Portopulmonary Hypertension  
—Hemodynamics, Pulmonary Angiography, and Configuration of the Heart—

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Background The goal of the present study was to examine the cardiac configuration and pulmonary vascular changes in patients with portopulmonary hypertension (PPHTN) and compare them with those of idiopathic pulmonary arterial hypertension (IPAH).

Methods and Results The subjects were 10 patients with PPHTN and 18 with IPAH. In PPHTN, the increases in the right ventricular end-diastolic volume index (89±19 vs 128±50 ml/m²; p=0.04), right end-systolic volume index (50±19 vs 95±47 ml/m²; p=0.02) and right ventricular mass index (47±18 g/m² vs 79±31; p=0.04) were low compared with IPAH. The decrease in the right ventricular ejection fraction was also low in PPHTN (45±10 vs 28±13%; p=0.01). The degree of sparse arborization and abrupt narrowing on wedged pulmonary angiography was moderate in PPHTN compared with IPAH. In PPHTN, the proximal pulmonary arteries were dilated near the segmental arteries, which were narrow in IPAH.

Conclusion Changes in the configuration of the heart were moderate in PPHTN compared with those in IPAH. The degree of sparse arborization and abrupt narrowing were also moderate in PPHTN. (Circ J 2005; 69: 1386 – 1393)

Key Words: Brain natriuretic peptide; Electron beam tomography; Idiopathic pulmonary arterial hypertension; Portopulmonary hypertension; Pulmonary angiography

Portopulmonary hypertension (PPHTN) was previously known as idiopathic pulmonary arterial hypertension (IPAH) with liver injury, but is now established as a clinical entity that is defined as pre-capillary pulmonary hypertension accompanied by hepatic dysfunction and/or portal hypertension. The appearance of PPHTN does not correlate with the severity of the liver dysfunction; there are no reports on the cardiac configuration, pulmonary vascular changes assessed by pulmonary angiography, and plasma levels of brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP), which are indices of loading to the heart. We hypothesized that the changes described would be less prominent in patients with PPHTN, compared with those in IPAH.

Methods

Our subjects were 10 patients with PPHTN (2 males, 8 females; mean age 38.5 years, range 22–57) (Table 1) and 18 patients with IPAH (3 males, 15 females, p=1.00; mean age 38.9 years, range 19–76, p=0.87). The severity of liver failure was classified as A, B or C by Child-Pugh’s score.

In all subjects, we measured the pulmonary arterial wedge pressure, pulmonary artery pressure, right atrial pressure, aortic pressure, oxygen content in the aorta and pulmonary artery, and cardiac output by routine catheter examination. Fractional pulse pressure was computed as the pulse pressure by the mean pulmonary artery pressure. Additionally, in 8 PPHTN patients and 14 IPAH patients, pulmonary angiography was carried out to examine the configuration of the pulmonary artery tree. Within 1 week after cardiac catheter examination, enhanced electron beam tomography (EBT) (Imatron C-150) was carried out to assess both the ventricular volume and myocardial mass in 5 PPHTN patients and 12 IPAH patients. Electrocardiographic electrodes were attached to each patient’s thorax to provide both continuous monitoring of the heart and a trigger signal to the scanner. Patients were placed in a supine position with a 17° axial (feet down) tilt and a 13° slope (to the patient’s right) to approximate the short-axis view of the heart. A total of 50–60 ml of iopamidol 370 contrast medium was injected into an antecubital vein at a rate of 0.8–1.2 ml/s. The gathering of data was started 40 s after the onset of injection. Ventricular and myocardial volumes were calculated using Simpson’s rule from 1-cm slice images (7 mm width and 3 mm gap) in the cine mode (Fig 1). End-diastole was defined according to the timing of the R wave on electrocardiography, and end-systole at the smallest ventricular size. Ventricular volumes were calculated at both end-diastole and end-systole. The left ventricular myocardial volume, including that of the interventricular
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Circulation Journal   Vol.69, November 2005

