Cirrhotic cardiomyopathy and hepatopulmonary syndrome: Prevalence and prognosis in a series of patients

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KEYWORDS
Carbon monoxide; Cirrhotic cardiomyopathy; Diastolic dysfunction; Liver disease; Hepatopulmonary syndrome

Summary
Hepatopulmonary syndrome (HPS) is of prognostic value in patients awaiting for orthotopic liver transplantation (OLT), but little is known about the effect of cirrhotic cardiomyopathy (CCM). The aim of the present study was to estimate the prevalence and possible relation between respiratory and cardiac abnormalities in a same series of patients awaiting OLT. Special attention was paid to the prognostic value of CCM in comparison to HPS.

Eighty-three patients were included (19 females, 64 males; 52.1 ± 10.0 yrs). All had lung function testing with arterial blood gases and echocardiographic evaluation at rest with a contrast echocardiography in case of arterial oxygenation defect. To estimate the presence of CCM, patients underwent a complete left and right echocardiography and Doppler...
Introductions

Liver diseases are associated with pulmonary complications in a significant number of patients. The most common complication is hepatopulmonary syndrome (HPS), which is defined as a defect in arterial oxygenation due to intrapulmonary vascular dilatation in the setting of liver disease, and is found in 10–30% of candidates for liver transplantation. Diagnosing this complication is essential, as it has been associated with pre- and post-transplantation mortality. Portopulmonary hypertension (PPH) is less common (in 3–5% of cases) and is defined as the combination of pulmonary and portal hypertension.

In addition to these pulmonary complications, purely cardiovascular complications, such as cirrhotic cardiomyopathy (CCM), have also been reported. CCM is defined as a cardiac dysfunction characterized by blunted contractile responsiveness to stress and/or diastolic dysfunction at rest and/or electrical conductance abnormalities (prolonged QT interval corrected for heart rate (QTc)) in the absence of other known cardiac disease. Orthotopic liver transplantation (OLT) has been reported to reverse some alterations, specifically diastolic dysfunction and the increase in wall thickness, as assessed by echocardiography. The prevalence of CCM is not accurately known, and to the best of our knowledge, its prognostic value for mortality and morbidity has not previously been estimated.

The exact mechanisms leading to HPS and CCM are still not completely understood but an overproduction of nitric oxide (NO) and carbon monoxide has been suspected to play a role. PPH is less common (in 5% of cases) and is defined as the combination of pulmonary and portal hypertension.

In addition, an echocardiogram was performed using an ATL HDI 5000 (Philips Medical System, Bothell, WA, USA).

Materials and methods

Eighty-three consecutive candidates for OLT (19 women and 64 men, aged 51.7 ± 2.5 and 53.5 ± 1.2 years, with a body mass index of 25.4 ± 1 and 27.1 ± 0.6, respectively) were included in the study. Forty-one patients had alcoholic cirrhosis, 16 had hepatitis C, eight had hepatitis B, four had primary biliary cirrhosis, and two had secondary biliary cirrhosis. Four patients presented with hepatitis B or C or biliary cirrhosis and abusive alcohol consumption. The eight remaining patients presented with less common liver diseases. The same day, a complete medical history and physical examination were performed, before the assessment and recording of all participants’ pulmonary and cardiac parameters.

The severity of liver disease was graded using the model for end-stage liver disease (MELD) score.

Based on coronary angiography or nuclear myocardial perfusion imaging, severe stable ischemic heart disease was observed in nine patients (none of whom were in the HPS group, see below). Sixty-four patients were receiving medical therapy in the form of beta-blockers and/or diuretics, or other antihypertensive treatments.

Informed consent was obtained from each patient. This study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the Institutional Review Board of the French Learned Society for Respiratory Medicine (Société de Pneumologie de Langue Française; CEPRO 2010-002).

