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## PULMONARY HEART DISEASE: RELATION OF PULMONARY HYPERTENSION TO ABNORMAL LUNG STRUCTURE AND FUNCTION\*

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FOR many years cor pulmonale was useful as a diagnostic entity because it emphasized the unifying role of pulmonary hypertension as a bridge between respiratory disease and its circulatory complications. This was especially important at a time when our knowledge of these disease processes was limited. With increased understanding, however, the emphasis has shifted. Cor pulmonale no longer can be regarded as a homogeneous disorder. Pulmonary hypertension now is known to stem from a variety of sources. Its clinical course is variable. Indeed, a spectrum of abnormalities can be identified whose management and prognosis vary with the specific cause. This discussion will emphasize the heterogeneous clinical behavior of pulmonary heart disease. Within the diversity apparent at the bedside, I shall characterize several coherent clinical patterns on the basis of our present understanding of the relation between abnormal structure and function of the lung and disturbed pulmonary hemodynamics.

Cor pulmonale stems directly from pulmonary hypertension. Hence, I shall begin with a consideration of the factors that determine blood pressure in the normal pulmonary circulation. Then I shall examine the mechanisms by which lung disease causes pulmonary hypertension, using three common clinical entities as model conditions: chronic bronchitis, diffuse interstitial lung disease, and pulmonary thromboembolic disease. Finally, the consequences of pulmonary hypertension in these diseases will be discussed—first, with respect to the pulmonary vasculature itself, and second, with respect to the behavior of the right ventricle. I shall close

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\*Presented as part of a *Symposium on Selected Aspects of Pulmonary Disease* held by the Section on Medicine of the New York Academy of Medicine March 3, 1976.

This research was supported in part by Public Health Service Research Grants HL 17813 and 07018 from the National Heart and Lung Institute, Bethesda, Md. and by a Grant-in-Aid from the New York Heart Association, New York, N.Y.

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with a few general remarks about the management of pulmonary heart disease.

#### DEFINITIONS

Cor pulmonale, or pulmonary heart disease, is an abnormality of structure or function of the right ventricle resulting from disturbed structure or function of the respiratory apparatus. Pulmonary arterial hypertension due to increased resistance to pulmonary blood flow is the underlying process which ultimately compromises right heart function. Two points, however, merit emphasis. First, the lung parenchyma or airways need not be involved by the disease process: disturbances of the nervous system, respiratory muscles, chest wall, and the pulmonary arterial tree itself also can be responsible. Second, many forms of heart disease, such as mitral stenosis or congenital malformations with left-to-right intracardiac shunts, also can produce an increase in resistance to pulmonary blood flow which may embarrass the right ventricle. These disease states, however, are not included under the heading of pulmonary heart disease.

*Pulmonary hypertension.* The upper limits of normal pulmonary arterial pressure in the adult are 27 mm. Hg systolic, 10 mm. diastolic, and 15 mm. mean when the subject is at rest. With moderate supine leg exercise, pressures do not normally rise above 30 mm. systolic, 14 mm. diastolic, and 20 mm. mean. Levels of pressure above these values indicate the presence of pulmonary hypertension.

#### THE NORMAL PULMONARY CIRCULATION

What factors are responsible for generating these pressures in the normal pulmonary circulation? In contrast to all the other regional beds in the body this vascular tree is unique in that it competes with no other organ for its share of the cardiac output. Rather, it must accommodate the entire stroke volume of the right ventricle. This requirement is met because resistance arteries are not present in the lung. The most heavily muscled vessel in the pulmonary circulation is some  $100\mu$  to  $300\mu$  in size. The media of such vessels is only 2 to 3% of their cross-sectional diameter. Further, these vessels have negligible autonomic innervation. As a consequence of the sparse smooth-muscle elements, scant nerve supply, and absence of valves, the bed is so distensible that intravascular pressures are quite low.

The determinants of pulmonary arterial pressure can be summarized rapidly by referring to Figure 1, in which a schematic representation of

