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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 PaO_2 and $PaCO_2$ 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 LaBourene [10], the left upper pulmonary vein was banded in six piglets (A group), and both the left upper and left 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.

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Table 1. Hemodynamic data at eight weeks after the operation

Group	sPAP (mmHg)	dPAP (mmHg)	mPAP (mmHg)	LPAWP (mmHg)	RPAWP (mmHg)	SVR (dyne.sec/cm^5)	PVR	PVR/SVR
Control	20.0 ± 1.0	10.4 ± 1.4	14.6 ± 0.8	9.0 ± 0.9	9.0 ± 0.9	26.1 ± 3.7	2.4 ± 0.4	0.09 ± 0.01
A	30.5 ± 2.2*	14.3 ± 1.5	19.8 ± 1.2*	9.5 ± 0.7	8.8 ± 0.7	30.4 ± 2.3	2.7 ± 0.3	0.09 ± 0.01
B	43.5 ± 1.6*†	16.2 ± 2.2	26.3 ± 1.6*†	14.8 ± 1.7*†	11.8 ± 1.1	35.4 ± 2.6	4.4 ± 0.4*†	0.12 ± 0.01*†

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.
$^{\dagger}p < 0.05$ 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 pericardiotomy, 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 Ps − mean RAP)/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 $D_{R=100\ \mu m}$ (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-