Pulmonary function testing

Lung volume, flow–volume curves, and diffusing capacity for carbon monoxide (DLCO) were determined with a Jaeger device (MasterScreen™ PFT, Jaeger GmbH, Würzburg, Germany). The European Coal and Steel Community reference values were used. Exhaled NO was measured before spirometry with a NIOX™ device (Aerocrine AB, Solna, Sweden) at an expiration rate of 50 mL min⁻¹ after a deep breath. Arterial blood gases (ABL725, Radiometer, Copenhagen, Denmark) were measured in the sitting position, exhaled gases were analyzed, and AaPO₂ was calculated using the simplified alveolar gas equation.

Electrocardiographic and echocardiographic measurements

A conventional electrocardiogram (ECG) was performed at rest on the same day. QT interval duration was automatically determined from the beginning of the QRS complex to the end of the T wave. The QTc was calculated using Bazett’s formula. A QTc > 440 ms was considered abnormal.

In addition, an echocardiogram was performed using an ATL HDI 5000 (Philips Medical System, Bothell, WA, USA).
Quantification of cardiac chamber size was carried out based on the guidelines of the American Society of Echocardiography. To assess left and right ventricular diastolic function, mitral and tricuspid pulsed-waves were used to measure peak early filling velocity (E, cm s\(^{-1}\)), peak late atrial filling velocity (A, cm s\(^{-1}\)), E/A ratio and E-wave deceleration time (EDT, ms). Tissue Doppler imaging was obtained on the lateral mitral or lateral tricuspid annulus, and systolic (S, cm s\(^{-1}\)) and peak early diastolic velocities (E', cm s\(^{-1}\)) were measured.

CCM was defined as altered systolic function at rest (EF < 55%) or diastolic dysfunction (with or without QTc prolongation) in the absence of a known cardiac disease or a known cause of myocardial dysfunction (i.e., coronary artery disease, diabetes mellitus, systemic hypertension, or less common diseases, such as hemochromatosis and pericardial fibrosis). Ventricular diastolic dysfunction was defined as an E/A ratio < 1 and an EDT > 200 ms for patients under 50 years of age, and >240 ms (LV) or > 220 ms (RV) for those over 50 years of age.

Cardiac output (CO; L min\(^{-1}\)) was calculated using the formula CO = VTI × HR × LVOT area, where VTI is the aortic velocity-time integral, HR the heart rate, and LVOT the left ventricular outflow track. LVOT area was calculated using the formula LVOT area = π × r\(^2\) (r = radius) derived from the measure of the valve annulus diameter. CI (in L min\(^{-1}\) m\(^{-2}\)) was calculated by dividing CO by the corporeal area.

Tricuspid regurgitation velocity was used (TRV, m s\(^{-1}\)) to estimate the systolic arterial pressure (SAP). Normal pulmonary arterial pressure was defined as a TRV ≤ 2.8 m s\(^{-1}\) and a SAP ≤ 36 mmHg.

Contrast echocardiography (CE) was performed in subjects presenting with an AaPO\(_2\) equal to or greater than 20 mmHg by injecting microbubbles (10 ml of Galactose, Echovist, Bayer Schering, Berlin, Germany) into a peripheral vein. Positive CE was defined as the appearance of microbubbles in the chambers of the left side of the heart in four to six heartbeats after their appearance in the right heart. The degree of intrapulmonary shunt was graded from 0 to IV. Patients with grades I to IV were considered to have a significant intrapulmonary shunt (HPS group).

Statistical analysis

The results were expressed as mean ± standard deviation (SD) or median and range (for non-normal distributions). The comparison between two groups was performed with Student’s t-test or the Mann–Whitney rank sum test (if normality or equal variance tests had failed). The comparison between two percentages was performed using Fisher’s Exact Test. Kaplan–Meier analysis and the log-rank test were used to evaluate and compare the survival of patients within four weeks of transplantation. The level of significance was set at \( p < 0.05 \).

