Liver Disease in Pulmonary Hypertension

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Background

• With success of liver transplantation (LT)
  • Liver – lung relationships more than academic interest
  • 6,000 LT/yr; 18,000 pts on waiting lists
  • 5% have clinically significant lung problems that may affect LT survival
Pulmonary Vascular Consequences of Hepatic Dysfunction

Vascular dilatation

1) precapillary and capillary dilatations
2) arteriovenous communications

“Hepatopulmonary Syndrome”

Vascular obstruction

Proliferation of endothelium and smooth muscle/fibrosis
± in situ thrombosis (anatomic shunts)
plexogenic arteriopathy

“Portopulmonary Hypertension”

Oxygenation issue ...
...hypoxemia

Hemodynamic issue ...
...right heart failure
Hemodynamic Patterns

- Liver may be an active or passive contributor to problems in PH
  - Liver disease leads to high cardiac output
    - PVR should be normal
    - \( \frac{(MPAP - PAOP)}{CO} = PVR \)
  - Liver disease may lead to excess volume
  - Liver disease may cause PH = POPH
    - By definition, PVR is increased
    - Hemodynamic abnormality – Right heart failure
Hemodynamic Patterns in Advanced Liver Disease

- **Hyperdynamic Circulatory State**
  - MPAP: ↑
  - PVR: ↓
  - CO: ↑
  - PAOP: ↓

- **Excess Volume**
  - MPAP: ↑
  - PVR: ↑
  - CO: ↓
  - PAOP: ↓

- **Vasoconstriction with vasoproliferation (e.g. POPH)**
  - MPAP: ↑
  - PVR: ↑
  - CO: ↑
  - PAOP: ↓
Doppler Echocardiography to Estimate RVsys Pressure

\[
\Delta p = 4(\text{TR})^2
\]

\[
\text{RVsys} = \text{RA est} + \Delta p
\]

If no TR…
RV size?
RV function?

TR=Tricuspid Regurgitant
Peak Velocity (m/sec)
Portopulmonary Hypertension

- Hemodynamics characterized at RHC
- **Definition**
  - MPAP > 25 mm Hg at rest
  - PVR > 240 dyne.s.cm\(^{-5}\) (> 3 WU)
  - Normal PAOP (<15 mm Hg) or abnormal TPG (> 12 mm Hg)
- Chronic liver disease
  - Associated with cirrhotic or non-cirrhotic portal hypertension
Portopulmonary Hypertension

- Pathologically similar to iPAH
  - Plexogenic lesions
  - Smooth muscle/intimal hypertrophy
- Classified in 1993 as a form of secondary PH *Chest* 1993;104:236
- Re-classified in 2003 as ‘associated with pulmonary arterial hypertension’ *Venice 2003 JACC 2004; 43:5S – 12S*
### Table 3. Revised Clinical Classification of Pulmonary Hypertension (Venice 2003)

1. Pulmonary arterial hypertension (PAH)
   1.1. **Idiopathic** (IPAH)
   1.2. Familial (FPAH)
   1.3. Associated with (APAH):
      - 1.3.1. Collagen vascular disease
      - 1.3.2. Congenital systemic-to-pulmonary shunts**
      - **1.3.3. Portal hypertension**
   1.3.4. HIV infection
   1.3.5. Drugs and toxins
   1.3.6. **Other** (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
1.4. Associated with **significant venous or capillary involvement**
   - 1.4.1. Pulmonary veno-occlusive disease (PVOD)
   - 1.4.2. Pulmonary capillary hemangiomatosis (PCH)
1.5. Persistent pulmonary hypertension of the newborn
Pulmonary Vascular Pathology in POPH

- In-situ thrombosis
- Proliferation/Plexogenic change
- Fibrosis
- Platelet aggregates
POPH MCR Experience

- 97 patients
  - 53 females (55%); 44 males
- Mean PAP = 46mm Hg (25 - 86)
- Mean PVR = 449 dynes.s.cm⁻⁵
- 24 pts underwent OLT (25%)
- 50 pts treated with prostanoid
  - 41 with intravenous epoprostenol
  - 11 with subcutaneous treprostinil
Median survival = 46 months [29, 95]

5 year survival = 45%
Survival months from dx

LT (n = 24)

No LT (n = 73)

P = .06
Surviving

Survival months from dx

No Treatment (n = 28)

LT Alone (n = 12)

LT + PAH Treatment (n = 11)

PAH Treatment (n = 46)

P = .02

Surviving
POPH in OLT Era

*Liver Transpl* 2004;10:174-182

N=66; multicenter Database (10 institutions; 1996-2001)

- 30 (45%) denied OLT due to severity of POPH
  - MPAP = 53 mmHg
  - PVR = 614 dynes.s.cm⁻⁵
- 36 (55%) had OLT (13 died - 36% mortality)
  - 5 died during transplant surgery
  - 8 died during transplant hospitalization (within 18 days of transplant)
  - If MPAP > 35 mm Hg, mortality 60%
  - only 1/13 had prostacyclin therapy pre-OLT
AASLD practice guidelines: Evaluation of the patient for liver transplantation (POPH)

- *Hepatology 2005; 41: 1407-1432*

Recommendations

8. All patients undergoing evaluation for potential liver transplantation should undergo screening for pulmonary hypertension (II-3).

