Vasoconstriction and Medial Hypertrophy in Pulmonary Hypertension

By C. A. WAGENVOORT, M.D.

That increased thickness of the medial layer of the muscular pulmonary arteries is an almost constant feature of pulmonary hypertension has been well established. Usually it is referred to as medial hypertrophy. This increase, however, is not necessarily an expression of hypertrophy, since it may result from vasoconstriction without any real increase of muscular tissue in the wall of the vessel.

In order to clarify this point the medial thickening of pulmonary arteries in cases of congenital cardiac disease with pulmonary hypertension was studied. Attention also was paid to differences in various parts of the same lung in cases of pulmonary hypertension and in normal persons.

Materials and Methods

One or both lungs in 10 cases without any evidence of cardiac or pulmonary disease were used as controls. These lungs were selected in so far as possible from patients in the same age group as the patients with pulmonary hypertension. The ages of these patients ranged from 6 weeks to 39 years. In addition one, sometimes both, lungs of 17 patients with pulmonary hypertension were studied. Ten of these patients had ventricular septal defects, 1 ostium atrio ventriculare commune, 5 atrial septal defects, and 1 patent ductus arteriosus with coarctation of the aorta. All patients died after cardiac operation. Only cases in which the pressure in the pulmonary artery or right ventricle had been measured during cardiac catheterization were included. The cases of pulmonary hypertension were divided into 2 groups according to the level of pulmonary arterial systolic pressure. A pressure of 80 mm. Hg systolic was arbitrarily chosen as the lower limit of the high pressure group. All lower pressures were included in the moderate pressure group. The youngest patient was 2 years old, the oldest 47.

One of the lungs, usually the right one, if not damaged at necropsy, was perfused via the pulmonary artery first with 4 per cent solution of formalin and then with barium sulfate-gelatin mixture at the systolic pressure recorded during life by cardiac catheterization. For normal lungs a pressure of 15 to 20 mm. Hg was used. The other lung was kept as a control if not needed for other purposes. Arteriograms were made of the whole perfused lung and of its segments after segmental dissection.1 In perfused lungs the number of vessels suitable for measurement was greater than in nonperfused lungs, in which the vessels are often more or less collapsed. Ten blocks of tissue were taken from 5 different segments of each lung, namely from the apical and pectoral segments of the upper lobe, the lateral segment of the middle lobe or the lingula, and the apical and the anterobasal segments of the lower lobe. One block was taken at the periphery and another nearer the hilum. Sections were cut 6 µ thick and stained with hematoxylin and with Weigert's method for elastin, counterstained with van Gieson's stain.

The method to be employed required careful consideration. It seemed necessary for our purpose to determine the thickness on cross section of the media of a great number of pulmonary arteries and to measure the diameter of these arteries in both control lungs and in lungs affected by pulmonary hypertension. Such measurements, however, give no reliable information about a possible increase in muscular tissue within the vessel wall. If the results so obtained in lungs with pulmonary hypertension differ from those in controls, it is not possible to state that a thicker-walled vessel has more muscle than a vessel with corresponding medial thickness in a control case or that the vessel is thicker because of spasm. Therefore further data were needed in order to give a quantitative expression of the amount of medial tissue present. It would have been possible to calculate the mean surface area of the muscular layer of a great number of vessels chosen at random in hypertensive lungs and to compare the results with the mean surface area of the muscular layer in arteries in normal lungs. This approach presupposes that the vessels under these different conditions are more or less comparable. There is, however, reason to believe that they are not comparable. It has been pointed out by Heath and Whitaker2 and Heath and Best3 that in pulmonary hypertension the number of the smallest arterial vessels increases, since many at the arteriole level, normally without a distinct media, possess a muscular coat. An increase in the number of small muscular arteries, however, will lead to a decrease

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Selection of Arteries

The following procedures were carried out: For our measurements only muscular arteries that were virtually circular on cross section and that had a definite muscular media, indicated by internal and external elastic membranes, were included. As transitions are found between large muscular arteries and elastic arteries in which only a limited number of elastic membranes are present, all transitional forms were excluded from study. The arteries were taken entirely at random, whenever a vessel, meeting the conditions stipulated, presented itself in the field of view. Although they were not selected for size, they were classified into 2 groups: arteries less than 100 μ in diameter and those 100 μ or more in diameter. In this way the frequency of large and small arteries was ascertained.

