Microatelectasis in Patients With Secundum Atrial Septal Defect and its Relation to Pulmonary Hypertension

Shigeo Yamaki, MD; Ai Abe, MD; Kaori Sato, MD; Tohru Takahashi, MD

In patients with secundum atrial septal defect, pulmonary hypertension appears to be attributable to microatelectasis of the lung. To confirm this hypothesis, pulmonary arteries in surgical biopsy specimens from 72 patients with atrial septal defect and pulmonary hypertension were subjected to morphometric examination. Thirtyeight of the 72 patients (53%) were found to have microatelectasis of the lung, which suggests that an even higher frequency would have been found if the entire organ had been examined. Atelectatic changes were found in 21 of 39 patients with plexogenic pulmonary arteriopathy (54%), 8 of 15 with muscular-elasticosis (53%), and 9 of 13 with both of these lesions (69%). No such changes were observed in 5 patients with atrial septal defect who showed thromboembolism-type lesions of the pulmonary arteries. On the other hand, microatelectasis was not observed in another 5 patients with atrial septal defect who did not exhibit pulmonary hypertension. The medial smooth muscles of pulmonary arteries in atelecatic areas were thicker (16.4±4.0 μm) than those in non-ateleastic areas (10.3±3.3 μm). The index of pulmonary vascular disease was not significantly different between atelecatic (2.0±0.6) and non-ateleastic areas (1.9±0.5). We conclude that in microateleastic areas, which may tend to develop after respiratory infections in patients with atrial septal defect, hypoxic vasoconstriction of the small pulmonary arteries is liable to occur, which causes hypertrophy of the media. This is likely to lead to the elevation of pulmonary arterial pressure and sustained pulmonary hypertension.

Key Words: Pulmonary hypertension; Pulmonary vascular disease; ASD; Microatelectasis

Pulmonary hypertension frequently develops in patients with atrial septal defect, although initially, unlike in patients with ventricular septal defect, there is no pressure load on the pulmonary arteries. The pathogenesis of this pulmonary hypertension has not yet been clarified. We speculated that the microatelectasis often seen in histological sections of the lung in atrial septal defect may be at least partially responsible for the induction of pulmonary hypertension. In the present study, we morphometrically analyzed pulmonary vascular disease in lung areas with and without microatelectasis.

Materials and Methods

The subjects consisted of 72 patients with atrial septal defect who underwent lung biopsy diagnosis of pulmonary vascular disease between 1985 and 1995. These patients had no other congenital heart disease. The pulmonary artery peak pressure was above 50 mmHg in all of the patients. Patients who showed clear clinical or histopathological signs of primary pulmonary hypertension were excluded from the study. There were 32 male and 40 female patients who ranged in age from 7 months to 66 years (mean 26.8 years).

Three autopsy and 2 biopsy specimens of lungs from patients who had atrial septal defect but not pulmonary hypertension were used as controls. They ranged in age from 1 to 74 years (mean 34.8 years).

Biopsy specimens were taken primarily from the middle lobe of the right lung and fixed in 10% formalin. Thirty semi-serial sections at 50-μm intervals were prepared and stained by Elastica-Goldner

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staining.

The thickness of the media of small pulmonary arteries was measured by a previously reported histometric method. In each case, about 15 cross-sections of small pulmonary arteries of various sizes were selected from lung areas with and without microatelectasis. Using a microprojector (Visapan, Reichert), cross-sections were magnified and projected onto a sheet of tracing paper. The external and internal elastic membranes were carefully delineated. The length of the internal elastic membrane (L) and the area of the media (S) were then measured using a digital image analyzer. From the resulting values for L and S, the radius (R) and the medial thickness (D) at a hypothetical state of complete extension of the lamina elastica intima were calculated as follows:

\[ R = S/(\sqrt{L^2 + 4\pi S} - L) \]
\[ D = (\sqrt{L^2 + 4\pi S} - L)/2\pi \]

The values of R and D were then plotted on a logarithmic scale. Using linear regression analysis, the medial thickness at a radius of 100 μm (D_{R = 100μm}) was calculated and compared among lung tissues with or without microatelectasis.

The severity of the intimal lesions of the small pulmonary arteries in isolated plexogenic pulmonary arteriopathy was expressed in terms of our previously reported index of pulmonary vascular disease.

