Pathology of the Pulmonary Vascular Tree

IV. Structural Changes in the Pulmonary Vessels in Chronic Left Ventricular Failure

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Previous studies in this series demonstrated structural changes in the pulmonary vascular bed as the result of mitral valvular disease and other cardiac disorders. The present study demonstrates changes in the lungs as the result of chronic left ventricular failure; these changes were like those produced by mitral stenosis. The most pronounced disturbance was medial hypertrophy. The exact mechanism is not known, but it probably is related to increased pulmonary venous pressure.

With the increased knowledge of cardiovascular physiology imparted by means of cardiac catheterization, parallel interest has been manifested in the structural changes that occur in the pulmonary vascular tree under various conditions, especially those associated with increased pulmonary arterial pressure. In earlier studies it has been demonstrated that in mitral stenosis and in mitral insufficiency, as well as in other cardiac disorders, structural changes may occur in the pulmonary vascular bed. When cardiac disease creates an impediment to pulmonary venous outflow, the pulmonary vascular changes are primarily those of medial hypertrophy of the muscular arteries.

Chronic left ventricular failure, like mitral stenosis or mitral insufficiency, is associated with impaired pulmonary venous outflow and increased pulmonary "capillary" and arterial pressures. The thought that this functional derangement might be associated with demonstrable structural changes in the pulmonary vascular tree led to the present study on histologic changes in the pulmonary vessels in cases of chronic left ventricular failure.

Material and Methods

Initially, it was desired to have three groups as follows: Group 1 included cases in which chronic left ventricular failure had resulted from calcific aortic stenosis or systemic hypertension. Group 2 included cases of calcific aortic stenosis or systemic hypertension without left ventricular failure. Group 3 included cases in which cardiovascular disease was absent. Later, a fourth group was studied; this group was made up of cases in which mitral stenosis was present.

Emphysema and other forms of pulmonary disease and aging may be associated with structural abnormalities in the pulmonary vascular tree. In order to exclude such cases as far as possible, records of patients 60 years of age or more were not included. Selection of cases for study included histologic examination of pulmonary tissue from persons potentially to be included in one group or another without knowledge at the time of this examination into which group the case would be placed if emphysema and other pulmonary diseases were not present. If pulmonary disease was present the case was not included.

After such elimination, the composition of the three groups was as follows: Group 1 was made up...
of 24 cases, in each of which chronic left ventricular failure had been present. The criteria for left ventricular failure were basically those given by White.\textsuperscript{11} The most constant feature was recurrent paroxysmal nocturnal dyspnea. Among the 24 cases in this group, six represented calcific aortic stenosis and 18 represented systemic hypertension. Healed myocardial infarction was also present in some of the cases in this group. Twelve of the patients were men and 12 were women; the ages ranged from 36 to 59 years, with a median age of 49 years. The mean cardiac weight in this group was 600 Gm., with a range of 420 to 920 Gm. In 17 of the cases, the cardiac weight was 600 Gm. or more. The duration of left ventricular failure varied from about 2 months to about 10 years; in the majority of cases, this functional disturbance had been present from about eight months to two years.

Group 2 also was composed of 24 cases; calcific aortic stenosis was present in two and systemic hypertension had been present in 22. None of these patients had presented clinical evidence of left ventricular failure. Nine were women and 15 were men. Their ages varied from 40 to 58 years, with a median age of 52 years.

Group 3 comprised 20 cases. No clinical or pathologic evidence of cardiac disease was present in any of these cases. Many of the patients in this group had died of cerebral neoplasms. Six were men and 14 were women. Their ages ranged from 39 to 58 years, with a median age of 46 years.

From each person included in the study two sections of lung, chosen at random as to lobes, were stained by Verhoeff's method for elastic tissue and counterstained by van Gieson's method for connective tissue. The sections were then examined histologically according to the methods to be described.

**Definition of Terms**

Since potential lack of uniformity exists regarding terminology, it is pertinent to designate the types of pulmonary vessels to which reference will be made and to describe their basic structures. In general the terminology to be employed is similar to that of Brenner.\textsuperscript{12} The classes of vessels studied were muscular arteries, arterioles, and veins.

