PRIMARY PULMONARY HYPERTENSION

Medical Grand Rounds

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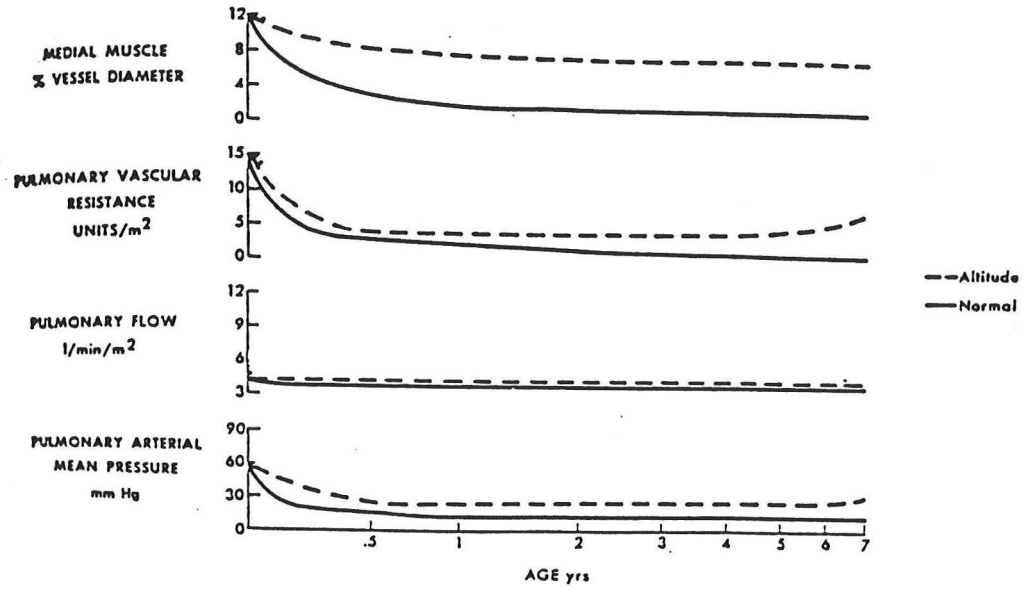
DEFINITION OF PULMONARY HYPERTENSION AND PHYSIOLOGY OF THE PULMONARY CIRCULATION

Pulmonary hypertension has been defined by the World Health Organization (1) as a mean pulmonary arterial pressure greater than 25 mmHg at rest or greater than 30 mmHg during exercise. In an adult population living at sea level, the normal range of values in the pulmonary circulation are:

Pulmonary artery pressure (mmHg)	
Systolic	18-25
Diastolic	6-10
Mean	12-16
Capillary wedge pressure (mmHg)	6-10
Cardiac Index (l/min/M^2)	2.6-4.2

The pulmonary vascular resistance is quantified as the ratio of pressure drop across the pulmonary bed (mean pulmonary artery pressure minus left atrial pressure) to cardiac ouptut. Resistance may be expressed in hybrid or Wood units or converted to metric units (dynes-sec-cm^{-5}) by multiplying the ratio by 80. The normal range for **pulmonary vascular resistance is 60-120 dynes-sec-cm^{-5} (or 1-1.5 units)**. Thus, in the normal adult, the pulmonary vascular bed is a ***low pressure, low resistance*** system which offers less than one-tenth the resistance to flow offered by the systemic vascular bed. That is not true at birth. At birth, pulmonary artery pressure is markedly elevated and equals systemic pressure. However, in normal infants, it rapidly falls secondary to the rise in PO_2, recruitment of new pulmonary vessels and anatomic changes with progressive thinning of the media of the muscular pulmonary arterioles. The major stimulus to the decline in pulmonary vascular resistance is the increase in alveolar PO_2. In the present of hypoxia, in fact, these changes do not occur. In infants born at high altitude, the fall in pulmonary arterial pressure is of lesser magnitude, slower in onset and the loss of muscle by the pulmonary arteries is reduced (Figure 1).

FIGURE 1



After birth, the pulmonary arterial pressure remains relatively constant through life; however, since cardiac output falls with advancing age, the pulmonary arteriolar resistance rises and by age 60, it doubles (Table 1).

TABLE 1

HEMODYNAMIC MEASUREMENTS IN MAN AS RELATED TO POST NATAL AGE

Age	Minutes	Hours		Days	Years				
	0-30	1-12	13-24	1-3	6-10	15-20	20-31	32-45	60-83
P_{PA} (mmHg)	60±13	40±10	32±8	26±4	14±3	14±3	13±4	14±1	16±3
P_W (mm Hg)	--	-2	-2	--	7±2	8±3	8±3	8±4	8±4
P_{AO} (mmHg)	58±12	54±7	53±11	58±7	84±11	90±5	88±8	101±16	102±11
CI (l/min/M^2)	--	--	--	--	4.3±9	42±.6	3.6±.7	3.2±.5	3.1±.7
PVR (units)	--	--	--	--	1.4±7	1.7±1.0	1.5±.6	1.8±.7	2.6±1.0

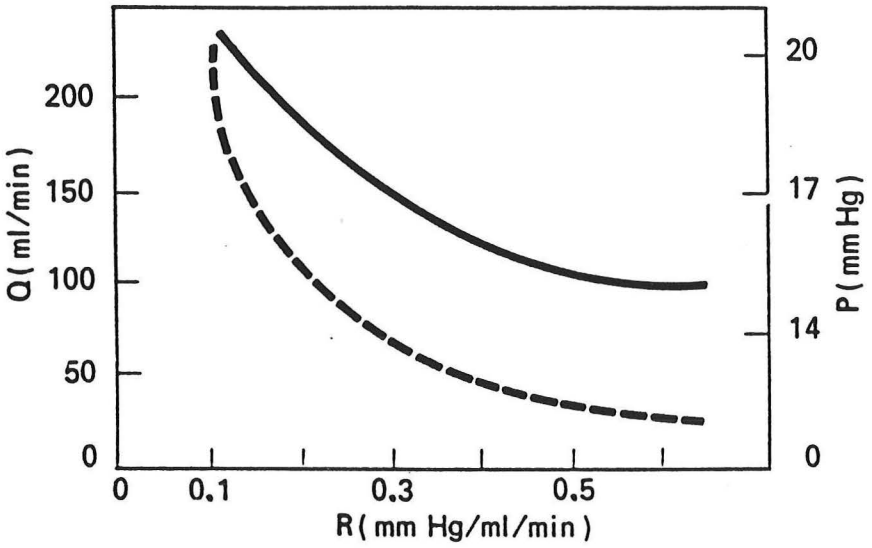
Two factors are responsible for the low resistance of the pulmonary vascular bed:

1. The pulmonary vascular bed is ***extremely distensible***. Due to its elevated content in elastic tissue, the cross-sectional area of the pulmonary vessels increases with an increase in flow and transmural pressure. Thus, pulmonary vascular resistance decreases passively with an increase in flow.

2. ***Recruitment of additional vascular channels*** -- The vessels in the upper pulmonary lobes are usually collapsed due to low hydrostatic pressure. If an increase in flow occurred, these vessels will open, thus decreasing pulmonary vascular resistance. The distensibility of the pulmonary vascular bed and the recruitment of additional vessels have been offered as the explanation for the lack of increase in pulmonary artery pressure with several fold increase in cardiac output as seen during exercise (2) or left to right intracardiac shunts of the pretricuspid variety (e.g. ASD) (Figure 2).

The anatomic characteristics of the pulmonary vascular bed explains why to produce pulmonary hypertension, more than 50% of the pulmonary bed has to be obstructed. In animals, acute balloon occlusion of one of the two pulmonary arteries does not produce pulmonary hypertension (3) and in humans, pulmonary hypertension does not develop after pneumectomy. Only when three-fourths of the pulmonary vascular bed are obstructed, pulmonary arterial pressure increases. Even if a mean pulmonary arterial pressure of 25 mmHg seems to represent only a modest increase from the normal value of 15 mmHg, to produce such an increase, extensive and severe obstruction of the pulmonary bed has to occur thus underscoring the fact that when pulmonary hypertension is diagnosed, severe damage was already done.

FIGURE 2



R = resistance
Q = pulmonary flow
P = mean pulmonary artery pressure

The development of medial hypertrophy, intimal fibrosis and thrombosis of the pulmonary vessels, as seen in different diseases (see under **"PATHOGENESIS"**), reduces the distensibility of the pulmonary vascular bed and limits the number of additional vessels which can be recruited. Under these circumstances, the pulmonary vascular bed turns from a low-pressure, low-resistance system into a high-resistance, high-pressure system and even a modest increase in flow will produce a marked increase in pressure (Figure 3).

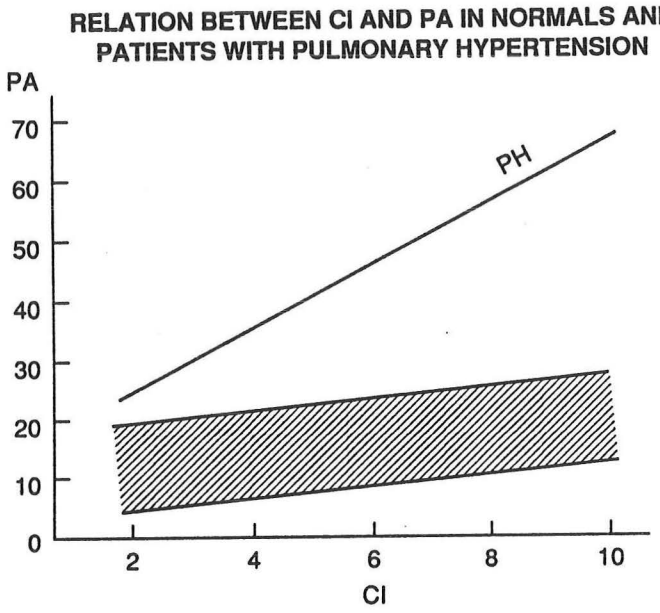
In addition to the anatomic structure of the pulmonary vessels, other factors control the pulmonary vascular resistance. They are listed in Table 2 .