Measurements Made

The diameter (d) of the vessel, exclusive of the adventitia, was measured and the thickness of the media (m) between the outer and inner elastic layer was measured also. At least 10 muscular arteries in each block of tissue, that is, at least 100 arteries were measured per lung, except in case 12 (fig. 1) in which not more than 88 pulmonary arterial branches could be found in the 10 sections studied. More than 100 vessels, indeed as many as 196 vessels, were measured in some cases in which great dimensional variations were apparent. From the measurements obtained, the thickness of the media was expressed as a percentage of the diameter.

Calculation of Area of Media on Cross Section

The cross-sectional area of the media (c), which gives a better indication for the presence of hypertrrophy, was deduced from the data already obtained according to the formula $c = \pi(dm - m^2)$. In this way the mean area of the media could be established both for small and larger arteries in each case. For the sake of convenience the area of the media surface was always expressed as an index of the cross-sectional area and the results of this calculation, therefore, were not multiplied by $\pi$.

Determination of Mean Cross-Sectional Area of Media per Unit of Lung Tissue

This was done by obtaining the mean cross-sectional area of the media of both the large and the small muscular arteries. This in turn was multiplied by the number of vessels per square centimeter of lung section. Since the measured vessels were relatively scarce per surface area of lung because of their having been selected for circular cross section, it was judged better not to confine ourselves to these for counting numbers. Since the small vessels can be counted only under high-power magnification, screening a big area in this way is a laborious and impractical procedure.

For that reason only muscular arteries of 100 μ or more in diameter were counted in all the sections previously used for measuring the vessels. If 2 successive countings yielded different results, the mean of these was taken. Ramifying arteries...
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Figure 2

a. Normal pulmonary artery (case 3, fig. 1) filled with injection mass. The medial thickness is about 3 per cent of the diameter. (Weigert's stain for elastin, counterstained with van Gieson's stain; × 350.)

b. Normal pulmonary artery (case 8, fig. 1) filled partly with blood and partly with injection mass. There is a marked thickening of the media (the ratio of the media to the diameter is about 16 per cent). This probably resulted from vasoconstriction. (Weigert's and van Gieson's stains; × 350.)

were counted as 1 vessel when they were connected in the section by a distinct common adventitia.

Then the surface area of all sections was measured with a planimeter, and the surface area of great bronchi or vessels, which could disturb the result, was deducted. Then the number of arteries measuring 100 μ or more was calculated per square centimeter of lung parenchyma. The ratio between vessels measuring less than 100 μ in diameter and those measuring 100 μ or more being known, the approximate number of the former could be calculated, and with the use of the mean cross-sectional area the total cross-sectional area of the media of arteries in both categories could be found. Their sum indicates an index of the amount of vascular muscle tissue per square centimeter of lung parenchyma. In figure 1 the method employed in determining the mean cross-sectional area of the media per square centimeter of tissue is illustrated.

Results

It seemed important to establish whether perfusion of the lungs with formalin and barium sulfate had an appreciable effect on the relative thickness of the media. When the left lung was not injected and could be used as a control, our measurements in both the normal and hypertensive groups showed a constant but slight difference in medial thickness, and the arteries that were not injected were somewhat more thick-walled than those that were injected. This decrease in the mean ratio of media to diameter of the vessel (—),

\[
\frac{m}{d}
\]
as a result of perfusion, was always less than 20 per cent and averaged no more than 7.8 per cent. Perfusion under controlled pressure, therefore, apparently has only a minor effect on the thickness of the arterial wall.

