The Pulmonary Arterial Tree in Atrial Septal Defect
A Quantitative Study of Anatomic Features in Fetuses, Infants, and Children

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IN CONTRAST to cases of ventricular septal defect in which pulmonary arterial lesions occur at a very early age, such changes are generally considered to be late phenomena in atrial septal defect. It is well known that pulmonary hypertension, when it occurs as a complication of a defect in the atrial septum, is usually not seen before adult life.1, 2 The pulmonary arteries are reported to be largely normal when the pressure in the pulmonary circulation is within normal limits.3 When the pressure is moderately elevated, intimal thickening of small muscular pulmonary arteries with subsequent narrowing of the lumen is believed to be an early change. In the presence of an increased flow, on the other hand, the pulmonary arterial tree in atrial septal defect is dilated,3 and it has been shown that dilatation of the vessels with stretching of the walls may mask the presence of medial hypertrophy.4

In view of the uncertainties regarding the changes in the pulmonary arterial tree, a study was undertaken of the pulmonary arterial branches in fetuses, infants, and children with uncomplicated atrial septal defect.

Material and Methods

Our material was derived from 12 subjects with uncomplicated atrial septal defect (table 1). Three of these were fetuses of 24, 30, and 36 weeks' gestation, one was a full-term stillborn infant, and the ages of the remaining eight ranged from 2 days to 11 years. Data from cardiac catheterization were available in two cases; in one of these (case 11) the pressure in the pulmonary artery appeared normal, and in the other (case 12) there was pronounced pulmonary hypertension. Of the 12 subjects, seven had died from causes not directly related to the cardiac malformation, as follows: prematurity (cases 1 and 2), prematurity and anencephaly (case 3), premature separation of the placenta (case 4), hyaline membrane disease of the lungs (case 5), duodenal atresia (case 6), and purulent meningitis (case 10). In the last case the atrial septal defect had been closed surgically 10 months before death. Three children died in cardiac failure (cases 7, 8, and 9) and two died shortly after operation, one as a result of a severe cerebral complication (case 11) and one because of pronounced pulmonary hypertension (case 12). The sex distribution was eight males and four females.

Only the right lung was used for histologic study. Sections from five segments of each right lung were stained with lawson's elastic stain, counterstained by van Gieson's connective-tissue stain.

For evaluation of medial hypertrophy, the mean relative medial thickness and the index of medial surface area were determined by quantitative analysis. The relative medial thickness is the thickness of the media expressed as a percentage of the external diameter of a muscular pulmonary artery. The mean relative medial thickness is the average percentage calculated for 100 arteries.

The index of medial surface area is an index of the ratio of the surface area of the media of muscular pulmonary arteries to the surface area of the pulmonary parenchyma in which these arteries lie. In other words, this index gives an expression of the amount of pulmonary arterial muscular tissue per unit of lung tissue.

The values for both the relative thickness and the index were compared with those found in a control series of fetuses, infants, and young children with normal hearts and lungs, described elsewhere.5 The techniques for determining the mean relative medial thickness and the index of medial surface area were described in detail previously4 and in outline in a study of ventricular septal defect.6 The histopathologic analysis was done blindly in that the sections were mixed with those from subjects with other conditions (ventricular...
septal defect, aortic atresia, and pulmonary atresia). Neither the nature of the condition nor the age of the subject was known at the time the pulmonary arteries were being measured.

**Results**

The relevant data obtained for the 12 subjects are listed in table 1. The values of the mean relative medial thickness and the index of medial surface area are shown also in figures 1 and 2, where they are compared with the results in a control group of corresponding ages.

During fetal life and in the newborn period (five cases), the mean thickness of the media was roughly within normal limits (figs. 1 and 3). However, in a 16-day-old infant (case 6), the value was somewhat higher than expected from corresponding data in the control group. In two subjects, 7 weeks and 4 months of age (cases 7 and 8, respectively), the mean thickness of the media reached an extremely high value for this age (table 1, fig. 4). A great number of small muscularized arterioles were present in these subjects (fig. 5). In three cases the medial thickness was at the upper range of normal (cases 9 and 11) or moderately increased (case 10). In the last subject of the series (case 12), who had a greatly elevated pulmonary arterial pressure, pronounced thickening of the media was present.

The index of medial surface area in the three fetuses with atrial septal defect (cases 1 to 3) was high as compared with that in fetuses with normal hearts and lungs (fig. 2). In the stillborn infant (case 4), the index was high but was in the upper range of normal. In five cases of the postnatal group (cases 5, 6, 9, 10, and 11), the index of medial surface area was within normal limits or only slightly elevated. In the three remaining postnatal cases (cases 7, 8, and 12), the index was high, as compared with that of the controls. In case 12, in which pronounced pulmonary hypertension was noted, the index was extremely high (table 1).