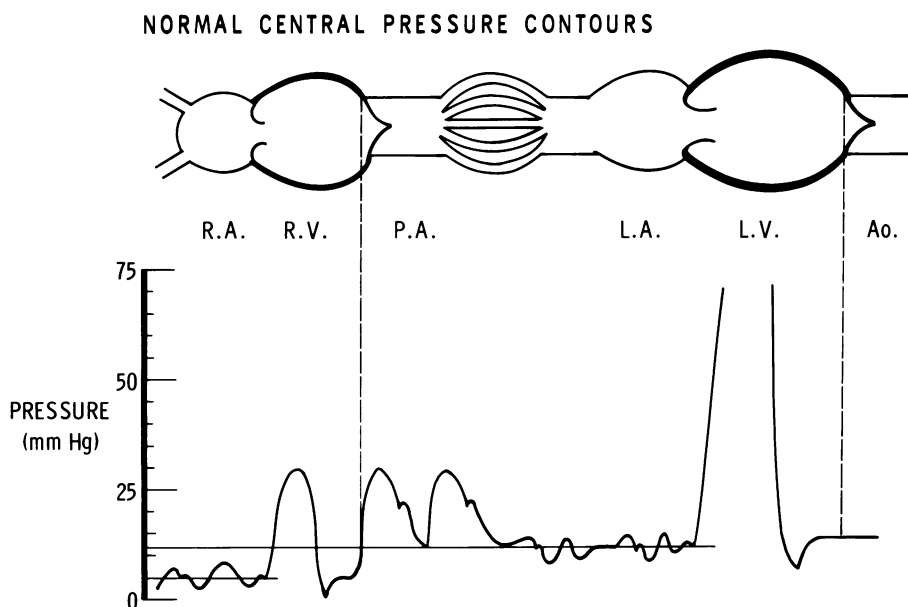


Fig. 1. Schematic representation of the central circulation. Above are the various vascular compartments, below are characteristic pressure contours recorded at each site. At the end of diastole the aortic and pulmonic valves are closed, the mitral valve is open. The entire bed between the closed semilunar valves behaves like a common pressure chamber. End-diastolic pressure lies at the same level in all segments of the chamber. End-diastolic pressure in the left ventricle determines pulmonary arterial diastolic pressure.

the central circulation and its characteristic blood pressure contours are depicted. Let us consider, for the moment, that instant in the heart cycle at the end of diastole just before the onset of left ventricular contraction. The mitral valve is open, while the aortic and pulmonary semilunar valves are closed. In the absence of valves, nerves, and significant smooth muscle elements, the entire bed between the aortic and pulmonic valves is a common pressure chamber at this instant. Hence, pressure at all points—left ventricular, left atrial, pulmonary venous, capillary, and arterial—is the same at end diastole.<sup>1</sup> As a corollary, in the absence of pressure gradients there is no pulmonary blood flow at that instant.<sup>2-4</sup> The sole determinant of pulmonary arterial diastolic pressure is the left ventricular diastolic pressure. Neither mean pulmonary blood flow nor the level of the stroke volume have an appreciable effect on the pulmonary arterial diastolic pressure.<sup>5</sup>

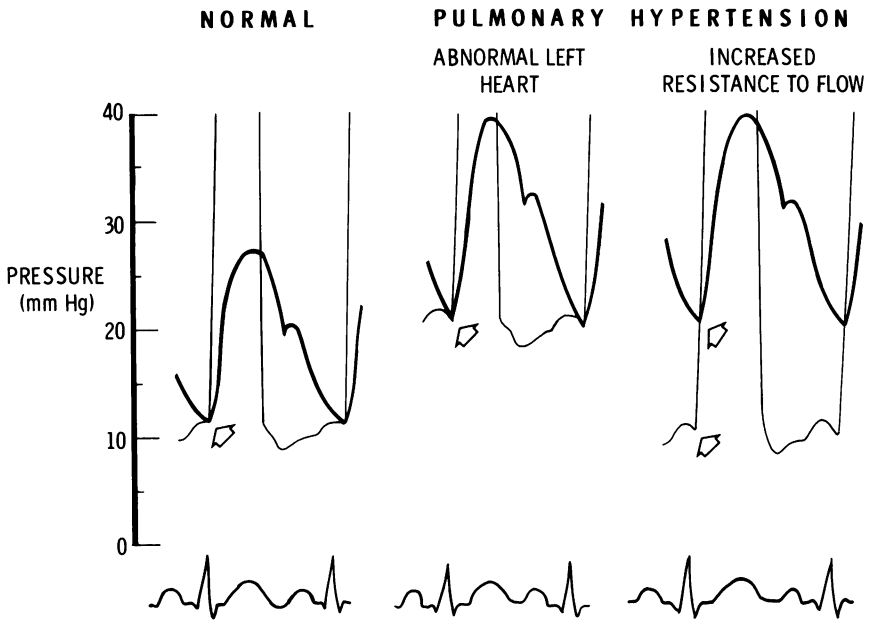


Fig. 2. Schematic representation of the relation between left ventricular (thin line) and pulmonary arterial (thick line) blood pressure contours. Peak left ventricular pressure lies off the diagram at this amplification. Under normal circumstances (left) end-diastolic pressure is identical at both sites (single arrow) and lies at the upper limit of normal valves. In the presence of abnormal left heart function (center panel) left ventricular end-diastolic pressure is elevated above normal levels, and pulmonary arterial diastolic pressure rises passively to the same extent (single arrow). When pulmonary hypertension stems from abnormal structure or function of the pulmonary vessels (right) pressure in the pulmonary artery exceeds left ventricular pressure at the end of the diastole (two arrows). The vertical distance between the arrows (pulmonary diastolic gradient) reflects the level of resistance to pulmonary blood flow. Reproduced by permission from Enson, Y., Thomas, H.M., III, Bosken, C.H., et al.: Pulmonary hypertension in interstitial lung disease: Relation of vascular resistance to abnormal lung structure. *Trans. Assoc. Am. Phys.* 88: 248, 1975.