Controls

In comparison to the arteries of the greater circulation the pulmonary vessels are thin-walled (fig. 2a). In our material the mean thickness of the media, expressed as a percentage of the diameter and calculated over all segments of the right lung, varied from 2.9 to 4.8 per cent in all lungs from normotensive controls older than 1 year. In the 2 youngest children (1 year old or less) these values were 5.5 and 6.3 per cent respectively. The latter finding is in agreement with the fact that thick-walled fetal pulmonary arteries only gradually diminish in size during the first 1 or 2 postnatal years of life.\(^5\)\(^6\) Although the media in a great majority of pulmonary arteries was thin, a certain variability occurred, so that occasionally the ratio of media to diameter was as high as 10 or even 20 per cent (fig. 2b). Since a small number of these exceptions could influence the mean ratio considerably, the characteristics of the distributions in all cases together are given in table 1

### Table 1

**Mean Medial Thickness, Standard Deviation, and Skewness of Frequency Curve of Pulmonary Arteries in Controls and in Moderate and Severe Pulmonary Hypertension**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Pulmonary hypertension</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Arteries studied</td>
<td>Medial thickness</td>
<td>Skewness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
<td>S.D.*</td>
<td>Mean</td>
</tr>
<tr>
<td>Controls</td>
<td>10</td>
<td>1539</td>
<td>4.64</td>
<td>1.08</td>
<td>1.85</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate pressure</td>
<td>6</td>
<td>809</td>
<td>7.61</td>
<td>1.98</td>
<td>1.02</td>
</tr>
<tr>
<td>High pressure</td>
<td>11</td>
<td>1982</td>
<td>11.88</td>
<td>1.94</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Significance of differences according to pressure

- Normal to moderate pressure
  - T = 2.44
  - P = 0.0156
- Normal to high pressure
  - T = 3.84
  - P = 0.0014
- Moderate pressure to high pressure
  - T = 2.30
  - P = 0.0214

*Standard deviation.

### Table 2

**Mean Medial Thickness in Various Zones of the Lung in Controls and in Groups with Moderate and High Pulmonary Hypertension**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Moderate pressure</th>
<th>High pressure</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arteries measured</td>
<td>Media, per cent of diameter</td>
<td>Arteries measured</td>
<td>Media, per cent of diameter</td>
<td>Arteries measured</td>
</tr>
<tr>
<td>Zone of lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper*</td>
<td>624</td>
<td>4.3</td>
<td>322</td>
<td>7.6</td>
<td>776</td>
</tr>
<tr>
<td>Middle†</td>
<td>612</td>
<td>4.4</td>
<td>321</td>
<td>7.4</td>
<td>818</td>
</tr>
<tr>
<td>Lower†</td>
<td>303</td>
<td>4.2</td>
<td>166</td>
<td>7.9</td>
<td>388</td>
</tr>
<tr>
<td>Blocks of lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>759</td>
<td>4.3</td>
<td>410</td>
<td>7.7</td>
<td>1006</td>
</tr>
<tr>
<td>Peripheral</td>
<td>780</td>
<td>4.3</td>
<td>399</td>
<td>7.5</td>
<td>976</td>
</tr>
</tbody>
</table>

*Measurements from apex and pectoral segments of upper lobe.
†Measurements from lateral portion of middle lobe, or lingula, and apex of lower lobe.
‡Measurements from anterobasal portion of lower lobe.
(see also figure 5). From these it appears that the peak frequency in the controls lies at 3 or 4 per cent or even lower. In the controls, no significant difference existed between the upper and lower parts of the same lung. The mean ratio for all the examined lungs was 4.3 for the upper zones, 4.4 for the middle zones, and 4.2 per cent for the lower zones. The hypertensive groups also did not differ significantly between the upper and lower regions (table 2).

The same was done for the blocks taken at the periphery of the lung and those taken at a more proximal level. For all the control lungs together both the peripheral arteries and the more proximally situated vessels yielded a mean ratio of 4.3 per cent. In the hypertensive groups the corresponding figures suggest a similar conformity of proximal and peripheral vessels (table 2).

Finally, the lingula was taken apart in 4 normotensive and 5 hypertensive cases in which the left lung was available; the mean ratio of the media of all the arteries to the diameter was calculated and compared with the corresponding groups of arteries of the left lung as a whole. The result both for normotensive and hypertensive arteries is given in table 3. No significant difference was found between the mean ratio for the lingula and that for the left lung as a whole, and the same is true for all other investigated segments.

A new division was introduced, namely, between arteries measuring less than 100 μ
and those measuring 100 μ or more in diameter. This may be important as the small vessels are likely to exert more influence on the pressure in the lesser circulation than the large ones. Therefore the same division was applied to the whole group of vessels.