TABLE 2

MEDIATORS OF VASCULAR TONE IN ADULT ANIMALS

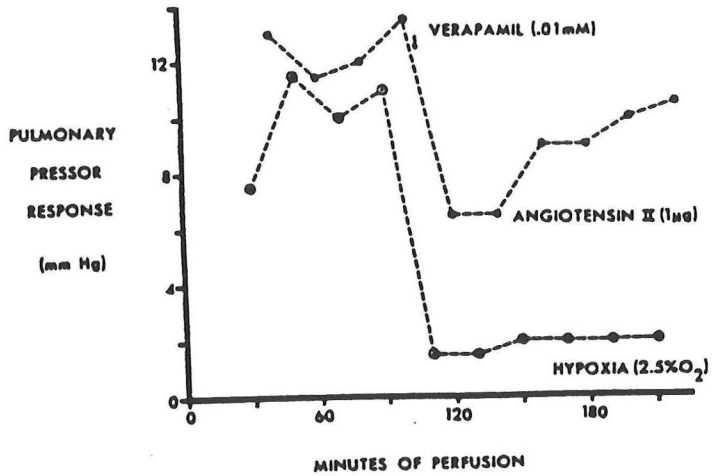
Vasoconstriction	Vasodilation
Hypoxia	Normoxia
H+	ANF
CO_2	EDRF
α-agonist	β-agonist
Acetylcholine	Acetylcholine
Histamine	Histamine
Bradykinin	Bradykinin
Serotonin	Vasopressin
Angiotensin II	VIP
Vasopressin	Substance P
Thromboxane A_2	PGI_2
PGH_2	PGE_1
PGF_2	PAF
PGE_2	Adenosine
ATP	ATP

FIGURE 3



Acute hypoxia produces pulmonary vasoconstriction; the degree of vasoconstriction is age-dependent (infants > adults) and species-dependent (cattle > humans > dogs > sheep). There is also strong evidence for a genetic determination, which may be relevant to the occurrence of familial primary hypertension. The mechanism(s) through which hypoxia produces pulmonary vasoconstriction are unknown. It seems that both the local release of histamine and increased entry of calcium into the vascular smooth muscle cells play a role in hypoxic pulmonary vasoconstriction. Both histamine receptor blockers and calcium channel blockers decrease pulmonary artery pressure during hypoxia (4,5). Figure 4 illustrates the effectiveness of verapamil, a calcium channel blocker, in reducing pulmonary hypertension due to hypoxia.

FIGURE 4



Relative susceptibilities of hypoxia- and angiotensin II-induced pressor responses to inhibition by verapamil, in isolated rat lung.

Tolazoline, a well known pulmonary vasodilating agent, among other actions, stimulates H_2 receptors. Acidemia seems to potentiate the vasoconstrictor effect of hypoxemia.

The media and adventitia of the large pulmonary arteries and veins have both α-adrenergic and β-adrenergic innervation (6). α-agonists produce pulmonary vasoconstriction and β-agonists dilate pulmonary vessels. However, while neural regulation may be important during fetal life and under particular circumstances, such as hypoxia, its role in regulating vascular tone in the normal adult population is uncertain and probably minimal. The role of other chemical substances and agents is uncertain as they exert different, often opposite effects, in different species. However, in all species, thromboxane has been shown to produce pulmonary vasoconstriction and prostacyclin vasodilation.

PATHOGENESIS OF PULMONARY HYPERTENSION

An increase in pulmonary artery pressure may occur as a result of an increase in flow through the pulmonary bed which exceeds the vasodilator reserve of the pulmonary vascular bed or of an increased resistance to flow, which may occur at a number of different sites within the pulmonary circulation. Pulmonary hypertension accounts for approximately 20% of all hospital admissions to a cardiologic unit. Utilizing the measurement of the right pulmonary artery diameter as an index of pulmonary hypertension, Rich and associates (7) have estimated that 13% of males over age 34 and 20% of males over age 65 in the U.S.A. have pulmonary hypertension. In more than 95% of patients, pulmonary hypertension is secondary to cardiac, pulmonary or systemic diseases. The most frequent causes of secondary pulmonary hypertension are listed in Table 3.

Congenital and acquired cardiac diseases can lead to pulmonary hypertension. Among congenital defects, left to right ventricular shunts at the post-tricuspid level, as in VSD and PDA, most frequently cause pulmonary hypertension. In this setting, the increase in pulmonary blood flow is associated with pulmonary pressure at systemic level. Both increased flow and pressure promote vascular changes which may become irreversible. The increase in pulmonary blood flow itself is not usually sufficient to produce severe pulmonary vascular changes as demonstrated by the fact that pulmonary hypertension is less common in patients with atrial septal defect.

Pulmonary hypertension may develop as a consequence of a persistent increase in left atrial pressure as in the setting of left ventricular failure, reduced left ventricular compliance, as seen in systemic hypertension or hypertrophic cardiomyopathy, in mitral valve disease, especially mitral stenosis, and left atrial or pulmonary venous obstruction.

Pulmonary parenchimal diseases represent the most common cause of pulmonary hypertension in the adult population. Chronic obstructive lung disease is responsible for the majority of cases of cor pulmonale (8). Several factors are

TABLE 3

SECONDARY PULMONARY HYPERTENSION

CARDIAC DISEASE

I. **Increased Pulmonary Flow with Secondary Pulmonary Vascular Disease as in VSD, PDA, ASD**

II. **Increased Resistance to Pulmonary Venous Drainage**
- Left ventricular failure (cardiomyopathy, valvular disease, CAD)
- Reduced LV compliance (HTN, hypertrophic CM)
- Mitral valve disease (MS)
- Left atrial mixoma, cor triatriatum
- Stenosis of pulmonary veins

PULMONARY PARENCHYMAL DISEASE
- Chronic obstructive pulmonary disease
- Restrictive lung disease
- Granulomatous disease (sacroidosis, TB, berylliosis)
- Cystic fibrosis

DISEASES OF RESPIRATORY FUNCTION
- Thoracic cage deformities
- Sleep apnea syndrome
- Obesity-hypoventilation syndromes
- neuromuscular diseases (myasthenia, poliomyelitis, spinal cord lesion)

PULMONARY VASCULAR DISEASE
- Pulmonary thromboembolism
- Pulmonary arteritis (Takayasu's disease)
- Collagen vascular disease
- Sickle cell anemia
- Schistosomiasis, filariosis
- Peripheral pulmonary artery stenosis
- Persistent fetal circulation
- Residence at high altitude

MISCELLANEOUS
- Intravenous drug abuse
- Aminorex fumarate
- Bush tea (crotalaria)
- Hepatic cirrhosis

implicated in the pathogenesis of pulmonary hypertension in patients with lung disease. They include (1) anatomical loss of pulmonary vessels, (2) arteriolar constriction secondary to hypoxia and acidosis, (3) increased blood viscosity.

Alveolar hypoventilation with the consequent hypoxia and acidosis is responsible for the development of pulmonary vasoconstriction and hypertension in patients with deformities of the thoracic cage, hypoventilation syndromes (sleep apnea, Pickwick's syndrome) and neuromuscular diseases (myasthenia gravis, poliomyelitis, spinal cord lesion).

A variety of conditions can produce anatomical obstruction to pulmonary blood flow. The most frequent, in the U.S.A., is pulmonary thromboemboli. It has been calculated that approximately 500,000 patients have 1 or more pulmonary emboli each year (9,10). Chronic pulmonary hypertension develops in 0.5-1.0% of them. Worldwide, the most common cause of obstruction to pulmonary flow is schistosomiasis (11).

Pulmonary hypertension has been described in I.V. drug abusers due to intravenous injection and pulmonary embolization of crushed powder (12). The role of anorectic drugs, and herbal extracts will be discussed in the pathogenesis of PPH. The incidence of pulmonary hypertension is higher in patients with hepatic cirrhosis than in the normal population (0.26% vs 0.02%). It has been speculated that endogenous or exogenous substances by by-passing the liver are not destroyed and can exert a vasoconstrictor effect on the pulmonary vessels (13). It has been also suggested that portal venous thrombosis may lead to pulmonary embolization. However, no evidence has been found at autopsy to support the latter hypothesis. In fact, the lesions of the pulmonary vessels in patients with hepatic cirrhosis closely resemble the changes seen in primary pulmonary hypertension.

In less than 5% of patients with pulmonary hypertension, no cardiac, pulmonary, neurological or systemic disease can be identified. The term "primary pulmonary hypertension" (PPH) is currently used to identify these cases. Probably different forms of pulmonary hypertension with different etiologies are currently grouped under the name of primary pulmonary hypertension (see **"PATHOGENESIS OF PPH"**).

HISTORY OF PRIMARY PULMONARY HYPERTENSION

The first description of a patient with primary pulmonary hypertension (PPH) was made in 1891 by Romberg (14), who described the findings at autopsy of sclerosis of the pulmonary arteries in the absence of underlying cardiac or lung disease. Sixteen autopsy cases of PPH were reviewed by Brenner (15) in 1935. However, it was not until 1951 that Dresdale (16) gave, in a series of 39 patients, the first detailed description of the clinical and hemodynamic characteristics of patients with unexplained pulmonary hypertension which he first named "primary pulmonary hypertension." In 1959, Wood (17) advanced the hypothesis that PPH was the result of abnormal vasoconstriction of the pulmonary arterioles and suggested the use of vasodilator drugs.

In the late 60s a sudden increase in the number of patients with unexplained pulmonary hypertension seen in several European countries and eventually linked to the use of a drug, aminorex fumarate, stimulated new worldwide interest in the study of PPH (18). In 1970, Wagenvoort (19) provided the first detailed description of the histopathology of PPH and identified 3 main different histologic forms (plexogenic, thrombotic, veno-occlusive). In 1973, the World Health Organization (1) proposed the current definition of pulmonary hypertension as mean pulmonary artery pressure exceeding 25 mmHg at rest and proposed the classification of patients with PPH in the 3 distinct histological subtypes described a few years earlier by Wagenvoort. In 1981, a national registry for the study of PPH was instituted in the United States sponsored by the NIH. Over a 5-year period, patients from 32 USA medical centers were enrolled. Follow-up was continued until 1989 in order to obtain data on the incidence, natural history and possibly treatment of this disease. The data collected have been published recently (20) and will be reviewed extensively in my presentation because they have provided new insights in the understanding of this disease and because they represent the only prospective data available in a large group of patients with this disease.

