Pulmonary Hypertension of Unknown Cause*

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Pulmonary hypertension occurs in a variety of conditions. It may exist as a congenital anomaly with or without an associated cardiac defect, or it may be acquired. One classification of acquired pulmonary hypertension is that suggested by Wood,1 including: (1) passive, (2) hyperkinetic, (3) obstructive, (4) obliterator, (5) vasoconstrictive, and (6) polygenic.

Congenital pulmonary hypertension is usually found in association with intracardiac defects and persists from birth. Some cases of isolated or unexplained pulmonary hypertension have been described in very young children with cardiac symptoms from birth and must be accepted as a congenital “primary” pulmonary hypertension.

Hypertrophy of the right ventricle in the absence of any obvious cause was first described by Romberg* in 1891. From that time until the beginning of the era of heart catheterization in 1941,* there was much dispute as to the relationship of hypertension of the lesser circulation to hypertrophy of the right ventricle. Many of these cases were published under such titles as “Right Ventricular Hypertrophy of Unknown Origin,” “Primary Pulmonary Vascular Sclerosis,” and “Isolated Hypertrophy of the Right Ventricle of the Heart of Unknown Cause.”

Since 1941, there have been many cases studied by right heart catheterization and proved at post-mortem examination. In 1951, Dresdale et al.† were able to find ten reported cases of pulmonary hypertension without discernable cause that had been studied by right heart catheterization. Since their report there have been many cases of unexplained or primary pulmonary hypertension in tabulations of cases encountered in catheterization laboratories. Several reviews have been published.

Recently we have had the privilege of studying a patient who developed unexplained pulmonary hypertension while being followed at the University of Minnesota Hospitals for an unrelated condition. This made it possible to obtain an interesting series of electrocardiograms (Fig. 1) and chest x-ray films (Figs. 2, 3, 4, and 5) that demonstrate the evolution of the disease. The patient was studied by right heart catheterization and material was obtained for pathologic study by open lung biopsy.

Case Report: Mrs. M. P., a 42 year-old white woman, had been followed since 1948. At that time, she was found to have anemia, neutropenia, and bone marrow that showed a maturation arrest of the granulocytic series with a normoblastic hyperplasia. A history of benzol exposure in 1945 was obtained, and she was thought to have bone marrow depression secondary to benzol exposure. No cardiac abnormality was noted on physical examination and chest x-ray film and ECG were normal.

She was found to have splenomegaly in 1952 and splenectomy was done. Again, no cardiac abnormality was noted and the chest x-ray film (Fig. 2) and ECG were normal. She was followed in the hematology clinic for the next three years with no specific complaint except for tiredness and a vague ache between her shoulder blades. Her hemoglobin was in the range of 11.0 to 12.5 Gm. during this time.

In May, 1955, she began to complain of a vague, aching, substernal pain that was usually associated with exercise and relieved by rest. This pain was not relieved by

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nitroglycerin and lasted longer than 10 to 15 minutes. The ECG (Fig. 1) was still normal, although the T wave had become inverted in V-1 through V-3. A Grade I apical systolic murmur was described.

In March, 1957, she developed a dry, chronic cough with occasional hemoptysis. Chest x-ray films (Fig. 4) were consistently normal and she was thought to have chronic bronchitis. In October, 1957, she complained of palpitation, dyspnea, and weakness on effort. An ECG at that time (Fig. 1) showed moderate T wave inversion in III, aVF, and V-1 through V-3 with ST depression in V-2 and V-3. A subendocardial infarction was suspected, but follow-up ECG's were unchanged and none of the other signs of myocardial infarction was found.

She noted gradual increase in weakness, palpitation, exertional dyspnea and chest pain during the next year. She was again seen in February, 1958, with the same complaints, was found to have no cardiac enlargement, clear lungs, and a soft Grade I apical systolic murmur. Her symptoms continued to increase until the later part of 1958, when she developed orthopnea, ankle edema, cyanosis and increased chest pain on effort. She was admitted to the hospital in October, 1958, for further diagnostic studies.

She was described as a thin, nervous, white woman in mild respiratory distress. There was slight cyanosis of the lips and nail beds at rest that became much more prominent on exercise. The vital signs were normal. There were a few petechiae over the skin of the chest. The lungs were clear to percussion and to auscultation. The heart was slightly enlarged to the left and there was a prominent right ventricular impulse just to the left of the sternum. The pulmonic second sound was palpable. There was a normal sinus rhythm with a blowing, Grade III systolic murmur heard over the entire precordium, but heard best just to the left of the sternum in the third and fourth intercostal spaces. The pulmonic second sound was much louder than the aortic and was widely split and fixed. There was no diastolic murmur either down the left sternal

**FIGURE 1:** Serial ECGs from July, 1955 through February, 1959 showing the evolution of the right ventricular hypertrophy and strain pattern.
border or at the apex. The liver was palpable 4 cm. below the right costal border and there was one plus pitting edema of the ankles.

