Cardiopulmonary Considerations in Patients awaiting Liver Transplantation

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Speaker Disclosure

- I have no financial conflicts, relationships or affiliations to disclose related to this topic.
The Endothelium: The Vital Organ
Endothelial Cells

- Vasoconstriction/Vasodilation: Blood Pressure
- Thrombosis/Fibrinolysis
- Produces Thrombomodulin
- Inflammation
- Passage: Transit of PMNs
- Glomeruli/Blood brain barrier
- Atherosclerosis
- Nitric oxide: Key modulator
Endothelium
Complications of Cirrhosis

- Coagulopathy
- Bleeding varices
- Ascites
- Hepatic Encephalopathy
- Portal Hypertension
- Hepatorenal syndrome
- Sepsis
- Hepatocellular Cancer
- Severe Debilitation
- Cirrhotic cardiomyopathy
- POPH/HPS
- Muscle wasting,
- Malnutrition
- Hypertrophic osteoarthropathy
- Gynecomastia
- Dupytrens
- Fetor hepaticus
- Jaundice
- Weakness/fatigue/anorexia
- Bruising/itching/fragile skin
Multi-Organ Dysfunction
Cirrhosis

- Named by René Laennec in 1819 – derives from Greek word meaning “Tawny”
Liver Cirrhosis – Scarring of the Liver
LIVER CIRRHOSIS
Portal Hypertension

- Portal venous system drains all the splanchnic blood to the liver where it is detoxified and nutrients are processed.
- In the cirrhotic scarred liver this portal blood backs up at increased pressure.
- This portal blood connects to other veins, bypassing the liver and forming varices.
- THIS IS NOT GOOD!
Portal Hypertension

- Splenomegaly: traps platelets
- Large varices: bleeding: esophagus, hemorrhoidal
- Ascites and edema
- The toxins bypass liver causing endothelial dysfunction and major organ dysfunction
- Portal hypertension may be relieved prior to surgery by Transjugular Intrahepatic Portosystemic Shunt (TIPS) procedure. This results in an increased cardiac output and may precipitate failure or worsen POPH
Major Cardiac Concerns for Patients on Transplant List

- Cirrhotic Cardiomyopathy
- Volume Overload
- High Cardiac Output: Low SVR
- Portopulmonary Hypertension
- Right Ventricular Dysfunction
- Coronary Artery Disease
Major Pulmonary Concerns

- Refractory Hepatic Hydrothorax: Abdominal Ascites
- Interstitial Lung Disease/Fibrosis: PBC, AILD, Hep C
- Hepatopulmonary Syndrome HPS
- Portopulmonary Hypertension POPH
- Advanced COPD: smoking related: Alpha-1 ATD emphysema
- Pulmonary AV malformations
- Pulmonary nodules: HCC mets
Refractory Hepatic Hydrothorax
Refractory Hepatic Hydrothorax

Krok & Cardenas. Semin Respir Crit Care Med 2012; 33: 3-10
Cardiomyopathy

- Cardiomyopathy may exist in all cirrhotics\textsuperscript{1}
- *Low SVR conceals poor LV function*
- More common in alcoholic disease
- *Reduced responsiveness to beta agonists*
- Severe cardiomyopathy may be unrecognized prior to OLT
- *Low threshold for dobutamine stress echo and volume challenge*

Molecular Basis of Blunted Cardiac Response
Figure 1 Clinical Basis of Blunted Cardiac Response
Figure 2: Clinical View on Relationship Between Clinical and Instrumental Abnormalities and Cardiac Function

<table>
<thead>
<tr>
<th>CLINICAL Findings</th>
<th>Hyperdynamic State</th>
<th>Hyperdynamic State ↑↑↑ Palpitations Tachycardia</th>
<th>Hypotension Cardiac Failure sign and symptoms Pulmonary edema</th>
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<tbody>
<tr>
<td>ECG abnormalities</td>
<td>QT prolongation</td>
<td>Multiple Extrasystoles QT prolongation ↑↑↑</td>
<td>Bundle branch block ST-segment depression Electrical and mechanical dyssynergy</td>
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<tr>
<td>Echocardiographic Findings</td>
<td>prolonged isovolumetric relaxation time</td>
<td>prolonged isovolumetric relaxation time (&gt;80ms) decreased pattern of contractility Diastolic dysfunction</td>
<td>- enlarged left atrium - decreased wall motion - increased wall thickness Systolic dysfunction</td>
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</table>
Cirrhotic Cardiomyopathy