EPIDEMIOLOGY

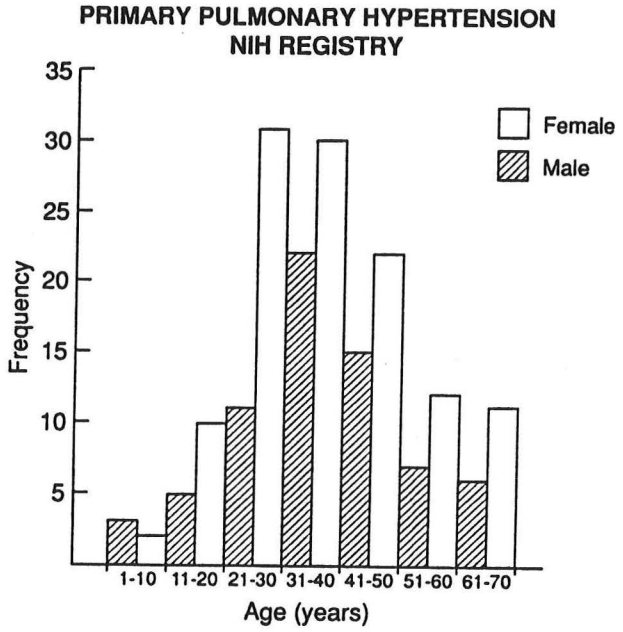
Primary pulmonary hypertension is a rare disease. Its true incidence is unknown and difficult to assess since patients may remain asymptomatic even when severe pulmonary hypertension is present. Clinically unsuspected primary pulmonary hypertension has been diagnosed in 0.02% of cases in a series of 10,000 autopsies (21). Based on data from different cardiac catheterization laboratories, it appears that primary pulmonary hypertension is diagnosed in approximately 1% of cath cases (22). One hundred eighty-seven patients were enrolled from July 1981 through 1985 in the NIH National Registry on PPH (20). This figure, however, underestimated the true incidence of the disease since only patients who were symptomatic and, therefore, sought medical attention were enrolled. Since patients may remain asymptomatic in face of severe pulmonary hypertension, several cases of PPH go undiagnosed.

PPH can occur at any age with the highest prevalence being in the third and fourth decades. The mean age of the patients enrolled in the NIH Registry was 36.4 years -- similar to the mean age of patients reported in the other series. However, in the NIH Registry, approximately 20% of patients were 50 years or older at the time of diagnosis. This finding corrects the previous belief that PPH is a disease which affects exclusively young people (Figure 5).

In childhood, the sex incidence is equal. After childhood, a greater incidence in women has been reported with a female to male ratio of 3:1. However, in the NIH Registry, the female to male ratio was only 1.7:1 and relatively constant for each decade. A higher female prevalence (4:1) was seen in the black population, which represented 12% of the cases enrolled in the Registry. Difference in the prevalence of PPH appears to exist worldwide. In 2 large series from India and Japan, a higher

prevalence in man has been reported (23,24). It is not clear whether the higher prevalence in men in these 2 countries is real or reflects the fact that women in India and Japan do not present as often as men to medical attention for socioeconomical reasons. The incidence of PPH varies from country to country. It appears, for example, that in India, the incidence is two-fold higher than in European countries (23). While it is possible that several cases are due to occult schistosomiasis, the existence of a genetic predisposition to a higher pulmonary vasomotor tone in the Indian population has been postulated to explain the higher incidence of pulmonary hypertension secondary to mitral stenosis and ASD found in India at younger ages (25). Several familial cases of PPH have been reported (26). In the NIH Registry (20), the incidence of familial PPH was 7%. An autosomal dominant inheritance with incomplete penetrance has been postulated (27).

FIGURE 5



PROGNOSIS

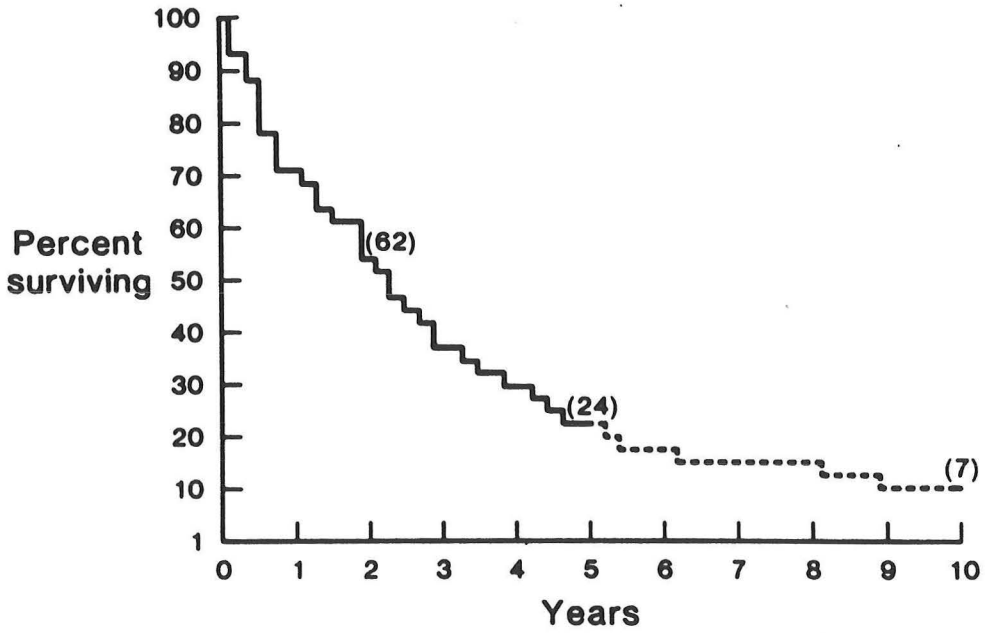
Patients with PPH usually present in the advanced stages of the disease when severe histological abnormalities are present and pulmonary artery pressure and resistance are markedly elevated. Consequently, there is little information, except for few case reports, on the duration of the presymptomatic phase. After the onset of symptoms, the mean survival is 2-3 years with even shorter survival reported in children (Figure 6). However, occasional patients have been reported who survived for more than 20 years after the disease was diagnosed (19,28). Spontaneous regression of the disease has been documented (29,30). The most important data on the natural history of PPH has been provided by the NIH Registry (20). Two important features have become apparent:

1. The clinical course is highly variable and cannot be predicted on the basis of the clinical presentation, hemodynamic data and even histological features. However, once right ventricular failure ensues, survival beyond 2 years is unlikely.

2. The hemodynamic abnormalities seem to follow a typical pattern, with patients in the asymptomatic or mildly symptomatic phases having elevated pulmonary artery pressure and resistance but relatively well preserved CO. Progression of the disease and clinical deterioration are associated with a drop in CO rather than an increase in PA (Figure 7). The findings of a CI <2.5, elevated RA pressure and arterial O_2 tension below 70 mmHg are indicative of an extremely poor prognosis with none of the patients showing all the above characteristics living more than 1 year (31-32). Patients with PPH usually die of intractable right ventricular failure or sudden death. Sudden death is probably due to several mechanisms, the most frequent being atrial tachyarrhythmia. The increase in rate and loss of atrial systole produce a marked decrease in CO. Other mechanisms are bradyarrhythmias and right ventricular infarct.

In a retrospective study (33), although patients receiving anticoagulant therapy had a better survival than patients not receiving anticoagulant therapy, so far, no medical therapy has been shown to change the prognosis of patients with PPH.

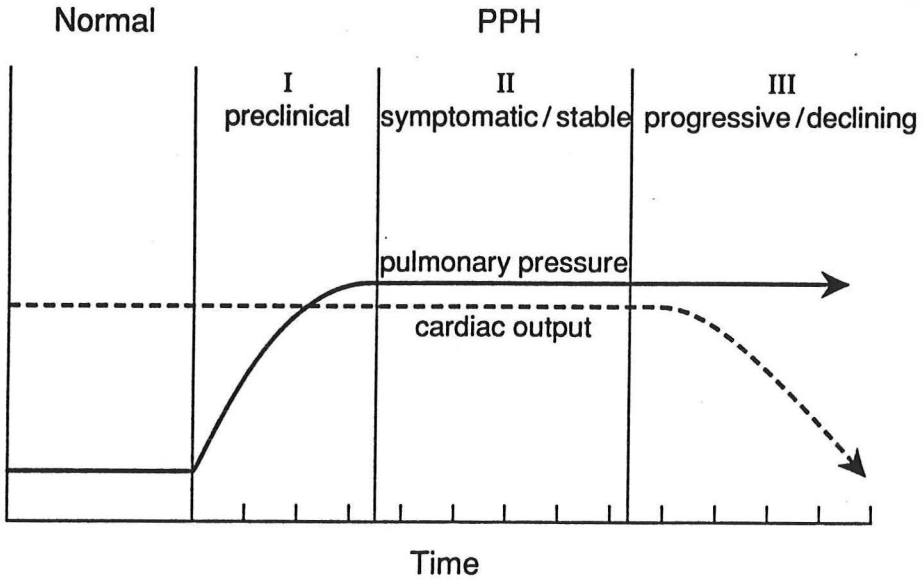
FIGURE 6



Observed survival to 10 years of patients with primary pulmonary hypertension (115 patients who survived diagnostic catheterization). Parentheses enclose numbers of living patients under observation at 2, 5, and 10 years.

FIGURE 7

CLINICAL COURSE OF PPH



HISTOPATHOLOGY

In primary pulmonary hypertension, the anatomic changes can occur at 2 different sites:

A. Obstruction at the level of the precapillary arterioles, so called ***pulmonary arteriopathy***. This type of obstruction is seen in more than 90% of patients with PPH. Two different histologic subtypes have been described: plexogenic pulmonary arteriopathy and thrombotic pulmonary arteriopathy (19,34-36) (Table 4).

B. Obstruction at the level of the pulmonary veins and venules. This entity has been called ***pulmonary veno-occlusive disease*** (PVOD) (37).

The obstruction at the precapillary level leads to an increase in pressure in the arterioles and major pulmonary arteries while pressure downstream (pulmonary capillaries, veins and left atrium) is normal. In PVOD, the obstruction on the venous site leads to elevation of pressure in the pulmonary arteries and capillaries, while pressure in the venules and left atrium is normal (Figure 8).