With ventricular systole the mitral valve closes, the semilunar valves open, and the right ventricular stroke volume enters the pulmonary artery. Volume distention of the elastic pulmonary artery generates the systolic pressure, which depends on the magnitude of the stroke volume, the level of the diastolic pressure, and the compliance characteristics of the central elastic vessels.<sup>6</sup> Pulmonary blood flow begins with injection of the right ventricular stroke volume and proceeds through diastole until the volume in the bed falls to a level which generates a blood pressure equal to that in the left ventricle. Flow then ceases and the cycle is complete. Pressure in

the systemic circulation is generated by the level of blood flow through thick-walled, relatively rigid vessels; pressure in the pulmonary circulation is generated by volume distention of thin-walled, highly compliant vessels.

#### CHARACTERIZATION OF PULMONARY HYPERTENSION

In considering the pulmonary circulation in a wide variety of diseases these remarks will provide a framework for assessing the nature of pulmonary hypertension. In Figure 2 pulmonary arterial (heavy line) and left ventricular (thin line) blood pressures are depicted under three conditions: 1) normal circumstances (left), 2) in the presence of abnormal left ventricular function, (center), and 3) in the presence of abnormal structure or function of the pulmonary vessels (right). In the first two instances blood pressure at both sites lies at the same level at the end of diastole (single arrow). The pulmonary hypertension shown in the center panel is a passive consequence of the high left ventricular end-diastolic pressure. The vessel walls remain thin and distensible under these conditions and do not impose an appreciable increase in resistance to blood flow.

In contrast, the panel on the right illustrates that when pulmonary hypertension stems from abnormal structure or function of the pulmonary vessels pressure in the pulmonary artery will exceed the left ventricular pressure at the end of diastole, as indicated by the two arrows. Disease has rendered the pulmonary vessels sufficiently rigid that they cause a detectible increase in resistance to blood flow. The vertical distance between the two arrows, the end-diastolic pressure gradient between the pulmonary artery and the left ventricle, reflects the level of pulmonary vascular resistance.<sup>1</sup> Hereafter I shall use the term pulmonary diastolic pressure gradient for this purpose.

#### EFFECT OF LUNG DISEASE ON PULMONARY ARTERY PRESSURE

Let us now examine the mechanisms by which abnormalities of the respiratory apparatus generate pulmonary arterial hypertension. First, consider the patient with chronic bronchitis: inflammatory changes in the airways and retained secretions markedly reduce alveolar ventilation in a large portion of the lung. The parenchyma, however, is usually not involved by disease and, hence, perfusion of the large, poorly ventilated space is maintained. The most heavily muscled portion of the pulmonary arterial tree, only some  $100\mu$  in diameter, is in intimate contact with surrounding alveolar spaces. Alveolar gases equilibrate by diffusion