### Results

Among the 72 patients from whom pulmonary histopathological samples were obtained, 38 (53%) showed microatelectasis; i.e., the formation of patchy, microscopic atelectatic areas, probably related to bronchiolitis, as suggested by the presence of subepithelial round cell infiltration in small membranous bronchioles or intraacinar respiratory bronchioles. The maximum size of the microatelectasis seen in semiserial sections was about 10 mm, and this assumed various shapes, i.e., round, cylindrical or star-shaped. In many patients, fibrosis was found within the atelectatic areas, and this appeared to be an irreversible change (Fig 1).

On the other hand, microatelectasis was not observed in any of the 5 control patients without

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**Table 1  The Ratio of Patients Having Microatelectasis**

<table>
<thead>
<tr>
<th>Type of pulmonary vascular disease</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plexogenic arteriopathy</td>
<td>8/20 (40%)</td>
<td>13/19 (68%)</td>
<td>21/39 (54%)</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>0/0 (0%)</td>
<td>0/5 (0%)</td>
<td>0/5 (0%)</td>
</tr>
<tr>
<td>Musculoelastosis</td>
<td>4/8 (50%)</td>
<td>4/7 (57%)</td>
<td>8/15 (53%)</td>
</tr>
<tr>
<td>Mixed type</td>
<td>3/5 (60%)</td>
<td>6/8 (75%)</td>
<td>9/13 (69%)</td>
</tr>
<tr>
<td>Total</td>
<td>15/33 (45%)</td>
<td>23/39 (59%)</td>
<td>38/72 (53%)</td>
</tr>
</tbody>
</table>

Mixed type shows a combination of plexogenic arteriopathy and musculoelastosis.
pulmonary hypertension, although in each of the 3 autopsy cases, as many as 5 sections from each lung lobe were examined. As we have previously reported, the changes in the pulmonary artery in atrial septal defect can be classified into 4 types: plexogenic pulmonary arteriopathy, thromboembolism in small pulmonary arteries, musculoelastosis consisting of longitudinal smooth muscle bundles and elastic fibers proliferating in the intima, and a combination of plexogenic pulmonary arteriopathy and musculoelastosis (mixed type). In the present study, plexogenic pulmonary arteriopathy was found in a total of 39 patients with an average age of 13.8 years (21 males, average age 9.4 years; 18 females, average age 18.9 years). Thromboembolism in small pulmonary arteries was found in 5 female patients (average age 41.8 years). Musculoelastosis was found in 15 patients (average age 47.7 years), including 7 males (average age 49.6 years) and 8 females (average age 40.0 years). Finally, a combination of plexogenic pulmonary arteriopathy and musculoelastosis was found in 13 patients (average age 39.2 years), including 5 males (average age 44.0 years) and 8 females (average age 31.3 years).

The frequencies of patients with microatelectasis were as follows: 21 of 39 (54%) in plexogenic pulmonary arteriopathy-type, 8 of 15 (53%) in musculoelastosis-type, and 9 of 13 (69%) in the combined type. None of the 5 patients with thromboembolism-type had microatelectasis (Table 1). Although microatelectasis was observed more often in female patients than in male patients, there was no significant gender difference.

The medial thickness of small pulmonary arteries was measured in all of the patients. A single linear regression line between D and R was obtained in patients without microatelectasis. However, in patients with microatelectasis, the characteristics of the arteries in the microatelectatic areas were different from those in the non-microatelectatic areas. The regression lines were

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**Fig. 2.** Correlation between the radius (R) and medial thickness (D) of small pulmonary arteries in Patient 1 (log scale). The regression line for arteries in microatelectatic areas (upper regression line) was clearly distinct from that for non-microatelectatic areas (lower regression line).

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**Fig. 3.** Small pulmonary arteries in a microatelectatic area (left) and in a non-microatelectatic area (right) from Patient 1. Note the marked difference in medial thickness. Elastica-Goldner stain.
clearly separated, as shown in Fig 2, and the medial thicknesses at a radius of 100 μm (D_{R=100 μm}) were much larger. In Fig 3, the microscopic appearance of small pulmonary arteries in a region of microatelectasis is compared with that of such arteries located outside a region of microatelectasis in the same patients. Fig 4 shows the relationship between the medial thickness at an R of 100 μm (D_{R=100 μm}) and the age of all 72 patients. Microatelectasis was found in patients ranging in age from 7 months to 62 years. In these patients, the medial thickness of the small pulmonary arteries was always thicker in microatelectatic areas than in non-microatelectatic areas. However, there was no significant relationship between medial thickness and age.

