Vascular Changes in Pulmonic Stenosis and Tetralogy of Fallot Studied in Lung Biopsies

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SUMMARY

The present study deals with the results of the histological investigation of lung biopsies from 44 patients with pulmonic stenosis and 117 with tetralogy of Fallot in correlation with their clinical and hemodynamic data. Particularly cases without additional complicating malformations have been considered.

Medial atrophy and luminal widening of the muscular pulmonary arteries and veins were confirmed in both isolated pulmonary stenosis and tetralogy of Fallot but were more marked in pulmonic stenosis. Intimal fibrosis in the pulmonary vessels on the other hand gave the impression of being greater in the cases of tetralogy of Fallot than in pulmonic stenosis even within the same age group, but this difference is not statistically significant. Intimal fibrosis was even more pronounced in tetralogy of Fallot with a previous shunt operation. The intimal fibrosis is thought to be based on organization of thrombi.

The explanations for the medial atrophy and the widening of the arterial lumen are unknown, but it is thought likely that the flatness of the pressure curve in the pulmonary artery plays a role in causation.

Additional Indexing Words:
Congenital heart disease
Pulmonary vascular disease
Potts’ operation
Blalock’s operation

The study of lung biopsies of patients, operated on for congenital or acquired heart disease, may give an important contribution to our understanding of the development of pulmonary vascular changes in these patients. In contrast to autopsy material, lung biopsies thus obtained provide us with a picture of the lung and its vasculature not just from a limited number of severe or terminal cases but from a much larger number of patients. These patients are selected only insofar as they are subject to operation. The advantage of having material from a large and varied group of cases well outweighs the disadvantage of having only a limited piece of lung tissue available for histological examination.

Over a prolonged period, from October 1962 to May 1966, we collected tissue from more than 1,000 lung biopsies on patients almost all of whom were operated on for various forms of cardiac disease.1 The present study deals with the results of the histological investigation of biopsies in correlation with clinical and hemodynamic data in patients with pulmonic stenosis and with tetralogy of Fallot.

Methods

Among these lung biopsies 44 were on patients with pulmonic stenosis and 117 on patients with tetralogy of Fallot. Both groups were divided

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into uncomplicated and complicated cases. A case of pulmonic stenosis, for instance, was considered uncomplicated when the stenosis was isolated, or at most accompanied by an atrial septal defect so small that it had no hemodynamic significance. There were 26 of these cases. The other 18 were complicated, that is, although the pulmonic stenosis was the predominant malformation, there was in addition a shunt at the level of the atrial septum indicated by cyanosis or by a diminished saturation of the arterial blood. In two cases there was a very small ventricular septal defect of less than 2 mm in diameter. The stenosis was valvular, infundibular, or combined.

Of the 117 patients with tetralogy of Fallot, seven had additional malformations such as a patent ductus arteriosus or agenesis of a main pulmonary artery. The remaining 110 were considered to have uncomplicated tetralogy although in some of them there was an additional atrial septal defect.

Cardiac catheterization was performed before operation in nearly all patients so that hemodynamic data were available. The lung biopsies were taken from the middle parts of the lungs. For reasons pointed out elsewhere, our control material was derived from autopsy cases of individuals without cardiovascular or pulmonary disease.

Histological sections of the paraffin-embedded lung tissue were stained routinely with hematoxylin and eosin, elastic-van Gieson stain, and Perl's iron stain. The sections were judged by one of us (C. A. W.) without advance knowledge as to age, sex, and clinical diagnosis of the patients, and the various lesions of the lung tissue and the vessels within the lung were graded with four grades ranging from normal (−) to severe (+++).

Results

To gain an impression of the vascular and other changes characteristic for pulmonic stenosis and tetralogy of Fallot, we have analyzed the results of the uncomplicated cases in relation to the clinical and hemodynamic data. The cases that were complicated one way or another are only briefly considered.

Our normal control group, composed of 77 individuals aged 2 to 54 years, with an average age of 22.2 years, was the same as that used in an earlier study. The findings in this group will be shown in connection with those from the cases of cardiac disease.

Pulmonic Stenosis

No Complicating Anomalies

Of the 26 patients with uncomplicated pulmonic stenosis, 11 were male and 15 female; they varied in age from 2 to 46 years with an average age of 16.7 years. In 23 of the cases hemodynamic data were available. In all these cases the right ventricular systolic pressure was over 60 mm Hg; in 17 cases it was over 100 mm Hg. The pressure in the pulmonary artery generally was unknown.

