Pulmonary Vascular Changes Induced by Unilateral Pulmonary Venous Obstruction

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Abstract. The relation of pulmonary hemodynamics to pathological change in the pulmonary vasculature was examined in a model of unilateral pulmonary venous (PV) obstruction. The left upper pulmonary vein (A group, n = 6) or both the left upper and left lower pulmonary veins (B group, n = 6) of two-week-old piglets were banded; the control group (n = 6) was sham operated. At eight weeks after PV banding, mean pulmonary arterial pressure was highest in the B group, intermediate in the A group and lowest in the control group. In all groups, the media of the pulmonary artery was equally thickened in both lungs, whereas the media of the pulmonary vein was thickened only in those lung lobes having stenotic pulmonary veins. For all animals from three groups, left pulmonary arterial wedge pressure (PAWP) correlated with medial thickness of the pulmonary arteries of the right lung (r = 0.76, p = 0.003), the left upper lobe (r = 0.54, p < 0.03), the left lower lobe (r = 0.49, p = 0.04). This finding suggests that the pathogenesis of PAWP-related medial thickening of the bilateral lung pulmonary artery begins with the sensing by the bilateral lung of PV pressure buildup in the unilateral lung.

Key words: Pulmonary venous obstruction — Pulmonary hypertension — Pulmonary vasculature

Cardiovascular anomalies, specifically those involving obstructive lesions of the pulmonary venous return, induce pulmonary hypertension. Pulmonary venous stenosis [14], pulmonary venous atresia [2], cor triatriatum [5], total anomalous pulmonary venous return [6], and mitral stenosis [15] are associated to varying degrees with pulmonary venous obstruction (PVO). These cardiac anomalies also induce pulmonary venous hypertension and pulmonary congestion. Severe pulmonary hypertension will reduce the efficacy of surgery to correct these anomalies [7]. The pathogenesis of pulmonary hypertension associated with these anomalies and of plexogenic pulmonary vascular disease is supposed to differ; the latter involves high left-to-right shunting of pulmonary blood flow [3, 17]. To elucidate the pathogenesis of PVO-induced pulmonary hypertension, the relation between hemodynamics and pulmonary vascular changes was examined in an animal model of unilateral pulmonary venous stenosis.

Materials and Methods

Two-week-old piglets were anesthetized by slow induction with halothane. General anesthesia was maintained by the inhalation of 0.5–1.0% halothane. Normal arterial blood PaO₂ and PaCO₂ were maintained by positive pressure ventilation with 30% oxygen and 70% nitrogen.

Pulmonary arterial pressure (PAP), pulmonary arterial wedge pressure (PAWP), right atrial pressure (RAP), cardiac output (CO), and systemic arterial pressure (Ps) were measured.

After hemodynamic measurement, left anterolateral thoracotomy was performed through the fifth intercostal space. Of the two left pulmonary veins reported by LaBoure [10], the left upper pulmonary vein was banded in six piglets (A group), and both the left upper and lower pulmonary veins draining the whole of the left lung were banded in six piglets (B group). For pulmonary venous (PV) banding, polyester tapes of 5-mm-width were placed in a nonrestrictive fashion around the pulmonary veins with no space between the vein and the band. This method avoids acute pulmonary congestion because pulmonary venous stenosis progresses only as fast as the piglets mature. Lung biopsy was performed just before the banding of the pulmonary veins. The control group (six piglets) underwent operative dissection around the right pulmonary veins.
Table 1. Hemodynamic data at eight weeks after the operation

<table>
<thead>
<tr>
<th>Group</th>
<th>sPAP (mmHg)</th>
<th>dPAP (mmHg)</th>
<th>mPAP (mmHg)</th>
<th>LPAWP (mmHg)</th>
<th>RPAWP (mmHg)</th>
<th>SVR (dynsec/cm²)</th>
<th>PVR</th>
<th>PVR/SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>20.0 ± 1.0</td>
<td>10.4 ± 1.4</td>
<td>14.6 ± 0.8</td>
<td>9.0 ± 0.9</td>
<td>9.0 ± 0.9</td>
<td>26.1 ± 3.7</td>
<td>2.4 ± 0.4</td>
<td>0.09 ± 0.01</td>
</tr>
<tr>
<td>A</td>
<td>30.5 ± 2.2*</td>
<td>14.3 ± 1.5</td>
<td>19.8 ± 1.2*</td>
<td>9.5 ± 0.7</td>
<td>8.8 ± 0.7</td>
<td>30.4 ± 2.3</td>
<td>2.7 ± 0.3</td>
<td>0.09 ± 0.01</td>
</tr>
<tr>
<td>B</td>
<td>43.5 ± 1.6†</td>
<td>16.2 ± 2.2</td>
<td>26.3 ± 1.6†</td>
<td>14.8 ± 1.7†</td>
<td>11.8 ± 1.1</td>
<td>35.4 ± 2.6</td>
<td>4.4 ± 0.4†</td>
<td>0.12 ± 0.01†</td>
</tr>
</tbody>
</table>

sPAP = systolic pulmonary arterial pressure, dPAP = diastolic pulmonary arterial pressure, mPAP = mean pulmonary arterial pressure, LPAWP = left pulmonary arterial wedge pressure, RPAWP = right pulmonary arterial wedge pressure, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance.

