Chronic Change in Pulmonary Vascular Response to Hypoxia in Hepatopulmonary Syndrome

Yoshinori Tanino\textsuperscript{a,b}, Hironi Makita\textsuperscript{a}, Ichizo Tsujino\textsuperscript{a}, Hideki Shinano\textsuperscript{a}, Masaharu Nishimura\textsuperscript{a}

\textsuperscript{a}First Department of Medicine, Hokkaido University School of Medicine, Sapporo, and \textsuperscript{b}Department of Pulmonary Medicine, Fukushima Medical University School of Medicine, Fukushima, Japan

**Established Facts**
- In hepatopulmonary syndrome, there have been only a few cases that reported spontaneous resolution of hypoxaemia with the development of pulmonary hypertension without liver transplantation.

**Novel Insights**
- This is the first report that shows remarkable change in the pulmonary vascular response to hypoxia before and after the spontaneous resolution of hypoxaemia in hepatopulmonary syndrome.

**Key Words**
Hepatopulmonary syndrome \cdot Spontaneous resolution \cdot Pulmonary hypertension \cdot Pulmonary vascular response

**Abstract**
Here we present a case of hepatopulmonary syndrome (HPS) where spontaneous resolution of severe hypoxaemia occurred with the development of pulmonary hypertension over several years after the initial diagnosis of HPS. The pulmonary vascular responses to hypoxia examined before and after the spontaneous resolution of HPS confirmed that the pathogenesis of HPS could be functional and reversible in nature. To the best of our knowledge, this is the first report demonstrating a remarkable change in the pulmonary vascular response to hypoxia before and after the spontaneous resolution of hypoxaemia in HPS.

**Introduction**
Hepatopulmonary syndrome (HPS) is characterized by a triad of chronic liver disease, oxygenation defect, and intrapulmonary vascular dilatation [1]. The hypoxaemia in HPS is generally progressive and no effective therapy...
Hypoxia in HPS

Pulmonary Vascular Response to Hypoxia in HPS

A 52-year-old man who had been diagnosed with HPS 40 months previously was admitted for further evaluation of improving hypoxaemia that had been noticed several months before. He had received a massive transfusion for leg injuries, and was further reduced to as low as 3.0% after 62 months. We then conducted right-sided heart catheterization for further haemodynamic evaluation. Circulatory parameters measured under room air breathing confirmed the development of PH. We examined the right to left shunt by breathing 100% oxygen. The right to left shunt calculated by the shunt equation was 3.0% at this time which was improved compared with 8.4% at the initial evaluation. Macroaggregated albumin lung perfusion scans showed a more dramatic change. The shunt value by this method was around 30% at the diagnosis. It was 10.3% after 40 months, and was further reduced to as low as 3.0% after 62 months. We then conducted right-sided heart catheterization and lung perfusion scans using macroaggregated albumin confirmed the chronological change in the pulmonary vascular response to hypoxia.

Case Report

A 52-year-old man who had been diagnosed with HPS 40 months previously was admitted for further evaluation of improving hypoxaemia that had been noticed several months before. He had received a massive transfusion for leg injuries, and was diagnosed as having post-transfusion liver cirrhosis (Child-Pugh score 5) at the age of 43. Long-term oxygen therapy had been prescribed because of severe hypoxaemia (table 1) and he complained of dyspnoea even on mild exercise at the first evaluation. However, he reported at this time that his exertional dyspnoea had been definitely getting better over the previous few months. His physical examination was remarkable for clubbed fingers, spider nevi scattered on the anterior chest and hepatomegaly. The breath sound was clear, as it had been at the initial diagnosis. The results of circulatory blood counts were unremarkable, and liver function tests showed no signs of deterioration. Chest roentgenograms demonstrated cardiomegaly with mottled vascular markings in bilateral lower lung fields.

Arterial blood gas analysis while breathing room air confirmed a marked improvement of the hypoxaemia (table 1: P\textsubscript{ACO}_2, 34.5 Torr, and P\textsubscript{AO}_2, 77.0 Torr). Spirometric measurement did not show apparent ventilatory dysfunction but a decline of the diffusing capacity [vital capacity, 3.04 liters (84.9% predicted), forced expiratory volume in 1 s/forced vital capacity, 71.0%, and diffusion capacity for carbon monoxide, 11.45 ml/min/mm Hg (50.4% predicted)].

We examined the right to left shunt by breathing 100% oxygen. The right to left shunt calculated by the shunt equation was 3.0% at this time which was improved compared with 8.4% at the initial evaluation. Macroaggregated albumin lung perfusion scans showed a more dramatic change. The shunt value by this method was around 30% at the diagnosis. It was 10.3% after 40 months, and was further reduced to as low as 3.0% after 62 months. We then conducted right-sided heart catheterization for further haemodynamic evaluation. Circulatory parameters measured under room air breathing confirmed the development of PH. We examined the pulmonary vascular responses to various arterial oxygen tensions as previously described [4]. Briefly, we let the patient receive 100% oxygen at first, and then attempted to control his oxygen saturation (S\textsubscript{O}_2) measured by a pulse oximeter by changing the inspiratory gas concentration. Measurements were done at least 3 min after a steady state was achieved at the S\textsubscript{O}_2 levels of nearly 100, 95, and 90% (fig. I). When the S\textsubscript{O}_2 reached 90%, the mean pulmonary arterial pressure (mPAP) was 41 mm Hg and the pulmonary vascular resistance (PVR) was 338 dyn s cm\textsuperscript{-5}, both of which were higher than the values obtained at the S\textsubscript{O}_2 levels of nearly 100% (35 mm Hg and 312 dyn s cm\textsuperscript{-5}, respectively). The pulmonary vascular response to graded arterial S\textsubscript{O}_2 indicated the presence of hypoxic pulmonary vasoconstriction (HPV), which was in sharp contrast with the finding at the initial evaluation. As previously reported, inhalation of 100% oxygen had evoked paradoxical pulmonary vasoconstriction 3 months after diagnosis [4].

