Hepatopulmonary Syndrome: An Update

Michael J. Krowka MD
Professor of Medicine
Division of Pulmonary and Critical Care
Division of Gastroenterology and Hepatology
Mayo Clinic
Falk Liver Week
October 11, 2006
Aims of this presentation

- Current concepts of Hepatopulmonary Syndrome (HPS)
- Specific HPS questions to be addressed
  - How should we screen for HPS?
  - What are the mediators of HPS pathophysiology?
  - Should HPS patients higher priority for liver transplantation?
The Liver-Lung Vascular Relationship

- Pulmonary circulation
  - Hepatopulmonary Syndrome
  - Portopulmonary Hypertension

- Portal bed
  - vascular obstruction

- Splanchnic bed
  - vasodilatation
Program Lectures and Discussions

JANUARY 11
Evening Registration 6:30 - 7:30 p.m.

JANUARY 12
7:30 a.m.  REGISTRATION  Continental Breakfast
8:10  WELCOME  Michael J. Krowka, M.D.  Mayo Clinic Jacksonville
8:15  ALPHA, ANTITRYPSIN DEFICIENCY: A Liver Disorder with Lung Manifestations
       Ronald C. Crystal, M.D.  National Institutes of Health, Bethesda, Maryland
8:45  HEPATO-PULMONARY SYNDROME
       Dame Sheila Sherlock, M.D., F.R.C.P.  Royal Free Hospital, London
9:15  PULMONARY VASCULAR PATHOLOGY IN LIVER DISEASE
       Lynne M. Reid, M.D.  Harvard University
9:45  NEUROPEPTIDES: A LIVER-LUNG RELATIONSHIP?
       Thomas M. O’Donnell, M.D.  Ohio State University
10:15  Discussion
10:30  Coffee
11:00  LIVER-LUNG GRANULOMAS
       D. Geraint James, M.D., F.R.C.P.  University of London
11:30  PRIMARY BILIARY CIRRHOSIS AND THE LUNG
       E. Rolland Dickson, M.D.  Mayo Clinic Rochester
12:00 p.m.  Discussion
12:30  Lunch
2:00  PULMONARY GAS EXCHANGE IN LIVER DISEASE
       Denis A. Cortese, M.D.  Mayo Clinic Rochester;
       Robert Rodriguez-Roisin, M.D.  University of Barcelona, Spain
3:00  Discussion
3:15  Coffee
3:30  LIVER TRANSPLANTATION: PERIOPERATIVE ICU EXPERIENCE
       David J. Plewak, M.D.  Mayo Clinic Rochester
4:00  EFFECT OF LIVER TRANSPLANTATION ON LUNG FUNCTION
       Michael J. Krowka, M.D.  Mayo Clinic Jacksonville
4:30  Discussion
4:45  OVERALL REVIEW:  Dame Sheila Sherlock
5:30  Cocktail Hour

For further information call (904) 223-2058

SYMPOSIUM: THE LIVER-LUNG INTERFACE
JANUARY 12, 1990
Background…with the success of orthotopic liver transplantation (LT)…

… liver-lung relationships are more than academic interest

… 6000 LTs/yr; 18,000 pts on wait lists in the US

… 5-10% have clinically significant lung problems that can affect LT survival
Major Pulmonary Vascular Consequences of Hepatic Dysfunction

Vascular dilatation
1) precapillary and capillary dilatations
2) arteriovenous communications (anatomic shunts)

“Hepatopulmonary Syndrome”

Vascular obstruction
Proliferation of endothelium and smooth muscle/fibrosis;
+ in situ thrombosis;
plexogenic arteriopathy

“Portopulmonary Hypertension”

Oxygenation issue ...hypoxemia

Hemodynamic issue ...right heart failure
HPS and POPH Papers Noted in Ovid MEDLINE Search (2000-2005)
37 yo female with cyanosis and clubbing; massive hemoptysis or hematemesis

“character of a paralytic dementia …coma then death”

Autopsy:
- Cirrhosis
- Syphilitic bones
- Dilated esophagus veins
- Dilated pulmonary veins
Case Reports

Multiple Pulmonary Arteriovenous Fistulas in Juvenile Cirrhosis

Robert Rydell, M.D. and F. W. Hoffbauer, M.D.
Minneapolis, Minnesota
The New England
Journal of Medicine

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Volume 274
FEBRUARY 10, 1966
Number 6

ARTERIAL CHANGES IN THE LUNGS IN CIRRHOSIS OF THE LIVER—LUNG SPIDER NEVI*

P. Berthelot, M.D.,† J. G. Walker, M.B.,§ Sheila Sherlock, M.D.,§ and Lynne Reid, M.D.¶

LONDON, ENGLAND
FIGURE 10. Photomicrograph of a Section through the Diaphragmatic Surface of the Lung in Case 13 at Site X (Fig. 3), Showing Numerous Dilated Vessels in the Region of Arteriovenous Shunting (Elastic-Tissue Van Gieson Stain, Original Magnification X45).

