Quantitative Analysis of Pulmonary Vascular Disease in Complete Transposition of the Great Arteries

SHIGEO YAMAKI, M.D., AND FUMIAKI TEZUKA, M.D.

SUMMARY  Forty autopsy cases of complete transposition of the great arteries (TGA) and 22 autopsy cases of ventricular septal defect (VSD) were analyzed histologically for evidence of vascular damage due to pulmonary vascular disease (PVD). Positive correlations were generally observed between an index of pulmonary vascular disease (IPVD) and blood pressure of pulmonary circulation. No significant difference in IPVD was found between TGA and VSD in the first five months of life, when cases of each disease were compared at similar blood pressure levels. After that age, however, IPVD was much higher in TGA, and particularly severe PVD in this disease was demonstrated histologically. Morphometrical analysis of the pulmonary artery revealed hypertrophy of the muscular coat in response to elevated blood pressure. However, the progress of medial hypertrophy was retarded in TGA in the first five months, and medial thickness in arteries of cases of TGA older than five months was only 70% of that in VSD at the same blood pressure levels. Suppression of this process of reinforcement of the arterial wall in response to the stress of high pulmonary pressure was regarded as one of the important factors precipitating severe pulmonary vascular disease in transposition of the great arteries.

DEVELOPMENT OF PULMONARY VASCULAR DISEASE (PVD) as a result of pulmonary hypertension in some congenital heart diseases is a major factor in the prognosis and postoperative course of patients. Although the role of pulmonary hypertension in inducing pulmonary vascular lesions is established in general terms, a number of authors have pointed out that complete transposition of the great arteries (TGA) in particular is characterized by early onset and development of severe vascular changes. The high vulnerability of the pulmonary artery in TGA suggests that factors other than elevated blood pressure also play a role in the production of vascular lesions. For this reason, a structural analysis of the arterial wall may contribute to the understanding of vascular lesions in this disease.

Histopathological studies seem to have been limited to direct correlation of histological vascular lesions with clinical records of blood pressure. The response of the pulmonary artery to elevated blood pressure prior to the appearance of vascular injuries has not yet been sufficiently investigated. Histometrical and histological methods are used in this study to quantitate hypertrophy of the arterial muscular coat and to estimate the grade of vascular lesions. These methods are expected to facilitate the analysis of the behavior of the muscular coat to elevated blood pressure and the relation of pulmonary hypertension to vascular lesions.

Materials and Methods

Forty autopsy cases of TGA at Tohoku University Hospital and Tokyo Women's Medical College in an eight-year period from 1967 to 1974 were examined in the present study. The age distribution was from 10 months of gestation to 20 years and included 17 cases under 5 months old. The examined cases of TGA comprised four groups: 11 cases of either intact ventricular septum or small VSD of less than 3 mm in diameter; 23 cases of large VSD; four cases of both large VSD and pulmonary stenosis (PS); and two cases of PS and either intact ventricular septum or small VSD. None were complicated by other serious cardiac malformations, except for three cases of associated coarctation of the aorta in the age group under 5 months. In three other cases, the patients had each undergone a Mustard procedure at least eight months before death.

For comparative analysis, 22 autopsy cases of VSD (aged from 46 days to 24 years), and 33 autopsy cases of apparently normal cardiovascular systems and normal pulmonary circulation (aged from 10 months of gestation to 32 years) were studied. Premature infants were excluded from the control group. Pulmonary arterial pressure had been recorded during catheterization within two months prior to death in 23 cases of TGA and in all the cases of VSD. From the record the peak systolic pressure was estimated in each case and used for correlation with vascular lesions and medial hypertrophy (table 1). About 30 samples of lung were randomly excised from formalin-fixed specimens of both lungs in each case. These were embedded in paraffin, sectioned at 5 μ, stained with Goldner's trichrome combined with Weigert's stain for elastic fibers and submitted to histological and histometrical examinations.

Grading of PVD

The well-known classification of PVD of Heath and Edwards is not adequate for an evaluation of the extent to which PVD is present throughout the arterial system of individual cases. The Heath-Edwards classification depends upon a fortuitous selection of arterial sections with severe histological changes. Different grades of arterial changes are usually observed even within a given case. In the present study, the severity of PVD in the entire pulmonary arterial system was determined.

Histological evidence of hypertensive arterial changes was variable. However, all changes may be regarded as deriving from the common process of intramural plasmal invasion, and the individual sections represent a continuous series from cellular intimal reaction to medial destruction. Consequently, a score from 1 to 4 was given to each arterial section according to the following histological findings.