Muscular arteries vary in diameter from 1 mm. to somewhat less than 0.1 mm. These vessels are further divided into large muscular arteries and small muscular arteries (fig. 1a, b and c). The large muscular arteries are associated with a small bronchus and arise by branching from elastic arteries. The small muscular arteries arise as right-angled branches from the large muscular arteries. Whether large or small, the muscular arteries have a thin intima composed of lining endothelium and a small amount of collagenous tissue resting on the internal elastic membrane. The media is composed of a well-defined band of muscle fibers arranged in a circular fashion lying between the internal and external elastic membranes. In the large muscular arteries occasional elastic fibers are interspersed along the muscle fibers of the media. The adventitia is composed of dense collagenous connective tissue.

The arterioles are designated as those vessels arising from the small muscular arteries and lying between the small muscular artery and the capillary bed (fig. 1d and e). The structure of this class of vessel is characterized by an endothelial lining and a small amount of connective tissue, including an elastic membrane, lying in a subendothelial position. The elastic membrane was continuous with the internal elastic lamina of the parent muscular artery. Although muscle fibers cannot be identified with certainty in the wall of the arteriole, at the same time their absence cannot be categorically denied.

The veins in this study were divided into two groups, large and small. The structure of the small veins, or venules, is like that of the arterioles (fig. 1f). In general venules are wider than arterioles, but it is difficult to distinguish these vessels from each other in random sections of lung. While attempts were made to classify the changes in arterioles and in venules, it is to be admitted that the distinction between these two classes of vessels was probably not always accurate. The large veins present an intimal layer that, as in the arteries, is thin. The media contains well-defined muscle bundles that are irregularly arranged and separated by connective tissue, mainly collagenous. The adventitia is composed of thick collagenous bundles, among which are varying numbers of elastic fibers. In contrast to the muscular arteries, in which the media is distinctly demarcated from the adventitia by the external elastic membrane, the large veins exhibit a poorly defined transition between these two layers.
Fig. 1. Pulmonary vessels. All sections were stained by Verhoeff's method for elastic tissue and counterstained by van Gieson's method for connective tissue. 
a. Normal small muscular artery (X 350). 
b. Large muscular artery with medial hypertrophy, grade 3 (X 115). 
c. Small muscular artery with intimal hyperplasia and fibrous proliferation grade 3 (X 330). 
d. Normal arteriole (X 430). 
e. Arteriole with intimal proliferation grade 4 (X 430). 
f. Normal small vein (X 245).

Grading of Vascular Changes and Determination of Index of Change

An attempt was made to approach a quantitative measurement of alteration in several elements of the pulmonary vascular tree. This was done by developing a method of determining an “index of change.” The units of the pulmonary vascular tree for which indexes of change were determined included the media and the intima of both large and small muscular arteries, as well as the intima of the arterioles, venules and the large veins.

The index of change was derived from (1) the
evaluation of the greatest degree of change, termed the "grade of severity," that was present in the vascular unit under study and (2) an estimation as to the extent of this change, termed the "grade of distribution."

**Grade of Severity.** The grade of severity with regard to the media of the muscular arteries was indicated on a basis of 0 to 4. A grade of 0 represented no discernible change; grade 1 indicated an increase in thickness of the media up to 100 per cent more than normal; grade 2 indicated thickening up to 200 per cent above normal; grade 3 indicated thickening up to 300 per cent and grade 4 represented thickening of more than 300 per cent of normal.

The grade of severity with regard to the intimal narrowing that the change in intimal tissue had caused. Intimal thickening of grade 0 was recorded when the intima was of normal thickness. Intimal changes considered as grade 1 were represented by thickening of the intima beyond the normal range but which produced narrowing of the luminal diameter of less than 25 per cent. Narrowing of the lumen ranging from 25 to 49 per cent of the diameter was considered as grade 2 intimal fibrous thickening; luminal narrowing ranging from 50 to 74 per cent represented grade 3, whereas grade 4 intimal fibrous thickening represented luminal narrowing of 75 per cent or more. The same method was used for the intimas of the muscular arteries, arterioles and venules. The grade of severity for the intimas of the large veins was determined from the ratio (expressed as per cent) of the intima to the total thickness of the wall of the vein. If the intima was of normal thickness, the changes were graded as 0. If intimal thickening amounted to as much as 25 per cent of the total thickness of the wall, it was graded 1; thickening up to 50 per cent was graded 2, thickening up to 75 per cent was graded 3 and that up to 100 per cent was graded 4.