Intimal proliferation generally was not an outstanding feature of the muscular pulmonary arteries in the present cases of atrial septal defect. In two patients, aged 7 weeks and 9 months (cases 7 and 9, respectively), a slight degree of intimal thickening was observed in a few branches. However, in case
12, pronounced oblitative lesions were noted in almost every branch (fig. 6a and b). In addition, two cases (cases 1 and 7) showed moderate intimal thickening of some elastic pulmonary arteries; one of these was a fetus of 24 weeks' gestation (fig. 7). In case 12 the elastic arteries were involved extensively in the generalized obliterating changes. In three patients (cases 8, 9, and 10), there was slight to moderate intimal proliferation in a small number of bronchial arteries (fig. 8a). Finally, slight to moderate intimal thickening was sometimes present also in pulmonary veins (cases 8 to 12) (fig. 8b).

Plexiform or glomerulus-like structures were numerous in case 12, but were not observed in other cases.

Discussion

In contrast to patients with ventricular septal defect, those with uncomplicated atrial septal defect rarely come to necropsy during infancy or childhood. Consequently, the number of such cases available for study will always be relatively small, and any conclusions drawn from such studies will require special and careful consideration. This is especially true in this series in view of the fact that some children died from causes unrelated to the atrial septal defect, and others died from cardiac failure or succumbed shortly after operation on the heart. It is possible that this group of cases does not generally reflect the natural history of the pulmonary vascular tree in atrial septal defect in this age group. This in part may account for some of the unexpected findings with regard to both mean relative medial thickness and index of medial surface area.

In the fetal and newborn periods the mean relative medial thickness did not differ greatly from the normal, although there was a tendency toward values in the upper range of normal. The index of the medial surface area, however, was considerably increased in the three fetuses of the series, indicating medial hypertrophy (fig. 2).

During fetal life the blood that enters the
right atrium flows in part to the right ventricle through the tricuspid valve and in part to the left atrium by way of the foramen ovale. In principle, a defect in the septum will not bring about any appreciable change in hemodynamics. It might be argued that if there is a pressure gradient at the foramen ovale, the presence of a large atrial septal defect might eliminate this gradient. In that case the left atrial pressure would be the same as that in the right atrium and thus higher than it would be in the absence of a defect. This difference in pressures must be small, however, if it exists at all, and it is unlikely to cause important changes in the pulmonary arterial tree.

Although it is possible that the high index of medial surface area observed in the fetuses represented a congenital anomaly of the pulmonary arteries rather than a reaction to hemodynamic changes, it must be admitted that our knowledge of the hemodynamic conditions in fetal life is limited.

It is not surprising that the medial thickness was not elevated in proportion to the increase in the index of medial surface area. In our experience the mean thickness of the media is never much higher than 20 per cent of the external diameter, regardless of age or pulmonary pressure, even though individual arteries may reach a relative thickness of as much as 35 per cent. Apparently, when a mean relative thickness of approximately 20 per cent is reached, increase of the index of medial surface area is brought about by expansion of the muscular coat along the length of an arterial segment rather than by further increase of the thickness of the media.

After the newborn period, the values for the mean relative thickness and index of medial surface area were above the normal values in all subjects (figs. 1 and 2). In two patients, aged 7 weeks and 4 months (cases 7 and 8, respectively), this increase was pronounced (fig. 4). In three others (cases 9,
a. Muscular pulmonary arterial branch, almost obliterated by intimal proliferation, in an 11-year-old child with atrial septal defect. Vessel tends to collapse (elastic stain). b. Large muscular pulmonary arterial branch with pronounced medial hypertrophy and intimal proliferation at origin of branch, in same case as in a. (elastic stain).

10, and 11), it was slight, sometimes being just within the upper range of normal. The last case, that of a girl of 11 years with pronounced pulmonary hypertension and extensive pulmonary vascular obstructive lesions (fig. 6a and b), conformed in all respects to the picture seen in adult patients with atrial septal defect complicated by pulmonary hypertension. Apart from the intimal lesions, excessive medial hypertrophy was present.

After birth a left-to-right shunt becomes established in patients with an atrial septal defect, although probably not immediately. This left-to-right shunt results in an increase in the pulmonary blood flow. In spite of this the pulmonary arterial pressure remains normal, since the pulmonary vascular resistance is low.

