The Liver-Lung Connection in Portopulmonary Hypertension

Pulmonary Hypertension Grand Rounds
Stanford University
May 8, 2017

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Disclosures

• No conflicts of interest
Objectives

• Compare and contrast the pathophysiology, management and prognosis of portopulmonary hypertension (POPH) and idiopathic pulmonary arterial hypertension

• Examine the role of liver transplantation in the management of POPH
A Case…

• What does my liver have to do with my lungs?
• Why do I have “pulmonary hypertension” when I have “hypotension” in the rest of my body?
• Will my pulmonary hypertension get better with liver transplant?
Portopulmonary Hypertension

- A subtype of WHO Group 1 pulmonary arterial hypertension (PAH) that develops as a complication of portal hypertension
- Affects 5-8% of patients evaluated for liver transplant
- 5% of PAH
- Pathologically indistinct from idiopathic PAH

Krowka et al. Hepatology 2006
Rodriguez-Roisin et al. ERJ 2004
Krowka et al. Liver Transplant 2000
Krowka et al. CHEST 2012
Clinical features

• Fatigue
• Exertional dyspnea
• Exertional syncope
• New or increased ascites
• Lower extremity edema
Screening

• Screening echocardiogram recommended in all LT candidates
• Mayo Clinic practice is to repeat echocardiogram annually and to refer all patients with RVSP>50mmHg for right heart catheterization
• RVSP>38mmHg: Sensitivity 100%, specificity 82%, NPV 100%, PPV 22%

Raevens et al. Liver Transplantation 2013
Cartin-Ceba et al. Advances in PH. 2013
Diagnosis

- mPAP >25mmHg
- PVR>3 Wood units
- PAWP<15mmHg
- Portal hypertension
- Absence of alternative etiologies of PAH
Hemodynamic profiles of pulmonary hypertension in liver disease

<table>
<thead>
<tr>
<th></th>
<th>mPAP</th>
<th>PVR</th>
<th>CO</th>
<th>PAWP</th>
<th>TPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperdynamic state</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Pulmonary venous congestion</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>POPH (Vasoconstriction and remodeling)</td>
<td>↑</td>
<td>↑</td>
<td>↘</td>
<td>←</td>
<td>↑</td>
</tr>
</tbody>
</table>

DuBrock et al. Exp Rev. 2015
Pathophysiology

• Not associated with:
  – Severity of liver disease

• Associated with:
  – Autoimmune liver disease
  – Female sex, genetic variations in aromatase and higher serum estradiol levels
  – Decreased prostacyclin synthase expression
  – Higher serum endothelin-1 levels
  – Higher prevalence of large spontaneous portosystemic shunts

Roberts et al AJRCCM 2009
Kawut et al Hepatology 2008
Benjaminov et al Gut 2003
Tuder et al AJRCCM 1999
Talwalkar et al Gastro 2011
Insights into Pathophysiology: Abernethy Malformation

- Rare congenital disease characterized by the absence of an intrahepatic portal vein
- Patients develop POPH (and/or hepatopulmonary syndrome) despite lack of intrinsic liver disease and POPH improves with liver transplant
The liver-lung connection and novel biomarkers of POPH

- Prospective case-control study
- Plasma sample collection from across pulmonary and systemic circulation in prevalent and incident cases of POPH and liver disease controls
- 31 controls and 21 cases with POPH
Antibody Microarray

Annotation:
- Angiopoietin-1
- Angiopoietin-2
- C-Reactive Protein
- CXCL8/IL-8
- Endoglin
- Endostatin
- Endothelin-1
- IFN-γ
- IL-13
- IL-6
- MIF
- MMP-8
- MMP-9
- Osteopontin
- PF4/CXCL4
- TIMP-1
- TIMP-4
- VEGF
Macrophage migration inhibitory factor (MIF)

- A pro-inflammatory and proliferative cytokine involved in the regulation of innate immunity
- MIF promoter polymorphisms and elevated MIF levels linked to susceptibility and severity of several autoimmune diseases, including autoimmune liver disease
- Elevated in idiopathic PAH and PH associated with ILD and scleroderma

Zhang et al. Mol Med 2012
Assis et al. Hepatology 2014
Le Hiress et al AJRCCM 2015
Maor Sauler et al AJP 2015
MIF is elevated in POPH

DuBrock et al. Pulmonary Circulation 2016
MIF is correlated with pulmonary hemodynamics and survival

DuBrook et al. Pulmonary Circulation 2016
Interim Summary

• The pathogenesis of POPH is poorly understood, but vasoactive factors from the gut that bypass the liver may play a role in disease development.