**Grade of Distribution.** A grade of distribution was recorded for the severest grade of change in each element. If the greatest degree of change present was observed in up to a fourth of the vascular elements under scrutiny, the grade of distribution was 1; it was grade 2 when about half the units were so involved; grade 3 indicated that about three fourths of the vascular units were so affected, whereas grade 4 indicated maximal changes in essentially all such elements.

**Index of Change.** As indicated previously, the index of change for each vascular unit in each section studied was determined by means of the grade of severity and the grade of distribution. This was done by obtaining the product of these two grades. To determine the index of change for the particular vascular unit in each case, the index of change for each of the two sections was determined and the two indexes were averaged.

The following is an example of the method used in determining the index of change for one vascular element. The greatest degree of intimal change among the large muscular arteries represented a grade of severity of 3. The distribution of this greatest degree of change involved about half of the large muscular arteries, yielding a grade of distribution of 2. The product of these two grades (3 times 2) gives an index of change of 6 for the intima in the large muscular arteries of that section. If the second section in the case being studied gave an index of change for the intima of the large muscular arteries of 8, the average index of change for this vascular element would be 7, which would be considered the index of change for the intima of the large muscular arteries in that particular case.

Averages for the index of change of each vascular element studied were made for each of the groups of cases studied. After the findings in these three groups were compared with each other, it was of interest to compare them with what might be found in mitral stenosis.

Accordingly, as previously mentioned, the records in 10 cases of established rheumatic mitral stenosis in which the patients had died of this valvular disease were collected to represent group 4. Five of the patients were women and five were men. The ages varied from 35 to 54 years, the median age being 42 years. The pulmonary tissue in these cases was examined by the same methods that were applied to the other groups.

As already indicated, at the time of examination of the histologic sections in groups 1, 2 and 3, it was not known in which of these groups the individual cases belonged. It was only after the indexes of change for the various vascular elements were determined in all the cases in these three groups that the key was exposed and the cases arranged according to their proper groups. However, when the sections in group 4 were examined, it was known that they were from cases of mitral stenosis.

**Results**

The general results of this study are summarized in table 1.

**Group 1 (Chronic Left Ventricular Failure)**

**Large Muscular Arteries.** Large muscular arteries were found in the sections in 21 of the 24 cases in which clinical evidence of chronic left ventricular failure had been present. The average index of change of the media of these arteries in this group was 5.0 (range, 0 to 12).
No changes (grade 0) were found in the media of the large muscular arteries in five cases; in seven, the indexes of change varied from 7.0 to 12.0, whereas the indexes ranged from 2.0 to 6.5 in the remaining nine cases. The average index of change in the intimal coat of the large muscular arteries in this group was 2.1 (range, 0.0 to 8.0). In nine of the cases no changes in the intimal coat were found (grade 0); in one case the index was 8.0, and in the remaining 11 the indexes ranged from 1.0 to 6.0.

Small Muscular Arteries. Small muscular arteries were present in the sections studied in all 24 cases in group 1. For the group the average index of change of the media of these small muscular arteries was 2.7 (range, 0 to 9.0). No change in the media coat (grade 0) was present in 5; in the remaining 19 cases, 3 had indexes of change in the intimal coat that varied from 7.0 to 9.0, whereas 16 had indexes that varied from 0.5 to 5.0. The average index of change in the intima of these small muscular arteries was 3.1 (range, 0 to 10.5). The intimal changes were classified as grade 0 in 8 cases; in the remaining 16 cases, 5 had indexes ranging from 7.5 to 10.5 and 11 had indexes ranging from 1.0 to 6.0.

Arterioles. The average index of change of the intima of the arterioles in group 1 was 4.4 (range, 1.0 to 10.5); the indexes ranged from 7.5 to 10.5 in 4 cases and from 1 to 6 in 20 cases.

Small Veins. The average index of change of the intima of the small veins in group 1 was 4.9 (range, 2.0 to 14.0); the indices varied from 7.0 to 14.0 in 6 cases and from 2.0 to 6.0 in 18 cases.

Large Veins. Large veins were present in the sections in 19 of the cases in group 1. The average index of change of the intima of these large veins was 5.2 (range, 0 to 16.0). No intimal changes were found in 1 case; in the remaining 18 cases, 5 had indexes that varied from 8.0 to 16.0, whereas 13 had indexes that ranged from 2.0 to 6.0.