Fig 5 compares the medial thickness of small pulmonary arteries in regions with and without microatelectasis in 38 patients. In non-microatelectatic areas, D at an R of 100 μm ranged from 4.2 to 16 μm, with a mean±standard deviation (SD) of 10.3±3.3 μm, while in microatelectatic areas, it ranged from 9.0 to 27.4 μm with a mean±SD of 16.4±4.0 μm. Thus, a significant thickening of media was observed in regions where microatelectasis was present (p < 0.0001).

Fig 6 shows the relationship between age and our index of pulmonary vascular disease in all of the 39 patients with plexogenic pulmonary arteriopathy. The values of this index ranged from 1.0 to 3.8 with a mean of 2.0. Older patients tended to have higher scores, but there were no notable differences between patients with and without microatelectasis.

The index of pulmonary vascular disease was also calculated for regions with and without microatelectasis among patients with microatelectasis. In microatelectatic regions, the index of pulmonary vascular disease was between 1.0 and 2.7, with a mean±SD of 2.0±0.6, whereas in regions without microatelectasis, it was between 1.0 and 2.7, with a mean±SD of 1.9±0.5. This difference was not statistically significant.
**Discussion**

The clinical onset of pulmonary hypertension relatively later in life is not uncommon in patients with atrial septal defect, but there have also been autopsy reports of elderly patients who did not exhibit pulmonary hypertension. Due to blood flow from the left atrium to the right atrium in atrial septal defect, there is increased flow into the pulmonary vascular bed, and this is considered to make such patients susceptible to respiratory infections, such as upper respiratory tract inflammation, bronchitis and pneumonia, which in fact are occasionally seen. Such infections may tend to produce small microatelectasis which is not detected in pulmonary X-rays. Since such microatelectasis can develop even after death, we examined its frequency in lung biopsy specimens. In this study, 37 of the 72 patients with atrial septal defect (51%) showed microatelectasis. Since microatelectasis was found in more than half of our patients even in very small lung biopsy samples, it is likely that additional lung samples from these same patients would have revealed a higher frequency of microatelectasis. Since microatelectatic areas are devoid of ventilation and become hypoxic, repeated vasoconstriction is believed to occur in the arteries supplying the area, which induces hypertrophy of medial smooth muscle cells. This in turn gives rise to an increase in the intraarterial pressure and the development of pulmonary hypertension. Previous reports that pulmonary hypertension is often seen in atrial septal defect patients with respiratory tract infections support this assumption. Our results indicate that surgical closure of atrial septal defect is justified when pulmonary infection has occurred to prevent the development of pulmonary hypertension. This is also true for patients who already show pulmonary hypertension.

In the cases of plexogenic pulmonary arteriopathy we examined, there was no significant difference in the degree of intimal changes between pulmonary arteries in microatelectatic and non-microatelectatic regions. This can be explained by the fact that small pulmonary arteries receive the same pressure load regardless of whether microatelectasis is present or not. As we previously reported, in patients with atrial septal defect and pulmonary hypertension, pulmonary arteries showed musculolastosis in addition to plexogenic pulmonary arteriopathy. When the patients were re-examined in terms of the type of pulmonary lesion, we found that microatelectasis was present in 53% of the patients with musculolastosis alone and in 69% of those with both plexogenic pulmonary arteriopathy and musculolastosis. In patients suffering from chronic lung disease with hypoxia such as bronchiectasis, longitudinal smooth muscle bundles have been reported to be present in pulmonary arteries. We have shown that microatelectasis and musculolastosis are frequently combined in atrial septal defect, which suggests that in this case also, longitudinal smooth muscle bundles may arise due to focal hypoxia of the small pulmonary arteries.

In this study, thromboembolism of the small pulmonary arteries was found in only 5 female patients who did not show microatelectasis. This suggests that
thromboembolism itself may cause pulmonary hypertension.

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References


