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Primary Pulmonary Hypertension —
Disease or Symptom?

A Retrospective Reclassification of 33 Cases

D.S. DasGupta, MBBS* and Ellet H. Drake, MD**

The hypertension which follows an intrinsic increase in pulmonary vascular resistance may be easily diagnosed by utilizing current catheterization and radiologic techniques. The real challenge is establishing a rational etiology in a given case before final pathological examination. Data from 33 proven cases are presented in an attempt to show that most of the proposed etiologic concepts may be represented in a large clinical series. Congenital and familial factors, multiple pulmonary embolization with resulting vasospastic sequela, arteritis, and degenerative states, were encountered, together with such specific clinical entities as scleroderma and systemic lupus erythematosus. Because the term “Primary Pulmonary Hypertension” implies only the exclusion of volume overloaded states, it requires further etiologic clarification.

By applying the principles of hydraulics to the human blood circulation, a student of cardiac physiology defines the determinants of pulmonary artery pressure as being proportional to 1) the volume inherent in the circuit (cardiac output) and 2) the resistance offered by the caliber and tone of the pulmonary vasculature. Pulmonary hypertension secondary to a volume overload is a well recognized and often remediable state. Its contributory causes are described in most modern text books. They range from congenital lesions, in the nature of shunts at various levels, to acquired valvular or structural defects leading to stagnation of blood in the pulmonary system.

Pulmonary hypertension resulting from an intrinsic increase in pulmonary vascular resistance remains an enigma, masquerading under such nomenclature as “primary” or “solitary” pulmonary hypertension. In the Cardiac Physiology Laboratory at Henry Ford Hospital, we reviewed the records of the past 12 years of 33 patients with established primary pulmonary hypertension (PPH). To our knowledge this is the largest collection reported so far from this country.

From the literature, we found that pioneer observers, some three hundred years ago, had designated PPH as being the counterpart of hypertension in the

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systemic circuit. They attributed the phenomenon to hypertensive and atheromatous changes in the pulmonary vasculature. In the eighteenth century Vieussens is generally regarded as the first person to have described sclerotic plaques in the pulmonary arteries at necropsy. A comprehensive study of the history of this disorder was presented in 1964 by Shane et al.1 Earlier this century, Posselt2 pointed out the various age and sex predilections of this entity. Detailed anatomical and pathological correlative studies were established by Ljungdahl3 and Brenner4 a few years later. Within the next two or three decades, further details of the gross and microscopic pathology involved were published.5-7

Controversy continued, however, over its clinical definition. In the absence of adequate facilities for detailed physiologic studies, differentiation of primary from secondary pulmonary hypertension very often was settled only at necropsy. With the advent of cardiac catheterization, early diagnosis and attempts at therapy have become possible.

A word of caution might be in order here about the advisability of pulmonary angiography in the presence of long-standing and severe pulmonary hypertension. Several authors have noted, and our experience has shown, that there is extreme, sometimes fatal, risk in the volume overload concurrent to the introduction of hyperosmolar dyes and the marked drop in arterial pH in such patients, with or without arterial oxygen unsaturation. Recognition of the problem and better laboratory facilities, however, have reduced the risk in recent years.

Findings

Twenty-one of the 33 patients included in our study are women. Seventeen patients are presently alive. Detailed autopsies were made of 13 of the 16 patients who died. Two of the three other patients, on whom autopsy procedures were refused, had antemortem biopsies which substantiated the diagnosis of PPH.

In the absence of an autopsy, the criteria we used to determine the diagnosis were: 1) cardiac catheterization studies demonstrating in every instance a pulmonary artery pressure of more than 60 mm of mercury systolic, with normal wedge or left arterial pressures; 2) demonstration by cardiac catheterization of the absence of any shunts, valvular disease, or any organic cardiac abnormalities; 3) absence of any significant lung disease demonstrated by x-ray, spirometry, or where indicated, by lung biopsy.