Table 1 Clinical Characteristics of Patients With Portopulmonary Hypertension

<table>
<thead>
<tr>
<th>Gender/Age (years)</th>
<th>Examination</th>
<th>NYHA functional class</th>
<th>Etiology of liver disease</th>
<th>Child’s class</th>
<th>Years after diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/29</td>
<td>Catheter/EBT</td>
<td>III</td>
<td>Idiopathic portal hypertension, Hepatitis type C</td>
<td>B</td>
<td>18</td>
</tr>
<tr>
<td>F/22</td>
<td>Catheter/EBT</td>
<td>II</td>
<td>Idiopathic portal hypertension</td>
<td>B</td>
<td>19</td>
</tr>
<tr>
<td>F/57</td>
<td>Catheter/EBT</td>
<td>III</td>
<td>Liver cirrhosis due to hepatitis B</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>F/44</td>
<td>Catheter/EBT</td>
<td>III</td>
<td>Liver cirrhosis</td>
<td>B</td>
<td>10</td>
</tr>
<tr>
<td>F/42</td>
<td>Catheter/EBT</td>
<td>IV</td>
<td>Hepatitis C</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>F/30</td>
<td>Catheter</td>
<td>III</td>
<td>Liver cirrhosis</td>
<td>A</td>
<td>5</td>
</tr>
<tr>
<td>F/49</td>
<td>Catheter</td>
<td>III</td>
<td>Chronic hepatitis</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>F/44</td>
<td>Catheter</td>
<td>II</td>
<td>Liver cirrhosis</td>
<td>C</td>
<td>8</td>
</tr>
<tr>
<td>F/68</td>
<td>Catheter</td>
<td>II</td>
<td>Hepatitis C</td>
<td>B</td>
<td>6</td>
</tr>
<tr>
<td>M/39</td>
<td>Catheter</td>
<td>III</td>
<td>Idiopathic portal hypertension</td>
<td>C</td>
<td>1</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; EBT, electron beam tomography.

Table 2 Laboratory Data

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>PPHTN</th>
<th>IPAH</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (10^9/l)</td>
<td>3.2–9.6</td>
<td>4.2±0.9</td>
<td>6.7±2.3</td>
<td>0.001</td>
</tr>
<tr>
<td>RBC (10^12/l)</td>
<td>3.93–5.03</td>
<td>4.48±0.48</td>
<td>4.89±0.49</td>
<td>0.05</td>
</tr>
<tr>
<td>Ph (10)</td>
<td>155–347</td>
<td>103±60</td>
<td>200±72</td>
<td>0.003</td>
</tr>
<tr>
<td>TP (g/dl)</td>
<td>6.3–8.2</td>
<td>6.5±1.1</td>
<td>6.9±0.6</td>
<td>0.42</td>
</tr>
<tr>
<td>Alb (g/dl)</td>
<td>4.2–5.3</td>
<td>3.6±0.6</td>
<td>4.2±0.5</td>
<td>0.005</td>
</tr>
<tr>
<td>T. Bil (mg/dl)</td>
<td>0.2–1.2</td>
<td>2.5±1.5</td>
<td>1.6±1.1</td>
<td>0.09</td>
</tr>
<tr>
<td>GOT (IU/L)</td>
<td>12–30</td>
<td>45±21</td>
<td>27±17</td>
<td>0.03</td>
</tr>
<tr>
<td>GPT (IU/L)</td>
<td>8–35</td>
<td>30±15</td>
<td>22±19</td>
<td>0.28</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>8–20</td>
<td>12±4</td>
<td>17±4</td>
<td>0.04</td>
</tr>
<tr>
<td>Cre (mg/dl)</td>
<td>0.4–1.0</td>
<td>0.7±0.5</td>
<td>0.8±0.2</td>
<td>0.90</td>
</tr>
<tr>
<td>CRP (mmol/L)</td>
<td>0.0–0.1</td>
<td>0.2±0.1</td>
<td>0.7±1.3</td>
<td>0.09</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>0–18.4</td>
<td>121±109</td>
<td>316±111</td>
<td>0.07</td>
</tr>
<tr>
<td>ANP (pg/ml)</td>
<td>0–43</td>
<td>43±56</td>
<td>192±409</td>
<td>0.04</td>
</tr>
</tbody>
</table>

