Polyneuropathy

**DIAGNOSIS:**

- Biopsy of clinically affected tissue, e.g. >80% involvement of the rectum
- Characteristic congo red staining.
- Immunohistochemical staining
- Electron microscopy suggestive but not diagnostic
- PCR for mutated gene.
Familial Amyloid Polyneuropathy

• **EVALUATION:**
  – Cardiac function: echocardiography, Holter monitoring, right heart catheterization
  – Gastrointestinal motility
  – Nerve conduction and autonomic function
  – Renal function
Familial Amyloid Polyneuropathy

• Rational for liver transplantation:
  – Eliminate site of abnormal protein synthesis
  – Stabilize or reverse stigmata of amyloid infiltration
  – Prevent accumulation of amyloid in other transplanted organs.

• Heart disease from amyloid deposition
  – Cardiac denervation
  – Restrictive cardiomyopathy
  – Conduction disturbances
  – Death
Cirrhotic Cardiomyopathy

- Closely related to the hemodynamic alterations that occur in cirrhosis
  - ↑ baseline CO with blunted ventricular response to stimuli
  - Systolic and Diastolic dysfunction, which are best observed in stress situations
  - Electrophysiological abnormalities

- Presence of portal hypertension make the accurate evaluation of the heart function difficult, because of the fluxes in load.
Pressure = Resistance \times Flow

Structural changes \quad Dynamic changes

Portal pressure = Increased intrahepatic resistance \times Increased portal venous flow

Splanchnic vasodilatation

Central hypovolemia

Activation of vasoactive systems (SNS, SRAA)

Sodium retention

Journal of Hepatology 2011 54, 810-822, DOI: (10.1016/j.jhep.2010.11.003)
# Pre-Transplant: Cardiac Diseases Outcome

<table>
<thead>
<tr>
<th></th>
<th>Pretransplant</th>
<th>During Transplant</th>
<th>Post-transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>Prevalence 6-26% [68-70]</td>
<td>Mortality 50% Morbidity among survivors 81% [136]</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>27.5% valvular dysfunction [83]</td>
<td>Valvular dysfunction associated to greater vasoactive drug and blood transfusion requirements [83]</td>
<td>Valvular dysfunction no differences in mortality rates [83]</td>
</tr>
<tr>
<td>Asymptomatic patent foramen ovale</td>
<td>Prevalence 4% [82]</td>
<td>Non significant trend to greater incidence of reperfusion syndrome [82]</td>
<td>Longer stay in ICU, no difference in morbidity or mortality [82]</td>
</tr>
</tbody>
</table>
| Cirrhotic Cardiomyopathy | Greater prevalence with more severe disease 40-90% prevalence prolonged cQT [41, 46, 149] | 23% abnormal cardiac response [6] | - 3.3-7% severe left heart failure [34, 87]  
- 45% mortality in those with severe left heart failure [127]  
- Progressive improvement of all abnormalities, although possible initial worsening of diastolic function [40, 50, 132] |
| Portopulmonary hypertension | Prevalence 2-14% [52-56] | MPAP >50mmHg 100% mortality  
MPAP 35-50mmHg 50% mortality  
MPAP <35 mmHg no disease related increase in mortality [57] |                                                                                                   |
- No improvement of sympathetic cardiac denervation, progression of cardiac amyloid infiltration [26, 128, 129] |
Cardiac Evaluation in LT: cMRI

- Detailed structural and functional evaluation
- Tissue characterization
- Hemochromatosis: degree of iron overload  
- Familial Amyloidosis: cardiac involvement detected by gadolinium enhancement with HIGH accuracy  
  *Maceira et al. Circulation 2005; 111:186-193*
- CAD: help identify scar and viable myocardium
Relationship During LT

• LT is a cardiovascular stressor:
  – Changes in preload
  – Changes in afterload
  – Sudden release of cytokine and vasoactive mediators