FIGURE 5. Photomicrograph of the Lung from a Patient with Cirrhosis of the Liver, Showing a Relative Increase of Small Blood Vessels in the Alveolar Walls (Elastic-Tissue Van Gieson Stain X45).

The difference in alveolar size is allowed for since the arterial count is expressed as a ratio of the alveoli.
Hypoxemia: 40-50%

“Hepatopulmonary Syndrome”
frequency: 5-10% (?)
Hepatopulmonary Syndrome

(Type I) Diffusion-perfusion defect

(Type II) Anatomic shunt

Excess perfusion (Low Ventilation/Perfusion ratio)
HPS and hypoxemia

- May be severe (PaO₂ < 50 mm Hg)
- Usually an excellent response to 100% inspired oxygen
- Orthodeoxia may exist
  - Worsening hypoxemia supine to standing
**HPS Diagnostic Criteria**

*J Hepatology 2005; 42: 924-927*

- Chronic liver disease (portal hypertension)
- Arterial hypoxemia
  - \( \text{PaO}_2 < 70 \text{ mmHg} \); or
  - Abnormal calculated alveolar-arterial oxygen gradient
    - > 15 mmHg
    - > 20 mm Hg if age greater than 64
- Pulmonary vascular dilatation
  - “positive” left atrial opacification via contrast echo > 3 cardiac cycles after right ventricle opacification
  - \(^{99}\text{TcMAA} \) lung perfusion with brain uptake > 6%
Transthoracic Contrast-Enhanced Echocardiogram
99m TcMAA Lung Scan with abnormal brain uptake

06-267 012
06/09/2005
NM Lung Scan Perfusion Only

Art/Right (Counts) | Post/Left (Counts) | GM (Counts)
LUNG      | 393110 | 357001 | 375044
BRAIN     | 12149  | 11332  | 12040

SHunted Counts: 92615

Shunt Index (%): 19.8%
Angiographic appearances of HPS

Type I

Type II
Pathophysiology?

- Genetic predisposition
- Which liver diseases???
  - Any cause of portal hypertension (+ cirrhosis)
  - Hypoxic hepatitis (“ischemic hepatitis”)

  *Gastroenterology* 2006; 131: 69-75

- Human
  - Increase exhaled nitric oxide
  - Increased carboxyhemoglobin
  - ↑ Circulating endothelin-1
  - Angiogenesis?
    - Increased numbers of capillaries abutting alveoli
Fig. 2. Potential mechanisms of intrapulmonary vasodilatation in experimental hepatopulmonary syndrome. See text for details. TNF-α, tumor necrosis factor alpha; ET₄R, endothelin B receptor; iNOS, inducible nitric oxide synthase; eNOS, endothelial nitric oxide synthase; HO-1, heme oxygenase 1; NO, nitric oxide; CO, carbon monoxide.
Endothelin receptor blockade in HPS?

- Rationale for selective antagonist
  - If $\text{ET}_b$ is “over expressed”, such an approach makes sense
- No human studies to date
Effects of Nebulized $N^G$-nitro-L-arginine Methyl Ester in Patients With Hepatopulmonary Syndrome

Federico P. Gómez, Joan A. Barberà, Josep Roca, Felip Burgos, Concepción Gistau, and Robert Rodríguez-Roisin