1) No intimal reaction
2) Cellular intimal reaction
3) Fibrous and fibroelastic proliferation of intima
4) Partial and total destruction of media

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An index of pulmonary vascular disease (IPVD) was then defined by:

$$\text{IPVD} = \frac{(1 \times n_1) + (2 \times n_2) + (3 \times n_3) + (4 \times n_4)}{n_1 + n_2 + n_3 + n_4}$$

where $n_1$, $n_2$, $n_3$, and $n_4$ were the numbers of arterial sections bearing the score of 1, 2, 3, and 4, respectively. This index expresses the grade of PVD in the whole pulmonary arterial system of each case and ranges from the minimum 1.00 to the maximum 4.00. The principle of scoring is much different from that of Heath and Edwards,4 and the scores in the present study cannot be immediately compared. In the case of grade 4 with the Heath and Edwards scoring, IPVDs were estimated at 2.14 to 3.98 with our own method. Bronchial arteries were of course excluded from the examination.

**Histometrical Estimation of Arterial Radius and Medial Thickness**

Because direct measurement of medial thickness of arteries is impaired by variable postmortem contraction, the arteries examined were standardized by the following procedure.5-8

Cross-sections of arterial branches were selected from the histological slide and projected onto a sheet of tracing paper. Arterial sections with severe PVD were discarded because secondary atrophy of the muscular coat might affect the histometrical result. The external and internal elastic membranes were exactly followed and delineated. The surface area (S) of the medial cross-section was planimetrically determined. The length (L) of the internal elastic membrane was measured by attaching a thin thread on the tracing. The arterial section was then transformed to a hypothetical state in which the internal elastic membrane was stretched to make an exact circle, and the cross-section of the muscular coat was replaced by a layer of uniform thickness throughout the entire circumference in such a manner that the surface area of the layer was equal to S. In this state, the radius (R), the distance from the center of the lumen to the middle point of the muscular layer, and the medial thickness (D) were obtained from the formulae:

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

The principle of the histometrical method is illustrated in figure 1.

In each case, the hypothetical radius (R) and medial thickness (D) were estimated for a number of cross-sections of muscular arteries of various dimensions. These

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**Table 1. Clinical Data**

<table>
<thead>
<tr>
<th></th>
<th>TGA</th>
<th>VSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases</td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td>Up to 5 mo</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Over 5 mo</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>PAP recorded</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Operated on</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: TGA = transposition of the great arteries; VSD = ventricular septal defect; PAP = pulmonary artery pressure.
measurements plotted together revealed a linear regression between R and D on a logarithmic coordinate system (fig. 2). D calculated at R = 100 μ from the regression equation of each case was used for comparative analysis. The arteries of muscular type smaller than 100 μ in R did not exist in normal lungs, while muscular coats were recognized even in arteriolar terminals of less than 100 μ in R in pulmonary hypertension.

In the present series, D could not be measured in two cases of TGA and one case of VSD because severe PVD interfered with exact histomterical determination.

**Results**

**IPVD Compared with Age and Systolic Pulmonary Arterial Pressure**

Pulmonary vascular lesions, expressed by IPVD, are plotted against age in figure 3. The index generally rose with age in both TGA and VSD. In the first five months of life, there was not a marked difference in IPVD between the two diseases. After that period, however, a distinct difference was found in the grade of pulmonary vascular lesions between TGA and VSD, and PVD developed more rapidly in the former disease. In view of this, it seemed appropriate to divide the cases into two groups: up to and over five months.

In each group, IPVD was correlated with intravascular blood pressure P, and the results for patients with VSD are shown in figure 4 and for those with TGA in figure 5. There was generally a positive correlation between P and IPVD, and the relation of the two quantities could be expressed as a linear regression. During five postnatal months no significant difference was found in the regression equation between TGA and VSD. After that period, however, the regression equation for TGA had remarkably higher elevation than that for VSD or the height of the regression line was larger in TGA; the slopes of the equations were almost equal. In this stage, TGA precipitated more severe arterial lesions than VSD did at the same blood pressure level.

**Thickness (D) of Muscular Coat Against Age and Systolic Pulmonary Arterial Pressure**

The estimates of D at R = 100 μ are plotted against age in figure 6. In cases of normal cardiovascular and respiratory systems, D declined after birth to reach a constant level of 5 to 7 μ by 5 months. The result indicated that physiological regression of the muscular coat of the pulmonary artery is
practically accomplished in 5 months. Our results were essentially the same as the reports of Phillips et al., Herzenberg and Ekerand, and Naeye. In the majority of the cases of TGA and VSD, attenuation of the muscular coat did not proceed after birth. This was apparently due to pulmonary hypertension complicating the two diseases. Larger scatter of individual values in TGA presumably corresponded to divergent blood pressure levels of the pulmonary circulation in this disease. In the first 5 months the reaction of the muscular coat to high blood pressure was expected to be different from that in later months. The cases of TGA and those of VSD were therefore divided into two groups, up to and older than 5 months, and D was examined in each group in relation to intravascular blood pressure P in clinical records.

