Liver → Lung

Gian-Reto Kleger
Liver ← Lung

or the otherway round

Gian-Reto Kleger
Liver (acute) → Lung

Dizier S. Early hepatic dysfunction is associated with a worse outcome in patients presenting with acute respiratory distress syndrome: A post hoc analysis of the ACURASYS and PROSEVA studies. PlosOne 2015
Liver (acute) → Lung

Dizier S. Early hepatic dysfunction is associated with a worse outcome in patients presenting with acute respiratory distress syndrome: A post hoc analysis of the ACURASYS and PROSEVA studies. PlosOne 2015
The increasing burden of liver diseases

The increasing burden of liver diseases

Asrani SK. Burden of liver diseases in the world. J Hepatol 2018
Liver → Lung

<table>
<thead>
<tr>
<th>condition</th>
<th>prevalence in ESLD</th>
<th>long-term mortality without transplant</th>
<th>long-term mortality with transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>hepatic hydrothorax</td>
<td>5-12%(^{10})</td>
<td>78%(^{12,a})</td>
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<td>portopulmonary hypertension</td>
<td>4-15%(^{4-6,11})</td>
<td>60-65%(^{7,8,a})</td>
<td>43%(^{9,a})</td>
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a) Five-year mortality  
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2) Swanson KL. Natural history of hepatopulmonary syndrome: impact of liver transplantation. Hepatology 2005  
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11) Savale L. Pulmonary hypertension in liver disease. Presse Medicale 2014  
12) Hung TH. The long-term outcomes of cirrhotic patients with pleural effusion. Saudi J. Gastroenterol 2018
Hepatic hydrothorax: Clinical aspects

Definition: Pleural effusion (transudate) in patients with advanced liver disease and exclusion of cardiopulmonary or malignant origin

retrospective, n = 77 (77/495, 16% of cirrhotic patients)
• most often with ascites (but reports with no or little ascites) →91%
• usually right sided only →73%
• usually large size (>500 ml) →71%
• MELD median 16 →16%
• symptoms: cough and shortness of breath →35%

Badillo R. Hepatic hydrothorax. Clinical features, management, and outcomes in 77 patients and review of the literature. Medicine 2014
Hepatic hydrothorax: Pathophysiology

<table>
<thead>
<tr>
<th>Treatments</th>
<th>n</th>
<th>Age (y) mean</th>
<th>Female</th>
<th>MELD (mean, range)</th>
<th>Ascites size</th>
<th>Cause of Death</th>
<th>Death n=44 (57%)</th>
<th>Pres. to Death (d) (or end of study*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>64/77 (83%)</td>
<td>52</td>
<td>23/64 (36%)</td>
<td>16 (4-46)</td>
<td>None = 6  Small = 34  Mod. = 16  Large = 8</td>
<td>None = 6  Small = 8  Mod. = 14  Large = 6</td>
<td>40/64 (63%)</td>
<td>321 ± 463</td>
</tr>
<tr>
<td>TIPS</td>
<td>8/77 (10%)</td>
<td>56</td>
<td>5/8 (63%)</td>
<td>12 (7-28)</td>
<td>None = 1  Small = 3  Mod. = 3  Large = 1</td>
<td>None = 1  Small = 3  Mod. = 3  Large = 1</td>
<td>4/8 (50%)</td>
<td>845 ± 407</td>
</tr>
<tr>
<td>LTx</td>
<td>5/77 (7%)</td>
<td>54</td>
<td>0</td>
<td>21 (10-40)</td>
<td>None = 1  Small = 1  Mod. = 1  Large = 1</td>
<td>None = 1  Small = 1  Mod. = 1  Large = 1</td>
<td>0</td>
<td>1’896 ± 1’752*</td>
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<tr>
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12) Hung TH. The long-term outcomes of cirrhotic patients with pleural effusion. Saudi J. Gastroenterol 2018
Hepatopulmonary syndrome HPS: Oxygenation failure

Definition: Oxygenation defect caused by pulmonary vascular dilatation in the setting of portal hypertension with or without cirrhosis

- mild: \[ \text{DpAaO}_2 \geq 2 \text{ kPa} \geq 3 \text{ kPa in } \uparrow 64 \text{ y} \] & \[ \text{paO}_2 \geq 10 \text{ kPa} \]
- moderate: \[ \text{DpAaO}_2 \geq 2 \text{ kPa} \geq 3 \text{ kPa in } \uparrow 64 \text{ y} \] & \[ \text{paO}_2 8 - 10 \text{ kPa} \]
- severe: \[ \text{DpAaO}_2 \geq 2 \text{ kPa} \geq 3 \text{ kPa in } \uparrow 64 \text{ y} \] & \[ \text{paO}_2 7 - 8 \text{ kPa} \]
- very severe: \[ \text{DpAaO}_2 \geq 2 \text{ kPa} \geq 3 \text{ kPa in } \uparrow 64 \text{ y} \] & \[ \text{paO}_2 < 7 \text{ kPa} \]
\[ \text{paO}_2 < 40 \text{ kPa, FiO}_2 1.0 \]