• Greatest impairment is when:
  – Clamp the hepatic vein
  – Time of reperfusion
• **Post-Reperfusion Syndrome**
  - Drop of MAP by at least 30% from baseline for at least 1 min in the first 5 min after reperfusion.
  - Thought to be secondary to cytokines and release of cardio-depressive substances
  - Associated with high levels of pro-inflammatory cytokines like IL-6.
Relationship During LT

- Study by Ripoll et al. 2008

Ripoll et al. Transplantation 2008; 85:1766-1772

- 209 patients with HCC or ESLD
- Examined intra-operative hemodynamics with continuous monitoring of right heart.
- 23% of patients had abnormal cardiac response:
  - ↓SV despite an ↑ in preload (PCWP)
- Patients who developed this seemed to have greater circulatory dysfunction
  - Lower CVP
  - Hyponatremia
- This abnormal cardiac response was associated with longer post-op tracheal intubation time
Relationship During LT

- Abnormal hemodynamic behavior (MAP <40mmHg or mPAP >40mmHg) also associated with negative surgical outcomes:
  - Presence of poor early graft function
  - Primary graft non-function
  - Death due to non-hemodynamic causes

Reich et al, J Cardiothorac Vasc Anest 2003;17:699-702
Relationship Post LT

• Hemodynamic changes in cirrhosis:
  – 2 weeks after LT: $\downarrow$CO, $\uparrow$SVR, normalization of portal hypertension

• Portopulmonary hypertension:
  – Vasodilators should be maintained for approximately 6 months post LT
  – Patients with portopulmonary hypertension have an increased requirement for ventilation and longer ICU stays
Relationship Post LT

- **CAD:** Plotkin et al. Liver Transplant Surg 1996;2:426-430
  - Retrospective review of the outcomes after LT has been reported in 32 patients with pre-existing CAD
    - 9 patients managed medically
    - 1 patient PCI
    - 22 patients surgery
  - Both medically and surgically managed patients had approximately 50% mortality rate at 3 years after LT
De novo presentation of cardiac disease:
- ↑ cardiovascular risk
- Longterm effects of immunosuppression:
  - Hypertension
  - DMII
  - Dyslipemia
  - Obesity
- The prevalence of metabolic syndrome in LT recipients has been reported between 43-58%
• ACS and MI in patients who had received LT has an incidence of almost 5% per year (mean follow-up 58 months)

• More frequent in patients with metabolic syndrome


• Another study observed a 3x ↑ in ischemic events and 2.5x ↑ in risk of cardiovascular death compared to age matched population

Johnston et al. Transplantation 2002;73:901-906
Combined Heart/Liver Tx

- Uncommonly performed and potentially life-saving
- Initial report: Lancet 1984 (Starzl)
  - 6 year old female with severe familial hypercholesterolemia
  - Heart failure due to coronary artery disease

"I don't know who I am. I have a donor heart, a donor kidney, a donor liver, a donor cornea, a donor lung..."
1963
First human liver transplant-
Dr. Thomas Starzl
(University of Colorado)
3 year old boy with biliary atresia – died on the table

1967
First successful human liver transplant-
(University of Colorado)
South African surgeon from Cape Town

First human heart transplant operation, assisted by his brother, Marius Barnard;

The operation lasted nine hours and used a team of thirty people.

The patient, Louis Washkansky, was a 54-year-old grocer, suffering from diabetes and incurable heart disease
TRIVIA

• **Stormie Dawn Jones** (May 30, 1977 – November 11, 1990) was the world's first recipient of a successful simultaneous heart and liver organ transplant.

• On **February 14, 1984**, Drs. Thomas E. Starzl and Henry T. Bahnson replaced the six-year-old's heart and liver at the Children's Hospital of Pittsburgh in Pittsburgh, Pennsylvania.

• Stormie had a condition which raised her blood cholesterol to 10 times normal levels. The condition, a severe form of familial hypercholesterolemia.

• The case showed that the liver controls blood cholesterol and that high cholesterol is controllable, and was part of the research on cholesterol and the liver that won Joseph L. Goldstein and Michael S. Brown the **Nobel prize in medicine in 1985**.