In all normal lungs without exception the mean ratio of the media in the small arteries was higher than that in the greater branches. For all lungs together the ratio of the former was 5.4 and that of the latter 3.9 per cent (table 4). This difference appears to be significant (p < 0.01; rank sign test). The same table shows the numbers of arteries in both groups which, since the vessels were taken at random, gives an indication of their frequencies as compared to each other. Arteries smaller than 100 μ are known to be relatively scarce in normal lungs. Still in 8 lungs used as controls obtained from persons more than 1 year of age, they comprised 25.8 per cent of all muscular arteries; in the 2 children less than that age they were even much more frequent (48.6 per cent) and were hardly outnumbered by the arteries of 100 μ or more in diameter. We could not confirm the finding of Heath and Best⁹ that these small vessels were exceptionally numerous in the lingula. As table 3 shows, 23 vessels less than 100 μ and 71 vessels of 100 μ or more in diameter were counted in the lingula of 4 control cases; the number of small vessels is 24.5 per cent of all arteries found. Since none of these belonged to the youngest age group, this percentage is in agreement with that found for the lung as a whole.

The mean number of arteries of 100 μ or more in diameter per square centimeter of normal lung sections is given in table 5, together with the calculated mean cross-sectional area of all medial tissue in both groups of arteries per square centimeter of lung parenchyma. There was a considerable variation in the number of arteries equal to or more than 100 μ in different controls (10.5 to 20.3), but this is independent of age, perfusion of pulmonary arteries or of the localization within the lung. The same applies to the total cross-sectional area of the media in small and large arteries.

**Patients with Pulmonary Hypertension**

Thickening of the medial layer of pulmonary arteries is a striking feature in most cases of pulmonary hypertension (fig. 3a and b). Although occasionally it may account for 25 or even 30 per cent of the diameter of the vessel, the mean value is 4.2 to 9.2 per cent of the diameter in the moderate pressure group and 8.1 to 15.4 per cent in the high pressure group. The distribution in both groups is shown in figure 4. In the group with pulmonary systolic pressure between 30 and 80 mm. Hg, the peak frequency is shifted to the right as compared with the control group. In the high pressure group this shift is more striking, and the peak is much lower. The differences in medial thickness and frequency between normal and high pressure groups are significant for the mean ratio, standard deviation, and skewness of frequency curve; those between moderate pressure group and both other groups are partly significant (mean ratio) and partly suggestive (test of Wilcoxon). As was pointed out previously, the mean ratio of the arterial media in cases of pulmonary hypertension was independent of the site of the vessels within the lung (tables 2 and 3). Whereas in control lungs the smaller arteries had a definitely thicker media than the large arteries, in the cases of high pulmonary hypertension, where the media of vessels of both sizes is so much thicker, this difference is almost entirely lost (table 4).

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**Table 3**

**Mean Medial Thickness in Arteries in Lingula and Whole Left Lung**

<table>
<thead>
<tr>
<th>Diameters of arteries</th>
<th>100 μ or more</th>
<th>Less than 100 μ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteries measured per cent of diameter</td>
<td>Arteries measured per cent of diameter</td>
<td></td>
</tr>
<tr>
<td>4 controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lingula</td>
<td>71</td>
<td>23</td>
</tr>
<tr>
<td>Whole left lung</td>
<td>295</td>
<td>113</td>
</tr>
<tr>
<td>5 cases of pulmonary hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lingula</td>
<td>47</td>
<td>93</td>
</tr>
<tr>
<td>Whole left lung</td>
<td>203</td>
<td>460</td>
</tr>
</tbody>
</table>

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The number of vessels with a diameter less than 100 &mu;m, however, is remarkably increased to such an extent that the ratio of small and great arteries, which was about 1:3 in normal lungs, was often reversed. The cross-sectional area of medial tissue per square centimeter of pulmonary parenchyma is also raised in both small arteries and large pulmonary arteries. There is a sharp rise in surface area of the small arteries. The mean surface area of the small arteries in the high pressure group is about 5 times that in the control group (fig. 5).

