Observations on the Pulmonary Vasculature in a Case of Centrilobular Emphysema with Hemosiderosis

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WHEN chronic and severe pulmonary arterial hypertension complicates acquired valvular and congenital heart disease, there is always associated occlusive vascular disease of the lung. Hence we were impressed by the finding of normal-looking pulmonary arteries in a case of centrilobular emphysema that had been complicated by cor pulmonale for many years. We report this case because this anomalous behavior of the pulmonary vasculature in emphysema with pulmonary hypertension is common in our experience and yet has not hitherto been stressed adequately.

Report of Case

The patient was a sales manager aged 31 years at the time of his death. He was first hospitalized at the age of 9 years with complaints of attacks of wheezing at night since the age of 5 years and recurring infantile eczema. A radiograph of the chest showed increased basal shadows in both lungs. A diagnosis of bronchial asthma of allergic basis was made. He was seen regularly as an outpatient until the age of 19 years, during which time he continued to have frequent attacks of wheezing. Three years later he developed left lower lobe pneumonia, which was treated successfully by penicillin. He was next hospitalized at the age of 21 years after discharge from the Royal Air Force because of frequent attacks of wheezing and coughing associated with respiratory infections. On examination he had kyphosis, poor chest expansion, clubbing of the fingers, and slight central cyanosis. Even at this stage a radiograph of the chest showed a prominent pulmonary conus with hyper translucent lung fields. An electrocardiogram showed the pattern of right ventricular hypertrophy, right axis deviation, and “P pulmonale.”

Ten years later he was readmitted to the hospital on account of breathlessness on exertion and ankle swelling of 5 months’ duration. A recent episode of cardiac failure had responded to diuretics. On admission there was no sign of heart failure, but there were central cyanosis and finger clubbing. There was also clinical evidence of right ventricular hypertrophy and accentuation of the second sound in the pulmonary area, indicating pulmonary hypertension. The systemic blood pressure was 140/90 mm. Hg. The hemoglobin level was 127 per cent (18.6 Gm. per cent). An electrocardiogram showed progressive right ventricular hypertrophy. A chest radiograph showed more pronounced dilatation of the main pulmonary arteries and attenuation of the smaller branches.

He was admitted for the final time at the age of 31 years. This time he was in severe congestive cardiac failure with extreme dyspnea and cyanosis, distended jugular veins and generalized edema. A radiograph of the chest showed gross cardiac enlargement. He did not respond to treatment and died. The diagnosis was obstructive airway disease associated with long-standing bronchial asthma and chronic bronchitis. The dominant clinical features for the last years of his illness were those of severe pulmonary hypertension.

At autopsy there was considerable cyanosis of the head and upper limbs. There was pronounced clubbing of the finger and toe nails and gross pitting edema of the lower limbs to the mid-thigh. Clear effusions in the right and left pleural cavities measured 1,850 ml. and 1,150 ml., respectively. The trachea and main bronchi were congested and contained watery sputum. The lungs were emphysematous, two forms of emphysema being present. Bullae were particularly prominent at the apices and along the anterior margins of the lungs; some of them measured as much as 3 cm. in diameter. The remainder of the lung parenchyma showed centrilobular emphysema. Both lungs were edematous. The pulmonary arteries were grossly atherosclerotic, every class of vessel from the pulmonary trunk to the quarternary branches being involved. No emboli were found. Areas of fibrosis, stained rusty brown with iron pigment, were scattered throughout the lungs.

The enlarged heart weighed 700 Gm., the right ventricle weighing 205 Gm., and the left ventricle weighing 295 Gm. (The upper limit of the normal weight of the right ventricle is 65 Gm.) The right atrium was dilated. The tricuspid valve was normal in structure but it was dilated, the circumference of the tricuspid valve ring being 15 cm. The right ventricle was dilated and so hypertrophied that it was almost as thick as the left ventricle.
The right ventricle was 13 mm. thick and the left ventricle was 14 mm. thick. The pulmonary valve was normal in structure but considerably dilated (10 cm. in circumference). The left atrium was normal in size, and both the mitral and aortic valves were normal in structure and circumference. The origin, course, and distribution of the coronary arteries were normal. These vessels, like the aorta and other systemic vessels, were virtually free from atheroma in contradistinction to the pulmonary arteries.

The liver (1,830 Gm.) showed chronic, passive venous congestion. The kidneys (606 Gm.) were congested and enlarged and included acute white infarcts, mainly at the upper pole of the right kidney. The spleen (405 Gm.) and the other abdominal viscera were congested. The brain (1,650 Gm.) was congested and edematous, showing considerable dilatation of the cerebral vessels.