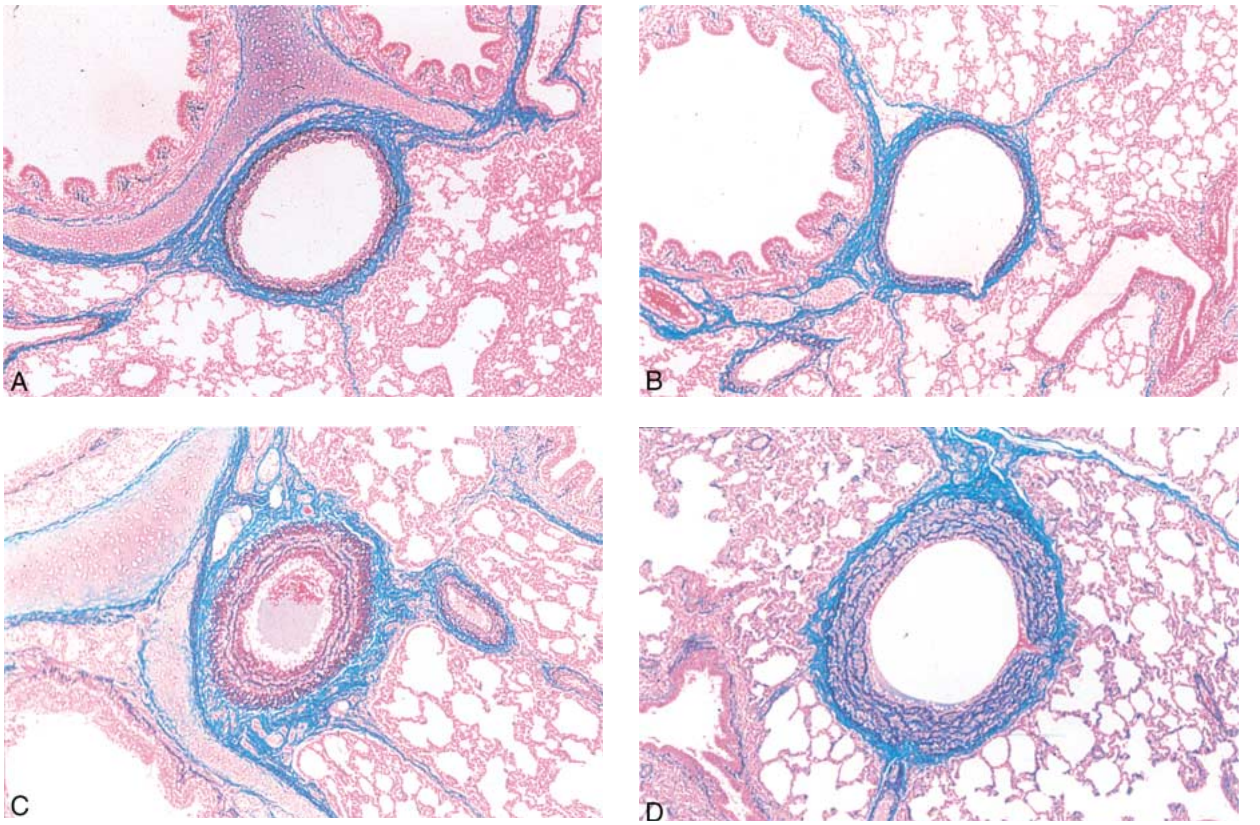

Fig. 1. Pulmonary vasculature. Pulmonary artery (**A**) and pulmonary vein (**B**) at the time of the operation. Pulmonary artery (**C**) and pulmonary vein (**D**) in the left lower lobe in B group at eight weeks after PV banding (Elastica Masson stain, ×100).

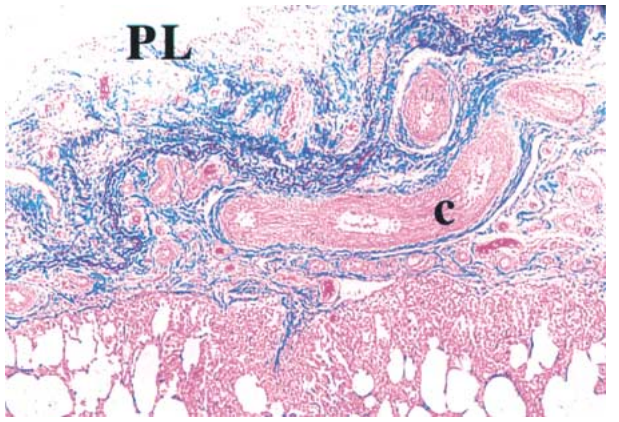

Fig. 2. Vessels (**c**) with abundant intimal cells beneath the visceral pleura (**PL**) (Elastica Masson stain, ×100).

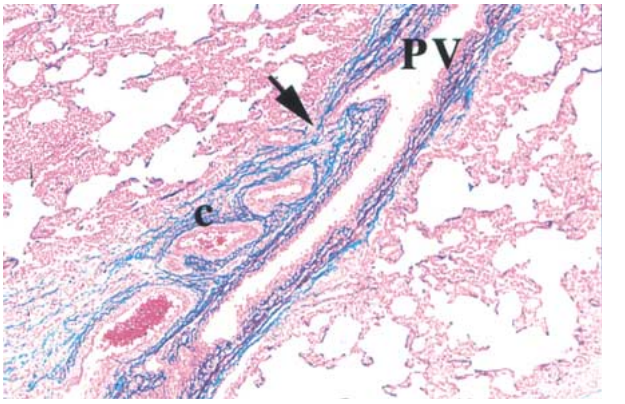

Fig. 3. Communication (arrow) between a pulmonary vein (**PV**) and a vessel with abundant intimal cells (**c**) (Elastica Masson stain, ×100).

phagiectasia were observed in the lung lobes of stenotic pulmonary veins.

Medial Thickness of Pulmonary Arteries and Pulmonary Veins

$D_{R=100\ \mu m}$ of pulmonary arteries in lungs taken at the time of operation ranged from 9.6 to 16.2 μm with the average of 12.2 ± 0.4 μm. $D_{R=100\ \mu m}$ of pulmonary veins ranged from 7.9 to 15.6 μm with the average of 12.1 ± 0.6 μm. At eight weeks after PV banding, $D_{R=100\ \mu m}$ of pulmonary arteries was not significantly different in the right lung, left upper lobe and left lower lobe for each group (Fig. 4). However, $D_{R=100\ \mu m}$ of pulmonary arteries in B group was