• Stormie died on November 11, 1990. Her death was related to rejection of the heart transplant she had received in 1984.
Combined Heart/Liver Tx

• Indications:
  – End-stage cardiac and liver disease because of related causes
  – End-stage cardiac and liver disease because of unrelated causes
  – End-stage heart disease with liver transplantation performed to correct and underlying disorder.
Combined Heart/Liver Tx

• Indications:
  – Familial amyloid polyneuropathy
  – Hemochromatosis (iron storage disease)
  – Familial Hypercholesterolemia
    • Homozygous
    • Heterozygous
  – Ischemic heart disease and congenital heart disease with cardiac cirrhosis
  – Alcoholic liver disease and heart failure
  – Other causes of cirrhosis and heart failure
Combined Heart/Liver Tx

• OPTN National Data Transplantation Report:
  – 163 combined heart and liver transplant (CHLT)
    • 141 combine heart and liver
    • 13 combined heart, liver and kidney
    • 12 combined heart, liver and lung
  – Graft survival after CHLT is similar to isolated liver or heart transplantation
    • 80% at 1 year and 70% at 10 years
Combined Heart/Liver Tx

• Allocation usually based on liver or heart and mainly local OPO
  – Organ recovered and packed separately
  – Absence of contraindication to the usage of organ
  – Usually not through expanded criteria donation
    • Immediate function of both organs
    • No stress on the heart after reperfusion of the liver
  – Heart implant first (reports on liver first in the presence of preformed antibodies)
Combined Heart/Liver Tx

- *Schaffer et al. AJT 2014:*

- UNOS database (at one year)
  - Wait list mortality higher in CHLT than HRT 26% vs 12% (p=0.001)
  - Wait list mortality higher in CHLT than LT 26% vs 14% (p=0.005)
  - There differences persist after stratifying by disease severity
  - Post Tx survival not different between CHLT and HRT or CHLT and LT
  - Multivariate model:
    - CHLT was associated with enhanced survival for CHLT candidates (HR 0.41; CI 0.21-0.79; p=0.008) but undergoing HRT alone was not.

- 90% of CHLT recipients were allocated an organ locally
  - 60% HRT candidates and 73% LT candidates (p<0.001)
Combined Heart/Liver Tx

Figure 1 Combined heart/liver transplants performed by year in the United States.

Cannon et al. Transplant International 2012; 25: 1223-1228
Liver graft survival of patients undergoing combined heart/liver transplantation versus isolated liver transplantation.

Cannon et al. Transplant International 2012; 25: 1223-1228
Heart graft survival of patients undergoing combined heart/liver transplantation versus isolated heart transplantation.

Cannon et al. Transplant International 2012; 25: 1223-1228
### Combined Heart/Liver Tx

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<tr>
<th></th>
<th>Amyloid indication</th>
<th>Other indications</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver graft survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>92.2%</td>
<td>80.2%</td>
<td>0.585</td>
</tr>
<tr>
<td>3 years</td>
<td>86.4%</td>
<td>67.8%</td>
<td></td>
</tr>
<tr>
<td>5 years</td>
<td>79.7%</td>
<td>67.8%</td>
<td></td>
</tr>
<tr>
<td>Heart graft survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>92.3%</td>
<td>80.3%</td>
<td>0.328</td>
</tr>
<tr>
<td>3 years</td>
<td>86.5%</td>
<td>68.1%</td>
<td></td>
</tr>
<tr>
<td>5 years</td>
<td>79.9%</td>
<td>68.1%</td>
<td></td>
</tr>
<tr>
<td>Patient survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>92.3%</td>
<td>81.5%</td>
<td>0.375</td>
</tr>
<tr>
<td>3 years</td>
<td>86.5%</td>
<td>69.1%</td>
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</tr>
<tr>
<td>5 years</td>
<td>79.9%</td>
<td>69.1%</td>
<td></td>
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</table>

Patient and graft survival for patients undergoing simultaneous cardiac-liver transplantation for amyloidosis versus other indications.