- Reduced ability to compensate for hemodynamic stressors.
- Prolonged QT
- Onset of atrial fibrillation
- Systolic and diastolic dysfunction
- Down regulation of beta -1 receptors PLUS Beta-blockers!
- THEY DON’T RESPOND TO USUAL DOSES OF INOTROPES!
- Consider norepinephrine, vasopressin, methylene blue
Effects of Portal Hypertension

Liver
- Portal hypertension
- Endothelin-1
- Shear stress
- Bacterial translocation / TNF-α
- MACROPHAGE
- VEGF
- NO
- CO
- Smooth muscle cell
- HPS
- Angiogenesis

Lung
- Vasoconstriction
- Remodeling
- POPH
Main histopathological features of pulmonary arteriopathy

Hepatopulmonary Syndrome

- Documented in 4-32% of patients evaluated for LT

- A Triad Defines HPS:
  - Liver disease
  - Arterial Hypoxemia due to:
    - Intrapulmonary vascular dilatations (Detected by Contrast ECHO or $^{99m}$Tc macroaggregated albumin lung-brain perfusion scanning)

Screening tool:
- Pulse oximetry
5 – 6 beat delay for appearance in left chambers
Hepatopulmonary Syndrome

- Basically ventilation perfusion mismatches, diffusion limitation and shunting appear to be the key physiological mechanisms seen in HPS.
Mechanisms of Arterial Hypoxemia in the Hepatopulmonary Syndrome in a Two-Compartment Model of Gas Exchange in the Lung

HPS Shunts

• Bypass of alveoli by pleural and hilar vessels
  • *Spider talangectasia on pleural surface*

• Portopulmonary anastomoses
  • *Big shunts*

• Dilated pulmonary capillaries
  • *$O_2$ travels further*
  • *Reduced transit time*
  • *RBC’s do not deform*
    • *Necessary to load & unload $O_2$*
HPS Clinical Features

- Cyanosis
- Digital clubbing
- Cutaneous telangectasia
- Platypnea – Orthodeoxia Syndrome: postural hypoxemia accompanied by breathlessness (dyspnea and hypoxia induced by upright posture)
Clinical Features of Severe Hepatopulmonary Syndrome in a 38-Year-Old Man

Hepatopulmonary Syndrome

- Diagnostic tools:
  - Pulse oximetry as a screening tool
  - Contrast echocardiography-agitated saline
  - Technetium-99m-labelled macroaggregated albumin perfusion scan.
Figure 1. Proposed screening algorithm for hepatopulmonary syndrome.
Grading of Severity of HPS (all with positive CEE)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
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<tr>
<td>MILD</td>
<td>Abnormal AaPO$_2$ ($\geq$ 15 mmHg)</td>
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<tr>
<td>MODERATE</td>
<td>60 mmHg &gt; PaO$_2$ &lt; 80 mmHg</td>
</tr>
<tr>
<td>SEVERE</td>
<td>50 mmHg &gt; PaO$_2$ &lt; 60 mmHg</td>
</tr>
<tr>
<td>VERY SEVERE</td>
<td>PaO$_2$ &lt; 50 mmHg and after 100% O$_2$ &lt; 300 mmHg</td>
</tr>
</tbody>
</table>

Survival curves from the time of HPS diagnosis for HPS patients and controls (from time of PaO$_2$ determination) undergoing OLT ($P=0.69$); and HPS patients and controls not undergoing OLT ($P=0.0003$).
Survival based on initial PaO$_2$ determinations at the time of HPS diagnosis in patients with HPS based on transplant status.

Swanson et al  Hepatology 2005;41:1122
Sequential oxygen assessments of 14 patients with HPS while awaiting liver transplantation.
Sequential oxygen assessments of 18 patients with HPS pre- to post-liver transplantation.
HPS increases Mortality Rate Following OLT  
Schiffer et al. AJT 2006;6:1430

- Complete recovery from HPS at 6 months
- Mortality 33% with PaO2 < 50 mmHg
- Cause of death: Sepsis, ARDS, MOF
Number of Days from OLT and Death and Cause of Death in Patients with HPS

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Time of Death (Days After OLT)</th>
<th>Cause of Death</th>
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<tbody>
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<td>Sepsis, pulmonary hypertension</td>
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<td>Respiratory failure, intracranial hemorrhage</td>
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<td>Atrial fibrillation, cerebrovascular accident</td>
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</table>
# Improved Survival after OLT in Patients with HPS