• MIF, a proinflammatory and proliferative cytokine, is associated with the presence and severity of POPH.
POPH is associated with significant morbidity and mortality

Krowka et al. Chest 2012
Perioperative mortality risk can be stratified by mPAP

<table>
<thead>
<tr>
<th>mPAP</th>
<th>Perioperative cardiopulmonary mortality in POPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35mmHg</td>
<td>0%</td>
</tr>
<tr>
<td>35-50mmHg</td>
<td>50%</td>
</tr>
<tr>
<td>&gt;50mmHg</td>
<td>100%</td>
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</tbody>
</table>
LT may be beneficial in POPH

<table>
<thead>
<tr>
<th>POPH Management</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PAH therapy or LT</td>
<td>14%</td>
</tr>
<tr>
<td>PAH therapy alone</td>
<td>45%</td>
</tr>
<tr>
<td>PAH therapy + LT</td>
<td>67%</td>
</tr>
</tbody>
</table>

Swanson et al. AJT 2008
# MELD Exception for Liver Transplant in POPH

<table>
<thead>
<tr>
<th>Criteria for MELD Exception</th>
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<tbody>
<tr>
<td><strong>Initial</strong></td>
</tr>
<tr>
<td>1. Diagnosis of POPH AND</td>
</tr>
<tr>
<td>2. Adequate hemodynamic response to PAH therapy (mPAP&lt;35mmHg AND PVR&lt;400 dynes•s•cm⁻⁵)</td>
</tr>
<tr>
<td><strong>Extension</strong></td>
</tr>
<tr>
<td>Sustained hemodynamic response to PAH therapy on follow-up right heart catheterization every 3 months</td>
</tr>
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</table>
Limitations of the MELD Exception for POPH

• The system does not allocate points based on disease severity or waitlist mortality risk
• It is not known whether POPH in the absence of decompensated liver disease should be an indication for liver transplant
• Misclassification of patients is common-47% of patients who received POPH MELD exception did not meet criteria

Goldberg et al. AJT 2015
POPH MELD Exceptions 2006-2014

- Retrospective analysis of UNOS database
- Patients with mPAP>25 and PVR>3 WU
- Aim: Identify predictors of waitlist mortality

DuBrock et al. Transplantation 2017
<table>
<thead>
<tr>
<th>Patient Characteristics (n=190)</th>
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<tbody>
<tr>
<td><strong>Age at listing, years</strong></td>
</tr>
<tr>
<td><strong>Male</strong></td>
</tr>
<tr>
<td><strong>Race</strong></td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
</tr>
<tr>
<td>Hepatitis C</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Hepatitis C and Alcohol</td>
</tr>
<tr>
<td>Autoimmune</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td><strong>Initial Native MELD Score</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Initial Pulmonary Hemodynamics</strong></td>
</tr>
<tr>
<td>mPAP, mmHg (n=190)</td>
</tr>
<tr>
<td>PVR, dynes (n=190)</td>
</tr>
<tr>
<td>CO, L/min (n=55)</td>
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</tbody>
</table>
## Predictors of Waitlist Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Model</th>
<th></th>
<th></th>
<th>Multivariate Model</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
<td>HR (95% CI)</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td><strong>Age at listing</strong></td>
<td>1.04 (1.00-1.08)</td>
<td>0.0499</td>
<td>1.05 (1.00-1.09)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td><strong>Female gender</strong></td>
<td>1.37 (0.76-2.48)</td>
<td>0.30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Initial Native MELD</strong></td>
<td>1.11 (1.05-1.17)</td>
<td>&lt;0.001</td>
<td>1.13 (1.08-1.20)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Initial Hemodynamics</strong></td>
<td></td>
<td></td>
<td>1.21 (1.09-1.33)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>1.02 (0.98-1.05)</td>
<td>0.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVR, per 100 dynes</td>
<td>1.12 (1.02-1.23)</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO, L/min (n=55)</td>
<td>0.67 (0.42-1.08)</td>
<td>0.10</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- MELD and PVR were not predictive of post-transplant mortality, but may have been under-powered
Back to our case...

- 56 year old man with cirrhosis and POPH treated with sildenafil and IV treprostinil on the liver transplant list
- MELD exception score 28
- Right heart catheterization demonstrates mPAP 38mmHg, PVR 2.1 WU, PAWP 15mmHg, CO 11L/min
- What next?
Management of an elevated mPAP and normal PVR in treated POPH

- Inactivate from transplant list?
- Appeal to regional review board?
- Diurese?
- Wean Treprostinil?
- Midodrine?
- Change the system?
mPAP > 35 mmHg at time of LT

• Single-center retrospective study
• 2010-2013
• mPAP ≥ 35 in 31/300 (10.3%) patients
• Transplant hospital mortality 0%
• 1-year mortality similar to those < 35 mmHg
• If normal PVR and RV function, it may be safe to proceed with LT in setting of mPAP 35-50 mmHg
Other Prognostic Factors: Intrapulmonary Vascular Dilatation

Fussner et al. Liver Transplantation 2016
A tale of two transplants...

- Case 1: POPH associated with autoimmune hepatitis, underwent liver transplant
- Case 2: POPH associated with portal hypertension secondary to portal vein thrombosis, received single lung transplant

Yoshida et al. Transplantation 1993
A tale of two transplants...

**TABLE 1. Case 1: pulmonary artery pressure (mmHg)\(^a\)**

<table>
<thead>
<tr>
<th></th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretransplant</td>
<td>75</td>
<td>26</td>
<td>45</td>
</tr>
<tr>
<td>Posttransplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Weeks</td>
<td>75</td>
<td>33</td>
<td>50</td>
</tr>
<tr>
<td>12 Months</td>
<td>42</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>22 Months</td>
<td>39</td>
<td>18</td>
<td>26</td>
</tr>
</tbody>
</table>

\(^a\) Case 1 received a liver transplant. PAP regressed posttransplant and has been sustained for 22 months.