The medial surface areas in both large and small arteries in normal lungs differ significantly from those in lungs with high pressure. Those in the moderate pressure group lie between, and differ significantly from, the normal, but not from the high pressure group (test of Wilcoxon) (see table 4).

**Comment and Conclusions**

Our finding that the mean ratio of the media to the diameter of the vessels in normal lungs is between 2.9 and 4.8 per cent, with a peak frequency at 3 to 4 or even 2 to 3 per cent, roughly corresponds with the figures of other authors. Heath and Best (1958), for instance, found the ratio to be 4.2 to 5.8 per cent for arteries less than 100 &mu;m and 2.8 to 6.8 per cent for arteries measuring between 100 to 300 &mu;m, and Granston (1958) found it to be 3 to 8 per cent, with an average of 4.4 per cent for all arteries together.

A small but rather constant number of arteries, both less than and more than 100 &mu;m in diameter, have a thicker media than would be expected. In most normal controls one or more arteries with a ratio \( \frac{m}{d} = 10 \) per cent were sometimes seen, and in several of them, vessels with a media comprising 15 per cent or even more of the diameter could be found. Often such an artery had several branches that were equally thick-walled. Vasoconstriction rather than increase in the amount of muscle tissue seems likely in these cases.

No differences in medial thickness could be found dependent of the localization of the vessels, neither in hypertensive nor in normotensive lungs. Since in our cases there was no reason to assume an increased venous pressure, the almost similar figures for media in the upper and the lower parts of the lung are in agreement with the results of Doyle and associates (1957), who have found such a difference only in mitral stenosis but not in their cases of congenital heart disease.

Since the medial thickness in the peripheral
arteries was exactly the same as that of arteries located nearer the hilum of the lung, we could not confirm the finding of Heath and Best3 (1958) that the lingula represents an exceptional situation in so far as the thickness of the wall of the vessels is concerned. Neither the lingula nor any other of the segments investigated in this respect differed significantly from the mean value.

There was a marked difference in medial thickness between small (less than 100 μ) and larger (100 μ or more) muscular arteries: 5.4 per cent against 3.9 per cent, but this held solely for normal lungs. In hypertension this difference disappeared gradually.

The increase in thickness of the media with rise of pressure in the lesser circulation is evident. The differences between the normal and hypertensive groups in mean ratio of media to diameter of the vessels (---) and incidence of muscularized arterioles are significant or almost significant. This indicates a correlation between thickness of the media and degree of pulmonary hypertension. Within the high pressure group, however, this correlation was not always maintained. Often the media in the presence of high pressure, for instance 120 mm. Hg, was not much thicker or was even thinner than that in the group.

Table 4

<table>
<thead>
<tr>
<th>Diameter of arteries</th>
<th>100 μ or more</th>
<th>Less than 100 μ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteries measured</td>
<td>Medial, per cent of diameter</td>
<td>Arteries measured</td>
</tr>
<tr>
<td>Controls</td>
<td>1075</td>
<td>3.9</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate pressure</td>
<td>402</td>
<td>7.0</td>
</tr>
<tr>
<td>High pressure</td>
<td>664</td>
<td>11.7</td>
</tr>
</tbody>
</table>

Significance of differences according to pressure

<table>
<thead>
<tr>
<th></th>
<th>Normal to moderate pressure</th>
<th>Normal to high pressure</th>
<th>Moderate pressure to high pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T = 2.96</td>
<td>T = 3.77</td>
<td>T = 0.12</td>
</tr>
<tr>
<td></td>
<td>P = 0.0029</td>
<td>P &lt; 0.001</td>
<td>P = 0.9044</td>
</tr>
</tbody>
</table>

Table 5

<table>
<thead>
<tr>
<th>Number of Arteries and Index of Medial Cross-Sectional Area per Square Centimeter of Lung Parenchyma in Controls and in Moderate and Severe Pulmonary Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean per cm.² of lung tissue</td>
</tr>
<tr>
<td>Mean number of arteries</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>Controls</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Moderate pressure</td>
</tr>
<tr>
<td>High pressure</td>
</tr>
</tbody>
</table>

Significance of differences according to pressure

<table>
<thead>
<tr>
<th></th>
<th>Normal to moderate pressure</th>
<th>Normal to high pressure</th>
<th>Moderate pressure to high pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T = 1.36</td>
<td>T = 2.43</td>
<td>T = 0.65</td>
</tr>
<tr>
<td></td>
<td>P = 0.1738</td>
<td>P = 0.0150</td>
<td>P = 0.5156</td>
</tr>
</tbody>
</table>
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with pressure of 80 mm. Hg. The presence of other vascular lesions such as intimal proliferation, glomerulus-like structures, and small thrombi, which are far more frequent than in the moderate pressure group, may have an additional influence on the pressure, to disturb the correlation between medial thickness and hypertension within this group.