*p < 0.05 versus control group.
†p < 0.05 versus A group.

Data are expressed as mean ± standard error of the mean.

At eight weeks after the operation, the piglets were anesthetized and intubated through tracheostomy. After median sternotomy and longitudinal pericardiomyotomy, left and right PAWP, PAP, RAP, Ps, and CO were measured. Left atrial pressure (LAP) was measured with the use of a catheter inserted into the left atrial appendage. Systemic vascular resistance (SVR) was calculated as (mean Pa – mean PAP). CO and pulmonary vascular resistance (PVR) was calculated as (mean PAP – mean LAP)/CO. After hemodynamic measurement, the piglets were sacrificed and their lungs were fixed in 10% formaldehyde solution. A block of tissue was obtained from the right lung, left upper lobe, and left lower lobe of each animal.

For histologic and histometric examinations, both biopsy and necropsy lung specimens were stained with the Elastica Masson method. The medial thickness of pulmonary arteries and pulmonary veins was measured using the computerized method proposed by Yamaki et al. [16]. The cross-section of the vessel was transformed to the hypothetical state in which the internal elastic lamina was completely stretched to the circle and surrounded by the ring of medial muscular layer. Each pulmonary artery and vein radius (R) and medial thickness (D) was calculated from measurements made on more than 15 cross-sections. Subsequently, from the regression line log R = log D for each case, D at an R of 100 μm was obtained and expressed as D = D_{R=100 μm} (the medical thickness of the artery or vein of radius 100 μm).

This experimental protocol was approved by the Animal Care Committee of Tohoku University School of Medicine.

Analysis of variance was used to evaluate the differences in each value among the three groups and multiple comparisons between the groups were done with Scheffe F-test. All values are expressed as the mean ± standard error of the mean (SEM). The correlation of the histometric values and hemodynamic data was evaluated and regarded as significant when the p-value was less than 0.05.

**Results**

**Body Weight**

The body weight of piglets at the time of the operation was 8.8 ± 0.4, 8.5 ± 0.6, and 8.8 ± 1.0 kg in the control, A, and B groups, respectively. At eight weeks after the operation, body weight approximately tripled in all groups to 28.4 ± 2.0, 30.0 ± 2.0 and 32.6 ± 3.1 kg in the control, A, and B groups respectively. There were no significant differences in body weight between the groups.

**Hemodynamics**

Before PV banding or sham operation, mean PAP ranged from 15.0 to 20.0 mmHg with the average of 17.1 ± 0.5 mmHg. Mean PAWP ranged from 6.0 to 11.0 mmHg with the average of 8.1 ± 0.3 mmHg.

Hemodynamic variables of pulmonary circulation at eight weeks after the operation are shown in Table 1. The A group had a higher mean PAP than the control group, but lower than the B group (p < 0.05).

The mean right PAWP was not different among the groups, but the mean left PAWP of the B group was higher than those of the control and A groups (p < 0.05).

The pulmonary vascular resistance (PVR) of the B group was higher than those of the control and A groups (p < 0.05).

**Pulmonary Vasculature**

In all lung specimens obtained at the time of PV banding or sham operation, thin medias and intact intimas were observed in both pulmonary arteries (Fig. 1A) and pulmonary veins (Fig. 1B). However, eight weeks after PV banding, the B group (Fig. 1C) when compared to the control and A groups had pulmonary arteries with thickened medial layers, which were equally thickened in both the right and left lungs of each animal. Medial thickening of the pulmonary vein was observed only in the lung lobes having stenotic pulmonary veins (Fig. 1D). In those veins with medial thickening, elastic fibers condensed into an internal and external elastic lamina, which is a process called “arterialization” [13]. Peculiar vessels characterized by abundant intimal cells were observed just beneath the visceral pleurae and around the bronchioles in the lung lobes with stenotic pulmonary veins (Fig. 2). In addition, connections between those vessels and intrapulmonary pulmonary veins were suggested (Fig. 3). Also, interstitial edema and lym-