Enhanced pulmonary production of nitric oxide (NO) has been implicated in the pathogenesis of hepatopulmonary syndrome (HPS). NO inhibition with $N^G$-nitro-L-arginine methyl ester (L-NAME) in both animals and humans with HPS has improved arterial hypoxemia. We assessed the role of enhanced NO production in the pathobiology of arterial deoxygenation in HPS and the potential therapeutic efficacy of selective pulmonary NO inhibition. We investigated the effects of nebulized L-NAME (162.0 mg) at 30 and 120 minutes on all intrapulmonary and extrapulmonary factors governing pulmonary gas exchange in 10 patients with HPS (60 ± 7 [SD] yr; alveolar–arterial oxygen gradient, range 19–76 mm Hg; arterial oxygen tension, range 37–89 mm Hg). Nebulized L-NAME maximally decreased exhaled NO (by −55%; $P < .001$), mixed venous nitrite/nitrate (by −12%; $P = .02$), and cardiac output (by −11%; $P = .002$) while increased systemic vascular resistance (by 11%; $P = .008$) and pulmonary vascular resistance (by 25%; $P = .03$). In contrast, ventilation-perfusion mismatching, intrapulmonary shunt and, in turn, arterial deoxygenation remained unchanged. In conclusion, gas exchange disturbances in HPS may be related to pulmonary vascular remodeling rather than to an ongoing vasodilator effect of enhanced NO production. (Hepatology 2006;43:1084–1091.)
Fig. 1. Individual exhaled NO data before and after L-NAME nebulization (arrow) in patients with HPS. Bold lines represent mean values. *P < .001 and **P = .001 compared with baseline. Patient numbers correspond to those in Table 1. FE\textsubscript{NO}, fractional exhaled NO concentration at a flow rate of 50 mL · s\textsuperscript{-1}; L-NAME, \textit{N}\textsuperscript{\textdagger}nitro-L-arginine methyl ester; BL, baseline.
 Editorial

VEGF-induced angiogenesis drives collateral circulation in portal hypertension

Richard Moreau*

Laboratoire d’Hémodynamique Splanchnique et de Biologie Vasculaire, INSERM, and Service d’Hépatologie, Hôpital Beaujon, F-92118 Clichy, France
How should we screen for HPS?

- N = 316
- O₂ sat < 92% or O₂ sat change > 4% (supine to upright)
- Detect clinically significant O₂ abnormality; not a prevalence study
How should we screen for HPS?
(cont)

- 17/316 abnormal (5.4%)
- 4 had HPS (contrast echo and nuc med shunt study)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Gender</th>
<th>Disease etiology</th>
<th>SaO₂ (%) supine</th>
<th>SaO₂ (%) upright</th>
<th>pO₂ (mmHg) upright</th>
<th>Shunt volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>†</td>
<td>HCV-cirrhosis</td>
<td>94</td>
<td>90</td>
<td>71</td>
<td>7</td>
</tr>
<tr>
<td>28</td>
<td>♀</td>
<td>Portal vein thrombosis</td>
<td>84</td>
<td>82</td>
<td>54</td>
<td>10</td>
</tr>
<tr>
<td>27</td>
<td>♀</td>
<td>Chronic EBV-infection</td>
<td>93</td>
<td>78</td>
<td>64</td>
<td>28</td>
</tr>
<tr>
<td>31</td>
<td>♀</td>
<td>Nodular regenerative hyperplasia</td>
<td>90</td>
<td>71</td>
<td>36</td>
<td>34</td>
</tr>
</tbody>
</table>
**Mayo Clinic Algorithm for HPS**

- **Screening ABG (sitting/room air)**
  
  - Is PaO₂ < 70 mm Hg?  Do Contrast Echo;
    
    - If Contrast Echo “positive” then obtain:
      - $^{99m}$TcMAA lung scan; and
      - Supine and standing ABGs (room air and 100% O₂)
Co-morbid conditions and HPS...what causes hypoxemia?

- Hepatic hydrothorax
- Massive ascites
- COPD
- Obesity
- Pulmonary fibrosis

- $^{99m}$TcMAA brain uptake very useful

Gastroenterology 2003
Chest 2000
J Hepatology 1999
HPS and prognosis
Schenk et al, Gastroenterology 2003;125:1042-1052

[Graph showing survival rates with and without HPS and OLT]
Treatment options for HPS

- Proven pharmacologic therapies that improve hypoxemia long-term...none

- “TIPS” - transjugular intrahepatic portosystemic shunt
  - reduce or normalize hepatic vein-portal vein pressure gradient (controversial...a few cases)

- Balloon Cavoplasty
  - noncirrhotic portal hypertension due to vena cava obstruction

*Gastroenterology 2002;122:897-903*
Abernethy malformation

Type I
- Complete absence of intrahepatic portal vein
- 19 cases reported

Type II
- Portal system completely formed but abnormal communication with systemic veins
- 6 cases reported
Abernethy malformation

Congenital portocaval fistula associated with hepatopulmonary syndrome: ligation vs liver transplantation