Results

Pulmonary assessment

Eighty-three consecutive candidates for OLT (19 women and 64 men, aged 52.1 ± 10.0 years) were included in the study. AaPO\(_2\) was equal to or greater than 20 mmHg in 35 of 81 patients. Two patients in whom this parameter was not measured had very severe hypoxemia and underwent CE, which confirmed the suspected shunt. Therefore, HPS was found in 14 of 83 patients (16.9%) included in the study, representing 34.3% of the patients who had increased AaPO\(_2\) (12/35).

There was no difference in medication between subjects with and without HPS. The severity of the shunt was: grade I in six patients, grade II in five, grade III in one and grade IV (very severe) in two cases. Pulmonary hypertension was found in two patients with systolic pulmonary arterial pressures of 40 and 75 mmHg. These two patients were excluded from further echocardiographic analysis.

No difference in MELD score was noted between the HPS group and the other patients (Table 1). Moreover, the most severe cases of shunts did not present high MELD scores (10 and 12).

Table 1 shows the pulmonary function test results. No difference between the HPS group and other patients was found regarding exhaled NO\(_x\), carboxyhemoglobin (COHb) and pH. As expected, AaPO\(_2\) was higher and PaO\(_2\) and PaCO\(_2\) were lower in the HPS group than in the non-HPS group. Moreover, single-breath DL\(_{\text{CO}}\) was lower in the HPS group than in the non-HPS group.

Four of 81 patients presented with non-contributive echocardiography (two pulmonary hypertensive patients were excluded from the analysis, see above). Right heart

| Table 1 | Characteristics of patients with (HPS) or without (Non-HPS) hepatopulmonary syndrome. |
|-----------------|---------------------------------|-----------------|
| **HPS** (n = 14) | **Non HPS** (n = 69) | NS |
| MELD score (units) | 14.0 (8–35) | 14.0 (6–40) |
| Exhaled NO (ppb) (n = 12) | 23.7 (9–54.6) | 17.6 (2.6–56.2) |
| HbCO (%) (n = 12) | 2.0 (1–3.9) | 1.9 (0.4–8.0) |
| DL\(_{\text{CO}}\) (mmHg) (n = 13) | 66.0 (40.0–91.0) | 77.0 (51.0–113.0) |
| DL\(_{\text{CO}}\)/AV (n = 13) | 72.5 ± 18.6 | 86.4 ± 16.1 |
| AaPO\(_2\) (mmHg) (n = 12) | 29.5 (23–42.2) | 15.3 (2.0–40.2) |
| PaO\(_2\) (mmHg) (n = 12) | 76.7 ± 12.8 | 91.8 ± 10.4 |
| PaCO\(_2\) (mmHg) (n = 12) | 31.3 ± 3.4 | 33.8 ± 4.5 |
| pH (units) (n = 65) | 7.46 (7.41–7.49) | 7.44 (7.36–7.55) |
| TLC (n = 68) | 86 (63–119) | 96.5 (60–134) |
| VE \(_{\text{f}}\)/VC (%) (n = 69) | 75.4 ± 5.8 | 76.0 ± 8.9 |

MELD: model for end-stage liver disease; NO: nitric oxide; HbCO: carboxyhemoglobin; DL\(_{\text{CO}}\): lung diffusing capacity for carbon monoxide; AV: alveolar volume; AaPO\(_2\): alveolar-arterial oxygen tension difference; TLC: total lung capacity; VE \(_{\text{f}}\)/VC: forced expiratory volume during the first second of expiration; VC: vital capacity.
Intrapulmonary shunt in liver diseases

Table 2  Echocardiographic data of patients with (HPS) or without (Non-HPS) hepatopulmonary syndrome.