PPHTN, portopulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension; WBC, white blood cell; RBC, red blood cell; Ph, platelet; TP, total protein; Alb, albmin; T. Bil, total bilirubin; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; BUN, blood urea nitrogen; Cre, creatinine; CRP, C-reactive protein; BNP, brain natriuretic peptide; ANP, atrial natriuretic peptide.

Table 3 Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>PPHTN</th>
<th>IPAH</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCWP (mmHg)</td>
<td>2–10</td>
<td>6±2</td>
<td>8±4</td>
<td>0.53</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>9–18</td>
<td>5±10</td>
<td>64±16</td>
<td>0.04</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>2–8</td>
<td>6±8</td>
<td>96±5</td>
<td>0.08</td>
</tr>
<tr>
<td>mAoP (mmHg)</td>
<td>70–105</td>
<td>90±19</td>
<td>88±12</td>
<td>0.67</td>
</tr>
<tr>
<td>CI (L·min⁻¹·m⁻²)</td>
<td>2.6–4.2</td>
<td>3.3±0.6</td>
<td>2.0±0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVR (dyne·s⁻¹·cm⁻⁵)</td>
<td>20–130</td>
<td>750±231</td>
<td>1,557±490</td>
<td>0.001</td>
</tr>
<tr>
<td>SVR (dyne·s⁻¹·cm⁻⁵)</td>
<td>700–1,600</td>
<td>1,332±558</td>
<td>1,239±359</td>
<td>0.001</td>
</tr>
<tr>
<td>PVR/SVR</td>
<td>NA</td>
<td>0.58±0.16</td>
<td>0.72±0.20</td>
<td>0.04</td>
</tr>
<tr>
<td>SVO₂ (%)</td>
<td>65–75</td>
<td>74±4</td>
<td>60±11</td>
<td>0.009</td>
</tr>
<tr>
<td>AVO₂ dif. (Vol %)</td>
<td>–5</td>
<td>3.8±0.6</td>
<td>6.7±1.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FPP</td>
<td>NA</td>
<td>0.92±0.17</td>
<td>0.83±0.14</td>
<td>0.25</td>
</tr>
</tbody>
</table>

PCWP, pulmonary capillary wedge pressure; mPAP, mean pulmonary arterial pressure; RAP, right atrial pressure; mAoP, mean aortic pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; NA, not available; SVO₂, mixed venous oxygen saturation; AVO₂ dif., arterio-venous difference in oxygen content; FPP, fractional pulse pressure. See Table 2 for other abbreviations.

Statistics

Statistical analysis was carried out using SPSS 13.0 (SPSS Inc, Chicago, ILL, USA). All continuous variables were analyzed by Mann-Whitney test and expressed as mean±standard deviation. Non-ordinal categorical data were analyzed by Fisher’s exact test. Survival data were analyzed by log rank test. All significant tests were two-tailed.

Results

Laboratory Data (Table 2)

The white blood cell, red blood cell and platelet counts, and the plasma levels of albumin and blood urea nitrogen were low, and the glutamic-oxaloacetic transaminase level were...
was high in PPHTN compared with the values in IPAH. The level of ANP was lower in PPHTN, as was the BNP level but not significantly.

**Hemodynamic Data (Table 3)**

The cardiac index was within the normal range in all 10 patients with PPHTN, and higher than that in IPAH patients. The mean pulmonary artery pressure, pulmonary vascular resistance and systemic vascular resistance were elevated in PPHTN, but were lower than those in IPAH. The pulmonary vascular to systemic vascular resistance ratio was low in PPHTN compared with that in IPAH. There was no significant difference in the mean arterial pressure, the pulmonary arterial wedge pressure and fractional pulse pressure between the 2 groups. Oxygen saturation at mixed venous was high and the arteriovenous difference in oxygen content was low in PPHTN compared with those in IPAH.