## PULMONARY HYPERTENSION IN CHRONIC BRONCHITIS

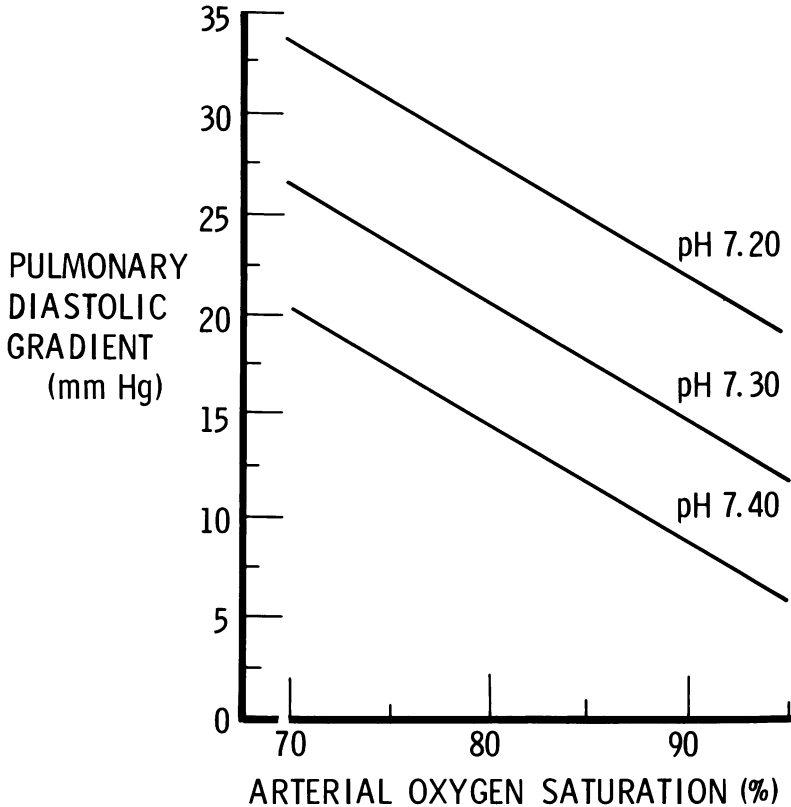


Fig. 3. Graphic representation of the relation among the pulmonary diastolic pressure gradient, arterial blood oxyhemoglobin saturation (reflecting alveolar oxygen tension, and blood pH in 45 patients with chronic bronchitis.<sup>5</sup> Pulmonary arterial wedge pressure is fixed at 10mm. Hg in this consideration.

across the walls of these precapillary vessels.<sup>7-9</sup> When the perivascular alveolar oxygen tension is reduced or the pH of the perfusing blood falls as a consequence of hypoventilation these vessels vasoconstrict,<sup>10-15</sup> increase resistance to blood flow, generate a diastolic pressure gradient, and cause pulmonary hypertension.

The determinants of the diastolic pressure gradient in a large population of patients with chronic bronchitis are summarized in Figure 3.<sup>5</sup> The level

of the pressure gradient is indicated on the vertical axis, while arterial blood oxygen saturation—used here as an index of the alveolar oxygen tension—appears on the horizontal axis. Isopleths of blood  $pH$ , reflecting the level of hypercapnic acidosis, are included. As saturation (i.e., alveolar oxygen tension) falls, or as acidemia becomes more severe, the level of the gradient rises. Alveolar oxygen tension and blood  $pH$  are interacting stimuli to vasoconstriction which determine the level of pulmonary arterial pressure in chronic bronchitis; the level of one either augments or attenuates the effect of the other. The intimate mechanism of this vasoconstrictive response is not yet clearly defined. It would appear that the immediate response to hypoxia results from the release of vasoactive substances from perivascular mast cells.<sup>16</sup> The response to sustained hypoxia may result from potassium fluxes across the smooth-muscle membrane caused directly by hypoxia.<sup>17</sup> Bergofsky recently has reviewed the current status of this problem in detail.<sup>18</sup>

The effect of this vasomotion is to decrease perfusion of poorly ventilated alveoli and to increase the perfusion of well-ventilated alveoli so that gas exchange may be maintained as efficiently as possible in the face of a disturbed distribution of ventilation. The reversibility of this type of pulmonary hypertension must be emphasized. With correction of hypoxia and acidemia by appropriate management, pulmonary arterial pressure returns toward normal levels.<sup>19</sup>

Let us turn, now, to the origins of pulmonary hypertension in patients with diffuse, interstitial lung disease. In contrast to the situation in chronic bronchitis, the pathologic process is limited here to the lung parenchyma. Chronic inflammatory changes and, ultimately, fibrosis of the interstitium have two major consequences: 1) lung volume—reflected by the vital capacity—is reduced and 2) the parenchymal disease gradually compresses and obliterates the small pulmonary vessels.

Figure 4 illustrates the consequences of this encroachment on the bed. On the vertical axis the pulmonary blood volume is plotted as a percentage of its main determinant, the total volume of circulating blood. Vital capacity (expressed as a percentage of predicted levels) is on the horizontal axis. When vital capacity lies at normal levels so does the pulmonary blood volume (some 10% of the total blood volume). As parenchymal disease encroaches progressively on the distal air spaces, the vital capacity falls; simultaneous impingement of parenchymal disease on the small pulmonary vessels causes the pulmonary blood volume to fall