1. Plexogenic Pulmonary Arteriopathy

Plexogenic pulmonary arteriopathy is typical, but not pathognomonic of PPH since it is seen in chronic pulmonary hypertension from a varity of etiologies, including congenital heart disease, cirrhosis, aminorex ingestion. All of these diseases are

characterized by increased pulmonary vasoconstriction. The sequence of lesions appear to be medial hypertrophy (Figure 9), intimal thickening with fibrosis, plexiform lesion (Figure 10). The intimal proliferation, usually lamellar and concentric, but often eccentric, may be so severe to produce obliteration of the lumen (onion-skin lesions). The plexiform lesion appears as a multichanneled outpouching of the pulmonary arterial wall. Its presence usually indicates advanced disease. Its cause(s) is/are unknown. It has been suggested that plexiform lesions represent aneurysmal dilations of the arteriolar wall or are reparative lesions in areas of previous fibrinoid necrosis. Since plexiform lesions are found only when pulmonary hypertension originates at the precapillary levels (not seen in pulmonary hypertension 2° to left ventricular dysfunction, mitral valve disease and pulmonary veno-occlusive disease), it has been suggested that plexiform lesions occur only when there is arteriolar pulmonary vasoconstriction.

Plexogenic pulmonary arteriopathy has been reported in 28 to 71% of patients with PPH (43% in the NIH Registry). It is more common in women and in younger patients. Its presence has been associated with survival poorer than in patients with thrombotic pulmonary arteriopathy.

TABLE 4

HISTOPATHOLOGIC CLASSIFICATION OF PPH

Previous Classification	Present Classification	Histologic Features
	Primary Pulmonary Arteriopathy with:	
	Plexiform lesions with or without thrombotic lesions	-- Eccentric or concentric laminar (onion-skin) intimal proliferation
Plexogenic pulmonary arteriopathy	Isolated medial hypertrophy	-- Medial hypertrophy, muscularization of intra-acinar arteries
	Intimal fibrosis and medial hypertrophy	-- Plexiform lesions
		-- Fibrinoid degeneration
Thromboembolic pulmonary arteriopathy	Thrombotic lesions	-- Thrombi (fresh, organized and recanalized)
Pulmonary veno-occlusive disease	***Pulmonary Veno-occlusive Disease***	*Veins*: Intimal fibrosis, recanalized thrombi, arterilization, alveolar edema, capillary congestion
		Arteries: Medial hypertropy, intimal fibrosis and thrombosis. No plexiform lesions.

FIGURE 8

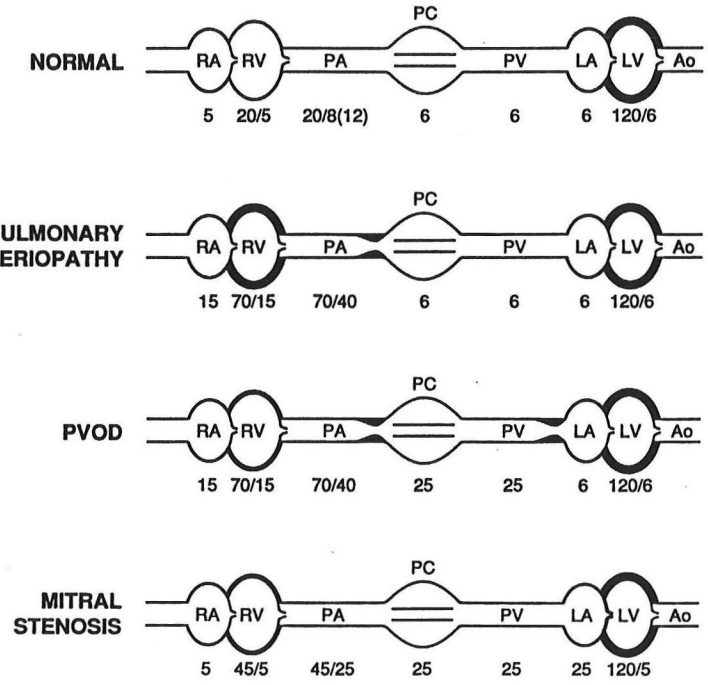


FIGURE 9

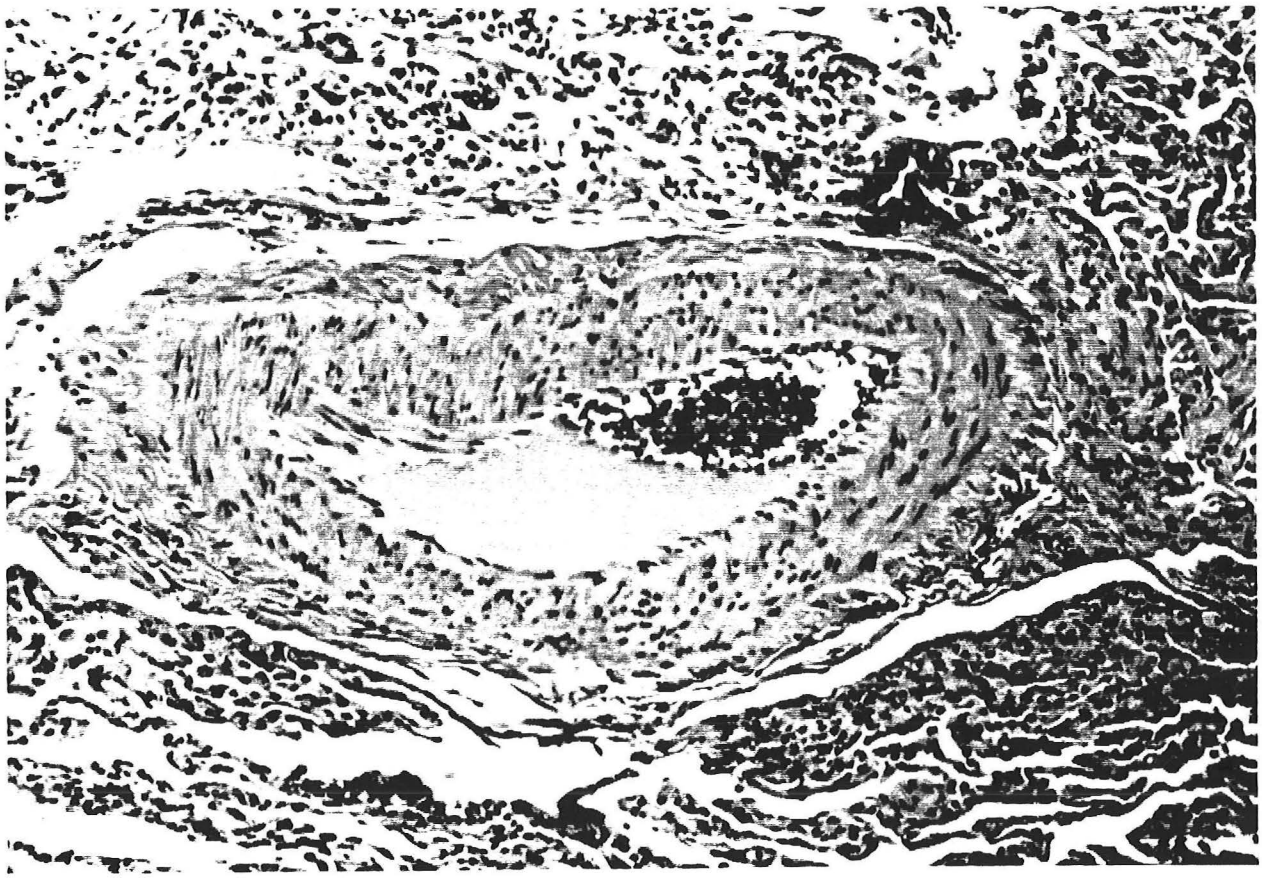
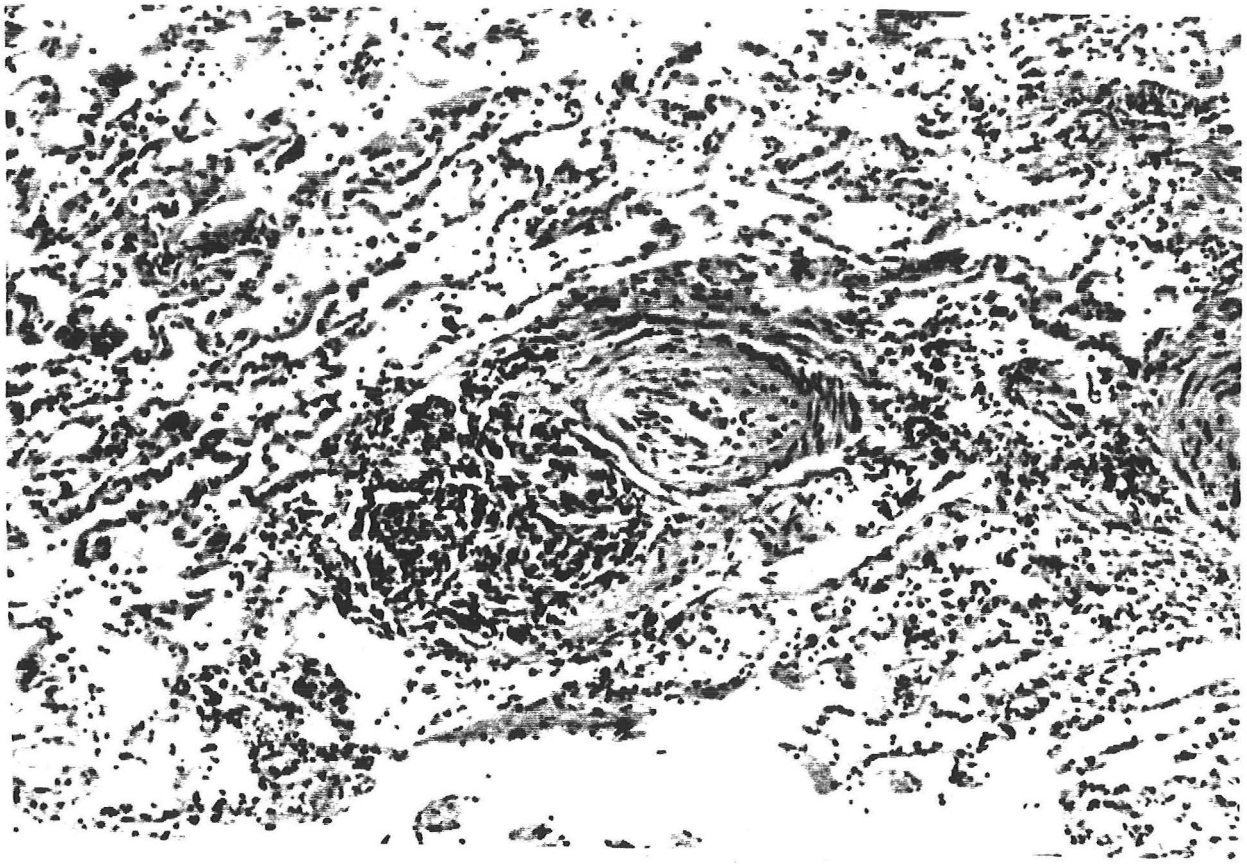