9. Doppler echocardiography is an excellent screening test in this setting; however, positive test results should be confirmed with right heart catheterization (II-2).

10. Patients with severe pulmonary hypertension should be considered for liver transplantation only if the condition can be effectively controlled with medical therapy (II-3).

No UNOS policy ...yet
POPH Experience

• Baylor University Dallas, Tx
  • 16 pts with mod-severe PH treated
  • MPAP fell to < 35 in 12 pts; 11 underwent LT
  • 1 yr survival = 91%; 5 yr survival = 67%
  • 9/11 off vasodilator therapy 9 months post-LT
    • Am J Transplantation 2007; 7:1-7

• Baylor University Houston, Tx
  • 8 pts treated with iv epoprostenol
  • 4 safely underwent LT – 2 now on oral PAH meds
    • Am J Transplantation 2006; 6:2177-2182
• **UCSF experience**
  - 19 pts treated with iv epoprostenol; 17 not treated
  - Hemodynamic improvements with epo but no survival difference
  - 2 pts in epo group underwent LT successfully
POPH Summary

- POPH uncommon, but serious
- Screen by transthoracic echocardiography
- Confirm by right heart catheterization
- Medical treatments evolving

...Liver transplantation can be done in carefully selected patients
...but long-term outcomes are to be defined
...cure vs control of POPH?
Portopulmonary Hypertension

Janet Pinson, NP
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October 12, 2007
How is Portopulmonary Hypertension different than IPAH?
PAH (WHO Group I)

- Idiopathic (IPAH)
- Familial (FPAH)
- Associated with (APAH)
  - Collagen vascular disease
  - Congenital systemic-to-pulmonary shunts
  - Portal hypertension
  - HIV infection
  - Drugs/toxins
  - Other
- Associated with significant venous or capillary involvement
  - Pulmonary veno-occlusive disease (PVOD)
  - Pulmonary capillary hemangiomatosis (PCH)
- Persistent pulmonary hypertension of the newborn

Epidemiology

- More common in 5th decade of life
- Male:Female 1:1
- No known genetic predisposition
- Poorer survival rate
Survival Curve

Goblin, et al., Clinics in Chest Medicine, March 2007, Vol.28, Issue 1
Possible Etiology

- Having PH does not correlate with etiology of the underlying liver disease
- Perhaps more circulating endothelin-1
- Circulating bacteria and bacterial endotoxins due to portosystemic shunts lead to release of cytokines which may trigger prostocyclin synthesis
Hemodynamics

- **Hyperdynamic circulatory state**
  - High cardiac output
  - Low pulmonary vascular resistance
- **Pulmonary artery pressure does not correlate with severity of liver disease**
- **Moderate PA pressures most common**
## Cardiopulmonary Hemodynamics Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PPHTN</th>
<th>L-Cont</th>
<th>P-Cont</th>
<th>pValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP, mmHg</td>
<td>10.8 ± 1.1</td>
<td>5.9 ± 0.9</td>
<td>11.4 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAS, mmHg</td>
<td>75.2 ± 3.7</td>
<td>26.3 ± 1.2</td>
<td>90.6 ± 4.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAD, mmHg</td>
<td>35.4 ± 1.8</td>
<td>11.3 ± 1.2</td>
<td>38.6 ± 2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>48.6 ± 2.1</td>
<td>16.3 ± 1.1</td>
<td>55.9 ± 3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI, L/mm/m</td>
<td>3.8 ± 0.3</td>
<td>3.9 ± 0.6</td>
<td>2.3 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVRI, mmHg/L/min/m</td>
<td>11.6 ± 1.6</td>
<td>1.6 ± 0.2</td>
<td>19.8 ± 1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVRI, mmHg/L/min/m</td>
<td>20.5 ± 1.7</td>
<td>20.5 ± 0.9</td>
<td>41.5 ± 2.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Kuo, PC, et al., Distinctive features of portopulmonary hypertension, Chest, 1997;112;980-986
Symptoms

- Often asymptomatic
- Dyspnea most common initial symptom
Physical Exam

- Ascites
- Lower extremity edema – PAH vs underlying liver disease
- Jaundice
Diagnostic Studies

- Less “pruning” of the vessels seen during pulmonary angiogram
- Pulmonary arteries dilated instead of narrowed in the segmental arteries
Pulmonary Function Testing

- Mild hypoxemia
- Respiratory alkalosis
- Reduced diffusion capacity
Vasodilator Trial

- Not done to assess for calcium channel blocker use, but to evaluate for staging and severity
- More reactive to nitric oxide than epoprostenol
- Etiology unknown, perhaps more endogenous NO production
Orthotopic Liver Transplant

- Moderate-severe PH associated with higher perioperative mortality
### Incidence & Mortality of PH in Patients Presenting for OLT

<table>
<thead>
<tr>
<th>No PH</th>
<th>Mild PH</th>
<th>Mod PH</th>
<th>Severe PH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Patients</td>
<td>1,103</td>
<td>81</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Mortality</td>
<td>308</td>
<td>27</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>28%</td>
<td>33%</td>
<td>35%</td>
<td>71%</td>
<td>29%</td>
</tr>
</tbody>
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