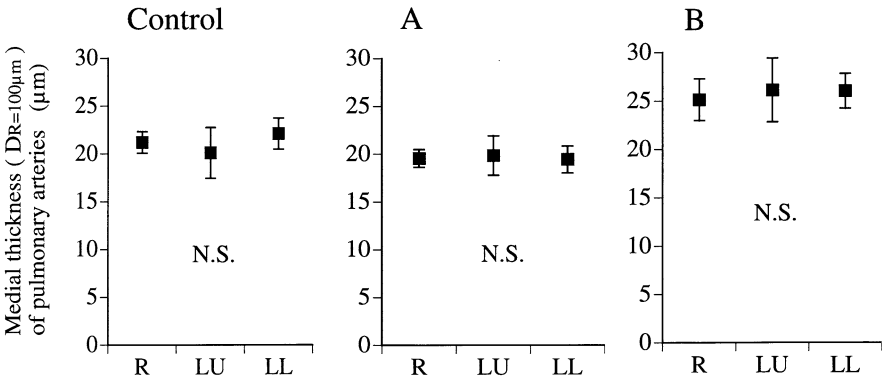

Fig. 4. Medial thickness ($D_{R=100\ \mu m}$) of pulmonary arteries at eight weeks after the operation. $D_{R=100\ \mu m}$ was not different in the right lung, left upper lobe, and left lower lobe in each group (R = right lung, LU = left upper lobe, LL = left lower lobe. N.S. = not significant). Data are expressed as mean, and error bars represent standard error of the mean.

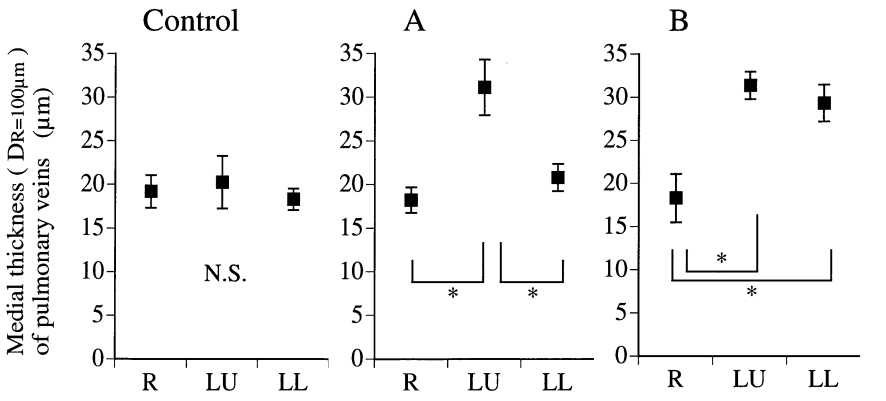

Fig. 5. Medial thickness ($D_{R=100\ \mu m}$) of pulmonary veins at eight weeks after the operation (R = right lung, LU = left upper lobe, LL = left lower lobe. N.S. = not significant. $*p < 0.05$.). Data are expressed as mean, and error bars represent standard error of the mean.

greater than those in the other groups ($p < 0.05$). $D_{R=100\ \mu m}$ of pulmonary veins was significantly greater in the lung lobes with banded pulmonary veins than in lobes with intact pulmonary veins (Fig. 5).

Correlation of Hemodynamics with Medial Thickness

In all piglets, there was a positive correlation between left PAWP and $D_{R=100\ \mu m}$ of pulmonary artery in the right lung ($r = 0.76$, $p = 0.0003$; Fig. 6). Left PAWP also was correlated positively with $D_{R=100\ \mu m}$ of pulmonary arteries of the left upper lobes ($r = 0.54$, $p < 0.03$) and the left lower lobes ($r = 0.49$, $p = 0.04$).