Pulmonary Vascular Pathology

There was considerable loss of pulmonary capillary bed as a result of emphysema and fibrosis of the alveolar walls. The emphysema was of the bullous and centrilobular varieties. The large air spaces of the bullae at the apices and anterior margins of the lungs were totally devoid of any pulmonary capillary network. Such areas of gross emphysema were localized, however, and involved a comparatively small portion of the pulmonary vasculature. In addition blocks taken from the remainder of both lungs showed "centrilobular" emphysema. These foci of emphysema occurred at the center of secondary lobules and surrounded the central bronchiole and its accompanying muscular pulmonary artery (fig. 1).

Much of the pulmonary capillary bed was obliterated by fibrous thickening of the alveolar walls (figs. 2A and B). This fibrosis seemed to be a reaction to breakdown and fragmentation of the elastic fibrils of the alveolar walls and subsequent deposition of iron salts. Many of the elastic fibrils had lost their fine, linear form and had become clumped into amorphous masses (fig. 2D). Small islands of early fibrosis and clumped elasticae were found (fig. 2A); many of them had become confluent, resulting in large fibrous masses (fig. 2B). The surrounding lung parenchyma was congested (fig. 2A).

The fibrous destruction of the vascular bed was modified and exaggerated by the incrustation of ferric salts on the disrupted elastic fibrils (fig. 2C). The source of these mineral salts was severe pulmonary hemosiderosis, which was widespread throughout all lobes of both lungs. Numerous alveolar spaces were filled with large collections of hemosiderin-containing macrophages. Ferric salts were deposited on the elastic fibrils of the alveolar walls and on the elastic laminae of muscular pulmonary arteries, and pulmonary arterioles (fig. 2D), venules, and veins. The greatest degree of iron inculstion affected the elastic fibrils of the alveolar walls; these fibrils were thickened, shortened, and distorted and in places had formed large amorphous clumps. A vigorous foreign-body giant-cell reaction had taken place around the iron-incrusted fibrils in the alveolar walls (fig. 2C) and to a much smaller extent in the walls of the blood vessels. These giant cells were large and numerous.

The pulmonary arterioles, which we considered to be arterial vessels less than 100 μ in diameter, were abnormal. In the normal lung their walls are composed of only a single elastic lamina. In the present case there was a distinct media of smooth muscle bounded by internal and external elastic laminae (fig. 3A). Muscularized arterioles with a diameter as small as 20 μ were seen; these could be regarded as precapillary vessels. Many of the pulmonary arterioles were occluded by what appeared to be organizing thrombus (fig. 3B). In some affected vessels this material had a cribriform pattern, as though the thrombus were recanalized (fig. 3C). Other arterioles were totally occluded by fibrous tissue (fig. 3D). There was slight intimal fibrosis in a few of the smallest muscular pulmonary arteries below 150 μ in diameter with atrophy of the underlying media. In the majority of cases the muscle was orientated circularly but in a few instances bundles of longitudinal muscle fibers were seen internal to the inner elastic lamina (fig. 4).

In our investigation we accepted the classifica-
Figure 2

A, upper left. Focus of fibrosis of alveolar walls with clumping of elastic tissue. (Elastic tissue-van Gieson × 250.) B, upper right. Area of lung showing more extensive fibrosis of the alveolar walls. (Hematoxylin and eosin × 100.) C, lower left. Section of lung to show deposition of ferric iron on the elastic laminae of a pulmonary arteriole (lower left) and on clumped elastic tissue (upper right). Vigorous foreign-body giant-cell reaction around the incrusted elastic tissue is seen. (Perls' hematoxylin × 450.) D, lower right. Two pulmonary arterioles showing iron incrustation of the inner and outer elastic laminae. (Perls' × 250.)

tion of Brenner,3 taking muscular pulmonary arteries to be vessels between 100 and 1,000 μ in diameter. Arteries of this class looked normal in every respect (fig. 5). They were composed of a thin media of circularly orientated smooth muscle sandwiched between internal and external elastic laminae (fig. 5). An insignificant increase in the thickness of the media was shown by its accurate measurement in 25 arteries in each of the five lobes of the lung. The mean medial thickness varied between 5.3 and 7.6 per cent of the external diameter of the arteries measured (table 1). A normal figure for percentage medial thickness is 4.6.4 Intimal proliferation and localized or generalized dilatation were not present.

The pulmonary venules and veins showed severe acellular intimal fibrosis.