Stéphane Tercier, Arnauld Delarue, Francis Rouault, Céline Roman, Jean Bréaud, Philippe Petit

Journal of Pediatric Surgery 2006; 41: E1-E3

- 4 year old boy (PaO₂ = 44 mg Hg)
- Type 2 Abernethy syndrome via cavofistulography
- Portal vein hypoplasia; successful ligation with transection of fistula
- No liver transplantation
Reduction of Intrapulmonary Shunt and Resolution of Digital Clubbing Associated with Primary Biliary Cirrhosis after Liver Transplantation

James K. Stoller,¹ Douglas Moodie, William A. Schiavone,²* David Vogt,⁵ Thomas Broughan,⁵ Eugene Winkelmann,² Patrice K. Rehm,⁴ and William D. Carey²

The Departments of ¹Pulmonary Disease, ²Gastroenterology, ³Cardiology, ⁴Radiology and ⁵General Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio 44195
HPS and Mortality Risk for OLT

  - N= 81; 16% mortality within 1 year
  - if PaO₂ < 50 mmHg… 30% mortality within 90 days

- Hepatology 2003:37:192-197  UAB/Mayo Clinic
  - N=24; 29% mortality within 12 months
  - PaO₂ < 50 mmHg and ⁹⁹mTcMAA brain uptake > 20% at highest risk

- Transplantation 2003; 75: 1482-1489  Paris, France
  - N= 23; 30.5 % mortality up to 60 months post-LT; 8.5% periop death

  - N=40; 16% (5/32) transplant hospitalization mortality
  - pre-OLT PaO₂ = 55 mmHg (survivors) vs 37 (died)
Hepatopulmonary Syndrome Increases the Postoperative Mortality Rate Following Liver Transplantation: A Prospective Study in 90 Patients

E. Schiffera,b,*, P. Majno, G. Mentha,b, E. Girostra, H. Burrd, C. E. Klopfenstein,b, M. Beaussier, P. Morelb, A. Hadenguec and C. M. Pastor

N= 9 with HPS
3 (33%) died post-LT in hospital
Each had 50 < PaO₂ <70 mm Hg
HPS and Resolution of Syndrome after OLT?

Normalization of oxygenation following OLT in most cases

- regardless of degree of hypoxemia
- time to resolution depends on severity of hypoxemia

-Gastroenterology 2003:32:192-197
-Transplantation 2003; 75:1482-1489

- mortality still significant post-OLT; and
  - DLCO may not normalize after LT
AASLD practice guidelines: Evaluation of the patient for liver transplantation (HPS)

**Hepatology 2005; 41: 1407-1432**

**Recommendation**

7. Because patients with cirrhosis and severe hepatopulmonary syndrome have an extremely poor prognosis without transplantation, they should have an expedited referral and evaluation for liver transplantation (II-2).

**NOTE:** The amendment to Policy 3.6.4.5 (Liver Candidates with Exceptional Cases) shall be approved and implemented pending distribution of appropriate notice and programming on the UNOS computer.

3.6.4.5.1 **Liver Candidates with Hepatopulmonary Syndrome (HPS).** Patients with a clinical evidence of portal hypertension, evidence of a shunt, and a PaO₂ < 60 on room air may be referred to the RRB for consideration of a MELD score that would provide them a reasonable probability of being transplanted within 3 months. Patients should have no significant clinical evidence of underlying primary pulmonary disease.
Should HPS patients receive higher priority for liver transplantation?

- Current US (UNOS) 2005 guidelines – “yes”
- New proposed MELD “exception” in the US
  - If PaO₂ < 60 mm Hg and
    - Breathing room air;
    - Sitting position;
    - At rest;
  - Then give enough MELD points (24-28?) for patient to receive LT within 3 months
HPS Summary

- Pathophysiology: vascular dilatation + angiogenesis?
- Liver transplantation is treatment of choice
  - rarely other measures may help
  - support with supplemental $O_2$
- In the United States higher priority for LT if $PaO_2 < 60\ \text{mmHg}$
- Resolution of hypoxemia (HPS) after OLT may take months
- Caveats…
  - co-morbid conditions cause hypoxemia
  - Post - LT mortality $\uparrow$ (8.5-33%)
  - $\uparrow$ risk if pre-LT $PaO_2 < 50\ \text{mmHg}$;
  - $\uparrow$ risk if $^{99}\text{mTcMAA}$ brain uptake $> 20\ %$