Gupta S et al. AJT 2010; 10:354-63

Table 3: Baseline HPS evaluation and type of liver transplant

<table>
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<tr>
<th>Patient no.</th>
<th>PaO₂ (RA) (mmHg)</th>
<th>AaDO₂ (mmHg)</th>
<th>PaO₂ (100%) (mmHg)</th>
<th>OSR (%)</th>
<th>MAA shunt (%)</th>
<th>DLCO (% predicted)</th>
<th>Clubbing</th>
<th>FIO₂ (L/min)¹</th>
<th>Type of LT</th>
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Mean (SD) 50.7 (11.8) 62.8 (14.7) 437.5 (107.6) 13 (6) 28.7 (17.9) 47.1 (9.9) − − −
## Post-Op Course

Table 5: Postoperative course

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<tr>
<th>Patient no.</th>
<th>Preoperative PaO₂ (RA) (mmHg)</th>
<th>Duration of intubation/tracheostomy (days)</th>
<th>Duration of MV (days)</th>
<th>Duration in ICU (days)</th>
<th>Duration of hospital stay (days)</th>
<th>Time to cessation of oxygen (days)</th>
<th>Current survival at study end (days)</th>
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# Survival Studies

## Table 4: Post liver transplant mortality

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<tr>
<th>Study</th>
<th>Overall mortality</th>
<th>Mortality in severe HPS</th>
<th>Follow-up period</th>
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<td>Current study</td>
<td>1/21 (5%)</td>
<td>1/11 (9%)</td>
<td>20 months (median)</td>
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<td>0/20 (0%)</td>
<td>0/11 (0%)</td>
<td>Transplant hospitalization</td>
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<tr>
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<td>0/19 (0%)</td>
<td>0/9 (0%)</td>
<td>3 months</td>
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<td>0/18 (0%)</td>
<td>0/9 (0%)</td>
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<td>1/14 (7%)</td>
<td>1/7 (14%)</td>
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<td>13/81 (16%)</td>
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<td>Krowka et al. (11)</td>
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<td>Taille et al. (10)</td>
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<td>Transplant hospitalization and 12 months</td>
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<td>Arguedas et al. (9)</td>
<td>7/23 (30%)</td>
<td>6/9 (67%)</td>
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<td>Krowka et al. (8)</td>
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<td>Swanson et al. (7)</td>
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<td>≥5/24 (21%)</td>
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AJT 2010; 10:354-63
Outcomes

AJT 2010; 10:354-63
After Liver Transplantation

- Hepatopulmonary syndrome
  Resolves: indication for OLT

- Portopulmonary hypertension
  Resolution uncertain
  May be unmasked by resolving hepatopulmonary syndrome
  NOT an indication for OLT
Pathophysiology of POPH

- Initial endothelial dysfunction resulting in vasoconstriction that is reversible
- Vascular remodeling; intimal proliferation, medial hypertrophy and plexogenic changes in the media.
- Fibrosis that is not reversible
Spectrum of Pulmonary Arteriolar/Capillary Injury

Fig. 1—The spectrum of portopulmonary hypertension. These color microphotographs of pulmonary arterial lesions, which also appear on the cover of this journal, show a) thrombotic type (autopsy), b) plexogenic type with platelet aggregates (autopsy), c) plexogenic type with microaneurysm (lung explant), and d) fibrotic type (autopsy).
Pulmonary Hypertension

- 20% of patients with advanced liver disease: increased CI and decreased PVRI and often increased PAOP

Portopulmonary Hypertension

- Present in 5.3% - 8.5% of patients with advanced liver disease

Pathophysiology of POPH


A. Normal Hemodynamics. Pulmonary artery pressure, cardiac output, PVR, and PCWP are normal.

B. PAH. Elevated pulmonary artery pressure caused by increased PVR with normal cardiac output and PCWP.

C. High-flow condition. Elevated pulmonary artery pressure caused by increased cardiac output but normal PVR and PCWP.

D. Pulmonary venous hypertension. Elevated pulmonary artery pressure caused by increased PCWP, normal cardiac output and PVR.
Recently, many investigators have followed the diagnostic criteria proposed by the European Respiratory Society–European Association for the Study of the Liver (ERS-EASL) Task Force on Hepatic-Pulmonary Vascular Disorders of POPH:

1. MPAP $\geq$ 25 mm Hg;
2. PVR $\geq$ 240 dynes/s/cm$^5$; and
3. TPG > 12 mmHg

PAOP may be elevated in POPH but NOT PAH

$PVR (\text{dynes.s.cm}^{-5}) = \frac{(\text{MPAP-PAOP})}{\text{CO}} \times 80$

Survival Worse for POPH than IPH

CHEST 2012; 141(4):906–915

![Graph showing survival rates for IPAH/FPAH and POPH with survival rates and number of participants at risk over time.]
Pulmonary Circulation

- Low pressure
- Low resistance
- Highly distensible – capable of handling significant increases in volume.
- Increase in blood flow results in minimal increase in pressure unless severe.
Right Ventricle