*Cannon et al. Transplant International 2012; 25: 1223-1228*
Combined Heart/Liver Tx

• No consensus statement on combined OHT-OLT exists
• Acceptable survival (like either of the organs alone)
  – 81% 1-year-survival
  – 72% 4-year-survival
• Indications are well known
• Early diagnosis of the problem and early liver transplantation (certain indications) could prevent further deterioration of other organs, e.g. Heart and decrease need for combined transplantation.
Part II: Lung in Liver Disease
Basics on Pulmonary Hypertension
What is PH?

- Pulmonary hypertension is a progressive disorder that affects both the pulmonary vasculature and the heart.
- Leads to right heart failure and eventually death across all PH groups.
- Significant mortality despite several treatment options (mainly PAH group)
  - Oral therapy
  - IV therapy
  - Lung Transplant
Classification

1. PAH
   - Idiopathic PAH
   - Heritable (BMPR2, ALK1, ENG, SMAD9, CAV1, KCNK3)
   - Drug- and toxin-induced
     - Associated with:
       - CTD
       - HIV infection
       - Portal hypertension
       - CHD (L -> R shunt)
       - Schistosomiasis

1’. PVOD and/or PCH ; 1”: PPHN

2. PH Owing to Left Heart Disease
   - Systolic dysfunction
   - Diastolic dysfunction
   - Valvular disease
   - Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH Owing to Lung Diseases and/or Hypoxia
   - COPD
   - ILD
   - Other pulmonary diseases with mixed restrictive and obstructive pattern
   - Sleep-disordered breathing
   - Alveolar hypoventilation disorders
   - Chronic exposure to high altitude
   - Developmental abnormalities

4. CTEPH

5. PH With Unclear Multifactorial Mechanisms
   - Hematologic disorders: splenectomy chronic hemolytic anemia
   - Systemic disorders
   - Metabolic disorders: Gaucher disease, thyroid d/o
   - Others: Segmental PH tumoral obstruction, fibrosing mediastinitis

Denotes change in classification.

Hemodynamic Definitions

- Pulmonary Hypertension – across ALL clinical groups:
  - Mean PAP ≥ 25mmHg

- Mean PAP (mmHg) = \[
\frac{(2 \times \text{Diastolic PAP}) + \text{Systolic PAP}}{3}
\]

- PVR (WU) = \[
\frac{(mPAP-mPCWP)}{CO}
\]
  - x80 = Dyn.s/cm^5
  - TPG, normal <7mmHg, >14-15 worry for Tx – may not get PVR down low enough
Pre-Capillary PH

**Characteristics:**
- Mean PAP ≥ 25mmHg
- PCWP <15mmHg
- CO normal or reduced
- * ↑PVR

**Clinical Groups:**
- Group 1: PAH
- Group 3: PH due to lung diseases
- Group 4: Chronic Thromboembolic PH
- Group 5: PH with unclear and/or multifactorial mechanisms
Post-Capillary PH

• Characteristics:
  – Mean PAP $\geq 25$mmHg
  – PCWP $> 15$mmHg
  – CO normal or reduced
  – PVR normal (pure sense)

• Clinical Groups:
  – Group 2: PH due to L Heart Disease
“Mixed” PH

- Group 2 PH – Left Heart Disease but Multifactorial

- Example:
  75F with scleroderma but has HTN, DM and OSA and ↑PCWP

- May not respond the same way to Group 1 therapy
Histopathology

Pan-Vasculopathy of SMALL pulmonary arteries

↑Cellular proliferation

↓Apoptosis

Vasoconstriction

Intimal hyperplasia, medial hypertrophy, adventitia proliferates, thrombosis in situ, inflammation → PLEXIFORM LESIONS
Pathology

Portopulmonary Hypertension (POPH)
Definition

- POPH is defined as PAH associated with portal hypertension, **whether or not** the portal hypertension is secondary to primary liver disease.

- Characterized by $\uparrow$PVR as a consequence of obstruction to pulmonary arterial blood flow.