**EBT Data (Table 4)**

The increase in the right ventricular end-diastolic volume index, volume index and mass index was low, and the decrease in right ventricular ejection fraction was also low in PPHTN compared with those in IPAH. Left ventricular end-diastolic volume index in PPHTN was slightly low, but larger than that in IPAH. The leftward shift of the interventricular septum was moderate in PPHTN (Fig 1).

**Pulmonary Angiography (Figs 2,3)**

The degree of sparse arborization (“pruned tree” appearance) and abrupt narrowing (tapering) on wedged pulmonary angiography was moderate in PPHTN compared with that in IPAH. In PPHTN, the proximal pulmonary arteries were dilated near the segmental arteries, which were narrow in IPAH. These angiographic findings were found in all cases with PPHTN.

**Management and Prognosis**

In PPHTN, 6 patients used calcium-antagonists, 4 the prostacyclin analogue beraprost sodium (1 received both a calcium-antagonist and beraprost sodium), and 1 was on intravenous prostacyclin. Two patients received warfarin, but thereafter one of them withdrew because of hemoptysis. In IPAH, 15 patients used intravenous prostacyclin (p=0.0003, vs PPHTN), and 3 were taking beraprost sodium (p=0.21, vs PPHTN). One of them used a calcium-antago-
ist (p=0.04, vs PPHTN). All of them received warfarin (p<0.0001, vs PPHTN) but 8 withdrew when the prostacyclin infusion rate reach approximately $15 \text{ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. However, warfarin was continued in cases with thrombotic risk as well as pulmonary hypertension or in cases treated medically except for prostacyclin. One patient died from hemoptysis while receiving both prostacyclin and warfarin. Mortality was lower in PPHTN than in IPAH, but was not significant (Fig 4).

Fig 2. Pulmonary angiograms in patients with portopulmonary hypertension (PPHTN). The degree of sparse arborization and tapering on wedged pulmonary angiography was more moderate in PPHTN than in idiopathic pulmonary artery hypertension (IPAH) (see Fig 3). The central pulmonary arteries are dilated near the subsegmental arteries, which are narrow in IPAH.

Fig 3. Pulmonary angiograms in patients with idiopathic pulmonary artery hypertension. Sparse arborization and tapering are marked compared with patients with portopulmonary hypertension (see Fig 2). Central pulmonary arteries are dilated. See Fig 2 for abbreviations.
Discussion

Hemodynamics

The mean pulmonary arterial pressure and pulmonary vascular resistance rose in PPHTN, whereas the cardiac index, pulmonary arterial wedge pressure, right atrial pressure, mean aortic pressure, systemic vascular resistance were within normal limits. These hemodynamic findings are consistent with previous reports. The elevation of both the mean pulmonary arterial pressure and pulmonary vascular resistance was mild in PPHTN compared with that in IPAH. The cardiac output was maintained in PPHTN but not in IPAH.

Nakayama et al described the usefulness of the fractional pulse pressure as an index of peripheral vascular lesions in the pulmonary arteries and they showed that in all patients with IPAH, in whom the peripheral pulmonary arteries were mainly injured, it was less than 1.1 and that in all patients with chronic thromboembolic pulmonary hypertension, in whom the proximal pulmonary arteries were mainly injured, it was over 1.1. In our subjects, the fractional pulse pressure was less than 1.0 in both PPHTN and IPAH patients, and there was no difference between the 2 groups. The present result indicates that the peripheral pulmonary arteries are mainly disturbed in PPHTN also.

Pulmonary Angiography

In the past, pulmonary angiography was thought to be contraindicated in patients with pulmonary hypertension, because catheter examination induced death in some cases, but it has since become safer because of improvements in both contrast media and the catheters. Since 1999 we have routinely performed pulmonary angiography and/or wedged pulmonary angiography in all patients with pulmonary hypertension, except those with New York Heart Association class IV, and have experienced no complications.