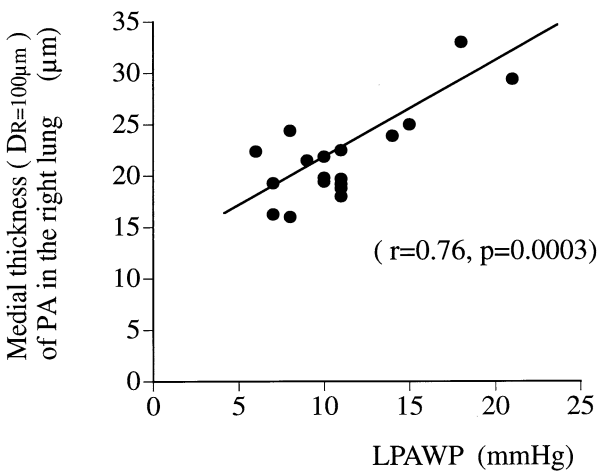

Fig. 6. Correlation between left PAWP and $D_R = 100$ μm of pulmonary arteries in the right lungs.

Discussion

Medial thickening and intimal fibrosis are characteristics of pulmonary vasculature induced by PVO-associated pulmonary hypertension [3, 18]. We [2] previously examined a case of unilateral right pulmonary venous atresia with severe pulmonary hypertension and showed that medial thickness of pulmonary arteries in the right and left lungs did not differ. Thus, the pulmonary artery media in the left lung with intact pulmonary veins became as thick as its counterpart in the right lung with obstructed pulmonary veins. An interaction between the right and left lungs seemed to be involved in the

pathogenesis of this case of pulmonary hypertension.

Narkiewicz [12] reported that ligation of the right lobar vein in cats induced hypertrophy of pulmonary arterial media equally in both left and right lungs.

In the present study, using the model of unilateral left PVO, the medias of pulmonary arteries also became equally thickened in both lungs. The increased blood flow to the right lung compared with the left lung was obvious, but the increase of pulmonary blood flow did not explain these vascular changes in bilateral lung. The positive correlation between PAWP on the PVO side with pulmonary arterial medial thickness on the non-PVO side suggested an intrapulmonary mechanism in which the pulmonary venous pressure (sensed on one side) regulates medial thickening of pulmonary arteries on the other side.

It was suggested in reports on the acute reaction to unilateral pulmonary venous distension by balloon angioplasty [8] that constriction of the pulmonary arterial wall is reactive. Also, it was reported that the stimulation of unilateral pulmonary veins by hypoxia [4] or hypertonic solution [1] increased pulmonary vascular resistance probably because of the constriction of pulmonary arterial wall in bilateral lung. These reports also suggested the existence of a mechanism by which lungs reciprocally coordinated the reaction of vascular constriction. In addition, it was suggested that chemoreceptors of the pulmonary venous system participated in the vascular reaction [15].

Intrapulmonary vasomotor regulation by autonomic nervous system [9, 11] has been pharmacologically investigated. Sympathetic and parasympathetic nerve supplies seem to form a sophisticated network connecting the right and left lungs. Persistent nerve stimulation inducing medial muscular constriction presumably produces medial hypertrophy and hyperplasia.

On the other hand, medial thickening of pulmonary veins in the lung lobes with PV banding was probably induced by the local reaction to the increased intraluminal pressure and interstitial edema.

Intimal fibrosis of pulmonary arteries and veins was not observed in this study. We previously demonstrated that intimal fibrosis correlated with the duration of PVO [3]. Therefore, longer-term observations on models of pulmonary venous obstruction might be necessary to detect intimal fibrosis.

Another important histological finding in this study was the peculiar vessels characterized by abundant intimal cells, which were found in the interstitium beneath the visceral pleurae or around the bronchioles in lung lobes with stenotic pulmonary veins. Because these vessels are seen connected to small pulmonary veins, they may function as collaterals of the pulmonary venous system. Impeded blood flow of the pulmonary veins probably drained through these collaterals into veins in the chest wall and around the pulmonary hilum.

Conclusions

The reciprocal mechanism between right and left lungs, which involves sensing hemodynamic changes of the pulmonary venous system and induction of medial thickening in pulmonary arteries, plays an important role in the pathogenesis of pulmonary hypertension associated with PVO. In addition, the local reaction of pulmonary venous stasis, interstitial edema and collateral formation also contribute to this pathogenesis.

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