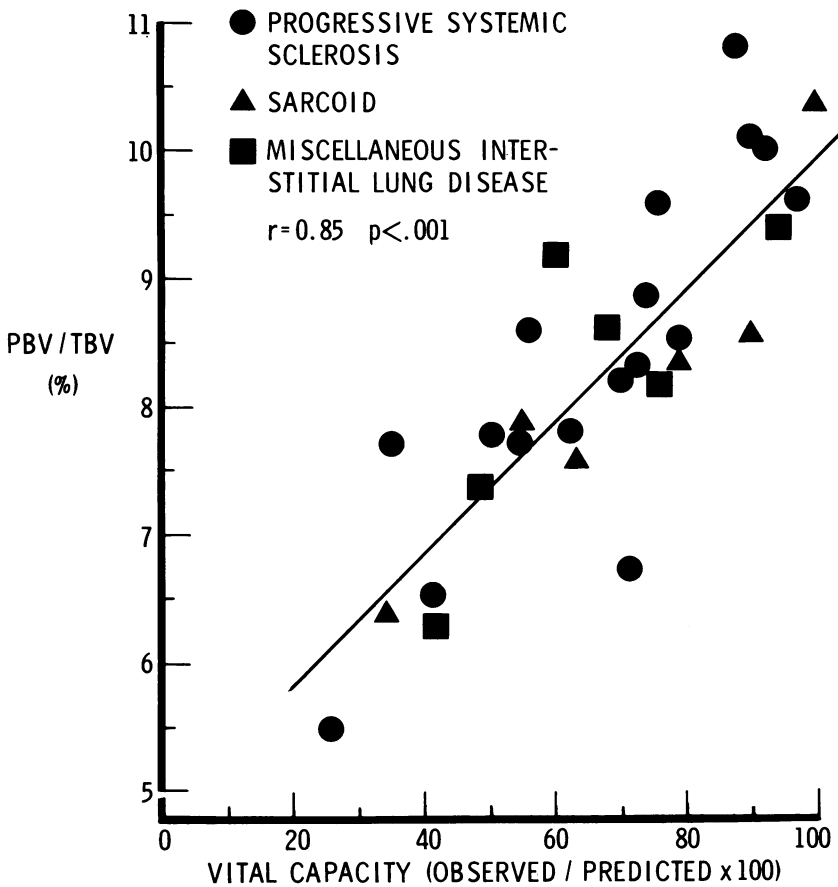


Fig. 4. Graphic representation of the relation between the ratio of pulmonary to total circulating blood volume (PBV/TBV) and vital capacity in 29 patients with diffuse interstitial lung disease. Reproduced by permission from Enson, Y., Thomas, H. M., III, Bosken, C. H., et al.: Pulmonary hypertension in interstitial lung disease: Relation of vascular resistance to abnormal lung structure. *Trans. Assoc. Am. Phys.* 88:248, 1975.

linearly with the decrease in vital capacity. The pulmonary diastolic pressure gradient rises hyperbolically as pulmonary blood volume decreases. Compression and obliteration of the small pulmonary vessels by interstitial disease causes an increased resistance to pulmonary blood flow.<sup>20</sup>

The parallel deterioration of pulmonary hemodynamics and lung mechanics is emphasized in Figure 5, where the diastolic pressure gradient is again on the vertical axis and vital capacity on the horizontal axis. The gradient increases hyperbolically as vital capacity falls. When the vital



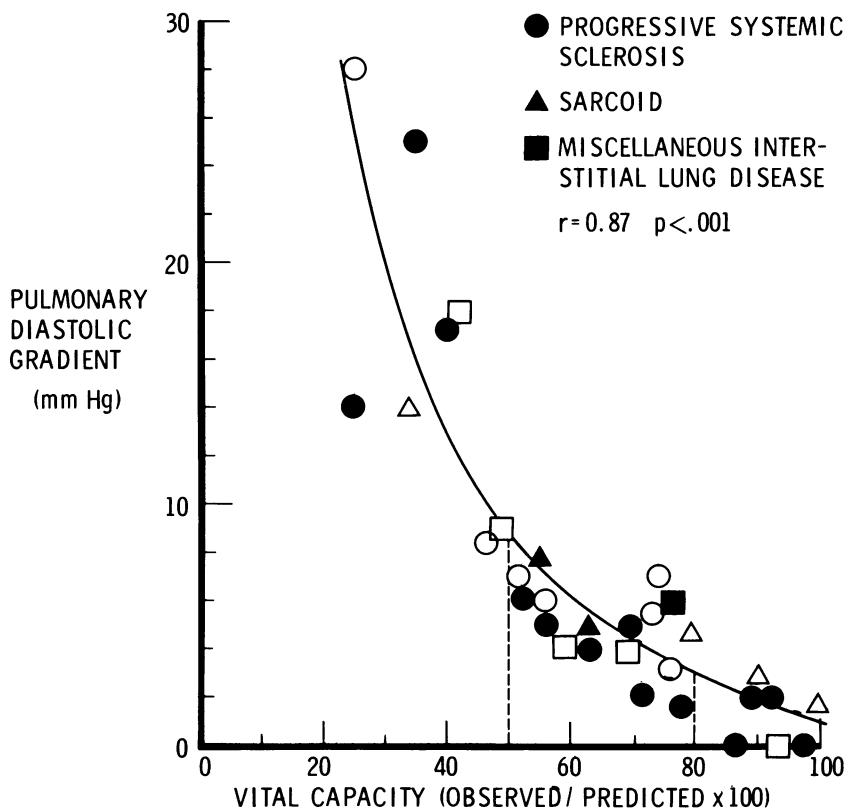


Fig. 5. Graphic relation between the pulmonary diastolic pressure gradient and the vital capacity in 32 patients with diffuse interstitial lung disease. Open symbols indicate patients who underwent open lung biopsy. Reproduced by permission from Enson, Y., Thomas, H.M., III, Bosken, C.H. et al.: Pulmonary hypertension in interstitial lung disease: Relation of vascular resistance to abnormal lung structure. *Trans. Assoc. Am. Phys.* 88: 248, 1975.