Typical angiograms of PPHTN and IPAH are shown in Figs. 2 and 3, respectively. Tapering of the peripheral arteries and sparse arborization were seen in IPAH whereas in PPHTN, the pulmonary arteries were dilated near the subsegmental arteries, which were narrow in IPAH, and then tapered acutely. The degree of sparse arborization was moderate in PPHTN compared with that in IPAH.

Histologically, pulmonary arteries are classified as elastic or muscular on the basis of the structure of their media. The elastic arteries include the pulmonary trunk and arteries with a diameter greater than 500 μm in diameter, and their media is characterized by a multilayered lattice of coarse elastic fibers. The muscular arteries, which have a diameter ranging between 500 μm and 100 μm, are characterized by a muscular media bounded by internal and external elastic laminae. Arterioles have been defined as precapillary arteries smaller than 100 μm in outer diameter, and these are composed solely of a thin intima and a single elastic lamina. The main lesions in IPAH are located in the muscular arteries and arterioles. Plexiform lesions, proliferative pulmonary arteriopathy with obliteration of the vessel lumen by endothelial cells and smooth muscle cells, and thromboembolic lesions are found in both PPHTN and IPAH. However, stenosis and/or obstruction in muscular arteries or arterioles cannot be seen using wedge pulmonary angiography. The images from wedge pulmonary angiography reflect the lumen of elastic arteries.

EBT

The increase of the right ventricular end-diastolic volume index, and the decrease in the right ventricular ejection fraction were moderate in PPHTN compared with IPAH. Additionally, the increase in the right ventricular mass index was also slight. On the other hand, no decrease in the left ventricular end-diastolic volume index, which occurred in IPAH, was seen in PPHTN.

Evaluation of the right ventricle is not easy because of its complex configuration. Imaging using EBT nuclear magnetic resonance imaging or multidetector row helical computed tomography has excellent time resolution without a blind spot and the quality of the imaging is barely influenced by the skill of the operator. Therefore, EBT is useful for assessing right ventricular function. Nootens et al reported that, in IPAH, the right ventricular end-diastolic volume and mass were increased, whereas the stroke volume and ejection fraction were reduced; the left ventricular end-diastolic volume was decreased, whereas the ejection fraction remained normal. Ours is the first report on PPHTN based on EBT data and our results show that the increases in right ventricular end-diastolic volume index and mass index were moderate and that the decline in the ejection fraction was also moderate in PPHTN compared with those in IPAH. The left ventricular end-diastolic volume index remained almost normal. These findings indicate that changes in heart configuration are moderate in PPHTN.

When the pulmonary vascular resistance increases and results in pulmonary hypertension, there is a compensatory mechanism by which the right ventricular preload increases to maintain the cardiac output and the long-term elevation of the right ventricular afterload causes the right ventricular myocardial mass to increase. The moderate increase in both the right ventricular end-diastolic volume index and mass index in PPHTN is thought to result from the increase in pulmonary vascular resistance and the elevation of the mean pulmonary artery pressure, which are moderate in PPHTN compared with IPAH.

The stroke volume was reduced in IPAH but not in PPHTN. If the stroke volume of the right ventricle is reduced, the amount of blood returning to the left-sided heart decreases via serial interaction, and then the left ventricular end-diastolic volume decreases. Furthermore, a leftward shift of the interventricular septum occurs because of the increase in the right ventricular end-diastolic volume and, in IPAH, also because of the decrease in the left ventricular end-diastolic volume. In PPHTN, the right ventricular afterload and end-diastolic volume were moderately increased. Moreover, blood return to the left-sided heart was maintained. Therefore, the change in the left ventricular shape was slight.

In summary, the changes in the configuration of both ventricles were moderate in PPHTN patients compared with those in IPAH patients. The difference in those changes resulted from the moderate elevation in pulmonary arterial pressure and pulmonary vascular resistance in PPHTN.