FIGURE 10



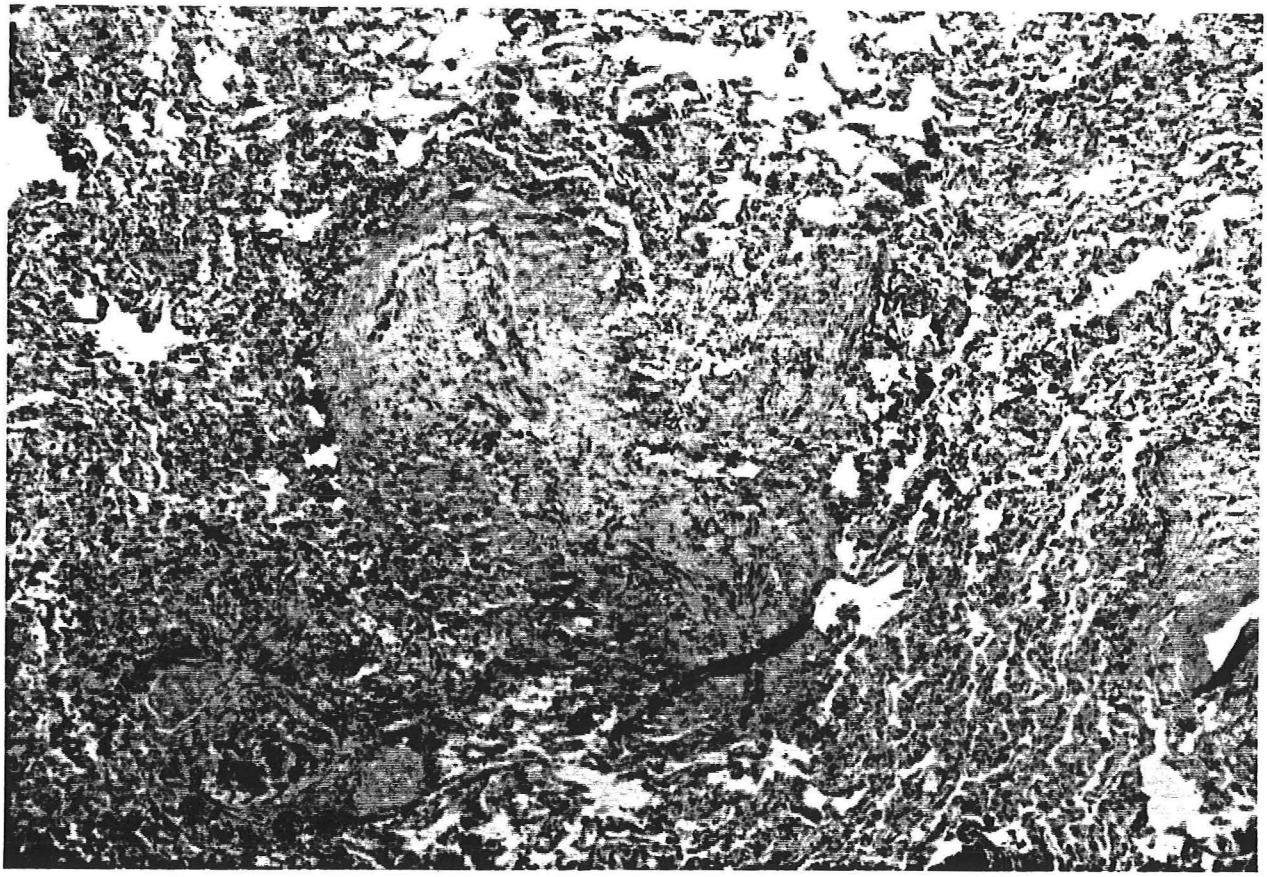
2. Thrombotic Pulmonary Arteriopathy

Thrombotic pulmonary arteriopathy describes another subset of pulmonary vascular lesions seen in 20-50% of cases (33% in the NIH Registry) with PPH. Thrombotic pulmonary arteriopathy has been found in older patients with PPH, and in contrast with plexogenic arteriopathy, is evenly divided between men and women. The prevailing lesions seen in thrombotic pulmonary arteriopathy are: eccentric intimal fibrosis, medial hypertrophy, and both fresh and old thrombi. Recanalized thrombi are frequently found (Figure 11). Recent research suggest that alterations of the endothelial cells by unknown mechanism(s) (virus, toxin, etc) provide the substrate for thrombosis *in situ* and intimal proliferation.

Until recently, plexogenic pulmonary arteriopathy and thrombotic pulmonary arteriopathy were considered 2 distinct entities with different pathogenesis: arteriolar vasoconstriction for the plexogenic form and primary endothelial damage for thrombotic arteriopathy. They are now considered two different aspects of the same process since both histological lesions can occur in the same patient (36) and in familial pulmonary

hypertension some members may present with plexogenic lesions and other members with the typical thrombotic arteriopathy (38). Moreover, in the few sequential pathologic studies available (39), changes from one form of arteriopathy to the other form have been observed and in animal models of pulmonary hypertension, the same injury may produce both type of lesions with thrombotic lesions usually found in the animals which survived for a longer period of time. In the NIH Registry, patients with plexiform lesions had worse hemodynamics and worse prognosis than patients with thrombotic lesions (40). In patients with plexiform lesions, higher pulmonary vascular resistance (44 ± 22 vs 28 ± 13 units, $p<0.05$), higher mean pulmonary arterial pressure (76 ± 22 vs 61 ± 10 mmHg, $p<0.05$) and lower cardiac index (1.7 ± 0.4 vs 2.4 ± 1.7 l/min/M^2, $p<0.05$) were observed suggesting that perhaps the severity of the initial insult is reponsible for the histological pattern.

FIGURE 11



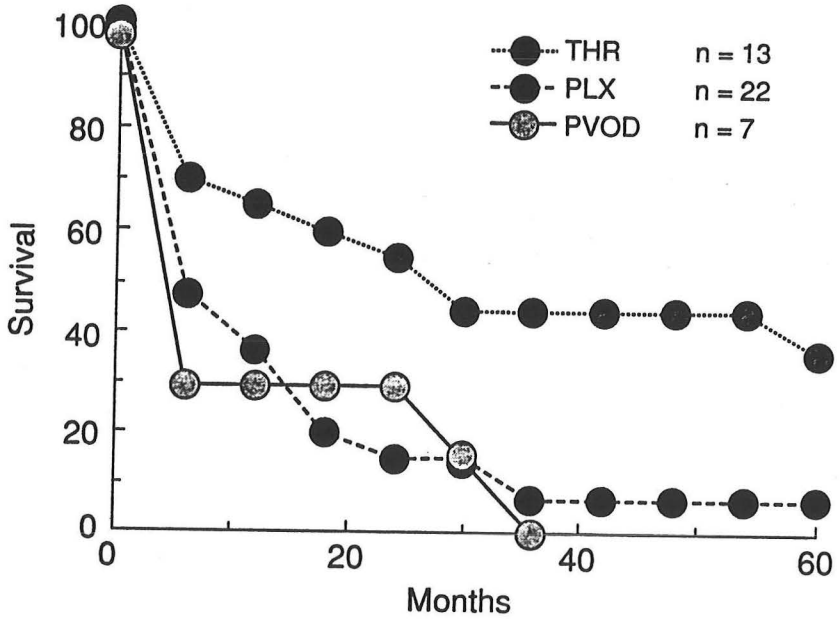
3. **Pulmonary Venous Occlusive Disease**

Pulmonary venous occlusive disease is the rarest form of primary pulmonary hypertension. It accounts for <7% of the cases of PPH with less than 100 cases described so far worldwide (20).

There is a slight predominance in men with ages ranging from infancy to the sixth decade. Patients with PVOD had the worse prognosis of all patients with PPH in the NIH Registry (40). In fact, the median survival was 858 days for patients with thrombotic lesions, 102 days for patients with plexiform lesions and only 84 days for patients with veno-occlusive disease. The 6 month mortality in this group was 71% (Figure 12). The typical histological features include widespread intimal proliferation and fibrosis of the intrapulmonary veins and venules (40,41). Venous thrombi are common and are frequently recanalized. Secondary changes of the pulmonary arterioles are frequently seen and consist mainly of medial hypertrophy. No plexiform or thrombotic lesions of the pulmonary arteries have been described. Cases of PVOD have been described after viral illness (42), chemotherapy and toxin exposure (43), suggesting that several agents may produce changes in the venous intima, leading to fibrosis and thrombosis. Familial cases of PVOD have been described (44).

FIGURE 12

SURVIVAL AND PATHOLOGY IN PPH



PATHOGENESIS OF PPH

Until recently, based on the pathological findings, it was thought that PPH was due to either one of two mechanisms: abnormal pulmonary **vasoconstriction** in patients with plexogenic arteriopathy and **thrombosis** in patients with thrombotic arteriopathy.

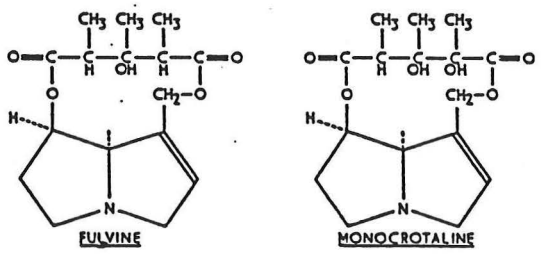
In favor of the vasoconstrictive hypothesis first formulated by Wood (17), were the findings that medial hypertrophy precedes plexogenic lesions (39) and that vasodilator agents are effective in reducing pulmonary resistance especially during the

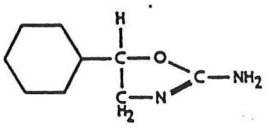
early phase of the disease when medial hypertrophy is indeed the prevailing lesion (36). In addition, plexogenic arteriopathy has been described in patients with liver cirrhosis (13) and in cases of diet-induced (crotalaria, aminorex) pulmonary hypertension leading to the speculation that vasoactive compounds may reach the pulmonary vessels and cause vasoconstriction. Ten percent of patients with PPH have Raynaud's phenomenon suggesting a generalized increase in vascular tone (20).