- Severity and prognosis depends on **both** the severity of PAH and the underlying liver disease.
Epidemiology & Prevalence

• Prevalence of POPH in patients with liver disease is approximately 2-5%.
• Prevalence of POPH in those undergoing liver transplant assessment-reported is 0.76-8.5%.
• *REVEAL* Registry-portal hypertension as a cause of all registered PH is 5.3%.
Etiology

CIRRHOTIC

NON-CIRRHOTIC

- Biliary atresia
- Extrahepatic portal vein obstruction
- Non-cirrhotic portal fibrosis
- Idiopathic Portal Hypertension
Epidemiology & Prevalence

• POPH commonly diagnosed in the 5th decade of life
• Diagnosis made on average 4-7 years after the diagnosis of portal hypertension
• Clinical Risk Factors:
  - Female sex
  - Autoimmune hepatitis
  - Portocaval shunts
  - Splenectomies
• Hepatitis C infection associated with ↓risk
Pathology & Histology
Pathology & Histology

Pathology & Histology

- Obstruction to blood flow is caused by a combination of:
  - Vasoconstriction
  - Pulmonary Endothelial/Smooth cell proliferation
  - Plexogenic arteriopathy
  - In-situ thrombosis

- ↑ ET-1
- ↓ Prostacyclin synthase levels

- Altered estrogen signaling is associated with cellular/growth apoptosis and oxidative stress — but no relationship with BMPR2 has been observed.
Pathophysiology

- 30-50% pts with cirrhosis have hyperdynamic circulation:
  - ↑CO
  - ↓SVR
  - ↓PVR
- mPAP may be elevated because of increase in CO and blood volume – but PVR will be low or normal.
Pathophysiology

• POPH
  – ↑PVR (>3wu)
  – ↑TPG (>12mmHg)
• Initially, ↑CO due to the underlying liver disease
• As severity of disease progresses, ↓CO
Clinical Features & Investigations

• Most common symptoms: Dyspnea on exertion.
  – Tense ascites
  – Cardiomyopathy
  – Hepatic hydrothorax
  – Hepatopulmonary syndrome

• As the severity of POPH increases, patients may develop:
  – Syncope
  – Chest pain on exertion
Clinical Features & Investigations

**Clinical examination:**

- **EARLY STAGES:**
  - Chronic liver disease
- **LATER STAGES:**
  - Signs of right sided HF – overwhelming fluid overload
- **BEWARE:**
  - Some patients remain asymptomatic – or only have signs of portal hypertension.
- Need to have high degree of suspicion, especially when evaluated for LTx.
Clinical Features & Investigations

• **EKG:**
  – RAE
  – RVH
  – RBBB
  – TWI V1-V4

• **PFTs:**
  – ↓ DLCO
  – Mild restrictive pattern

• **CXR:**
  – Right-sided cardiac hypertrophy

• **V/Q Scan:**
  – “Mosaic pattern” of hypertrophy
Hepatopulmonary Syndrome

• Characterized by triad of
  – Arterial deoxygenation (a widened $P_{A-a,o2}$) with or without hypoxaemia
  – Intrapulmonary vascular dilatation
  – Liver disease

• Can occur with any degree of liver disease, ranging from well-compensated chronic liver disease without cirrhosis to non-cirrhotic portal hypertension and cirrhosis.
Hepatopulmonary Syndrome

• The consequence of the intrapulmonary vasodilation is arterial doxygenation by three mechanisms:
  – Ventilation/perfusion (V/Q) mismatch
  – Intrapulmonary shunting
  – Limitation of the oxygen diffusion

• The main mechanism is related to V/Q mismatch
  – Usually improves when breathing 100% O2
## POPH vs. HPS

<table>
<thead>
<tr>
<th></th>
<th>PPHTN</th>
<th>HPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Similar to primary pulmonary hypertension with intense vasoconstriction of pulmonary capillaries as well as remodeled, thickened pulmonary vasculature</td>
<td>Arteriovenous (AV) shunting in the lung, predominantly at the bases. “Spider angiomata” in the lung.</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Dyspnea on exertion, syncope, orthopnea</td>
<td>Platypnea</td>
</tr>
<tr>
<td><strong>Physical findings</strong></td>
<td>Loud P2, RV heave, TR murmur, hypoxemia worsens with exercise (normal O₂ saturation at rest is common)</td>
<td>Hypoxemia, orthodeoxia</td>
</tr>
<tr>
<td><strong>Echocardiogram</strong></td>
<td>Elevated pulmonary artery systolic pressure</td>
<td>Positive bubble study</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Same as primary pulmonary hypertension; if mean PAP &lt; 40 mmHg, can safely undergo liver transplantation.</td>
<td>Liver transplantation</td>
</tr>
</tbody>
</table>
Hemodynamics