In the absence of complications the only visible change in the pulmonary arteries in most cases of atrial septal defect is dilatation of the vessels. It seems possible that gradually an increase of the absolute amount of medial tissue occurs as a result of this dilatation. When the cross section of an artery becomes
greater, there are fewer medial muscle fibers in this cross section to maintain the pressure. This might well result in a reactive increase in the number of muscle fibers. In any event, dilatation of an artery without such an increase of medial tissue must lead to thinning of the wall as compared to the normal condition. Such thinning has never been described; generally, the relative medial thickness in cases of uncomplicated atrial septal defect has been reported to be normal.\textsuperscript{3} A few cases of atrial septal defect in adults have been described; the medial thickness was not far from normal, but the index of medial surface area was considerably increased.\textsuperscript{4}

These considerations do not explain the findings in two of our cases (cases 7 and 8), in which both the medial thickness and the index were far above normal values. Although

\begin{center}
\textbf{Table 1}
\end{center}

\textbf{Data in Twelve Cases of Atrial Septal Defect in Fetuses, Infants, and Children}

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, sex</th>
<th>Medial thickness, per cent of diameter</th>
<th>Index of medial surface area</th>
<th>Location and grade of intimal proliferation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24 fetal wk. M</td>
<td>17.8</td>
<td>441</td>
<td>Elastic pulmonary arteries; moderate</td>
</tr>
<tr>
<td>2</td>
<td>30 fetal wk. M</td>
<td>19.8</td>
<td>495</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>36 fetal wk. F</td>
<td>18.6</td>
<td>439</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Stillborn M</td>
<td>18.8</td>
<td>373</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2 days F</td>
<td>14.7</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>16 days M</td>
<td>16.4</td>
<td>245</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>7 wk. M</td>
<td>20.0</td>
<td>448</td>
<td>Elastic pulmonary arteries; moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Muscular pulmonary arteries; slight</td>
</tr>
<tr>
<td>8</td>
<td>4 mo. M</td>
<td>18.6</td>
<td>444</td>
<td>Bronchial arteries; slight</td>
</tr>
<tr>
<td>9</td>
<td>9 mo. M</td>
<td>8.5</td>
<td>243</td>
<td>Pulmonary veins; slight</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Muscular pulmonary arteries; slight</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bronchial arteries; moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pulmonary veins; moderate</td>
</tr>
<tr>
<td>10</td>
<td>22 mo. M</td>
<td>8.6</td>
<td>240</td>
<td>Bronchial arteries; slight</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pulmonary veins; slight</td>
</tr>
<tr>
<td>11*</td>
<td>9 yr. F</td>
<td>6.4</td>
<td>188</td>
<td>Pulmonary arteries (elastic and muscular); severe</td>
</tr>
<tr>
<td>12*</td>
<td>11 yr. F</td>
<td>10.8</td>
<td>1024</td>
<td>Pulmonary veins; moderate</td>
</tr>
</tbody>
</table>

*Pulmonary arterial pressures obtained by cardiac catheterization in cases 11 and 12 were normal and hypertensive (96/56), respectively.
we are not able to offer any acceptable explanation for these unexpected findings, it should be kept in mind that both children died in cardiac failure, presumably as a result of their congenital cardiac defect. This clinical course, as unfortunate as it is unusual in patients with atrial septal defect of this age, might well be related to, or even caused by, the equally rare (in this age group) pulmonary vascular manifestations.

Intimal proliferation was a feature of several types of pulmonary blood vessels, although it was of a severe nature in only one case. It was found in muscular and elastic pulmonary arteries, in bronchial arteries, and in pulmonary veins. The significance of these changes is not understood except in the subject with pronounced pulmonary hypertension (case 12), in whom these intimal lesions reflected a familiar, although not entirely explained, picture. Intimal proliferation in muscular pulmonary arteries and in pulmonary veins has been described before; it has been attributed to the large flow.\textsuperscript{7-9} This may be the explanation in general, but it does not explain the presence of intimal proliferation in one of the fetuses.

**Summary**

The pulmonary vascular tree was studied in 12 cases of uncomplicated atrial septal defect in fetuses, infants, and children. The ages of these subjects ranged from 24 weeks of fetal life to 11 years. A quantitative analysis was made of the medial thickness and of the index of medial surface area (ratio of medial tissue to pulmonary parenchyma) of the pulmonary arterial branches. In contrast to subjects with ventricular septal defect in corresponding age groups, the three fetuses in this series had medial hypertrophy, as indicated by a high index of medial surface area. In the postnatal group, both the medial thickness and the index of medial surface area were also usually greater than in the controls of corresponding ages, notably in two patients, who, at the ages of 7 weeks and 4 months, died of cardiac failure. No satisfactory explanation for these unexpected findings can be offered.

Slight to moderate intimal proliferation was observed in some muscular and elastic pulmonary arteries, in bronchial arteries, and in pulmonary veins in several subjects. Thickening of the intima in elastic arteries was observed in a fetus of 26 weeks' gestation. Pronounced oblitative intimal changes were found in only one subject, an 11-year-old girl with severe pulmonary hypertension.

**References**

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