Hepatopulmonary syndrome (HPS): Hypotheses on pathophysiology

Hepatopulmonary syndrome HPS: Hypotheses on pathophysiology

Control patients

Patients with HPS

Clichy, n = 2'280, 1997-2015
19 HPS vs. 57 matched controls

intrahepatic portal venule thrombosis

fibrous septa with vascular proliferation

wall thickening of centrilobular venule

intrahepatic hepatic venule thrombosis

Lejealle C. Evidence for an association between intrahepatic vascular changes and the development of hepatopulmonary syndrome. Chest 2019
### Hepatopulmonary syndrome HPS: Diagnostic approach

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<th>limitations</th>
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<td>VWF antigen↑</td>
<td>More studies needed</td>
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Hepatopulmonary syndrome HPS: Contrast TTE

Fuhrmann V. Hepatopulmonary syndrome. J Hepatol 2018
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Grilo-Bensusan I. Hepatopulmonary syndrome: What we know and what we would like to know. W J Gastroenterol 2016
Hepatopulmonary syndrome HPS: Diagnostic approach

Patient presenting with Shortness of Breath

Demonstrates Platypnea/Orthodeoxia

Cardiac Echocardiography with contrast and bubble study and/or perfusion scan with scintigraphy

Positive

Bubble Study Positive Within 3 Cardiac Cycles

- Patent Foramen Ovale/Atrial Septal Defect
  - Consider Cardiology Consultation and Surgical Management

Bubble Study Positive After 3 Cardiac Cycles

- Consider CT Pulmonary Angiogram and/or pulmonary arteriography
  - Positive
  - Negative
    - Consider treatment for Pulmonary AV malformation.
    - Consider hepatopulmonary syndrome.

Negative

- Consider CT of the chest to discern alveolar or interstitial diseases (Zone I Phenomenon)
  - Consider Miscellaneous Causes Like:
    - Severe kyphosis
    - Hemidiaphragm paralysis
    - Paraesophageal hernia
    - Large hepatic hydatid cyst, etc.

Agrawal A. The multiple dimensions of platypnea-orthodeoxa syndrome: A review. Respir Medicine 2017
Hachulla AL. Impact of liver diseases on heart and lungs. JACC 2019
### Liver → Lung

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a) Five-year mortality  
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12. Hung TH. The long-term outcomes of cirrhotic patients with pleural effusion. Saudi J. Gastroenterol 2018
Portopulmonary hypertension (POPH): Updated classification of PH 2019

1 PAH
   1.1 Idiopathic PAH
   1.2 Heritable PAH
   1.3 Drug- and toxin-induced PAH (table 3)
   1.4 PAH associated with:
      1.4.1 Connective tissue disease
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 Congenital heart disease
      1.4.5 Schistosomiasis
   1.5 PAH long-term responders to calcium channel blockers (table 4)
   1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
   1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease
   2.1 PH due to heart failure with preserved LVEF
   2.2 PH due to heart failure with reduced LVEF
   2.3 Valvular heart disease
   2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia
   3.1 Obstructive lung disease
   3.2 Restrictive lung disease
   3.3 Other lung disease with mixed restrictive/obstructive pattern
   3.4 Hypoxia without lung disease
   3.5 Developmental lung disorders

4 PH due to pulmonary artery obstructions (table 6)
   4.1 Chronic thromboembolic PH
   4.2 Other pulmonary artery obstructions

5 PH with unclear and/or multifactorial mechanisms (table 7)
   5.1 Haematological disorders
   5.2 Systemic and metabolic disorders
   5.3 Others
   5.4 Complex congenital heart disease

Simonneau G. Hemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019
Portopulmonary hypertension POPH: Hypotheses on pathophysiology

- Portal hypertension ± cirrhosis
  - Cirrhosis
  - Porto-systemic shunts
- Systemic endotoxinemia
- Hyperdynamic circulatory syndrome
- Inbalance between pro and anti-angiogenic factors
- Systemic inflammation
- Shear stress

Endothelial dysfunction / local inflammation

- Autoimmunity
- Female

Pulmonary vascular remodelling

Genetics factors
Toxic exposure
Portopulmonary hypertension (POPH): Hemodynamics

Excess Volume
- mPAP: ↑
- PAWP: ↑
- CO: ↑
- PVR: ↓

Hyperdynamic circulatory state
- mPAP: ↑
- PAWP: –
- CO: ↑
- PVR: ↓

Pulmonary arterial hypertension
- mPAP: ↑↑
- PAWP: –
- CO: ↑
- PVR: ↑

Portopulmonary hypertension POPH: Hemodynamics

Simonneau G. Hemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019
Herve P. Criteria for diagnosis of exercise pulmonary hypertension. Eur Respir j 2015
Portopulmonary hypertension (POPH): Screening pathway

PoPH screening
All patients candidates for liver transplantation / Symptomatic patients with portal hypertension

Transthoracic echocardiography

TRV ≤ 2.8 m/s and no other signs of PH
Low probability of PoPH
No RHC

TRV ≤ 2.8 m/s and other signs of PH or TRV ≥ 2.9 m/s
Intermediate or high probability of PoPH

RHC

mPAP < 25 mmHg
No PoPH

Early PoPH?
Close monitoring

mPAP ≥ 25 mmHg
PCWP < 15 mmHg
PVR 2 to 3WU
No PoPH

PoPH associated with postcapillary component?

mPAP ≥ 25 mmHg
PCWP ≥ 15 mmHg
DPG ≥ 7 mmHg and PVR > 3WU

Gr. 2, 5

Gr. 1, 3, 4 and 5

Savale L. Portopulmonary hypertension. Semin Respir Crit Care Med 2017
Simonneau G. Hemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019
Portopulmonary hypertension (POPH): Drug treatment

Problem: POPH patients are usually excluded from studies!!!