<table>
<thead>
<tr>
<th></th>
<th>HPS</th>
<th>Non HPS</th>
<th>HPS</th>
<th>Non HPS</th>
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<tbody>
<tr>
<td><strong>Left heart</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LA (cm)</td>
<td>44.1 ± 4.4</td>
<td>42.3 ± 6.3</td>
<td>84.9 ± 23.6</td>
<td>76.4 ± 20.2</td>
</tr>
<tr>
<td>LAA (cm²/m²)</td>
<td>23.4 ± 1.7</td>
<td>19.8 ± 3.1a</td>
<td>77.1 ± 13.5</td>
<td>69.6 ± 19.9</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>49.1 ± 3.6</td>
<td>49.6 ± 5.9</td>
<td>1.12 ± 0.29</td>
<td>1.16 ± 0.39</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>10.0 ± 1.5</td>
<td>10.4 ± 1.5</td>
<td>231 ± 32</td>
<td>241 ± 48</td>
</tr>
<tr>
<td>LVPW (mm)</td>
<td>9.8 ± 1.8</td>
<td>9.6 ± 1.6</td>
<td>12.4 ± 2.2</td>
<td>13.3 ± 2.9</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>64 ± 7</td>
<td>65 ± 8</td>
<td>7.0 ± 1.6</td>
<td>5.9 ± 2.2</td>
</tr>
<tr>
<td><strong>Right heart</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVEDD (mm)</td>
<td>26.8 ± 4.3</td>
<td>23.1 ± 6.0b</td>
<td>57.9 ± 10.1</td>
<td>52.3 ± 12.4</td>
</tr>
<tr>
<td>RVEDA (cm²/m²)</td>
<td>9.7 ± 1.6</td>
<td>10.2 ± 2.3</td>
<td>55.2 ± 15.0</td>
<td>44.3 ± 13.7</td>
</tr>
<tr>
<td>RVESA (cm²/m²)</td>
<td>5.2 ± 1.7</td>
<td>5.1 ± 1.4</td>
<td>1.11 ± 0.24</td>
<td>1.25 ± 0.38</td>
</tr>
<tr>
<td>RVFAC</td>
<td>49 ± 11</td>
<td>47 ± 10</td>
<td>232 ± 46</td>
<td>248 ± 56</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>24.6 ± 3.7</td>
<td>23.4 ± 5.3</td>
<td>13.9 ± 2.2</td>
<td>13.7 ± 3.6</td>
</tr>
<tr>
<td>RAA (cm²)</td>
<td>20.7 ± 3.7</td>
<td>17.8 ± 4.0d</td>
<td>4.5 ± 1.5</td>
<td>4.0 ± 1.3</td>
</tr>
</tbody>
</table>

LA: left atrium; LAA: left atrium area; LVEDD: left ventricle end-diastolic diameter; LVEF: left ventricle ejection fraction; EDT: E-wave deceleration time; E/E’ peak early diastolic mitral or tricuspid velocity.  

The highest CIs were found in the three patients with a grade III or IV shunt (4.6; 4.3 and 6.5 L min⁻¹ m⁻² for the grade III and the two patients with grade IV shunts, respectively). A significant correlation was found for the whole set of patients between CI and both LAA (r = 0.42; p < 0.0001) and RAA (r = 0.32; p = 0.008).

No correlation was found between hemodynamic data and MELD score.

Table 3  Pulmonary and echocardiographic data of patients with (CCM) or without (Non-CCM) cirrhotic cardiomyopathy.