The hemoglobin was 15.7 gm. and the white blood count was 8950 with 25 neutrophiles, 67 lymphocytes, 4 monocytes, 3 eosinophils and 1 basophil. The urinalysis was negative and the blood urea nitrogen, fasting blood sugar, total serum proteins and albumin/globulin ratio were normal. The blood Kline reaction was negative. The platelet count was 180,000 per cu. mm. and the clot retraction was normal. The red cells were mildly macrocytic and hyperchromic and the reticulocyte count was 5.6 per cent. Free acid was found on gastric analysis, and the bone marrow examination was unchanged. All of the liver functions tests were normal as were bleeding, clotting and prothrombin times. Prior to exercise, the arterial oxygen saturation was 91.2 per cent. This fell to 78.6 per cent after mild exercise. The venous pressure was 130 mm. of saline solution and the arm to tongue circulation time was 27 sec.

Cardiac fluoroscopy (Fig. 5) was thought to show biventricular enlargement with no enlargement of the left atrium. The pulmonary artery segment was prominent, as were the hilar vessels, but the peripheral lung vasculature was thought to be normal or slightly decreased. A “hilar dance” was not thought to be present. An ECG (Fig. 1) showed right axis deviation with the pattern of right ventricular hypertrophy and strain. Pulmonary function studies (Table 1) were only slightly abnormal, and were not thought to indicate pulmonary disease of any severity.

**TABLE 1**

<table>
<thead>
<tr>
<th>Pulmonary Function Tests</th>
<th>Observed</th>
<th>Per cent of Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal Volume</td>
<td>500-575 ml.</td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Minute Volume</td>
<td>8 1/min.</td>
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| Inspiratory Capacity           | 1500     | 88                    |
| Expir. Res. Volume             | 850      | 108                   |
| Vital Capacity                 | 2500     |                       |
| Residual Volume                | 600      |                       |
| Total Lung Capacity            | 2900     |                       |

**Timed Vital Capacity**

| 1st second | 1800 | 75 per cent |
| 2nd second | 2070 | 87 per cent |
| 3rd second | 2200 | 93 per cent |
| Total      | 2400 |            |

Maximum Breathing Capacity 60 L./min. 100 per cent of predicted

CONCL: Essentially normal respiratory function.

FIGURE 2: Chest x-ray films of February 8, 1952 reported normal. FIGURE 3: Chest x-ray film of March 21, 1955 showing early cardiac enlargement.
TABLE 2 — CATHETERIZATION DATA

<p>| | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Right Atrium, mean</td>
<td>15 mm. Hg.</td>
<td></td>
</tr>
<tr>
<td>Right ventricle</td>
<td>82/5-20</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>78/32</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery, mean</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Pulmonary capillary, &quot;wedge&quot;</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Femoral artery</td>
<td>127/80</td>
<td></td>
</tr>
<tr>
<td>Femoral artery, mean</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Cardiac output</td>
<td>2.6 L./min.</td>
<td></td>
</tr>
<tr>
<td>Pulmonary resistance</td>
<td>1800 dyne sec. cm.*</td>
<td></td>
</tr>
</tbody>
</table>

She was given digitalis, but showed no response whatsoever. She did become edema free on a low salt diet and occasional injections of mercurial diuretics. Her clinical status remained stable and she was readmitted for right heart catheterization on January 22, 1959. The physical findings and laboratory data were unchanged. The ECG (Fig. 1) showed a more pronounced right ventricular hypertrophy and strain pattern with the development of "P Pulmonale" P waves. The catheterization results are summarized in Table 2. No evidence of a left to right or right to left shunt was found and the pulmonary capillary "wedge" pressure was normal. Following the right heart catheterization, an open lung biopsy was performed. The patient tolerated the procedure well.

The pathologic report of the lung biopsy is in part as follows: "In the small arteries (Fig. 6 and 7) and in the arterioles (Fig. 8 and 9) there are profound changes with marked luminal narrowing of these vessels due primarily to medial thickness, but with some fibrous intimal proliferation as well. The degree of luminal narrowing is somewhat variable although virtually all of the small arteries and arterioles show an estimated 50 per cent diminution in luminal size. Frequently this narrowing is so marked that small muscular arteries can accommodate only three to ten erythrocytes in their widest diameter. Except for the vascular narrowing and moderate emphysema, no other structural alterations are noted. There is no fibrosis or evidence of either recent or remote inflammation and no pigment laden macrophages are found within the alveoli."