Our assessment of the clinical signs and symptoms of PPH is essentially the same as has been reported by others.8-10 The disease generally manifests itself within the third to fifth decade of a patient's life, with obvious preponderance among women. Dyspnea, effort intolerance, syncopal episodes, marked fatigue, and, occasionally, chest pain with palpituation were the usual symptoms among our patients. Though occasionally indistinguishable from coronary distress, chest pain conformed with the type of pain associated with pulmonary hypertension as described by Viar and Harrison.11 Cough and cyanosis, noted in some, were not invariable features. Hemodynamic systolic as well as diastolic pulmonary murmurs were present in most instances.

Marked right ventricular hypertrophy with a diastolic overload pattern, with or without right bundle branch block, was universal. In more than 95% of our cases the typical features of pulmonary hypertension were noted by the radiologist in results of chest x-ray, fluoroscopy, and
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Pulmonary angiography studies. Radiologic results showed prominent pulmonary artery trunks and central branches rapidly tapering to a point, with the outer third of the lung fields virtually free of vascular shadows.

Symptoms and signs of progressive congestive heart failure, mostly right sided, were present in all patients. Previously described polycythemia and false positive serologies were noted in approximately 20% of our patients. Average time of survival after onset of symptoms in the 16 patients who died was 1.8 years. However, some patients in our series have now been followed for as long as 6 years since the initial diagnosis was made.

Discussion

Paul Wood and others have established the physiologic criteria for diagnosis of this disease as high pulmonary artery pressure with normal pulmonary capillary wedge pressures, in the absence of any other heart or lung pathology. They held that this was a distinct pathological entity, its features confined exclusively to the pulmonary vasculature. Various authors have reported cases with different etiological factors, which they offered as causes for this elusive disease.

The purpose of our study was to determine which of these divergent claims applied to our series of patients. Table 1 compares our results with the literature.

The diversity of the causes listed prompted us to review our series of patients from an etiological approach, as follows:

1. Familial or Congenital

In 1960 Fleming had reported the existence of this disorder in a mother and her daughter. A handful of reports followed, including a demonstration of the disease established in a pair of twins. Our series included a man whose father had died of PPH. The pathologist’s autopsy report of the father indicated that the disease was an end result of multiple pulmonary emboli. The necropsy report on the son fits the description of degenerative arteriopathy offered by James.

In the same vein, others have commented on a possible congenital origin for this disease. Their contention is that, as resistance in the pulmonary circuit is necessarily very high in utero, perhaps PPH results from a failure of this system to become normal after birth.

### Table 1

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<tr>
<th>Comparison of Henry Ford Hospital Experience with Literature</th>
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<tr>
<td>1) Familial or congenital[^13,14,15]</td>
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<tr>
<td>2) Multiple pulmonary emboli[^16,17,18]</td>
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<tr>
<td>a) Obstruction and recanalization</td>
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<td>b) Intrinsic vascular and vasospastic changes as a response to repeated emboli.</td>
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<td>3) Changes in pulmonary vascular tree[^19,20,21,22]</td>
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<tr>
<td>a) Pulmonary vascular arteriosclerosis</td>
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<td>b) Congenital hypoplasia of the media of the arterioles with secondary intimal thickening</td>
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<tr>
<td>c) Pulmonary vascular arteritis e.g., Polyarteritis nodosa, lupus, etc.</td>
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<tr>
<td>d) Degenerative arteriopathy</td>
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<td>4) Associated with scleroderma[^23,24,25,26]</td>
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<tr>
<td>a) Established scleroderma</td>
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<td>b) C.R.S.T. syndrome.</td>
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<td>5) Broncho pulmonary communications[^27]</td>
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We found three individual instances in our patients in which a congenital etiology might be considered. The first was a 23-year-old woman with multiple stenotic lesions in the small peripheral branches of the pulmonary tree. The second was a 35-year-old woman, with hypoplastic aortic and pulmonary arteries; the third was a 15-year-old boy whose age in itself would indicate a congenital possibility.