Comparison of Degree of Change with Duration of Left Ventricular Failure and with Underlying Disease. When the duration of left ventricular failure, as determined from the clinical history, was plotted against the degree of change, as expressed by the summation of the indexes of medial and intimal changes in the large and small muscular arteries, the resultant scattergram showed no obvious correlation with the duration of left ventricular failure. Likewise, no clear correlation was seen when the duration of left ventricular failure was plotted against the summation of the indexes of change found in all the elements graded in each particular case. Considerable difference was noted in these indexes when the cases were separated into those in which calcific aortic stenosis was present and those in which systemic hypertension was present. In general, a greater index of change was associated with calcific aortic stenosis than with systemic hypertension in the cases studied (table 2).
### Table 2.—Average Indexes of Change in the Pulmonary Vascular Tree in Chronic Left Ventricular Failure and in Mitral Stenosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Large muscular arteries</th>
<th>Small muscular arteries</th>
<th>Arterioles*</th>
<th>Small veins*</th>
<th>Large veins*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcific aortic stenosis with left ventricular failure (subdivision of group 1)</td>
<td>7.7 (4-12)</td>
<td>1.7 (0-6)</td>
<td>4.7 (3-7.5)</td>
<td>5.6 (1-10)</td>
<td>8.0 (2-14)</td>
</tr>
<tr>
<td>Hypertensive cardiovascular disease with left ventricular failure (subdivision of group 1)</td>
<td>4.0 (0-12)</td>
<td>2.3 (0-8)</td>
<td>2.0 (0-9)</td>
<td>3.8 (1-10.5)</td>
<td>3.7 (2-4)</td>
</tr>
<tr>
<td>Mitral stenosis (group 4)</td>
<td>8.8 (0-16)</td>
<td>1.2 (0-4)</td>
<td>3.6 (0-7)</td>
<td>4.5 (2-8)</td>
<td>4.9 (2-5.8)</td>
</tr>
</tbody>
</table>

* Only intimal changes graded. † Range of indexes of change.

**Group 2** *(Calcific Aortic Stenosis or Systemic Hypertension without Left Ventricular Failure)*

**Large Muscular Arteries.** Sections in 22 of the cases in group 2 contained large pulmonary muscular arteries. The average index of change of the media of these large muscular arteries was 0.7 (range, 0 to 8.0). In 16 cases, the index of change was classified as 0; in 1 case the index was 8.0, and in the remaining 5 cases the indexes ranged from 0.5 to 4.0. The average index of change of the intima was 0.8 (range, 0 to 4.0); in 16 cases the indexes were 0, whereas in 6 cases they ranged from 2.0 to 4.0.

**Small Muscular Arteries.** All the sections in this group contained small muscular arteries. The average index of change of the media of these small muscular arteries was 0.5 (range, 0 to 4.0). No change was noted in 18 cases, whereas the indexes ranged from 0.5 to 4.0 in 6 cases. The average index of change of the intima of these small muscular arteries for the entire group was 1.5 (range, 0 to 6.5). The intimal changes in 11 cases were classified as 0; in the remaining 13 cases, the indexes ranged from 1.0 to 6.5.

**Arterioles.** The average index of change of the intima of the arterioles in the 24 cases in this group was 1.9 (range, 0 to 9.0). In 9 cases, the changes were classified as 0; in 2 cases, the indexes were 6.5 and 9.0, whereas the remaining 13 had indexes that ranged from 1.0 to 4.0.

**Small Veins.** The average index of change of the intima of the small veins was 2.9 (range, 0 to 8.0). No change was noted in 4 cases; 1 case had an index of 8.0, and the remaining 19 showed indexes that ranged from 2.0 to 4.0.

**Large Veins.** Large veins were found in sections in 23 cases in this group. The average index of change of the intima of these large veins was 1.9 (range, 0 to 8.0). In 11 of the cases the intimal change was classified as 0; in 1 case the index was 8.0, and the remaining 11 cases had indexes that ranged from 2.0 to 6.0.

**Group 3** *(Normal Controls)*

**Large Muscular Arteries.** The average index of change of the media of the large muscular arteries in this group was 0.2 (range, 0 to 2.0); the average index of change of the intima was 0.25 (range, 0 to 2.0).

**Small Muscular Arteries.** The average index of change of the media in the small muscular arteries was 0.1. In 19 of the cases, the medial changes were classified as 0; in the remaining case, the index was 1.5. The average index of change of the intima was 1.0 (range, 0 to 4.0).