Discussion

This case is similar to many that have been reported in detail in the literature, and there is no need to review the characteristic clinical and laboratory findings, or to comment on the results of the right heart catheterization. It is of interest, however, to point out the evolution of the ECG from normal in 1952, through the development

FIGURE 4

FIGURE 5

FIGURE 4: Chest x-ray film of March 29, 1957 showing further cardiac enlargement with beginning prominence of the pulmonary artery segment.

FIGURE 5: Chest x-ray film of October 13, 1958 showing further cardiac enlargement with congestion of the hilar vessels but with relatively avascular peripheral lung fields.
of early right ventricular strain, to right ventricular hypertrophy, and finally to the
development of the classical "P Pulmonale" P waves of right atrial hypertrophy and
dilatation. The serial chest x-ray films, while less striking, again show the gradual
evolution of the increasing pulmonary vascular congestion with the development
of right ventricular hypertrophy.

It is clear that this case represents acquired rather than congenital pulmonary
hypertension. The possibility that this pulmonary hypertension was secondary to some
other disease process was eliminated by pulmonary function studies and by right heart
catheterization. With the other possibilities excluded, one is left with the diagnosis
of acquired primary pulmonary hypertension. In discussing the etiology or patho-
genesis of this disease, it is important to try to separate the congenital from the
acquired form. This is not often done in the case reports in the literature. There are
probably two reasons for this. The clinical picture is much the same whether the
disease is found in a young infant, who presumably had the disease from birth, or in
a young or middle-aged adult who must have acquired the disease. The pathologic
picture is also rather non-specific and offers no distinguishing features between the
congenital and the acquired form of the disease. The common lesions on pathologic
examination of the lungs are pulmonary atherosclerosis and arteriolosclerosis, which
are likely to be secondary to the hypertension, and hypertrophy of the media of the
small arteries.

Goodale and Thomas14 found medial hypertrophy to be the predominant lesion in
two cases of primary pulmonary hypertension in children seven months and ten years
of age. They concluded that this change represented persistence of the thick walled
fetal pulmonary arterioles. However, they also found medial hypertrophy of a similar
degree in five cases of congenital heart disease, but felt that in this situation, the
medial hypertrophy was a compensatory mechanism in response to the abnormally

FIGURE 6: Photomicrograph of a small artery showing marked intimal proliferation.
FIGURE 7: Photomicrograph of a small artery stained with an elastic tissue stain
showing the internal and external lamina. There is marked intimal proliferation with
a very narrow lumen.

FIGURE 8: Photomicrograph of a pulmonary arteriole showing marked medial
hypertrophy with very little intimal thickening. Note the minute lumen.
FIGURE 9: Photomicrograph of a pulmonary arteriole stained with an elastic tissue
stain showing reduplication of the elastic membrane with some medial hypertrophy
and some proliferation of the intima.
A large amount of blood flowing through the pulmonary vascular tree. They felt that the proliferation and fibrous thickening of the intima found in all varieties of pulmonary hypertension were secondary to the hypertension itself.

The varying degrees of inflammatory reaction that have been described in the pulmonary arterioles of patients with primary and secondary pulmonary hypertension are probably also secondary reactions to the hypertension, as are the small thrombi that have been described in the arterioles.

In the majority of the cases of acquired primary pulmonary hypertension in the literature, as in the present case, medial hypertrophy is a prominent pathologic finding. The hypothesis of persistence of the thick-walled fetal arterioles does not explain the pathologic picture found in these cases. There are reported cases that have been shown to have primary pulmonary hypertension during life who have no pathologic pulmonary vascular changes at post mortem examination. The most satisfactory hypothesis to explain the varied pathologic picture is that proposed by Dresdale in 1951 and reaffirmed in 1954. He suggested that the increased pressure was secondary to increase in the pulmonary vascular resistance caused by increased tone in the pre-capillary arterioles. He produced evidence that at least some of the pulmonary vascular resistance was vasospastic in nature by demonstrating a fall in pulmonary artery pressure with an increase in cardiac output after injection of Priscoline into the pulmonary artery of several patients with primary pulmonary hypertension.