2. Multiple Pulmonary Emboli

In this group, we included 10 patients in whom we found evidence for multiple pulmonary emboli. The diagnoses in six instances were made at autopsy. In the other four there were convincing clinical episodes of pulmonary embolism corroborated by lung scans and pulmonary angiography. In five of these ten patients a possible source for the emboli was in the lower extremities. In three of the six patients on whom autopsies were done, the pathologist felt that the extent of compromise to the pulmonary circulation, secondary to the aberration of normal architecture by organized and recanalized clots, was sufficient to explain the pulmonary hypertension. Though there was ample evidence of multiple organizing thrombi in the pulmonary circuit in the other three, sclerotic changes in the pulmonary vessels were regarded to be the primary causative factors. Pulmonary emboli, in such instances, may be merely co-existent, or may serve as an inciting factor responsible for triggering the changes in the pulmonary vessels. Two more of our patients were noted to have clear vessels on initial study by pulmonary angiography. On subsequent angiography, with progress of the disease, they were noted to have obstructed vessels. This supports the hypothesis that the thrombi noted in the disease may be a result of, rather than a cause of, PPH. The pathological changes in the diseased intima, by exposing the circulating constituents of blood to a rough surface, might serve as regional foci for thrombus formation. An interesting feature, noted at autopsy in one of our patients, was the presence of infarcts in the spleen, liver and kidneys. This, coupled with the fact that some 15% of our patients had very low platelet counts (in some as low as 70,000) raises the possibility of diffuse intravascular coagulopathy associated with this disorder. Hematological surveys in our patients were not complete enough to pursue this possibility.

3. Changes in Pulmonary Vascular Tree

In the third group were 13 patients whom we divided into four separate categories, as shown. Long-standing pulmonary hypertension results in irreversible sclerotic changes in the pulmonary vasculature. Larger arteries have obvious atheromatous plaques, while smaller vessels show endothelial proliferation, intimal thickening and medial hypertrophy often with cystic medial necrosis. Some investigators have contended that vascular changes in this group come first, and result later in pulmonary hypertension. In the literature, arteritis has also been invoked as a cause for such vascular changes. We found one patient in this group with typical changes of polyarteritis and fibrinoid necrosis at autopsy, consistent with Zeek's description of the arteritides. Two other patients had established diagnoses of systemic lupus erythematosus, with positive LE preps, a "butterfly" rash and "wire looping" in the kidney. In one of them, the diagnosis of lupus was made two years after the discovery of her pulmonary hypertension.
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Severe intimal thickening with almost total occlusion of smaller vessels was found in one patient, with patchy medial necrosis. It has been postulated that intimal proliferation in such patients may be in response to a congenitally weak media. However, the patchy degenerative process found in the media in this instance would be hard to distinguish from that found in generally arteriosclerotic vessels.

A systemic degenerative arteriopathy present in vessels in other parts of the body was found in one patient, perhaps exemplifying the stand taken by James, who demonstrated similar changes in the sinus node artery of a group of patients with PPH and claimed that their syncopal episodes could be related to this change. The rest of the patients in this group we felt had this arteriopathic disorder with predominantly sclerotic changes, and without any evidence of organizing thrombi.

4. Associated with Scleroderma
We found six patients with a history of Raynaud’s phenomenon, three of them with established scleroderma, including sclerodactyly typical skin changes and positive ANF. One patient had extensive interstitial calcinosis, and yet another had associated telangiectasia. The last patient in this group developed a positive ANF one year after the initial diagnosis of PPH was made. This was associated with thickening of the peridontal membranes, which the oral surgeons claimed was a feature of scleroderma. The calcinois, Raynaud’s, sclerodactyly and telangiectasia syndrome (CRST) with PPH first described by Winterbauer has impressed observers sufficiently to warrant the suggestion that Raynaud’s phenomenon associated with PPH should be considered as evidence of scleroderma or an allied collagen disorder.

5. Broncho Pulmonary Communications
We found no evidence of broncho pulmonary arterial communications in our group of 33 patients. Plexiform vessels were noted occasionally at autopsy but were felt to be a result of recanalizing after occlusion of the vessels by thrombi.

Conclusion
The possibilities inherent in the diagnosis of primary pulmonary hypertension cover such a wide spectrum that even if the patient meets all the criteria for the disease, the clinician should, in the pursuit of professional excellence, not just bask in the definition of the syndrome, but must actively exclude all underlying disease entities, which share in common the clinical features of primary pulmonary hypertension (PPH). If one makes an exhaustive analysis of the various clinical associations of this entity, an honest student would be forced to conclude that perhaps PPH is not so primary after all — but should be considered as a syndrome manifestly present in a wide variety of complex vascular diseases.

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