- Thin walled chamber
- Very little muscle
- Unable to respond to an acute increase in afterload
- Under resistance will dilate leading to dilated atrium, increased CVP and congested liver.
- What does the RV look like on this patient?
Figure 1 Pathophysiology of acute pulmonary hypertension causing right ventricle failure

LVEF, left ventricular ejection fraction; PAH, pulmonary arterial hypertension; RV, right ventricle.  
Ramsay  Cur Opin Anaesth  2010;23:145
Portopulmonary Hypertension

- Progressive disease
- Results in RV failure and death
- Life expectancy without liver transplantation:
  - Median survival 8 months to 2.3 years
  - Le Pavec\(^1\) – 88% at 1 year, 75% at 3 years
  - Kawut\(^2\) - 85% at 1 year, 38% at 3 years

1. Am J Respir Crit Care Med 2008;178:637
2. Hepatology 2008;48:196-203
RV Dilatation
Survival Considerations with Liver Transplantation

1. The Patient – RV Dysfunction – RV Failure – Death

2. The Graft – RV Dysfunction – Graft Congestion – Graft Failure
Screening for POPH

- Transthoracic Doppler echocardiography screening for all patients with portal hypertension on waiting list for liver transplant
- Requires presence of tricuspid regurgitant jet to calculate RV systolic pressure RVSP
  - $RVSP = 4(TRV)^2 + RAP$
- Negative predictive value of 100% for PASP > 30 mm Hg
- Positive predictive value of 59%
  - Hepatology 2003;37:401-9
- 97% sensitivity 77% specificity
  - Liver Transpl 2000;6:453-458
Screening for POPH

Farzaneh-Far et al AJC 2008;101:259-262

- RVSP > 50 mmHg are referred for right heart catheterization.

- Ratio of peak tricuspid regurgitant velocity (TVR) to right ventricular outflow tract velocity time integral ($VTI_{RVOT}$) is superior to RVSP and may decrease need for right heart catheterization
RSVP

PULMONARY HYPERTENSION:

- 20% of patients with advanced liver disease: increased CI and decreased PVRI and often increased PAOP: This is the result of a very hyperdynamic circulation and frequently volume overload and maybe compromised by cirrhotic cardiomyopathy.

PORTOPULMONARY HYPERTENSION (POPH)

- True POPH is found in 5-8% (adults and children) of patients with PORTAL HYPERTENSION.
- POPH does NOT correlate with severity of liver disease
Outcomes: POPH after OLT

71% mortality over 36 months after liver transplantation in patients with severe POPH treated with conventional therapy (prior to epoprostenol)

## POPH & Perioperative Mortality

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>mPAP 25-35 mmHg PVR &lt; 240 No increase in mortality</td>
</tr>
<tr>
<td>Moderate</td>
<td>mPAP 35-45 mmHg PVR &lt; 240 Increased mortality: up to 50%</td>
</tr>
<tr>
<td>Severe</td>
<td>mPAP &gt;45 mmHg PVR &gt;240 Mortality 70–100%</td>
</tr>
</tbody>
</table>
Major Decision Determinants for OLT

- Right ventricular function

  - Assess with transesophageal echocardiogram on the OR table
Decision Tree

**Needs ECHO**

1. \( \text{mPAP} < 35 \text{ mmHg} \) → \( \text{PVR} < 240 \text{ dynes.s.cm}^{-5} \) → Good \( Q_T \) and right ventricular function → **TRANSPLANT**

2. \( \text{mPAP} 35 – 40 \text{ mmHg} \) → \( \text{PVR} > 240 \text{ dynes.s.cm}^{-5} \) → Good cardiac function determined by TEE challenge → **TRANSPLANT**

   Attempt to reduce \( \text{mPAP} < 35 \text{ mmHg} \) and \( \text{PVR} < 240 \text{ dynes.s.cm}^{-5} \)

   Irreversible, but right ventricular function is good (dobutamine and fluid challenge OK) → **TRANSPLANT**

   Poor ventricular function or dilated right heart → **DEFER SURGERY**

3. \( \text{mPAP} > 40 \text{ mmHg} \) → \( \text{PVR} > 240 \text{ dynes.s.cm}^{-5} \) → **DEFER SURGERY**

   Initiate vasodilator therapy
TREATMENT for POPH

- **Prostacyclin:**
  - Epoprostenol IV > 2ng/kg/day
  - Inhaled Iloprost 5 µg 6 x day