Media and Width of the Lumen of Pulmonary Arteries. The muscular pulmonary arteries in the lung biopsies usually showed a thin media. The grading of this medial atrophy appeared to be more difficult than that of medial hypertrophy as observed in cases of pulmonary hypertension. The reason is that the media of a normal muscular pulmonary artery is already relatively thin. When expressed as a percentage of the external diameter of the artery, its diameter is in the range of 4 to 5%, as we have shown in earlier, fully quantitative studies of autopsy cases. In cases of extreme medial atrophy, smooth muscle fibers may be lacking in part of, or even in the whole of, the circumference of pulmonary arteries, which, according to their caliber and close connection with bronchioles, should have a distinct and complete muscular media. Lesser degrees of atrophy, however, may easily overlap the normally occurring variations in medial thickness. In medial hypertrophy the differences are much greater and this makes the grading of its degrees more reliable than that of medial atrophy. It was therefore particularly important that in this study the biopsies were judged by the blind-test method to avoid bias.

The results for the pulmonary arterial medial thickness are shown in figure 1. When compared with the control group, it is evident that the pulmonary arterial media in pulmonic stenosis is very thin (fig. 2), the difference being significant (*P < 0.001*). Although cases

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*Here and elsewhere in this paper P is the one-sided tail probability, using Wilcoxon's one-sided two-sample test.
Incidence of degrees of medial thickness of pulmonary arteries in cases of pulmonic stenosis with intact ventricular septum, tetralogy of Fallot, and tetralogy of Fallot with previous shunt operation according to Blalock or Potts (B.P.) procedure, compared with normal controls. Especially in the first two groups the media is thinner than in controls.

of extreme atrophy (+++ ) did not occur in the uncomplicated group, individual arteries with such extreme atrophy, that is, with hardly any muscle in their walls (fig. 3), were occasionally observed, but the grading was then influenced by the presence of other arteries in the same biopsy with more muscle tissue in their media.

Another characteristic of the muscular pulmonary arteries in pulmonic stenosis is the width of their lumina (figs. 2 and 3). Here again it must be stipulated that this feature is hard to evaluate, especially when only a limited number of vessels is available. In a number of biopsies the wide lumina of the arteries and arterioles were so striking as to leave no doubt whatsoever. In other cases its evaluation caused great difficulties since exact criteria were hard to apply. Com-

Figure 2
Wide lumen and thin wall in a pulmonary artery in a case of pulmonic stenosis with slight intimal fibrosis in the right upper part of the vessel. Elastic-van Gieson stain; × 200.

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years, its thickness increases by subendothelial fibrosis. Initially, this fibrotic layer is very thin, but from an age of 40 years upward it may attain a considerable thickness.

This necessitated comparison of similar age groups, but since most of our patients with pulmonic stenosis were young, the results for the intimal fibrosis have been shown only for the age group of 2 to 19 years (fig. 5). In this group it appeared that intimal fibrosis was more often found in pulmonic stenosis than it was in the normal series ($P=0.0046$).

In all instances the type of intimal alteration was patchy, rather than concentric, as in cases of pulmonary arterial hypertension. It was suggestive that it originated from organization of thrombi. Recognizable thrombi, either recent or organizing, were never frequent, but their incidence was higher (three of 26) than in the control group (three of 77), in spite of a lower overall age. In only one case

parison with the luminal width of the accompanying bronchiole proved to be helpful, but sometimes we had to rely on the general impression; thus, again, elimination of bias was of utmost importance.

As may be seen in figure 4, the width of the lumina of the pulmonary arteries and arterioles, as compared to that in the control group, is striking and statistically significant ($P<0.001$).

Intimal Fibrosis and Thrombotic Lesions. While the medial thickness of normal pulmonary arteries is unaffected by age, intimal thickening occurs as a regular age change, as we have shown before. In children the intima consists of a single endothelial layer. Gradually, after the age of approximately 20

Figure 3
Wide lumen and thin wall in a pulmonary artery in a case of pulmonic stenosis. In some segments of the arterial wall all muscle tissue has disappeared. Patchy intimal fibrosis in the left upper part of the vessel. Elastic-van Gieson stain; $\times$ 500.

Figure 4
Incidence of degrees of luminal widening of pulmonary arteries in cases of pulmonic stenosis and of tetralogy of Fallot without or with previous shunt operation (B.P.) As compared with normal controls, the media is wider in all groups, especially in pulmonic stenosis.

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that in the uncomplicated cases, even in the presence of marked cyanosis, that is, with an arterial oxygen saturation of 80% or less at rest. There were, however, only nine such cases. No differences were found between cases of valvular stenosis and those of infundibular stenosis or a combination of both.