<table>
<thead>
<tr>
<th></th>
<th>CCM</th>
<th>Non CCM</th>
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<tr>
<td><strong>Hemodynamic</strong></td>
<td></td>
<td></td>
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<tr>
<td>MELD score (units)</td>
<td>12.7 (6–21)</td>
<td>15.8 (7–40)</td>
</tr>
<tr>
<td>Exhaled NO (ppb)</td>
<td>20.5 (9–56.2) 21.9 (4.4–36.9) NS</td>
<td></td>
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<tr>
<td>HbcO (%)</td>
<td>2.7 (1.4–8) 1.9 (0.4–4.2) 0.02</td>
<td></td>
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<tr>
<td>(all patients)</td>
<td>(n = 15)  (n = 30)</td>
<td></td>
</tr>
<tr>
<td>HbcO (%)</td>
<td>2.5 (1.4–8) 1.45 (0.4–3.1) 0.01</td>
<td></td>
</tr>
<tr>
<td>(ex-or no-smokers)</td>
<td>(n = 15)  (n = 48)</td>
<td></td>
</tr>
<tr>
<td>HPS (n, %)</td>
<td>1; 6.7% 13; 26.5% NS</td>
<td></td>
</tr>
<tr>
<td>Smokers (n, %)</td>
<td>3; 20% 17; 34.6% NS</td>
<td></td>
</tr>
<tr>
<td>E/A</td>
<td>0.83 ± 0.14 1.23 ± 0.32 &lt; 0.0001</td>
<td></td>
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<tr>
<td>(left ventricle)</td>
<td>(n = 15)  (n = 30)</td>
<td></td>
</tr>
<tr>
<td>E/A</td>
<td>1.17 ± 0.29 1.29 ± 0.40 NS</td>
<td></td>
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<tr>
<td>(right ventricle)</td>
<td>(n = 15)  (n = 30)</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac output</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO (l min⁻¹)</td>
<td>5.4 ± 1.3  5.5 ± 1.5 NS</td>
<td></td>
</tr>
<tr>
<td>CI (l min⁻¹ m⁻²)</td>
<td>2.9 ± 0.8  3.0 ± 0.9 NS</td>
<td></td>
</tr>
</tbody>
</table>

MELD: model for end-stage liver disease; HbCO: carboxyhemoglobin; HPS: hepatopulmonary syndrome; MELD: model for end-stage liver disease; NO: nitric oxide; E: peak early filling velocity; A: peak late atrial filling velocity; CO: cardiac output; CI: cardiac index.

Dimensions and Doppler measurements could not be assessed with accuracy in seven and 13 patients, respectively. Therefore, complete (i.e., right and left) Doppler echocardiographic evaluation was obtained for 64 patients (Table 3).

No case of systolic dysfunction was found. An isolated left and/or right ventricular diastolic dysfunction was found in 32 of 64 patients. When patients with a diastolic dysfunction related to an etiology other than liver disease were excluded, the global prevalence of CCM was 23.4% (15 of 64 patients), so about half (46.8%) that of patients with CCM and non-CCM patients (data not shown).

Among all participants, the prevalence of increased QTc was 28% (23 of 83). No difference in the rate of increased QTc was observed in HPS vs. non-HPS patients or in CCM (as defined above) vs. non-CCM patients (data not shown).

Only one patient presented with both moderate HPS (grade II) and CCM (Table 3). In contrast with what was observed in the HPS group, a significantly higher COHb was found in the CCM group, even when excluding smokers (Table 3).

On comparing patients with or without HPS, we found a significantly higher left and right atrium area (LAA and RAA) and a right ventricular enlargement in the HPS group (Table 2).

Patients with HPS presented with a higher cardiac output (CO) at rest (6.6 ± 1.7 vs. 5.2 ± 1.1 L min⁻¹; p = 0.007) and cardiac index (CI) (3.6 ± 1.0 vs. 2.8 ± 0.7 L min⁻¹ m⁻²; p = 0.006). Furthermore, the highest CIs were found in the three patients with a grade III or IV shunt (4.6; 4.3 and 6.5 L min⁻¹ m⁻² for the grade III and the two patients with grade IV shunts, respectively).
Outcome before and after OLT

Sixty-eight patients underwent OLT.

Influence of HPS: Global pre- and post-OLT mortality was not significantly different in patients with or without HPS [4/14 (28.6%) vs. 11/69 (15.9%), respectively]. However, there was a tendency (p = 0.06) for a higher number of serious adverse events (death or prolonged intensive care, i.e., length of stay in the intensive care unit of more than five days) after OLT in the HPS group (3/10) than in the non-HPS group (5/58) (Fig. 1).

Influence of CCM: Global pre- and post-OLT mortality was not significantly different in patients with or without CCM [3/15 (20%) vs. 9/49 (18.4%), respectively]. In the group of patients who underwent complete echocardiographic evaluation, 52 had OLT. The occurrence of serious adverse events immediately after OLT did not differ between CCM (2/12) and non-CCM patients (5/40) (Fig. 1).