- **Endothelin receptor antagonist**
  - Bosentan oral 125 mg bid

- **Phosphodiesterase inhibitor**
  - Sildenafil oral 20 mg tid

- **HMG-CoA reductase inhibitor**
  - Simvastatin oral 40 mg/day

- **Chronic iNO**
## Hemodynamic/Right Ventricular Responses to Epoprostenol Therapy

<table>
<thead>
<tr>
<th>Timeline</th>
<th>mPAP (mmHg)</th>
<th>PVR (dyne·s·cm⁻⁵)</th>
<th>CI (L/m²)</th>
<th>RVEDV (ml)</th>
<th>RVESV (ml)</th>
<th>RVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial</strong></td>
<td>55</td>
<td>445</td>
<td>3.6</td>
<td>176</td>
<td>140.5</td>
<td>20</td>
</tr>
<tr>
<td><strong>At OLT</strong></td>
<td>45</td>
<td>180</td>
<td>5.1</td>
<td>102.1</td>
<td>66.9</td>
<td>34.2</td>
</tr>
<tr>
<td><strong>Post-op</strong></td>
<td>38</td>
<td>211</td>
<td>5.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Patient 1</strong></td>
<td><strong>Initial</strong></td>
<td>40</td>
<td>406</td>
<td>2.57</td>
<td>67.8</td>
<td>36.3</td>
</tr>
<tr>
<td><strong>At OLT</strong></td>
<td>39</td>
<td>366</td>
<td>4.5</td>
<td>79.2</td>
<td>24.8</td>
<td>69</td>
</tr>
<tr>
<td><strong>Post-op</strong></td>
<td>39</td>
<td>432</td>
<td>2.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Patient 2</strong></td>
<td><strong>Initial</strong></td>
<td>43</td>
<td>275</td>
<td>4.5</td>
<td>176</td>
<td>140.5</td>
</tr>
<tr>
<td><strong>At OLT</strong></td>
<td>46</td>
<td>298</td>
<td>4.4</td>
<td>38.3</td>
<td>18.1</td>
<td>52</td>
</tr>
<tr>
<td><strong>Post-op</strong></td>
<td>36</td>
<td>336</td>
<td>3.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Patient 3</strong></td>
<td><strong>Initial</strong></td>
<td>60</td>
<td>447</td>
<td>3.6</td>
<td>55.7</td>
<td>32.9</td>
</tr>
<tr>
<td><strong>At OLT</strong></td>
<td>50</td>
<td>180</td>
<td>5.1</td>
<td>46.4</td>
<td>15.8</td>
<td>66</td>
</tr>
<tr>
<td><strong>Post-op</strong></td>
<td>38</td>
<td>211</td>
<td>5.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
Acute Elevation in mPAP

- Following reperfusion of the new liver graft there is an unpredictable increase in cardiac output
- CO typically increases 5 – 18%* however, 300% increase may occur
- Results in a large increase in mPAP

Graphic Trends

Pressure (mmHg)

Time (hr:min)

Cardiac Output

Reperfusion

15.7
5.9
12.5

PA2-S
PA2-D
PA2-M
Acute Increase in MPAP

Treatment

- iNO
- Epoprostenol IV or inhaled (limited by systemic hypotension)
- Sildenafil via NG tube
- Consider atrial septostomy
- Right ventricular assist device or AV ECMO
CVP 5  CVP 15  CVP 17  CVP 12

CO 16 l/min

iNO 20 ppm  5 ppm  0 ppm  20 ppm

CO 16 l/min
Portopulmonary Hypertension

- Increased pulmonary vascular resistance: vasoconstriction, structural vascular remodeling and eventual fibrosis.
- Right ventricular overload
- Right heart failure
- Death
Management of POPH

- Liver Transplantation: increased risk and may not reverse POPH
- Anticoagulation: may prevent thromboembolism and microthrombosis but patients at increased risk of variceal bleeding
- TIPS: may worsen POPH because of increase in preload, CO and mPAP
- Calcium channel blockers: may increase hepatic venous pressure gradient and worsen portal hypertension
Specific Therapies for POPH

- Prostanoids
- Endothelin receptor antagonists
- Phosphodiesterase inhibitors
- Inhaled nitric oxide
- Combination therapies
- Liver transplantation in selected patients
- ??V-A ECMO ??RVAD
- Liver combined with bilateral lung transplantation
- Antiproliferation therapy
- Research innovation
The combination of pulmonary hypertension and hepatopulmonary syndrome has been reported.

Autopsy: hypertensive pulmonary arteriopathy together with dilation of precapillary arterioles

Unmasking Pulmonary Hypertension with OLT

- Development of severe pulmonary hypertension and amelioration of severe hepatopulmonary syndrome after liver transplantation

Thanks for your attention