It has now been recently proposed that abnormalities of the endothelial cells may lead to pulmonary vasoconstriction (45). It is possible that the release of endothelial derived relaxing factors contributes to the maintenance of low pulmonary resistance in the normal state (46). Animal (47) and clinical (48) data demonstrating that acetylcholine, which stimulates the release of EDRF, is often an effective pulmonary vasodilator suggests impaired function of the pulmonary endothelium in patients with pulmonary hypertension. Histological studies in patients with pulmonary hypertension secondary to congenital cardiac disease have revealed ultrastructural abnormalities of the endothelial cells (increased microvilli and rough endoplasmic reticulum) which suggest heightened metabolic function (49). These changes were not seen in patients with congenital cardiac disease without pulmonary hypertension.

Different herbs and plants, crotalaria and ragwort, found in India, Africa, Australia and Central America, produce pulmonary hypertension in animals (50-52) and in humans drinking the so called "bush tea" which is made with extracts from seeds and leaves of these plants (53). Two alkaloids, monocrotaline and fulvine (Figure 13), contained in these leaves have been shown to produce acute endothelial cell injury followed by endothelial cell proliferation and several weeks later by an increase in vascular smooth muscle cells (52,54). The pulmonary hypertension seen after aminorex ingestion (which will be discussed later) may have similar etiology (55). Aminorex resembles adrenalin and amphetamine in its chemical structure. The early stage of intimal proliferation appear to result from migration of smooth muscle cells through the internal elastic lamina in response presumably to a chemotactic or growth factor released by endothelial cells and/or platelets.

FIGURE 13





AMINOREX

The findings in at least one-third of patients with PPH of thrombi involving the small pulmonary arteries without any evidence at autopsy for a source for recurrent embolization (40) supports the hypothesis that in several patients PPH may be due to *in situ* thrombosis as a result of endothelial abnormalities, defective coagulation-fibrinolysis or abnormalities of the platelets. The hypothesis is attractive and intriguing but the evidence in its favor is, so far, scanty. Reduced fibrinolytic activity following occlusion of a peripheral vein has been described in 13 patients with PPH (56). PPH has been reported in patients with hemophilia chronically receiving factor VIII and an increase in factor VIII has been reported in some patients with PPH (57,58). In several patients with PPH, Rich and associates (59) reported elevated levels of fibrinopeptide A, which normalized with the intravenous administration of heparin. Some type of acquired fibrinolytic defect is likely since the patients had normal levels of cross-linked fibrin degradation products and elevated levels of plasminogen activator inhibitor 1 activity.

Recently (40), a unitarian hypothesis has been formulated which postulates that the initial insult in PPH is localized at the level of the pulmonary endothelium and may lead to either intimal proliferation with smooth muscle hypertrophy or intimal proliferation with intravascular thrombosis. According to this hypothesis, different stimuli (shear forces, viruses, drugs, hypoxia, etc) can injure the endothelium. The histologic expression of the injury is probably determined by the genetic substrate, the age, the extent of initial damage, the presence of associated fibrinolytic defect or vascular hyperreactivity. In other words, the same etiologic factor may produce two different histologic patterns. This hypothesis is supported by the findings that the same stimulus may cause plexogenic pulmonary arteriopathy in some patients (or animals), thrombotic arteriopathy in others and in some patients, both lesions may be present. This has been observed in familial cases of pulmonary hypertension (60) and following administration of aminorex (55), and crotalaria (54).

Still unknown, in most cases of PHP, is the factor(s) which may cause endothelial injury. So far, no single etiologic factor has been identified but several have been proposed (Table 5).

A sharp increase (18,55) in the incidence of pulmonary hypertension was seen in Switzerland, West Germany, and Austria in the late 60s (Figure 14). It followed the introduction on the market in these countries of an appetite-suppressant drug, aminorex fumarate. The epidemic was limited to the countries where the drug was sold and terminated shortly after the drug was revocated. Aminorex exerts a sympathomimetic activity, similar to monocrotaline, and the lesions are similar to the ones observed in animals fed crotaline. Only 2 out of 1000 patients taking the drug actually developed pulmonary hypertension. Its severity varied from patient to patient and was unrelated to the amount ingested or length of administration of the drug thus suggesting, as for other forms of pulmonary hypertension, some kind of genetic susceptibility.

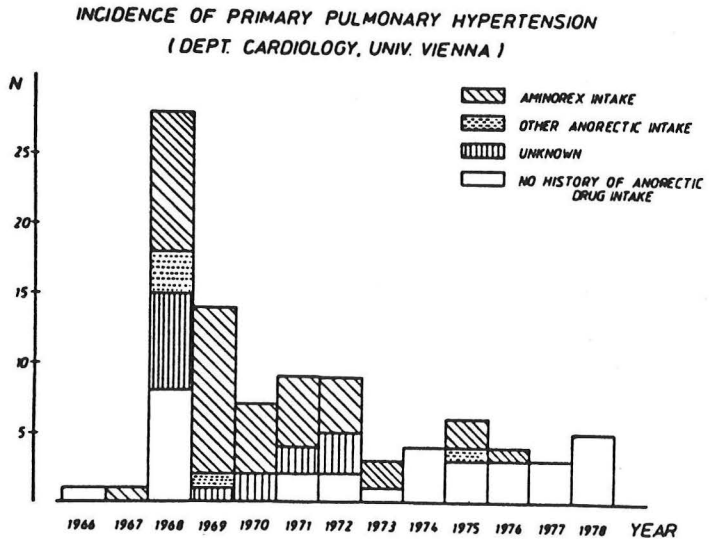
Several other drugs have been implicated in the pathogenesis of PPH, including other appetite suppressants, such as fenfluramine (61,62) and oral hypoglycemic agents,

such as phenformin (63). Since phenformin can produce lactic acidosis and pulmonary vasoconstriction occurs in animals following infusion of lactic acid into the pulmonary artery, pulmonary hypertension in these cases has been related to the metabolic acidosis.

TABLE 5
FACTORS IMPLICATED IN THE ETIOLOGY OF PPH

DRUGS	--	Aminorex fumarate
	--	Fenfluramine
	--	Phenformin
	--	Indomethacin ?
	--	H_2 inhibitors ?
DIET	--	Crotalaria (retusa, fulva, spectabilis)
	--	Senecio jacobea (ragwort)
	--	"bush" tea
	--	Rapeseed oil denatured with aniline (toxic-oil syndrome)
VIRAL INFECTION	--	HIV
PREGNANCY		
ORAL CONTRACEPTIVES		
ANTINUCLEAR ANTIBODIES		

FIGURE 14



Increase in incidence of pulmonary hypertension of unknown origin in Vienna 1968.

Pulmonary hypertension has been described, as mentioned previously, in animals fed crotalaria and in consumers of "bush tea" (50-53). Another form of dietary pulmonary hypertension has been described in Spain in the mid 80s following the ingestion of contaminated rapeseed oid. The so-called "toxic oil syndrome" due to rapeseed oil denatured with aniline, affected more than 20,000 people and caused 369 deaths (64,65). The incidence of pulmonary hypertension was 3.5% and pulmonary hypertension accounted for almost 10% of deaths (32 people). Both plexiform and thrombotic lesions were seen. Endothelial damage has been well documented with rapeseed oil and was probably due to the release of free peroxide radicals (65).

Viral infections have been described to precede the onset of PPH (20,42). PPH has been recently described in HIV infected patients (66). Since histological lesions similar to that seen in PPH have been described in the coronary arteries of cardiac transplant recipients (67) and normal subjects following herpes simplex and cytomegalovirus infections (68), it is conceivable that viruses, by producing endothelial damage, may cause pulmonary vascular changes in genetically predisposed individuals.

PPH is often first noticed during pregnancy (69-70). However, it is possible that pulmonary hypertension was present prior to pregnancy and patients become symptomatic during pregnancy because of the increase in cardiac output and tachycardia. An increased incidence of PPH has been suggested in women taking oral contraceptives (71,72). However, no relation between pregnancy, use of oral contraceptives and PPH has been found in the NIH Registry (20). In fact, the incidence of pregnancy and pill consumption in women with biopsy proven PPH was not higher than in a normal population of similar age. It is likely that several patients described in the previous studies suggesting a relation with pregnancy or oral contraceptives did not have PPH but pulmonary hypertension as a result of pulmonary emboli. During the menstrual period, increased vasomotion has been described, not only in the arteries supplying the endometrium, but in the congiuntival arteries (73). Whether similar changes occur in the pulmonary vascular bed of selected patients is unknown. It may explain the higher incidence of PPH seen in female patients after puberty.

Rich, et al (74) found positive antinuclear antibodies at titers of 1:80 dilutions or greater in 40% of 43 patients with PPH, while the incidence in the same study in patients with secondary forms of pulmonary hypertension was 6%, similar to that in the normal population. A positive antinuclear antibody test has been reported in the NIH Registry (20) in approximately one-third of the patients. These findings, in addition to the prevalence of PPH in females, the presence of Raynaud's phenomena in 10% of patients with PPH (20) and the occurrence of pulmonary hypertension in patients with connective tissue disease suggests the possibility that PPH is an autoimmune disorder.

CLINICAL MANIFESTATIONS OF PPH

1. Symptoms

PPH is characterized by a slow, insidious onset with progressive clinical deterioration. Initial symptoms can be very mild and vague. Patients with PPH have been frequently misdiagnosed as having hyperventilation, depression and psychiatric illness. On average, patients are usually symptomatic for almost 2 years before seeking medical attention and before the correct diagnosis is made (20). It should be kept in mind that pulmonary hypertension is initially well tolerated and when patients become symptomatic, the disease is already in advanced stages and pulmonary arterial pressure is usually 2 or 3 times the normal value. Usually, the appearance of symptoms coincides with a decrease in cardiac output and with the onset of right ventricular failure (see Figure 7).

It is unknown how long the asymptomatic phase lasts. As mentioned before, several patients may remain completely asymptomatic and the disease may be diagnosed only at autopsy. Based on a few cases in which the diagnoses was incidentally made in a completely asymptomatic patient, 3-5 years may elapse before the patient becomes symptomatic (39). The most common presenting symptom is dyspnea on effort. Ninety percent of the patients enrolled in the NIH Registry complained of dyspnea (20). As the disease progresses, dyspnea is present at rest. In pulmonary venous occlusive disease, dyspnea is due to the increased capillary pulmonary pressure and alveolar edema. Patients with pulmonary plexogenic or thrombotic arteriopathy hyperventilate to compensate for arterial hypoxemia due to reduced cardiac output, decreased diffusion capacity, diminished lung capacity and ventilation-perfusion mismatches. Chest pain, which often presents with the typical anginal characteristic is a common symptom in patients with PPH (75). Since, with few exceptions, (76) coronary arteries are usually normal in patients with PPH, chest pain is probably the result of relative underperfusion of the hypertrophic right ventricle. Histological evidence of right ventricular infarct has been found at autopsy in patients with PPH in the presence of normal epicardial vessels. It has been postulated that, at least in some patients, chest pain could be due to stretching of the large pulmonary arteries.