Discussion

The main results of our study are as follows: i) we observed a "pure" CCM in 23.4% (n = 15/64) of the 64 patients with complete Doppler assessment; ii) HPS was present in 16.9% (n = 14/83) of the patients included in our study; iii) although common factors have been suspected to lead to HPS and CCM, there was no relation between these complications in our series of patients; and iv) CCM was not of prognostic value before or after OLT.

One important finding of our study is that CCM was detected in 23.4% (n = 15/64) of patients screened before OLT and for whom complete echocardiographic assessment could be obtained. The exact prevalence of CCM is difficult to determine. Its diagnosis has been defined variously, based on at rest and/or stress echocardiographic criteria and/or ECG abnormalities.11,31 More recently, it has been suggested that brain natriuretic peptide plasma levels could also be of help.32,33 In our study, CCM was defined as systolic or diastolic dysfunction at rest and in the absence of any other clear cause for cardiac impairment. A diagnosis of CCM was not retained in cases with an isolated increase in QTc. The prevalence of CCM in our series of patients was rather high, and we can then conclude that CCM in patients awaiting OLT is far from rare.

Higher CO, LAA and RAA were found in HPS patients than non-HPS patients. This is probably mainly explained by the case of hyperdynamic syndrome found in the group of HPS patients.16,17 Nevertheless, this increase in cardiac parameters was not, in our series, related to diastolic dysfunction, which suggests CCM.

Our results showed that HPS and CCM were not correlated with the severity of hepatic disease. This is not surprising for HPS since it has been reported in previous studies.28,29 Interestingly, we observed that HPS and CCM are independent complications of liver disease. This is rather surprising since identical mechanisms leading to both complications have been suggested.10,11,15,34–38

As for HPS, the precise pathophysiological mechanisms leading to CCM have not been fully elucidated. In the literature, systolic dysfunction in patients awaiting OLT has been associated with increased endocannabinoid levels, impaired β-adrenergic receptor signaling, and overproduction of NO or carbon monoxide.10,11,15 Interestingly, an increase in COHb was noted in patients with CCM in comparison with other patients, suggesting that carbon monoxide is implicated in the occurrence of diastolic dysfunction. It is noteworthy that COHb was increased in CCM but not HPS patients, which suggests that different factors may lead to these two complications of liver diseases. It has been reported in animal20,21 and human studies34–36 that increased NO is one of the factors leading to HPS or CCM.37,38 In our series we did not observe any difference in inhaled NO in patients with or without HPS or in those with or without CCM. This could be explained by the method used to measure NO (during an expiration rate of 50 mL min⁻¹), which cannot estimate accurately the NO output from the alveolar compartment, which is the main source of NO in cirrhosis.34

Clinical studies have shown that HPS is of prognostic value in patients awaiting liver transplantation, and also after OLT. In our study, a tendency toward a higher rate of serious adverse events after transplantation was noted in HPS patients. The lack of a clearly significant difference could be explained by the weak statistical power of the study due to the small number of HPS patients, or by actual better outcomes due to optimum management of patients with known HPS during the transplantation period. We observed an early post-operative mortality of 20% in HPS.
patients vs. 6.9% in non-HPS patients, which is similar to what has been reported in other studies.\textsuperscript{35,36}

In contrast to HPS, CCM was not related to prognosis before and immediately after OLT in the present study. To the best of our knowledge, this has not been reported before.

In summary, both HPS and CCM could be found in our series of patients awaiting OLT, but not in the same patients. HPS patients were more likely to have a serious adverse event after OLT than non-HPS patients. Conversely, CCM was not of prognostic value for survival before and immediately after OLT, or for the occurrence of adverse events after OLT. To our knowledge, this is the first study to evaluate the prevalence and prognostic value of both pulmonary and cardiac abnormalities in a series of consecutive patients awaiting OLT.

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**Conflict of interest**

The authors have no conflict of interest to report.

**References**