There was a positive correlation between P and D, and D could be expressed as an exponential function of P with a positive exponent (figs. 7 and 8). The equations were as follows, with D expressed in μ and P in mm Hg.

<table>
<thead>
<tr>
<th>Group</th>
<th>Equation</th>
<th>Exponent</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD</td>
<td>$D = 2.600e^{0.28x10 -3P}$</td>
<td>0.28x10 -3</td>
</tr>
<tr>
<td>TGA</td>
<td>$D = 2.654e^{0.27x10 -2P}$</td>
<td>0.27x10 -2</td>
</tr>
</tbody>
</table>

There was no significant difference in the exponent or in the elevation of the equations for VSD between the groups within and after five months. Consequently, the measurements of the two groups were pooled and the following single equation was derived for all ages.

$$D = 2.655e^{0.27x10 -2P}$$

In TGA patients, statistical analysis revealed that the exponent in the equation for the earlier period was significantly lower ($P < 0.05$) than that for later months of this disease and also significantly lower than that in the equation for VSD ($P < 0.05$). The results indicated rather suppressed development of medial hypertrophy in response to elevated blood pressure in the early postnatal months of TGA. The tendency was not observed in VSD.

After five months, the behavior of the muscular coat in TGA was entirely different. The comparison of the equation for TGA in this stage with that for VSD did not show any statistically significant difference in the exponent. However, the elevation of the equation for TGA was distinctly lower ($P < 0.01$) than that for VSD, and the thickness of the muscular coat in TGA was only about 70% of that in VSD at

**Figure 6.** Postnatal change in medial thickness (D) estimated at $R = 100\mu$. Dotted vertical line marks the break at 5 months. In normal cases, D declines after birth to reach a constant level of 5 to 7μ by 5 months. On the contrary, D increases gradually in the majority of the cases of TGA and VSD.

**Figure 7.** Medial thickness (D) at $R = 100\mu$ is correlated with arterial pressure (P) in VSD. A close linear regression is observed, plotted on a semilogarithmic coordinate system.
the same blood pressure level. Medial hypertrophy due to elevation of blood pressure proceeded almost at the same rate in both diseases, but the initial condition of the muscular coat was different. Transposition of the great arteries was consequently characterized by weak muscular coat of the pulmonary artery. This condition developed only after five months, and the behavior of the muscular coat in the earlier period of this disease seemed to present a transitional response. In patients who had surgical treatment the thickness of the muscular coat reached the level of that of the VSD.

Discussion

Ferencz, Viles et al., and Newfeld et al. noticed in their histological studies early onset and remarkable development of severe PVD in TGA. Our results agreed with their observations with respect to the severity of PVD. It was further revealed in the present study that a pronounced aggravation of PVD took place only after the first five months of life.

The grade of PVD expressed as an index IPVD could be roughly correlated with blood pressure levels of pulmonary circulation in TGA as well as in VSD. The result suggests an important role of mechanical factors in precipitating PVD. It is therefore easy to understand that the capacity of the artery to resist mechanical impingement will be determined mostly by the strength of its wall. Our quantitative structural analysis of the pulmonary artery demonstrated hypertrophy of its muscular coat in response to elevated blood pressure. The reinforcement of the muscular coat will contribute much to protecting the arterial wall from mechanical stress. One of the important findings in the present study was the weak muscular coat found in TGA after five months of life. Even under a blood pressure load of the same magnitude, the medial thickness D was much lower in TGA than in VSD. This may account for the high vulnerability of the pulmonary artery in TGA to elevated blood pressure.

In the first five postnatal months, where physiological attenuation of the muscular coat proceeds under normal pulmonary circulation, the behavior of the muscular coat seems to be different from that in later months. The lack of this change in the weak muscular coat in TGA has not yet been established in this stage of life, and IPVD does not exhibit any significant difference from that for VSD. However, the response of the muscular coat to elevated blood pressure is suppressed in TGA, but not in VSD in this early period, so that the difference in the medial thickness between TGA and VSD becomes evident at the end of five months.

The low incidence of PVD in the first five months of TGA may be attributed to maintenance of some level of strength in the muscular coat. Thus it appears reasonable to recommend surgical treatment before the pulmonary artery becomes highly susceptible to pulmonary hypertension. It is interesting that in three cases of operated TGA in the present series the medial thickness of the pulmonary arteries matches that of arteries in VSD, a disease in which PVD does not inflict as much damage (fig. 8).

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