Fatigue with dyspnea is the most common symptom at presentation and it is due to low, fixed cardiac output. According to the Registry, syncope has been the presenting symptom in 10% of the patients; its incidence increases with the progression of the disease and its appearance usually indicates a poor prognosis at short term. While syncope usually occurs during or immediately after exercise due to the inability to increase cardiac output, it may occur even at rest in the advanced stages of the disease. The role of arrhythmia in the pathogenesis of syncopal episodes in patients with PPH has not been investigated. However, in patient with PPH, even a relatively benign atrial tachyarrhythmia can produce severe systemic hypotension. In terminal cases, bradyarrhythmias have been documented and attributed to abnormal vagal

reflexes arising from the distended right ventricle or in a few cases, in whom alterations of the coronary arteries supplying the sinus and atrioventricular nodes have been documented (76), to acute ischemia.

Less frequent symptoms include cough, hemoptysis, and hoarseness due to compression of the recurrent laryngeal nerve by an enlarged pulmonary artery (77). Raynaud's phenomenon has been described in 10% of patients (20). When right ventricular dysfunction is present, patients will additionally present with symptoms related to right ventricular failure such as peripheral edema, ascites and due to intestinal congestion, nausea, anorexia, poor absorption and muscle wasting. Patients with PPH usually die of refractory right ventricular failure or sudden death.

2. **Signs**

Physical exam is extremely important. In fact, the presence of pulmonary hypertension is often suspected on the basis of the findings on physical exam of a loud P_2. In patients suspected of having PPH, the physical exam helps in excluding several secondary forms of pulmonary hypertension such as COPD, anomalies of the thoracic cage, neuromuscular disorder, and congenital or acquired cardiac diseases. However, it should be kept in mind that a diagnosis of PPH cannot be made solely on the basis of physical exam since it is often impossible to differentiate clinically between PPH and other secondary forms of pulmonary hypertension such as thromboembolic pulmonary hypertension and even Eisenmenger's syndrome. The most frequent findings in patients with PPH are:

1. Increased P_2 -- the pulmonary component of the second heart sound is loud and often louder than the aortic component.

2. Left parasternal lift as a result of right ventricular hypertrophy.

3. Palpable systolic impulse of the pulmonary artery in the 2nd left intercostal space. Often the closure of the pulmonic valve is also palpable.

4. Right-sided third and fourth heart sounds are common as well as: (a) pulmonary ejection and (b) tricuspid regurgitation murmurs

With the onset of right ventricular failure and tricuspid regurgitation, distended jugular veins, pulsatile and enlarged liver, ascites and peripheral edema become prominent physical findings.

Cyanosis is usually mild but may become a prominent feature in the presence of right ventricular failure and low cardiac output. More commonly, cyanosis is due to right to left shunting across a patent foramen ovale. The presence of a patent foramen ovale has been demonstrated in approximately 10% of patients with PPH. Clubbing is rarely seen; in fact, its presence should alert the physician to the presence of an undiagnosed congenital cardiac defect or COPD.

The lungs are usually clear except in the rare patient in whom PPH is due to pulmonary venous occlusive disease. In patients with PVOD, bibasilar rales are usually present due to capillary congestion.

CHEST X-RAY

Chest x-ray is an important initial screening test in the evaluation of patients with clinical signs of pulmonary hypertension to exclude the presence of pulmonary and cardiac disease. It should, however, be kept in mind that the finding of normal lung fields does not exclude the possibility of interstitial lung disease.

Typical findings (20) in primary pulmonary hypertension include enlargement of the main and hilar pulmonary arteries, present in 90% of the cases, and pruning of the peripheral arteries, present in 51% of patients (Figure 15a,b). The presence of all 3 abnormalities has been associated with higher pulmonary artery pressure (66 vs 53 mmHg, $p<0.001$) and lower CI (2.0 vs 2.4, $p<0.05$). It has been suggested that survival in patients with PPH correlates inversely with the size of the main pulmonary artery and the latter correlates with the pulmonary artery pressure. In PPH, the left ventricle is normal in size, while right ventricular enlargement is usually present. The lung fields are generally clear. This finding when associated with the pruning of the peripheral arteries differentiate PPH from pulmonary hypertension secondary to left to right shunts or to increased capillary venous pressure as seen in left ventricular failure and mitral disease. Increased bronchovascular markings and Kerley B lines, however, have been described in patients with pulmonary veno-occlusive disease (78). The radiographic findings of pulmonary congestion, in the presence of a normal left atrial pressure, are considered diagnostic of pulmonary veno-occlusive disease. Chest x-ray has been reported to be completely normal in 6% of patients with PPH confirmed at catheterization.

ELECTROCARDIOGRAM

The electrocardiogram is usually abnormal and reflects the presence of right ventricular hypertrophy (79). The most common findings are: right axis deviation, (QRS axis $>90°$), tall R waves in V_1-V_2. ST segment depression and T wave inversion indicative of right ventricular strain, can occur in the same leads. Right bundle branch conduction defects are often present. The P waves tend to be tall and peaked; however, the finding of "P pulmonale" is not as common as in pulmonary hypertension secondary to lung disease. Atrial arrhythmias are quite rare. In the NIH Registry, none of the 187 patients had atrial arrhythmias (20). The absence of atrial arrhythmia in

patients with PPH contrasts with their frequent occurrence in patients with cor pulmonale. It has been suggested that in PPH, because of low, fixed cardiac output, an increase in rate and the loss of atrial contraction produce such a rapid hemodynamic deterioration to be incompatible with survival.

FIGURE 15a
PLEXIFORM ARTERIOPATHY

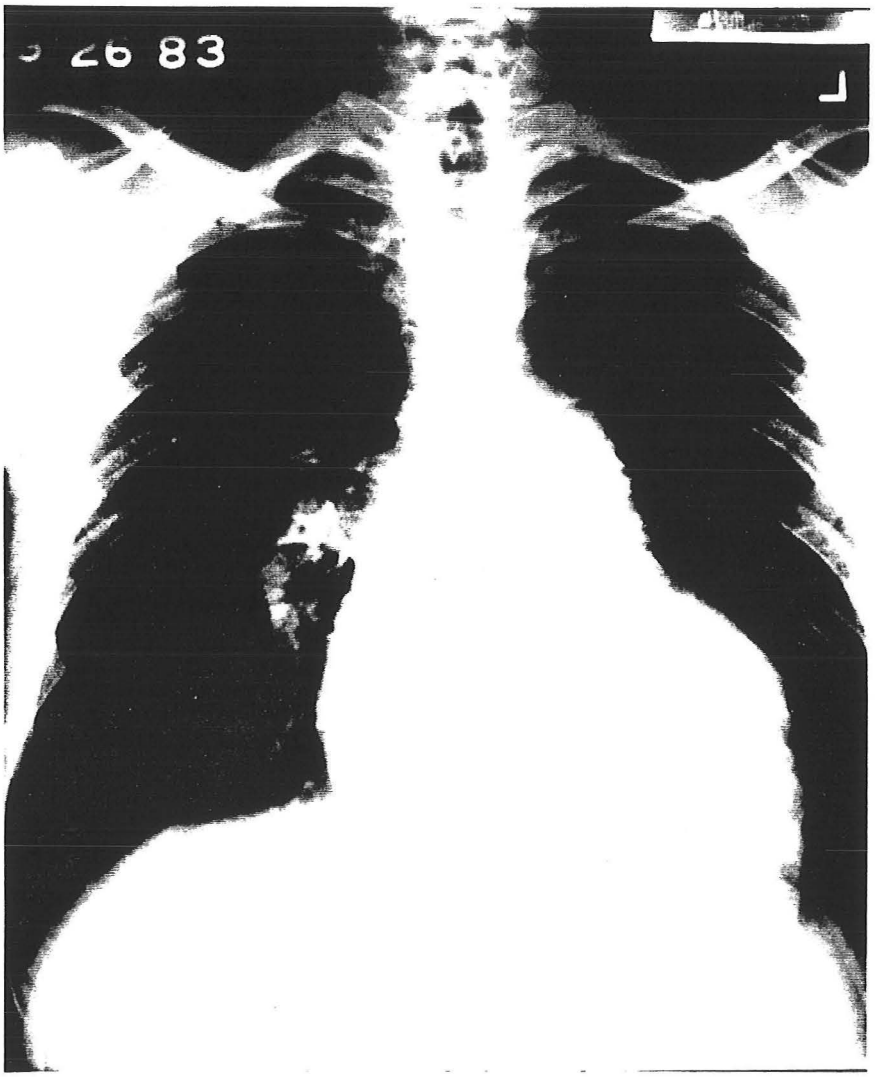
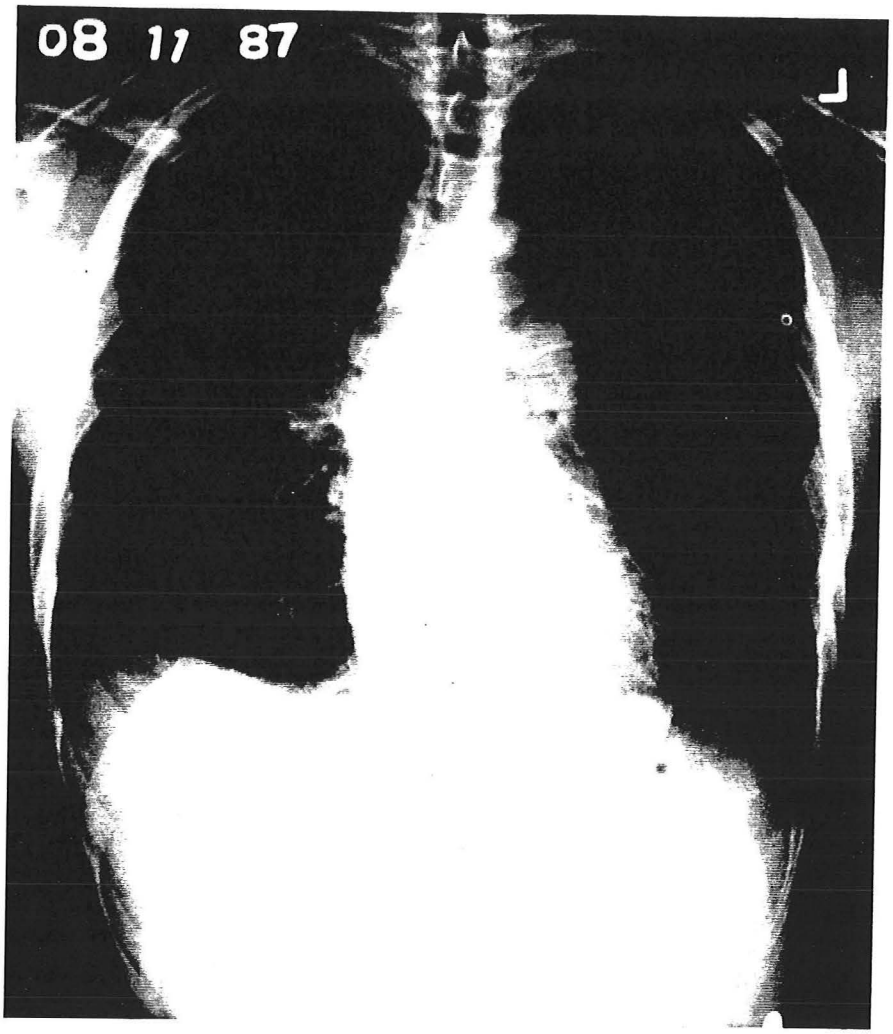