Tetralogy of Fallot

The total group of tetralogy of Fallot comprised 117 patients. In seven there were complicating malformations, such as agenesis of one main pulmonary artery, patent ductus arteriosus, or slight aortic stenosis. An additional shunt on the level of the atrial septum was not considered a complication.

No Complicating Anomalies

Of the uncomplicated group, 35 patients had been operated on prior to the operation.
of the medial thickness was necessary since normally young infants have a thicker media, which could have been misjudged, the age being unknown at the time of the original grading.

Also the width of the lumina of these vessels was significantly greater than that in the control series (P = 0.0047) (fig. 4), though not quite to the same extent as in pulmonic stenosis.

*Intimal Fibrosis and Thrombotic Lesions.* Intimal fibrosis in both groups was significantly more pronounced than in controls (P < 0.001) and slightly more marked in tetralogy of Fallot than in pulmonic stenosis (fig. 5), in spite of the fact that the average age within the age group up to 19 years was lower in tetralogy of Fallot. The fact that in this group some infants below the age of 2 years were

*Figure 7*
Pulmonary artery in a case of tetralogy of Fallot with multiple thin septa. Elastic-van Gieson stain; × 200.

at which the biopsy was carried out. In 28 patients, the previous operation was a shunt-operation of the Blalock or Potts type; in seven it was a Brock infundibulectomy. Since these previous operations may have influenced the structure of the pulmonary vasculature, we have eliminated them for our more extensive study. In this way 75 patients with uncomplicated tetralogy, not previously operated on, were available; 48 of these were male and 27 female. Their ages ranged from 5 months to 43 years with an average of 8.1 years.

*Media and Width of the Lumina of Pulmonary Arteries.* Also in tetralogy of Fallot the muscular pulmonary arteries tended to be thin-walled (fig. 1), the difference with regard to the controls being significant (P = 0.0012). In the few instances in which the age of the patients was less than 1 year, a later correction

*Figure 8*
Pulmonary veins with wide lumina and thin walls in a case of tetralogy of Fallot. Elastic-van Gieson stain; × 80.
Included is of no consequence since, normally, intimal fibrosis is never seen in young children.

The type of intimal fibrosis corresponds to that found in pulmonic stenosis, that is, it seemed to be based on the organization of thrombi (fig. 6). Recognizable thrombi, recent or organized, were found in seven of the 75 cases; in addition seven biopsy specimens contained intra-arterial septa (fig. 7), known to result from recanalization of thrombi.4, 5

In tetralogy of Fallot, also, the pulmonary veins sometimes showed a thin media and a wide lumen (fig. 8), but not as regularly as in pulmonic stenosis. Intimal fibrosis in veins did occur slightly more often than in pulmonic stenosis. The incidence of hemosiderosis and interstitial fibrosis was not greater than in normal lungs.

Complicating Anomalies

The lung biopsies from the seven cases of complicated tetralogy of Fallot and from the 35 cases in which there had been a previous operation in most respects showed a similar picture to that of the uncomplicated group. However, in the 28 cases with a previous shunt-operation, the incidence of intimal fibrosis was significantly higher than in our standard group of cases of tetralogy of Fallot (P = 0.00065) (fig. 5). In addition in nine of the 28 cases recognizable thrombi and in another six cases intra-arterial septa were found. In the group of seven complicated cases of tetralogy of Fallot, there was one more biopsy with septa. The number of collateral vessels in the pleura was only increased in cases previously operated on.

Discussion

In many cases of pulmonic stenosis and tetralogy of Fallot, the muscular pulmonary arteries are known to be wide and thin-walled. Also intimal fibrosis and thrombotic lesions especially the intra-arterial septa are frequently observed in these instances. An additional feature is the development of a collateral circulation. The literature on this subject has been reviewed by Wagenvoort, and associates.5 The reports on these vascular changes are almost exclusively based on autopsy material and thus on the more severe cases.

Little is known about the morphological differences in the lung between pulmonic stenosis with intact ventricular septum on the one hand and tetralogy of Fallot on the other.

In the present study the occurrence of medial atrophy of the muscular pulmonary arteries was confirmed both in isolated pulmonic stenosis and in tetralogy of Fallot, but the medial thinning was more pronounced in the former anomaly (fig. 1) and the same applied to the luminal widening of the pulmonary arteries (fig. 4).