As we have seen, a thick media might be the expression of constriction. O'Neal and associates 4 (1955) explained all thickening of the media in small pulmonary arteries in mitral stenosis in this way. An increase in the amount of muscle tissue within a certain quantity of parenchyma of the lung, however, indicates real muscular hypertrophy. This study indicates that the vascular muscle tissue both in small and large arteries is significantly raised in patients with severe pulmonary hypertension over that of normal controls.

There are more strong arguments for the occurrence of medial hypertrophy. This study indicates that in normal lungs the number of arteries of 100 μ or more in diameter is far greater than the number of small arteries (table 4). In cases of moderate pressure these numbers were about equal and in the high pressure group the small arteries were twice as numerous as the large ones. It is not possible to explain this enormous increase in arteries of the smallest category merely by a process of vasoconstriction. New muscular vessels must have been formed by the development of muscle fibers around arterioles, previously without a muscular layer (fig. 6). That this form of medial hypertrophy occurs was denied by Short  8 (1957), who considered these small arteries the result of arterial contraction, but it was accepted by Edwards 9 and Heath and Best.  3 Proof of this can be obtained from consideration of the relatively large number of arteries with a diameter of about 30 μ and a medial thickness of about 3 μ in the lungs in cases of severe hypertension. When it is recalled that as a rule the media is never less than about 2.5 μ thick,
which is the thickness of one single muscle fiber, the area of the media on cross section remaining the same, such a vessel could only have arisen from an arteriole with a diameter of 35 \( \mu \) and a media that was 2.5 \( \mu \) thick by mere vasoconstrictive action. The diameter could not have been greater at the same cross section unless the medial thickness had decreased and this is not possible. Arteries of 35 \( \mu \) or thereabout, however, are not found in normal lungs. In a similar way the largest muscular arteries provide evidence for the existence of hypertrophy of their media. Muscular arteries of about 400 \( \mu \) in diameter with a media of 70 \( \mu \) can be found, though not frequently, in lungs affected by pulmonary hypertension. If these vessels were products of vasoconstriction, they would have arisen from far larger arteries. A calculation shows that, if the cross-sectional area of the media remained the same and the original ratio between media and diameter were normal, that is about 4 per cent, the vessel originally must have had a diameter of about 775 \( \mu \) and a media 31 \( \mu \) thick. But in our control series, arteries of this size were always of the elastic and not of the muscular type. Although these findings are pointing strongly to a real increase in vascular muscle tissue, this, of course, does not mean that vasoconstriction plays no part in medial thickening. It is now fairly well established that the pulmonary arteries have a tone and are capable of constriction.

Shepherd and Wood\textsuperscript{10} (1959) recently reviewed this topic. They concluded that a continuously increased tone, regardless of the mechanism that maintains it, probably will

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**Figure 7**

*Diagram for comparing the index of medial cross-sectional area per square centimeter of lung tissue and the mean medial thickness in normotensive and hypertensive cases. N = normal, V = ventricular septal defect, A = atrial septal defect, AC = ostium atrio-ventricular commune, DC = patent ductus arteriosus and coarctation of aorta, DV = ventricular septal defect; a patent ductus arteriosus was closed 3 years prior to death. The pressures were recorded in the pulmonary artery in all except the 5 cases (underlined) in which the pressures in the right ventricle only were available. Age and sex in all cases should be noted also.*