**Arterioles.** The average index of change of the intima of the arterioles was 2.2 (range, 0 to 5.5).

**Small Veins.** The average index of change of the intima of the small veins was 3.0 (range, 0 to 6.0).

**Large Veins.** The average index of change of the intima of the large veins was 1.9 (range, 0 to 8.0). No intimal changes were noted in 10 cases; in 1 case the index was 8.0, and in the remaining 9 cases the indexes ranged from 2.0 to 4.0.
Group 4 (Mitral Stenosis)

The average indexes of change of the various pulmonary vascular elements in the 10 cases of mitral stenosis are given in table 1.

Comment

It is obvious from the summary in table 1 that the average change of each of the vascular elements studied in group 1 differed noticeably from the averages in groups 2 and 3. On the average, the changes in chronic left ventricular failure approximated the changes in mitral stenosis. The data are even more striking when the findings in mitral stenosis are compared with those of the two subdivisions of group 1 (table 2); it is apparent that the changes in calcific aortic stenosis associated with left ventricular failure were similar to those in mitral stenosis.

The most striking deviations from the control group occurred in the media of the muscular arteries in the other three groups. Averages for indexes of change in the intimal layer of these arteries were greatest in groups 1 and 4; however, the differences from control figures were not so great as in the case of the media of the muscular arteries. These findings conform to the observation of Larrabee and associates that medial hypertrophy appears to be the earliest recognizable structural change in the small pulmonary vessels in mitral stenosis. It has been stated that the medial vascular changes in mitral stenosis are a true effect of the valvular disease, while accompanying intimal changes represent incidental aging processes. Our results would not appear to support unequivocally the latter opinion but suggest that one element responsible for the intimal change may be age.

It was noted that the indexes of change in 8 of the 24 cases of calcific aortic stenosis or systemic hypertension without left ventricular failure (group 2) were greater than those in certain cases in the group with chronic left ventricular failure (group 1). This may be explained in one of two ways. A simple explanation would be that left ventricular failure had been present in some cases in group 2 despite a negative history. The other possibility is that the vascular changes in the lungs may represent the anatomic expression of a functional response to left ventricular failure, a response which, although the left ventricle had failed, had prevented the occurrence of pulmonary edema and so had prevented the important clinical basis for the recognition or failure of the left ventricle.

It will be recognized that the argument just presented implies essentially the same explanation for the prevention of pulmonary edema in some cases of chronic left ventricular failure that has been applied for the prevention of pulmonary edema in mitral stenosis.1 "Protective" contraction of the small pulmonary arterial vessels is considered to be the underlying factor responsible for the medial hypertrophy that was seen in the muscular arteries in cases of chronic left ventricular failure (group 1), in cases without ventricular failure (group 2) and in cases of mitral stenosis (group 4).

While it is recognized that great resistance to flow through small pulmonary arterial vessels in mitral stenosis is associated with medial hypertrophy of muscular arteries and is protective against the development of pulmonary edema, it is not known by what specific mechanism this arterial response is brought about. Similarly, while the mechanism for the hypertrophy of the muscular arteries seen in groups 1 and 2 is not understood, it is considered to be related to increased pulmonary venous pressure resulting from a failing left ventricle. The mechanism in these three groups is probably identical.

Summary

Structural vascular changes in the lungs in cases of chronic left ventricular failure were found to be qualitatively similar to those seen in mitral stenosis. The exact mechanism of the changes, the most striking of which was medial hypertrophy of the muscular arteries, is not known but would appear to be related to increase in left atrial and pulmonary venous pressures. Thus, the mechanism for the development of the pulmonary vascular changes in left ventricular failure appears to be like that operative in mitral stenosis.
SUMARIO ESPAÑOL

Los cambios estructurales en los pulmones en casos de descompensación crónica del ventrículo izquierdo fueron encontrados ser cualitativamente similares a aquellos observados en la estenosis mitral. El mecanismo exacto de estos cambios, el más significativo de los cuales fue la hipertrofia medial de las arterias musculares, no se sabe, pero aparece estar relacionado al aumento en la presión atrial izquierda y en la presión pulmonar venosa. De manera, que el mecanismo del desarrollo de cambios vasculares pulmonares en la descompensación ventricular izquierda aparenta operar similarmente a la estenosis mitral.

REFERENCES

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