↓↓↓ prognosis

↓↓ small numbers

hepatotoxicity

Portopulmonary hypertension POPH: LTx yes or no? Which patients?

- **mPAP ≥ 35 mmHg**
  - PAH-targeted therapies
  - **mPAP < 35 mmHg or 35 ≤ mPAP < 45-50 mmHg and PVR < 3-4 WU**
  - Yes: Inscription on waiting list for liver transplantation (MELD exception)
  - No: Definitive contra-indication for liver transplantation

**Multivariate retrospective analysis**

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>1.05 (1.00-1.09)</td>
<td>0.03</td>
</tr>
<tr>
<td>MELD</td>
<td>1.13 (1.08-1.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVR</td>
<td>1.21 (1.09-1.33)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

(Per 100 d*s*cm5)

**Peri-operative right heart failure:**
- Fluid volume optimization
- Cardiac output and systemic pressure optimization (use of catecholamines)
- Inhaled NO
- Reinforcement of PAH-targeted therapies

**Refractory right heart failure:**
- ECMO?
Gattinoni L. The future of mechanical ventilation: lessons from the present and the past. Crit Care 2017
Liver ← Lung

endotoxemic 13 pig’s abdominal edema formation was estimated by isotope technique

Lattuda M. Mechanical ventilation worsens abdominal edema and inflammation in porcine endotoxemia. Crit Care 2013
Liver ← Lung

Liver ↔ Lung

Assessed for eligibility (n = 273)
Excluded (n = 236)
- Not meeting inclusion criteria / exclusion criteria at time informed consent could have been asked (n = 199)
- Refused to participate (n = 24)
- Missing human resources (n = 14)
- Participation in competing study (n = 1)
Included (n = 37)
Lost to follow-up (n = 0)
Excluded from analysis (n = 1)
- Technical failure to record hepatic vein oxygen saturation
Analyzed (n = 36)

Ventilator-related procedures (n = 181)
- Airway suctioning
- Adjustment of ventilator settings
- Change of respiratory tubing
- Extubation/ intubation
- Change of dressings
- Change of sheets
- Oral care
- Washing
- Blood sampling
- Bolus of sedative/vasoactive drug
- Intravenous injection
- Assessment of level of sedation
- Examination (nurse)
- Bedside examination (e.g., rectscopy)
- Rectal enema
- Examination (physician)
- Electrocardiogram recording
- Chest radiograph
- Radiograph, other than chest
- Insertion/ removal of catheters
- Insertion/ removal of drains
- Insertion/ removal of nasogastric tube
- Physiotherapy
- Bedside visits
- Patient moving, fighting ventilator, attempting to speak
- Coughing
- Change in position

Hygiene (n = 130)

Physical examinations, blood sampling, and drug administration (n = 513)

Patient movement (n = 311)

Jakob S. Increased splanchnic oxygen extraction because of routine nursing procedures. Crit Care Med 2009
Increased splanchnic oxygen extraction because of routine nursing procedures. Crit Care Med 2009
Summary

- Hepatic diseases may increase oxygenation failure:
  - preexisting pulmonary vascular anomaly (HPS)
  - atelectasis and pleural effusion (e.g. hepatic hydrothorax)
  - pneumonia (cirrhosis related immune dysfunction)
  - ARDS (pneumonia, TRALI, aspiration)
  - volume overload

- Hepatic diseases may decrease cardiac function (esp. right ventricular function)
  - PoPH
  - HPS with chronically elevated CO

- Lung diseases (needing mechanical ventilation) may decrease liver function
  - PEEP and PIP may decrease preload and CO
  - increase visceral edema
  - abdominal compartment syndrome needs ↑ ventilation pressure

Any respiratory failure and mechanical ventilation may worse liver failure 
&
any liver failure (esp. chronic liver failure) may worse respiratory failure
These articles have been selected by our editors as the most important published by JAMA between 2010 and 2019. Click below to read them for free.

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)
Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; et al

Audio Interview: Consensus Definitions for Sepsis and Septic Shock
Video Interview: Consensus Definitions for Sepsis and Septic Shock
Video: Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)
Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; et al

Audio Interview: 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis: The APPAC Randomized Clinical Trial
Paulina Salminen, MD, PhD; Hannu Paajanen, MD, PhD; Tero Rautio, MD, PhD; et al

Clinical Review Audio: Treating Appendicitis Without Surgery – 5-Year Follow-up From a Randomized Clinical Trial of Antibiotic Treatment

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