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The table and diagram are not transcribed here. However, the values for Patient number, Sex, Age in years, Condition, Pulmonary pressure, and so on, are shown.
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lead to medial hypertrophy and although increase of tone does not necessarily cause vasoconstriction, it may cause it; therefore, the combination of medial hypertrophy and a certain degree of constriction can be expected more or less regularly. In the series studied the number of arteries of 100 \( \mu \) or more in diameter per square centimeter of lung tissue showed a marked tendency to decrease in hypertensive lungs as compared with controls (table 5). The high pressure group differed significantly from the controls; the number in the moderate pressure group lay between but the difference for either group was not significant (test of Wilcoxon). Since in general vasoconstriction the diameters of all vessels tend to diminish, it might be suggested that such a constriction is responsible for this decrease in number. It is difficult to measure the degree of vasoconstriction from morphologic criteria, especially when it coincides with hypertrophy, but when a marked medial thickening is found together with a relatively low value for the medial cross-sectional area, then vasoconstriction is likely to prevail.

Therefore, the medial thickness \((\frac{m}{d})\) and the medial cross-surface area in all cases studied were put together in one diagram (fig. 7). That the medial thickness and cross-sectional area fell together in most cases was of course coincidence, since this depends on the choice of the scales for both factors. It is important, however, that these two factors show a rather close correlation in controls as well as in cases of hypertension. It may be useful to consider those cases in which a certain discrepancy exists between thickness and surface area of the media. In case 22, a case of ventricular septal defect, and in case 24 (fig. 7), a case of patent ductus with coarctation, the vasoconstriction seems to be more important than the hypertrophy, since the surface area of the media is relatively small as compared with its thickness. The reverse is found in cases 14 and 16 (fig. 7) in which a normal or moderately raised ratio of media to diameter is combined with a high cross-sectional area of the media. This suggests just the opposite of vasoconstriction, that is, passive dilatation of the vessels. It may be significant that both patients had an atrial septal defect with high flow, which could explain a certain dilatation of the pulmonary arterial system.

Summary

To determine whether thickening of the media of pulmonary muscular arteries in cases of pulmonary hypertension is the result of vasoconstriction or of hypertrophy or of both, a method for calculating the amount of arterial muscular tissue per unit of pulmonary tissue was devised. Comparison of the mean medial thickness, expressed as a percentage of the diameters of the arteries, with the amount of arterial muscular tissue per unit of lung, will give an impression as to whether vasoconstriction or hypertrophy prevails in a certain case. This method was applied to sections of pulmonary tissue from 10 normal controls and 17 patients with congenital cardiac disease with pulmonary hypertension. Medial hypertrophy was present in all cases of congenital heart disease studied as compared with controls, and was more pronounced in severe than in moderate pulmonary hypertension. In some cases also vasoconstriction appeared to play an important or even a dominant role in the thickening of the medial layer. In 2 cases of atrial septal defect with large pulmonary flow, hypertrophy was masked by dilatation of the vessels resulting in a relatively thin media.

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**Summario in Interlingua**

Pro determinar si le spissification del media de arterias pulmono-muscular in casos de hypertension pulmonar es le resultato de vasoconstriction o de hypertrophia o del duo in combination, un metodo esseva elaborate pro le calculation del quantitate de tissu arterio-muscular per unitate de tissu pulmonar. Le comparation del spissitate medie del media (exprimite como procentage del diametro del arterias) con le quantitate de tissu arterio-muscular per unitate de pulmon permitte nos formar un idea de si, in un certo caso, il ha prevalentia de vasoconstriction o de hypertrophia. Iste metodo esseva applicate a sectiones de tissu pulmonar ab 10 normal subjectos de controlo e ab 17 patientes con congenite morbo cardiaco e hypertension pulmonar. Hypertrophia del media esseva presente in omné le casos de congenite morbo cardiaco studiate e esseva plus pronunciate in sever que in moderate hypertension pulmonar. In piure casos, vasoconstriction etiam pareva haber un rolo significativo o mesmo dominante in le spissification del tunica media. In 2 casos de defecto atrio-septal con mareate fluxo pulmonar, hypertrophia esseva muscate per dilatation del vasos con le resultato de un relativamente tenue media.

**References**


**Heredity**

Two and two do not always make four, in the matter of hereditary descent of qualities. Sometimes they make three and sometimes five.—Oliver Wendell Holmes, M.D. The Poet at the Breakfast Table, 1872.
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