### POPH Criteria:
- mPAP >25mmHg at rest
- PVR >3WU
- PCWP <15mmHg
- Portal pressure >10mmHg

<table>
<thead>
<tr>
<th></th>
<th>mPAP</th>
<th>CO</th>
<th>PCWP</th>
<th>PVR</th>
<th>TPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>High cardiac output and vasodilated</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓↓</td>
<td>N↑</td>
</tr>
<tr>
<td>Fluid overload or diastolic dysfunction</td>
<td>↑</td>
<td>N↑</td>
<td>↑↑</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>POPH</td>
<td>↑↑</td>
<td>↓↓</td>
<td>N</td>
<td>↑↑</td>
<td>↑</td>
</tr>
</tbody>
</table>
Management

• POPH is considered WHO Group 1 PAH, and therefore should be amenable to all the FDA approved therapy for this group of pts

• HOWEVER, POPH patients were excluded from clinical trials for these agents

• Data is limited to case series and observational studies
  – Lack for RCTs
General Management

- Diuretics
- Oxygen (maintain sats >90%)
- CCB contraindicated because may increase hepatic venous congestion gradient
  - Bleeding of gastroesophageal varices
- BB may worsen exercise capacity and pulmonary hemodynamics
Endothelin Antagonists

AGENTS:
- Bosentan
- Ambrisentan

ENDOTHELIN:
- Vasoconstrictor
- Smooth muscle proliferation
- Vascular remodeling

In PAH pts ↑ET-1
- c/w dz severity
- c/w outcome

↑6MWD, exercise capacity and hemodynamics in PAH
- Limited data in POPH
Endothelin Antagonists

• Bosentan has shown improvement in exercise capacity and survival in small, single center, uncontrolled, observational trials

• Bosentan limited on POPH population because of hepatotoxicity (in approx. 10% of pts)
  – Likely related to its inhibition of a bile salt transporter, and is reversible with drug discontinuation

• Ambrisentan – no hepatotoxicity
  – Single center, uncontrolled, observational trial in POPH from the Mayo Clinic reported a significant improvement in mPAP and PVR with treatment and no hepatotoxic events.
Phosphodiesterase Type 5 Inhibitors

AGENTS:
- Sildenafil
- Tadalafil

Nitric Oxide (NO)
- Potent vasodilator & anti-proliferative
- Activates soluble guanylate cyclase - $\uparrow$ cGMP
- cGMP (degraded by PDE)

**Mechanism PDEi:**
- cGMP-dependent vasodilation
PDE5i

• Small uncontrolled observational trials reveal that sildenafil treatment of POPH
  – ↑6MWD
  – ↓NT-pro-BNP

Correlate with better prognosis in PAH pts

• Reported hemodynamic response is mixed
  – 1 observational trial reporting improved PVR in 3/5 pts at 1 year
  – 1 observational trial reporting improved PVR in all 9 pts at a f/u time varying between 95-282 days
Prostacyclins

AGENTS
- Epoprostenol (IV)
- Treprostinil (IV or S/C)
- Iloprost (inhaled US, IV Europe)

Patients with PAH
- Decreased production of prostacyclin

Prostacyclin activated adenyl cyclase – converts ATP to cAMP
- Vasodilation
- Anti-proliferation
- Inhibition of plt aggregation
Prostacyclins

• Uncontrolled single center series have consistently demonstrated that prostacyclin infusions result in significant improvements in mean PAP, CO and PVR in patients with POPH

• Prostacyclin infusions have been successfully used to improve hemodynamics in pts with POPH to the degree that liver transplantation can be safely pursued