Wood also found a fall in pulmonary artery pressure in five of six patients with primary pulmonary hypertension when he injected 1 mg. of acetylcholine into the pulmonary artery. In fact, he found a greater response to acetylcholine in this condition than in any other type of pulmonary hypertension. He felt that this was good evidence that a significant degree of pulmonary vasoconstriction existed in primary pulmonary hypertension.

The situation may well be analogous to hypertension of the systemic circulation. The primary process may be an arteriolar vasoconstrictive response to some unknown stimuli, with the secondary development of varied pathologic lesions in different patients.

**SUMMARY**

A 42 year-old woman, observed since 1948 for a blood disorder, developed physical signs of pulmonary hypertension. The electrocardiogram changed from normal to right ventricular strain and hypertrophy while heart fluoroscopy showed increasing prominence of the pulmonary artery and right ventricle. Lung function studies were normal. Heart catheterization revealed a pulmonary artery pressure of 78/32 mm. Hg. and a pulmonary capillary pressure of 2 mm. Hg. The total pulmonary vascular resistance was 1800 dynes cm.\(^{-2}\) secs. There was no evidence of intracardiac shunt. Lung biopsy showed marked medial hypertrophy of the arterioles plus modest intimal proliferation.

The cause of pulmonary hypertension in this case is not known, but it is clearly acquired. There is no evidence that the marked medial arterial hypertrophy is a consequence of previous vasospasm although a vasospastic element has been demonstrated in similar cases. Medial arterial hypertrophy occurs in both the congenital and acquired forms of primary pulmonary hypertension and hence is not a helpful differential diagnostic point.

**RESUMEN**

Una mujer de 42 años, observada desde 1948 con motivo de un padecimiento hemático, presentó signos de hipertensión pulmonar. El electrocardiograma cambió de normal a manifestaciones de esfuerzo ventricular derecho e hipertrofía en tanto que la fluoroscopia del corazón mostró prominencia creciente de la arteria pulmonar y del ventrículo derecho.

Los estudios de la función pulmonar dieron datos normales. La cateterización del corazón reveló presión de la arteria pulmonar de 78/32 mm. Hg. y la presión pulmonar capilar fue de 2 mm. Hg.

La resistencia vascular pulmonar total fue de 1800 dynes cm.\(^{-2}\) segs. No hubo evidencia de intercomunicación de cavidades cardiacas.

La biopsia de pulmón señaló hipertrofia de la capa media de las arteriolas y ademas moderada proliferación de la íntima.

La causa de la hipertensión pulmonar en este caso no se conoce pero evidentemente es adquirida. No hay evidencia de que la hipertrofia de la media arterial sea consecuencia de espasmo previo aunque un elemento vasoespástico se ha demostrado en casos similares.

La hipertrofia de la capa media arterial acontece tanto en las formas mas congénitas como en las adquiridas de la hipertensión pulmonar primaria y por tanto, no es una ayuda para el diagnóstico diferencial en este punto.

**RESUMÉ**

Une femme âgée de 42 ans, suivie depuis 1948 pour des troubles hématiques, a présen- té des signes physiques d’hypertension pulmonaire. L’électrocardiogramme se modifia : deux ans de cette observation une fatigue ventriculaire droite et une hypertrophie tandis que la radioscopie cardiaque montrait une augmentation de la saillie de l’artère
Belastung hypertrophielement montra cm.': pulmonaire de 17 cm. 

La cause de l'hypertension pulmonaire dans ce cas n'a été décelée mais il s'agit certainement d'une affection acquise. Il n'y a aucune preuve que la nette hypertrophie de la média de l'artériole soit une conséquence du vasospasme antérieur, bien qu'un élément de spasme vasculaire ait été mis en évidence dans des cas semblables. Une hypertrophie de la média de l'artériole peut se voir aussi bien dans les formes congenitales que dans les formes acquises d'hypertension pulmonaire primaire et ne permet donc pas d'aler le diagnostic différentiel.

ZUSAMMENFASSUNG


Die Ursache für den pulmonalen Hochdruck dieses Falles ist nicht bekannt, sie ist aber doch bestimmt eine erworbene. Es findet sich kein Anhalt dafür, daß die ausgeprägte Hypertrophie der Media der Arteriolen die Folge eines vorausgegangen Gefäßspasmus darstellt, obwohl ein vasospastisches Element in analogen Fällen nachgewiesen wurde. Media-Hypertrophie der Arteriolen tritt wohl in angeborenen wie in erworbener primären pulmonalen Hypertensionfällen auf und läßt sich daher nicht bei differential-diagnosticschen Erwägungen zu Hilfe nehmen.

REFERENCES