Many elastic pulmonary arteries were severely atherosclerotic with focal collections of lipophages and surrounding fibrous reaction to give rise to

Table 1

<table>
<thead>
<tr>
<th>Lobe of lung</th>
<th>Left upper</th>
<th>Left lower</th>
<th>Right upper</th>
<th>Right middle</th>
<th>Right lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>3.9 to 8.2</td>
<td>5.4 to 10.0</td>
<td>4.9 to 7.3</td>
<td>5.3 to 7.8</td>
<td>5.0 to 10.8</td>
</tr>
<tr>
<td>Mean</td>
<td>5.3</td>
<td>7.3</td>
<td>6.1</td>
<td>6.5</td>
<td>7.6</td>
</tr>
</tbody>
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Figure 3

A, upper left. Hypertensive pulmonary arteriole showing a muscular media sandwiched between internal and external elastic laminae. A group of hemosiderin-laden macrophages is present in the alveolar space to the upper left. (Elastic tissue-van Gieson × 250.)

B, upper right. Hypertensive pulmonary arteriole with a distinct muscular media and almost total occlusion of the lumen by intimal fibrosis, which appears to be due to organization of thrombus. (Elastic tissue-van Gieson × 450.)

C, lower right. Pulmonary arteriole largely occluded by what appears to be recanalized organized thrombus. (Elastic tissue-van Gieson × 250.)

D, lower right. Hypertensive pulmonary arteriole almost totally occluded by intimal fibroelastosis. (Elastic tissue-van Gieson × 250.)

considerable thickening of the intima. The pattern of the elastic tissue of the media of the pulmonary trunk was of adult pulmonary type. The bronchial arteries were hypertrophied. Plexuses of dilated, thin-walled vessels were present in the walls of the bronchi, both within the submucosal layer and around the muscle of the bronchial walls. These were probably bronchial venules.

**Discussion**

The significant feature of this case is the failure of the pulmonary arteries to show the expected degree of medial hypertrophy secondary to long-standing severe pulmonary hypertension. That this patient had a considerably raised pulmonary arterial pressure there seems to be little doubt, although this was never directly confirmed by cardiac catheterization. In the absence of such direct proof one may accept instead evidence of hypertrophy of the right ventricle which, in the absence of a structural abnormality of the pulmonary valve or infundibular stenosis (as in this case), occurs only as the result of increased work of this chamber. Such increased work may result from either increased pulmonary flow or increased pulmonary vascular resistance. In this connection Wade and Bishop have recently collected evidence to show that the earlier view that congestive car-
Hypertensive pulmonary arteriole with a distinct muscular media. A fasciculus of longitudinal muscle internal to the inner elastic lamina is seen to the left of the vessel. (Elastic tissue-van Gieson × 450.)

diac failure in emphysema is usually of high output type⁶ is erroneous. Collecting the reported data of 216 observations on the level of pulmonary flow in 201 patients with emphysema, either with or without pulmonary hypertension, in or out of congestive failure, they found that the pulmonary flow was normal in 87 per cent of these cases, diminished in 5 per cent, and slightly increased in only 8 per cent. Hence we may assume that right ventricular hypertrophy in emphysema is a result of increased pulmonary vascular resistance and pulmonary arterial hypertension. Further points in support of this contention in the present case are the presence of pulmonary fibrosis, which tends to diminish pulmonary flow, and the fact that the left ventricle did not share in the hypertrophy of the myocardium such as would have occurred if the right ventricular enlargement was due to increased cardiac output.

Moreover, the pulmonary hypertension had been present for at least 10 years, as shown by the dilated pulmonary cones in the chest radiograph of 10 years ago. All the classical clinical and pathologic criteria for sustained hypertension in the lesser circulation were present. The weight of the right ventricle was three times that accepted as normal¹ and the right ventricular wall was as thick as the left. The major pulmonary arteries were also dilated and severely atherosclerotic, a finding usually associated with raised pulmonary arterial pressure in the young.⁷ All the abdominal viseera showed the effects of long-standing congestion secondary to right ventricular failure.

Not only were the macroscopic effects of severe chronic pulmonary hypertension present but also the histologie evidence of its cause. The pulmonary arterioles were unequivocally abnormal in showing a distinct muscular media with internal and external elastic laminae and also various stages of occlusion of the lumen by intimal proliferation of a type suggesting organization of thrombus (fig. 3). The etiology of such hypertensive changes is no doubt related to loss of much of the pulmonary capillary bed by centrilobular emphysema and interstitial pulmonary fibrosis. Be that as it may, there is no doubt that the pulmonary arterioles in this case showed changes that are known to characterize all forms of

Transverse section of muscular pulmonary artery. The media is thin. No form of intimal proliferation is present. Such normal features characterized all the blood vessels of this class throughout the lungs. (Elastic tissue-van Gieson × 250.)
hypertensive pulmonary vascular disease, be it produced by mitral stenosis, congenital cardiac shunt, or idiopathic pulmonary hypertension.  