So far no satisfactory explanation has been brought forward for the medial atrophy in these cases. Since medial hypertrophy is related to elevated pulmonary arterial pressure rather than to increased flow, as has been shown in cases of congenital heart disease with pulmonary hypertension,1 it is enticing to regard medial atrophy as resulting from a diminished pulmonary arterial pressure.

Although data on pressure in the pulmonary artery in our cases generally were not available, we know that the mean pressure distal to a pulmonic stenosis is only a few millimeters of mercury lower than that normally occurring in a pulmonary artery6 which makes it unlikely that the extreme medial atrophy, occasionally observed, results from so slight a difference in mean pressure. The systolic pulmonary arterial pressure, however, is more influenced by the stenosis, and the pressure curve as a rule is flatter than it is in pulmonary arteries of normal individuals. It may be assumed that the systolic peaks in the normal pressure curves are largely responsible for maintaining the medial thickness at its normal level, while a flat pressure curve leads to medial atrophy. In this respect it remains undecided whether the actual height or the steepness (dp/dt) of the peaks eventually is the main factor.

An increased luminal width of the muscular pulmonary arteries and of the pulmonary

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veins is particularly observed in cases of pulmonic stenosis and to a lesser extent in tetralogy of Fallot. Here again the significance of this alteration is unknown. It can not merely be regarded as a poststenotic dilatation, since it is a feature not only of the small pulmonary arteries and arterioles but of the pulmonary veins as well.

There is evidence that the increased width of the vessels can be brought about by different mechanisms. In cases of complete transposition of the great vessels without pulmonic stenosis or ventricular septal defect, we have repeatedly observed very wide and thin-walled vessels in the lung. In these cases it is difficult to accept that for the development of the thin-walled, wide vessels, the same causal factors are responsible as in pulmonic stenosis. In our cases the vessels tended to be wider and more thin-walled with increasing hematocrit values. If this factor played a role however, for instance by way of increased blood volume and resulting increased distention pressure, it could do so in cases of transposition and tetralogy of Fallot but not in the uncomplicated cases of stenosis in which hematocrit values were always within normal range. We also know from experimental work that ligation of a pulmonary artery on one side produces these changes only in the lung on that side.

Possibly the underdevelopment of the muscular media, supposedly due to the absence of systolic pressure peaks, is basic to a dilatation of the vessels. In the occasional cases in which thin-walled and more thick-walled arteries occurred in the same lung, only the thin-walled arteries were dilated. However, although such a mechanism could explain the vascular alterations in pulmonic stenosis and tetralogy of Fallot, it could not apply to cases of uncomplicated transposition. Further study for an explanation of these phenomena is required.

The widening of the pulmonary arterial bed is clearly demonstrated by the “moss-like” appearance shown in postmortem angiograms in cases of tetralogy of Fallot as well as of pulmonic stenosis. It should be kept in mind, however, that this may be due in part to dilatation of the thin-walled vessels brought about by the pressure exerted during injection of contrast medium. For demonstrating the original luminal width of the arteries, the angiographic method thus may not be reliable.

The concept that intimal fibrosis in cases of pulmonic stenosis and tetralogy of Fallot results from organization of thrombi is sustained by the findings of our present study. It is indicated by the morphological aspect of the intimal lesions in some instances and also by the correlation of intimal fibrosis with recognizable thrombotic lesions and with intra-arterial septa. The latter alterations, first described by Rich, have been repeatedly shown to originate from organization and recanalization of thrombi or emboli. The tendency to thrombosis is likely to be enhanced by the slow blood stream within the wide vessels and by the increased viscosity of the blood. Not only were these vascular changes much more common in tetralogy of Fallot than in pulmonic stenosis, but there was indeed a positive correlation in cases of tetralogy between the grade of the hematocrit on the one hand and the intimal fibrosis and arterial septa on the other. It should be pointed out, however, that a similar correlation existed between hematocrit on the one hand and medial atrophy and luminal width of pulmonary arteries on the other. Possibly these morphological changes, therefore, were merely more pronounced in the more severe cases of tetralogy of Fallot.

Intimal fibrosis in pulmonary arteries was somewhat more marked in our cases of tetralogy than in the cases of pulmonic stenosis, even within the same age group (fig. 5), and the same applied to intimal lesions in the veins. The differences, however, were not significant. A pronounced and significant increase in intimal fibrosis was observed in those patients with tetralogy of Fallot who had undergone operation prior to the one at which a biopsy was carried out. Here again it must be kept in mind that such cases are almost
certainly the more severe ones. That the creation of a shunt may lead to a breakdown of thrombotic lesions and fibrotic patches, as has been claimed by Ferencz, is not supported by our findings.

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