BNP and ANP

The ANP level was lower and the BNP level tended to be lower in PPHTN compared with IPAH. There have been reports on ANP and BNP in IPAH, but not in PPHTN. Nagaya et al reported that the plasma BNP level was higher in patients with right ventricular pressure overload than in...
those with volume overload, and positively correlated with the mean pulmonary artery pressure, pulmonary vascular resistance, mean right atrial pressure and right ventricular myocardial mass, and negatively with the cardiac output and right ventricular ejection fraction.27 A high level of plasma BNP is associated with increased mortality in patients with IPAH.3 The difference in the ANP and BNP levels between PPHTN and IPAH in the present study can be explained by differences in the hemodynamics and right ventricular mass.

Management and Prognosis

There were a few PPHTN cases that received both prostacyclin and warfarin, although the use of warfarin is not recommended, even in the West, because of its tendency to cause bleeding.29 Warfarin was used at the start of prostacyclin administration in all patients with IPAH, but thereafter was stopped in 50% of the patients. Retrospective studies in Western countries reported that warfarin improves the mortality in IPAH patients30–32 but it was shown recently that alveolar hemorrhage, which can be fatal, was increased in Japanese patients with IPAH who received combined warfarin and prostacyclin therapy.33 One of the present patients who received the combined therapy died from hemoptysis and after that experience, we stopped warfarin when the prostacyclin dosage reached approximately 15 ng·kg−1·min−1. The efficacy of epoprostenol to prevent platelet aggregation in hemodialysis has been assessed at doses ranging from 3 to 5 ng·kg−1·min−1.34–37 In the United Kingdom, the usual dose of epoprostenol for renal dialysis is 4 ng·kg−1·min−1 in cases with a contraindication for heparin, but this is not relevant to the prevention of pulmonary thrombosis in pulmonary artery hypertension as well as that of platelet aggregation in hemodialysis. Therefore, the following problems remain: should warfarin be stopped in patients treated with epoprostenol, and if so, when?

The prognosis was better in PPHTN compared with IPAH, but not significantly, similar to other findings.3 The 5-year survival rate of IPAH was equal to that in the West, approximately 60%28,38,39 Recently, epoprostenol, beraprost, bosentan and sildenafil have been used in the treatment for pulmonary arterial hypertension in Japan40–42 and have improved the prognosis. In the present study, the 5-year survival rate with PPHTN was approximately 80%, which is good compared with the previous reports and one reason may be the use of these medicines.

PPHTN Cases in Japan

In Japan, 147 cases with PPHTN (39.6±20.3 years old) have been reported, but many of them only in abstract form and therefore patient information is limited. The mean pulmonary arterial pressure was 51.7±15.4 mmHg (n=67), and the cardiac index was 3.12±1.02 L ·min−1·m−2 (n=16). Liver diseases and cause of death in PPHTN patients are summarized in Tables 5 and 6. Half of the cases of liver disease in PPHTN were liver cirrhosis, including alcoholic cirrhosis and primary biliary cirrhosis, and half of the deaths were from cardiac events, including right heart failure and sudden death.

In 2002 Japan, mortality from liver cirrhosis was 9,231 persons/year44 and the number of patients with liver cirrhosis was 88,000.45 PPHTN was found in 0.73% of deaths from liver cirrhosis and in 0.61% of clinical cases with liver cirrhosis.46 Therefore, it is estimated that there are 70 deaths/year with PPHTN and 540 patients with PPHTN of those with liver cirrhosis. This number of patients is larger than the estimated number of patients with IPAH (230 patients; 95% confidence interval, 200–260).47

Conclusion

Changes in the hemodynamics and configuration of the heart were moderate in PPHTN compared with IPAH. The degree of sparse arborization was moderate in PPHTN, and
pulmonary arteries were dilated near the subsegmental arteries, which were narrow in IPAH. The level of ANP was lower in PPHTN and the BNP level was lower in PPHTN but not significantly.

Acknowledgment
This study was partly supported by a grant from the Respiratory Failure Research Group from the Ministry of Health, Labour and Welfare, Japan.

References