capacity is greater than 80% pulmonary hemodynamics are normal. When vital capacity lies between 50% and 80%, vascular resistance is increased, but resting pulmonary artery pressure lies at the upper limits of normal. With exercise, however, patients in this group develop pulmonary hypertension. When vital capacity is less than 50%, pulmonary hypertension is present at rest. There is no evidence that vasoconstriction plays a role in the development of pulmonary hypertension in these patients.<sup>20</sup>

The reversibility of pulmonary hypertension in these patients is problematic. When the vital capacity is greater than 50% of its predicted

## PULMONARY HYPERTENSION IN ACUTE EMBOLIC DISEASE

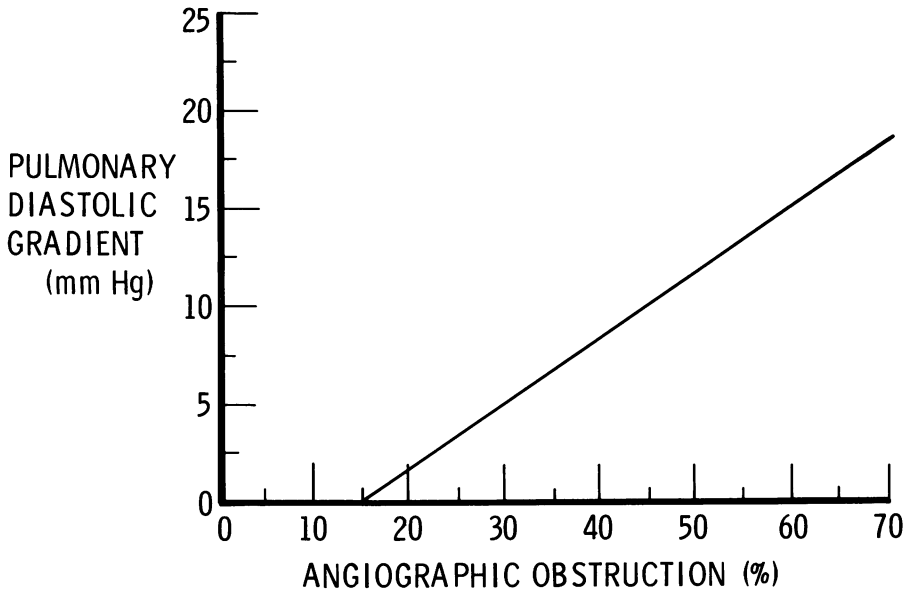


Fig. 6. Graphic representation of the relation between the pulmonary diastolic pressure gradient and the percentage of the pulmonary arterial tree obstructed by emboli as assessed by angiographic examination. Derived from data of McIntyre and Sasahara.<sup>21,22</sup>

value, chronic inflammatory changes are present in the alveolar septa and interstitium. Hence, the use of anti-inflammatory agents in this group may prevent the development of pulmonary hypertension. In contrast, when the vital capacity is lower than 50%, i.e., when pulmonary hypertension is present at rest, interstitial fibrosis dominates the picture.<sup>20</sup> It is not likely that fibrosis will respond to anti-inflammatory agents. We cannot expect, then, that established pulmonary hypertension will improve with treatment.

The origins of pulmonary hypertension in patients with pulmonary thromboemboli involve mechanisms similar to those present in both preceding conditions. For simplicity we shall consider only those patients who experience embolization of the lung in the absence of antecedent cardiopulmonary disease. Figure 6 illustrates the relation in such subjects between the diastolic pressure gradient (vertical axis) and the percentage of the pulmonary arterial tree obstructed by emboli as assessed by angio-