• Less data exists for inhaled iloprost
Liver Transplantation (LT)

- HISTORY IS CONTROVERSIAL
- EARLY experiences, POPH pts:
  - Not treated
  - Not under care of a medical team familiar with critical care of the POPH pt
  - Not surprisingly, intraop death from decompensated RHF was common
  - Longterm outcome was also affected
    - sPAP >60mmHg had a 9-month post-transplant survival of 58%

With experience and the advents of new treatment modalities for PAH
- Successful liver transplants
- Regression of POPH after liver transplantation

2006 – BUMC
- 8 sequential cases of severe POPH who were treated with IV epoprostenol
- 7/8 had significant hemodynamic improvement with epoprostenol
- 6/8 were listed for LT
- 4/6 were successfully transplanted
LT

- Of those transplanted, survival was 100% at 5 years
- Retrospective RHC screening analysis published from Mayo clinic documented:
  - lowest 5-year survival in POPH pts who were neither transplanted nor treated for PH
  - Highest 5-year survival (64%) in those both treated for PH and transplanted
• Retrospective studies have identified risk factors for perioperative mortality:
  – mPAP <35mmHg AND normal RV function, perioperative mortality approaches those without portopulmonary hypertension
  – mPAP >50mmHg at time of transplant, mortality approaches 100%
LT

• UNOS has allowed for upgrade points in the model for end-stage liver disease (MELD) system for POPH patients who meet criteria, to expedite liver transplantation.

• MELD system prioritizes LT for the sickest pts with liver dz
  – Exception allows extra points for pts whose mortality risk is not reflected in their MELD score
• Guidelines currently state:
  – If a pt is diagnosed with POPH
    • (using mPAP, PVR and TPG)
  – AND, are treated with pulmonary vasodilator therapy to attain
    • mPAP <35 mmHg
    • PVR <5 wu

→ They are eligible for a MELD exception to 22 points, with an increase in their MELD by 10% every 3 months until they are transplanted
• Peri-op course may be difficult – even in pts WITHOUT POPH

• “Reperfusion Syndrome” at time of allograft reperfusion
  – Acute ↑ in both CO and PAP
  – Acute decompensated RV failure

• Use of intra-op prostacyclin infusions, inhaled NO or IV milrinone has been reported with mixed results.
• Limited data exists regarding the clinical course of POPH after liver transplantation

• POPH progression, stability, improvement and resolution have all been reported

• In MOST cases, pts are able to wean from their prostacyclin infusion over a period of months, but some remain on oral pulmonary vasodilators

• Available data suggests that 40-50% of patients may be able to be weaned from all pulmonary vasodilators given enough time.

Take Home Points

• Heart, lung and liver are closely related and influence each other in health and disease states.
• In the pre-transplant patients with liver disease, attention should be placed on identification of subclinical cardiac disease that influences surgical risk and long term outcome.
• Portopulmonary hypertension identified on screening test should be further characterized with right heart catheterization. Treatment with vasodilators in patients with moderate or severe portal hypertension can be attempted.
Take Home Points

• Don’t confuse POPH (development of PH in a cirrhotic pt) with HPS (shunting and V/Q mismatch due to AVM in the lung

• Most common symptoms of POPH
  – Dyspnea on exertion

• Previously thought to be a contraindication to liver transplantation, now can be pre-treated with pulmonary vasodilators to achieve mPAP <35mmHg, PVR <5wu
Take Home Points

• Screening for coronary artery disease is recommended in high risk patients, although clear recommendations regarding management of these patients remain to be elucidated.

• During LT, close surveillance of hemodynamic factors can improve outcome. Patients with greatest hemodynamic derangement (Child-Pugh class C), portopulmonary hypertension and familial amyloid polyneuropathy have the greatest difficulties of intraoperative management.
Take Home Points

• Cardiovascular events are an important cause of morbidity and mortality in the post-LT period.
• Special care of previous disease and effort to control newly developed risk factors should be attempted.
Take Home Points
Thank you

Be An Organ Donor; Save a Life