Sixty-two months after the diagnosis, long-term oxygen therapy was discontinued according to the patient’s request because of further improvement of hypoxaemia and exertional dyspnoea.

Table 1. Results of right-sided heart catheterization and shunt value estimated by a macroaggregated albumin lung scan

<table>
<thead>
<tr>
<th></th>
<th>At diagnosis</th>
<th>Time after diagnosis</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>3 months</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>69</td>
<td>73</td>
</tr>
<tr>
<td>SBP s/d/m, mm Hg</td>
<td>95/57/69</td>
<td>109/59/75</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>PAP s/d/m, mm Hg</td>
<td>19/9/12</td>
<td>25/14/20</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>8.24</td>
<td>8.98</td>
</tr>
<tr>
<td>CI, l/min/m\textsuperscript{2}</td>
<td>4.31</td>
<td>4.70</td>
</tr>
<tr>
<td>PVR, dyn s cm\textsuperscript{-5}</td>
<td>29</td>
<td>53</td>
</tr>
<tr>
<td>SVR, dyn s cm\textsuperscript{-5}</td>
<td>641</td>
<td>579</td>
</tr>
<tr>
<td>Shunt value, %\textsuperscript{1}</td>
<td>29.3</td>
<td>33.2</td>
</tr>
<tr>
<td>P\textsubscript{ACO}\textsubscript{2}, Torr</td>
<td>26.6</td>
<td>24.4</td>
</tr>
<tr>
<td>P\textsubscript{AO}\textsubscript{2}, Torr</td>
<td>63.4</td>
<td>58.2</td>
</tr>
</tbody>
</table>

SBP s/d/m = Systemic blood pressure, systolic, diastolic, mean; RAP = right atrial pressure; CO = cardiac output; CI = cardiac index; SVR = systemic vascular resistance.
although the PAP estimated by a Doppler echocardiogram remained high or even higher than before. At this time, we conducted right-sided heart catheterization again and confirmed that the mPAP (48 mm Hg) and the PVR (534 dyn-s-\(\text{cm}^{-5}\)) were further elevated while the CO or CI was decreased compared to the values of 22 months before (table 1).

**Discussion**

In the present case, the pulmonary artery had constricted on exposure to hyperoxia and then gradually dilated during progressive hypoxic inhalation at the first admission [4]. Interestingly, this paradoxical response has disappeared and normal HPV was observed after 37 months. Such a paradoxical response in the pulmonary artery should result in abnormal VA/Q relationships in the lungs, thus further contributing to the hypoxaemia observed in HPS. In general, the presence of HPS in chronic liver diseases is considered to indicate a poor prognosis. Indeed, median survival was reported to be 24 months among patients who were not candidates for liver transplantation [5]. However, spontaneous resolution of hypoxaemia and dyspnoea occurred over the next several years after the initial diagnosis in this case, and this surprising event was associated with the new development of PH. In fact, there are a few earlier cases that showed such spontaneous resolution of hypoxaemia in HPS with the development of PH [3, 4]. However, we demonstrated for the first time that the pulmonary vascular response could be returned to normal from paradoxical. In other words, we could confirm the recovery of HPV with a resolution of hypoxaemia in this case, which should potentially contribute to the improvement of hypoxaemia. Although the pathogenesis of HPS remains to be elucidated, these findings indicate that HPS could be functional and reversible in nature and may lead to the future discovery of pharmacological therapy for HPS.

In cirrhotic patients, Daoud et al. [6] demonstrated the complete loss of HPV and concluded that this phenomenon resulted in abnormal VA/Q relationships and hypoxaemia. In contrast, Naeije et al. [7] reported HPV was preserved in the majority of individuals with cirrhosis. The mechanism by which the pulmonary vascular response to hypoxaemia changed over the years in this case was unclear. In general, the pulmonary vascular response is considered to be determined by the net balance between vasoconstrictor and vasodilatory factors. Therefore, the chronological change in the pulmonary vascular response in this case may suggest changes in vasodilatory factors as well as vasoconstrictive mechanisms. A balance of vasoconstrictive and vasodilatory factors such as endothelin-1 (ET-1) and nitric oxide may possibly be involved in our case [8–10].

Like HPS, PH is another well-known complication of chronic liver disease, although its prevalence is reported to be as low as 2% in cirrhosis and portal hypertension [9]. The haemodynamic features of HPS and portopulmonary hypertension are seemingly opposite, with PVR being low in the former and elevated in the latter. Although the precise pathogenesis of portopulmonary hypertension has not been clarified, recent evidence suggests the possible role of ET-1 [11]. Because ET-1 is also considered to be involved in HPS, Umeda et al. [3] have
discussed a biphasic property of ET-1 in liver cirrhosis (at first vasodilation, then vasoconstriction). From this point of view, it is interesting to see the two complications in the same patient.

In conclusion, the change in pulmonary vascular responses which we presented here indicates that the pathogenesis of HPS could be functional and reversible in nature. Although the precise mechanism remains to be clarified, these findings provide insight into the pathogenesis and mechanisms of pulmonary vascular abnormalities associated with chronic liver disease.

References