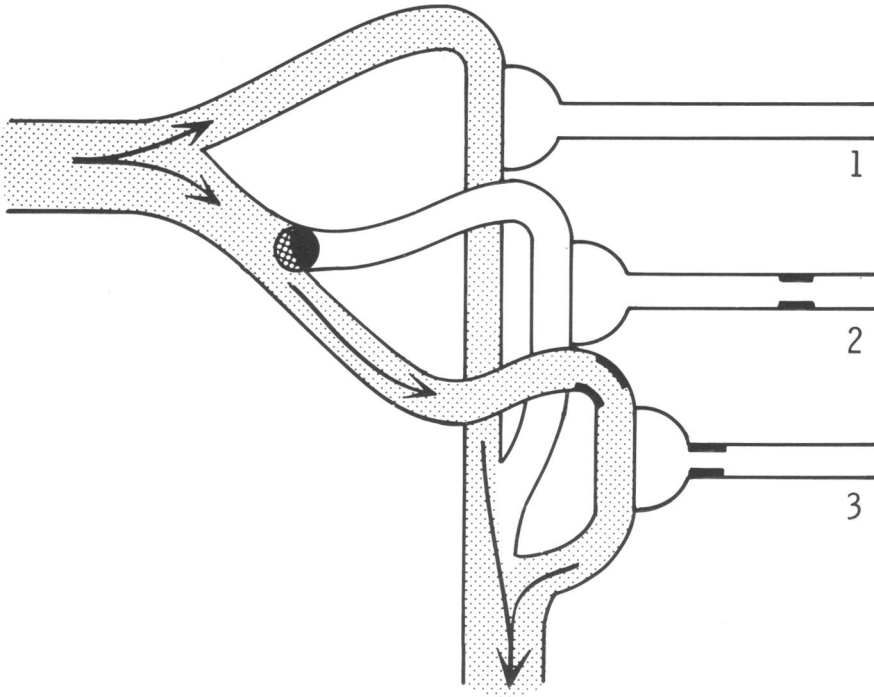


Fig. 7. Schematic representation of the effects of embolization of the lung. A clot (dark circle) is shown at a vessel bifurcation completely obstructing blood flow (shaded area) to one branch and only partially occluding the other. The hatched area indicates fibrin and platelets aggregated on the free surface of the clot which is bathed by flowing blood. Vasoactive substances liberated by platelet degranulation are carried to precapillary vessels downstream of the clot.

graphic techniques (horizontal axis). It is apparent that as the obstructed portion of the bed increases, pressure rises linearly.<sup>21,22</sup> However, closer examination of the data indicates that the degree of mechanical obstruction cannot be the sole determinant of the level of pressure.

Recall that a significant portion of the normal lung is underperfused as a result of gravitational forces. Considering the low level of blood pressure in the pulmonary circulation and the height of the apices of the lungs above the atrial level in the erect position, it is obvious why blood flow is least in the apical region of the lung and greatest in its most dependent portions.<sup>23</sup> Pulmonary arterial pressure does not rise, therefore, after pneumonectomy if the remaining lung is normal; recruitment of previously underperfused vessels in the remaining lung occurs, and the bed is distensible enough to

accommodate the entire output of the right ventricle without an increase in blood pressure. Indeed, in the experimental animal it is necessary to remove some 60% to 70% of the arterial tree before blood pressure rises.

The data in Figure 6, however, indicate that quite a substantial rise in pressure has occurred when 50% of the arterial tree is occluded by emboli. Therefore, nonoccluded vessels also must participate in this process to account for the levels of pressure encountered. Current ideas about the response to embolization of the lung are summarized in Figure 7. Emboli lodge at sites of narrowing of the pulmonary vessels. This occurs at vessel bifurcations, so that an embolus usually completely obstructs one branch and only partially occludes the other. Fibrin and platelets aggregate on the free surface of the clot which is accessible to flowing blood. The platelets interact with thrombin in the blood bathing this free surface, degranulate, and release vasoactive substances into the bloodstream.<sup>24</sup> Although the precise nature of these substances has not yet been characterized, some evidence indicates that serotonin may play a role.<sup>25-28</sup> The downstream precapillary vessels respond to these substances by vasoconstricting and thus augment the effect of mechanical obstruction on pulmonary arterial pressure. In thromboembolic disease, then, pulmonary hypertension stems from a combination of mechanical curtailment of the bed and vasomotion.

How reversible is this type of pulmonary hypertension? Organization of the fibrin mesh, clot retraction, and fibrinolysis reverse both the vasomotor and mechanical contributions to pulmonary hypertension. Only a small number of patients, certainly less than 5%, continue to have repeated and often asymptomatic showers of emboli and pass into a chronic phase of sustained pulmonary hypertension.<sup>29</sup>

#### THE CONSEQUENCES OF PULMONARY HYPERTENSION

Once established, what are the effects of pulmonary hypertension on the pulmonary vessels? A sustained increase in resistance to pulmonary blood flow produces anatomic changes in the walls of small pulmonary arteries 100  $\mu$  to 300  $\mu$  in diameter. This was readily apparent in studies we conducted through biopsy of patients with diffuse interstitial lung disease.<sup>20</sup> When resistance to flow was increased modestly, medial hypertrophy was observed. In the presence of more significantly elevated resistance, intimal hyperplasia also was noted. Finally, when pulmonary hypertension at rest was moderately severe, intimal fibrosis—on occasion almost to the point of occluding the lumen—also was present.