In the presence of increased pulmonary vascular resistance of this organic basis, the appearance of the muscular pulmonary arteries throughout both lungs is anomalous. These vessels showed no form of intimal proliferation, so that there was no diminution in the diameter of the lumen. At the same time there was an insignificant increase in the thickness of the media (fig. 5), an observation confirmed by mensuration of 125 arteries in all five lobes (table 1). Hence we are faced with the coexistence of normal-looking muscular pulmonary arteries, exhibiting none of the histologic features of hypertensive pulmonary vascular disease, with pulmonary hypertension that gave rise to a right ventricle that was 13 mm. thick and weighed 205 Gm.

This peculiar disparity between the thickness of the right ventricle and the medial thickness of the muscular pulmonary arteries in emphysema has been pointed out before. Leopold and Gough2 found right ventricular hypertrophy, defined by them as a right ventricular thickness of 6 mm. or more, in 41 of 75 cases of centrilobular emphysema. They found no statistically significant difference in the degree of thickening of the small pulmonary arteries in cases with and without right ventricular hypertrophy. Cameron9 found the pulmonary arteries to be "not obviously hypertrophied" in a case of emphysema complicated by pulmonary hemosiderosis and considerable right ventricular hypertrophy very similar to that reported here. Heath and Best10 also found the increase in medial thickness of the pulmonary arteries in emphysema complicated by pulmonary hypertension to be insignificant. They studied the pulmonary blood vessels in three patients with primary lung disease in whom the pulmonary arterial mean blood pressure was proved directly by catheterization to equal or exceed 60 mm. Hg. Dunnill,11 who investigated the anatomic factors concerned in the production of cor pulmonale in emphysema, also found little or no evidence of hypertensive pulmonary vascular disease in cases of centrilobular emphysema in which the right ventricle was hypertrophied. He found right ventricular hypertrophy, defined by him as a right ventricular thickness of 7 mm. or more, in 27 of 30 cases of centrilobular emphysema, but, with one exception, the "muscular pulmonary arteries showed remarkably little change."

Dunnill11 formulated a hypothesis to account for the coexistence of an increased pulmonary vascular resistance and pulmonary arteries of normal histologic appearance in centrilobular emphysema. In this disease the muscular pulmonary artery enters the secondary lung lobe with its accompanying bronchiole as though at the apex of a pyramid. With the development of centrilobular emphysema this artery is suspended in the center of a lobule surrounded by an air sac. The air pressure in this sac is considerably elevated during the prolonged phase of expiration which characterizes emphysema. This increased pressure, Dunnill believed, pushes in the walls of the artery, thus partially occluding the lumen and giving rise to increased pulmonary vascular resistance. This theory does not explain why those pulmonary arteries proximal to the multiple foci of vascular collapse do not develop hypertensive changes as a reaction to the elevated pressure. Furthermore, in our present case we know the site of increased vascular resistance, for we have demonstrated this histologically. Rather we have failed to explain why, in the presence of such increased resistance, hypertensive changes have not developed in the muscular pulmonary arteries.

We do not believe the case reported here to be an example of idiopathic pulmonary hemosiderosis12 but consider it to be analogous to the two cases of pulmonary hemosiderosis reported by Cameron9, which complicated emphysema and bronchiectasis, respectively. The hemosiderosis may have followed terminal failure of the left ventricle brought about by
hypoxia of the myocardium, itself a result of low output and reduced arterial oxygen saturation. Less likely, there may have been direct interference of left ventricular filling and contraction as a result of the gross right ventricular hypertrophy.

Summary

A 31-year-old man with centrilobular emphysema complicated by pulmonary hemosiderosis suffered from cor pulmonale for many years and eventually died from congestive cardiac failure. At autopsy the right ventricle was 13 mm. thick and was three times the normal weight. The pulmonary arterioles showed classical hypertensive changes, but the pulmonary arteries showed no abnormality apart from an insignificant increase in medial thickness. These findings support the view that hypertensive pulmonary vascular disease is not a passive phenomenon due to the effect of increased pressure on vessels but is brought about by active response to stimuli, which were apparently not present in this case.

References


Congenital Heart Disease and Endocarditis

The liability of grossly congenitally deformed valves to become infected was first pointed out in 1844 by James Paget in recording what is now recognizable as acute gonococcal endocarditis of the pulmonary valves; Ormerod in 1851 quoted Paget's statement as a general law, but otherwise it appears to have been forgotten, for in 1886 Osler independently brought out the frequency with which malignant endocarditis supervened on bicuspid aortic valves, and A. E. Garrod (1897) did the same. Recently Lewis and Grant have gone exhaustively into the presence and influence of minute abnormalities of the aortic valves, and Maude Abbott into the statistical aspect, thus proving the correctness of Paget's conception of eighty-four years ago.—Sir Humphry Davy Rolleston. The Harveian Oration. Great Britain, Cambridge University Press, 1928, p. 36.
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