**TABLE 3. Case 2:\(^a\) pulmonary artery pressure and right ventricular pressure**

<table>
<thead>
<tr>
<th></th>
<th>PAP</th>
<th>RVP (systolic)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Pretransplant</td>
<td>95</td>
<td>44</td>
</tr>
<tr>
<td>Posttransplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Months</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5 Months</td>
<td>64</td>
<td>25</td>
</tr>
<tr>
<td>9 Months</td>
<td>67</td>
<td>47</td>
</tr>
</tbody>
</table>

\(^a\) Case 2 received a single-lung transplant. Pulmonary hypertension regressed but recurred by 5 months posttransplant.
Post-transplant outcomes

United States UNOS 2002-2010
- 85% 1-year survival, 81% 3-year survival
- Patient and graft survival inferior to non-POPH exception patients

UK LT Registry 1992-2012
- 5 year post-transplant survival 53.8%
- 12 patients (42.9%) died within 5 years of LT with the majority of deaths (10/12) of deaths within 6 months post-transplant
- Only 8 (28.6%) of patients were on PH therapy
- 1992-2002: 60% early post-operative mortality vs. 27% early post-operative mortality 2002-2012
Post-transplant outcomes

French PH Registry

- 35 patients who underwent LT
- 8 (23%) died after LT, including 5 due to POPH (Deaths at 1 and 7 days, 1 month, 2 and 6 months)
- Among survivors, all patients treated with epoprostenol were weaned off
- ERA or PDE5 were continued in 15/27 (55%)
- Post-LT survival 80%, 77%, 77% at 6 months, 1 year and 3 years, respectively
- “Stabilization or reversibility of POPH seems to be an attainable goal using the combination of PAH targeted therapy and LT”

Savale et al Hepatology 2017
Hemodynamic outcomes

A

- Pulmonary vascular resistance, WU

Baseline | 3.1 months (median) after LT | 15 months (median) after LT
---|---|---

B

- Pulmonary vascular resistance, WU

Baseline | Before LT | 3.6 months (median) after LT | 14 months (median) after LT
---|---|---|---

Savale et al Hepatology 2017
**PAH Targeted Therapy**

- Similar to other subtypes of Group 1 PAH

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Therapeutic Class</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitric Oxide</td>
<td>Phosphodiesterase-5 inhibitors</td>
<td>Sildenafil, Tadalafil</td>
</tr>
<tr>
<td></td>
<td>Soluble guanylate cyclase stimulators</td>
<td>Riociguat</td>
</tr>
<tr>
<td>Endothelin</td>
<td>Endothelin receptor antagonists</td>
<td>Bosentan, Ambrisentan, Macitentan</td>
</tr>
<tr>
<td>Prostacyclin</td>
<td>Prostacyclin analogues</td>
<td>Epoprostenol, Treprostinil, Iloprost</td>
</tr>
<tr>
<td></td>
<td>Prostacyclin IP receptor agonist</td>
<td>Selexipag</td>
</tr>
</tbody>
</table>
PAH Therapy in POPH

- Improved 6MWD and pulmonary hemodynamics

Faisal M et al Pulm Med 2014
Special Considerations Regarding PAH Therapy in Liver Disease

• Use of parenteral prostanoids has been associated with worsening thrombocytopenia, splenomegaly and ascites
• Typically use lower doses of parenteral prostanoids
• Calcium channel blockers not recommended
• Treatment goals often driven by liver transplantation candidacy
• If MELD score is high, important to treat PH aggressively to facilitate LT
Perioperative Management

• Monitoring
  – Swan-Ganz catheter
  – Intra-operative transesophageal echocardiogram

• Treatment
  – Inhaled nitric oxide
  – Intravenous epoprostenol
  – Milrinone
  – ECMO

Krowka et al. Transplantation 2016
Additional Management

• Diuretics
• Supplemental Oxygen
• Consider discontinuation of prophylactic beta blockers
• Avoid TIPS
• Liver Transplant
Why don’t we know more about POPH?

• Small sample sizes
• Most studies are retrospective and often include patients over a long period of time
• Misclassification of patients with pulmonary hypertension associated with a hyperdynamic state or postcapillary pulmonary hypertension
• Difficult to study outcomes in isolation of liver transplantation
• Is all POPH created equal?
Future Directions

- Identify non-invasive biomarkers to improve screening for POPH and to monitor treatment response and disease progression
- Define the short-term and long-term effects of liver transplant on pulmonary hemodynamics and POPH outcomes
- Identify predictors of hemodynamic improvement with liver transplant… does immunosuppression play a role?
Conclusions

• The pathogenesis of POPH is poorly understood, but vasoactive factors that bypass the liver may play a role in disease development

• Compared to idiopathic PAH, POPH is associated with worse survival

• LT is beneficial in a select group of patients with POPH, but pulmonary hemodynamics may worsen within the first 6 months
Questions

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