These vascular changes closely resemble the abnormalities encountered in other conditions characterized by sustained pulmonary hypertension such as mitral stenosis<sup>30</sup> and congenital heart disease with left to right intracardiac shunts.<sup>31</sup> They themselves increase resistance to blood flow, contribute to the level of pulmonary arterial pressure, and may well account for the hyperbolic rise in pulmonary arterial pressure previously noted in diffuse interstitial disease (Figure 5). Sustained pulmonary hypertension, then, is a progressive rather than a static condition. Once a sustained increase in pulmonary vascular resistance is established, a vicious cycle of deterioration is initiated. While medial hypertrophy and intimal proliferation regress when the source of pulmonary hypertension is corrected, the more severe fibrotic changes do not. Hence, correction of the cause of severe pulmonary hypertension in the presence of such lesions may not improve the patient's status appreciably.

Such vascular lesions are not encountered in patients with chronic bronchitis.<sup>32</sup> Pulmonary hypertension in these patients is not sustained, but fluctuates with the degree of impairment of respiratory gas exchange. Indeed, if respiratory failure were sustained, death would ensue before such lesions had sufficient time to develop. Neither are such lesions found in the vast majority of patients with pulmonary emboli, since pulmonary arterial pressure returns to normal with resolution of the process. However, in the small portion of patients who go into a chronic phase of hypertension, these lesions do develop and contribute significantly to the clinical picture.

The response of the right ventricle to pulmonary hypertension varies with the severity and rapidity of evolution of the hypertensive process. In general, the right ventricular myocardium responds to the increased work load of pulmonary hypertension by increased protein synthesis and hypertrophy.<sup>33</sup> With progression of the hypertension or sudden exacerbations the myocardium, ultimately, is unable to meet the increasing demands imposed upon it and the chamber dilates and fails. This is especially true when pulmonary hypertension is associated with a volume overload (such as occurs in the polycythemia that accompanies sustained hypoxemia) so that the right ventricle is subjected to the double challenge of an increased preload and afterload.

The time course of this process depends upon the rapidity with which pulmonary hypertension develops. At one end of the spectrum a massive pulmonary embolus may produce sudden, catastrophic right ventricular

dilatation and failure without evidence of hypertrophy. Respiratory failure due to chronic bronchitis is associated with more slowly evolving pulmonary hypertension. Hence, some myocardial hypertrophy does occur. However, hypoxemia causes both renal retention of salt and water and polycythemia so that the chamber soon sustains both an increasing preload and fluctuating afterload. Under these circumstances dilatation and failure occur relatively early. Finally, at the far end of the spectrum the insidiously progressive pulmonary hypertension of interstitial lung disease affords ample opportunity for extensive myocardial hypertrophy to occur. In this condition pulmonary blood flow is maintained, even when the pulmonary arterial pressure is considerably elevated.<sup>20</sup> In effect, the right ventricle behaves like a left ventricle. Failure occurs only late in the course of the disease.

I shall close this discussion with some remarks about the management of pulmonary heart disease. In general, if pulmonary hypertension is reversible, correction of the accompanying cardiac abnormalities is best achieved by treating the cause of the pulmonary hypertension. If the cause of pulmonary hypertension is not reversible (as may be the case following recurrent showers of pulmonary emboli or in severe interstitial lung disease) digitalis and bed rest may increase the ability of the right ventricle to sustain the afterload imposed upon it, while diuretics, phlebotomy, and continuous low-flow oxygen may lower the level of blood volume and decrease its preload.

#### CONCLUSIONS

First, diseases of the respiratory apparatus may impose anatomic changes on the pulmonary vessels either from within by embolization or from without by compression. Alternatively, they may expose the bed to vasoconstricting stimuli. In both instances pulmonary hypertension may develop which is independent of any primary cardiac abnormality.

Second, the pulmonary hypertension so produced may be intermittent and short-lived or sustained and slowly progressive. In the former instance minor secondary abnormalities may occur in the vessel walls. When pulmonary hypertension is sustained, however, secondary anatomic changes occur which ultimately become severe, contribute in themselves to the level of pulmonary hypertension, and may determine the course of the underlying disease and its response to therapy.

Third, the behavior of the right ventricle also is determined by the

nature of the pulmonary hypertension. Two responses can be identified: With slowly developing, sustained pulmonary hypertension, the right ventricle hypertrophies, maintains the cardiac output within normal levels, and fails only very late in the course of the disease. In the face of rapidly developing, intermittent, pulmonary hypertension, however, the ability of the right ventricle to meet the increased work load is exceeded easily, and the right heart fails early in the course of the disease.

Finally, prognosis in patients with pulmonary heart disease depends upon the reversibility of the hypertensive process. Appropriate management in the acute phase of respiratory failure, then, is directed at the underlying cause of the pulmonary hypertension, not at the manifestations of circulatory embarrassment.

#### ACKNOWLEDGEMENT

I wish to thank Dr. Réjane M. Harvey, who contributed heavily to the concepts expressed herein, and Ms. Mariam Heath for her help in preparing the manuscript.

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