FIGURE 15b
PULMONARY VENO-OCCLUSIVE DISEASE



PULMONARY FUNCTION TESTS

Pulmonary function tests are routinely performed in the evaluation of patients with suspected PPH to exclude underlying obstructive or restrictive lung disease (Table 6). Pulmonary function tests are frequently abnormal in patients with PPH. A mild, but significant, reduction in total lung capacity and vital capacity has been found in the patients enrolled in the NIH Registry (20) confirming data obtained in previous series (80).

TABLE 6
PULMONARY FUNCTION TESTS - NIH REGISTRY ON PPH
(n = 187)

Total lung capacity (% predicted)	89 ± 17
FVC (% predicted)	79 ± 19
FEV_1 (% predicted)	83 ± 17
FEV_1/FVC	82 ± 9
DLCO (% predicted)	73 ± 24
Arterial PO_2	72 ± 16
Arterial PCO_2	31 ± 5

Ann Int Med 1987;107:216.

The mild restrictive pattern has been attributed to increased stiffness of the lungs. The diffusion capacity for carbon monoxide (DLCO) is usually reduced and it has been attributed to the pulmonary vascular lesions increasing the capillary-alveolar distance (80). Hypoxemia is a routine finding in patients with PPH and is due to ventilation-perfusion mismatches and in some patients, to right-to-left shunt across a patent foramen ovale. No correlation has been found between pulmonary function tests, pulmonary artery pressure values and any other clinical index of severity (20). However, an arterial O_2 tension of <70 mmHg is associated with worse prognosis (33).

PERFUSION-VENTILATION LUNG SCAN

A perfusion-ventilation lung scan should routinely be obtained in all the patients suspected of having PPH to exclude chronic pulmonary emboli. The absence of a clinical history for pulmonary emboli is not sufficient for excluding the possibility of pulmonary embolization, which can occur silently in more than half of the cases. The differentiation of primary pulmonary hypertension from hypertension secondary to chronic pulmonary thromboemboli is extremely important especially now that thromboembolectomy is feasible with a relatively low mortality and has been shown to produce remarkable short and long-term improvement (81,82).

Approximately 40% of patients with PPH have a normal perfusion-ventilation scan, 60% have abnormal scans with the majority of patients having patchy defects and a

minority single subsegmental defects (20). Segmental and lobar defects are usually suggestive of thromboemboli and, when found, a pulmonary angiography should always be performed.

While the severity of abnormalities seen on lung scan does not correlate with the hemodynamic and clinical data, a correlation has been found between perfusion patterns and underlying pathologic lesions (83). A normal perfusion scan has been usually found in patients with plexogenic pulmonary arteriopathy, while a patchy distribution has been found more often in patients with thrombotic pulmonary arteriopathy and pulmonary veno-occlusive disease.

No morbid event has been associated with lung scanning in the NIH Registry (20); however, in the past, at least 3 deaths in PPH patients have been attributed to occlusion of pulmonary vessels by albumin macroaggregates during perfusion scan (84,85).

PULMONARY ANGIOGRAPHY

In patients suspected of having PPH, a pulmonary angiogram should be performed only when the lung scan shows a single or multiple, segmental or lobar, defects in order to exclude chronic thromboembolic disease. In chronic thromboembolic disease, angiography will generally show cut offs of the large proximal vessels, while in PPH, the angiogram will show dilation of the main and hilar pulmonary vessels which taper rapidly with marked pruning of the distal vessels (Figure 16) (86). It has been suggested that the level of pulmonary artery pressure in patients with PPH could be correctly estimated by the morphology of the pulmonary vessels and their rate of tapering (87).

There has been considerable concern in performing pulmonary angiograms in patients with elevated pulmonary artery pressure since fatalities have been reported and dye injection into the pulmonary artery produces a 10-15% increase in the already elevated pressure (88). While deaths have been reported in patients with elevated right ventricular end-diastolic pressure when injection has been made in the main pulmonary artery, the risk of the procedure can be minimized by selective injections into the right and left pulmonary arteries, by the use of non-ionic contrast agents and by premedication with atropine to reduce the risk for hypotension and bradycardia (89,90). By following this protocol, no death or significant morbid events have occurred in the NIH Registry (20) and in another large series (91).

ECHOCARDIOGRAPHY AND DOPPLER STUDY

Echocardiographic imaging and Doppler studies play an important role in excluding congenital and valvular heart diseases and left ventricular dysfunction as a cause of pulmonary hypertension. In addition, they allow quantification of the degree of pulmonary hypertension.

FIGURE 16

Typically, in patients with PPH, the right ventricle and right atrium are dilated while the left ventricular cavity is normal or even reduced in size. In the NIH Registry (20), an inverse correlation was found between left ventricular diameter and pulmonary vascular resistance suggesting that under filling of the left ventricle is a reflection of the severity of the pulmonary vascular disease (92). No such correlation was found between right ventricular dimension and pulmonary resistance. Right ventricular

hypertrophy is usually present and the interventricular septum usually shows paradoxical movement as a result of the elevated right ventricular pressure. Other common findings are midsystolic closure of the pulmonic valve and pulmonic and tricuspic regurgitation by Doppler. The usefulness of serial Doppler studies has been advocated for the noninvasive follow up of patients with PPH on vasodilator therapy (93). However, the precision with which Doppler can detect minor changes in pulmonary pressure is questionable and Doppler ultrasound is not currently used for the routine follow up of patients with PPH. The presence of a patent foramen ovale has been detected by echo in approximately 10% of patients with PPH (20).

CARDIAC CATHETERIZATION

The diagnosis of PPH cannot be made without heart catheterization. Catheterization not only allows exclusion of other cardiac diseases as the cause for pulmonary hypertension, but allows accurate determination of pulmonary artery pressure and resistance. The risk of catheterization in patients with pulmonary hypertension is relatively high. Catheterization should be performed only by trained cardiologists in the cardiac catheterization laboratory and should never be performed in patients with PH as bedside procedure because of the risk for pulmonary artery rupture and bradyarrhythmia. In the Mayo Clinic series, 5 deaths in 120 patients studied were directly related to cardiac catheterization (33). In the NIH Registry, 10 of 187 patients who underwent right heart catheterization experienced severe morbid events (extreme hypotension, hemoptysis) during catheterization. No death occurred as a consequence of catheterization in the NIH series (20).

At the time of catheterization, hydrogen or green dye curves and a full oximetry run should be obtained to exclude the presence of intracardiac shunts even if the clinical suspicion was low. Congenital diseases, in fact, especially ostium secundum ASD, can often be missed and a patent foramen ovale can be present in 10% of patients with PPH. The most extensive series of hemodynamic measurements has been collected through the NIH Registry (20). Hemodynamic data from the NIH Registry are summarized in Table 7.

The typical hemodynamic findings are:

1. Elevated pulmonary artery pressure.

2. Normal pulmonary capillary wedge pressure except in patients with PVOD in whom wedge may be elevated. If PVOD is suspected, direct left atrial pressure should be obtained by retrograde catheterization of the left atrium. In PVOD, the left atrial pressure is normal while the wedge is elevated reflecting the presence of obstruction at the level of the pulmonary veins; in contrast in patients with mitral valve disease or LV dysfunction, both capillary wedge pressure and left atrial pressure are elevated (see Figure 8).

3. Normal or low cardiac output -- CO is usually normal in the early stages of the disease and declines during its progression. A cardiac index of less than 2.0 is an index of poor survival in patients with PPH. Even when normal at rest, CO fails to rise normally during exercise due to the presence of fixed pulmonary resistance. The lack of increase in CO during exercise is responsible for the syncopal episodes and dyspnea patients experience.

4. The calculated pulmonary vascular resistance is elevated.

5. Right atrial and right ventricular end-diastolic pressures are elevated. Higher is the right atrial pressure and poorer is the prognosis in patients with PPH.

TABLE 7
PRIMARY PULMONARY HYPERTENSION
HEMODYNAMIC DATA AT ENTRY INTO NIH REGISTRY (n = 187)

	Males	Females
Heart rate (b/min)	82 ± 14	89 ± 19
Right atrial pressure (mmHg)	10 ± 6	9 ± 6
Pulmonary artery pressure (mmHg)		
Systolic	90 ± 27	91 ± 23
Diastolic	45 ± 16	43 ± 14
Mean	60 ± 19	60 ± 16
Capillary wedge pressure (mmHg)	8 ± 3	8 ± 3
Cardiac index (l/min/M^2)	2.3 ± 1.0	2.2 ± 0.9
Pulmonary vascular resistance Index (units)	23 ± 11	27 ± 16

Ann Int Med 1987;107:216.

Patients with more severe symptoms (functional class III and IV) have worse hemodynamic data with higher mean pulmonary artery pressure (62 mmHg vs 56 mmHg, $p<0.05$), higher right atrial pressure (11 mmHg vs 7, $p<0.0001$) and lower cardiac index (2.0 vs 2.7 l/min/M^2, $p<0.001$) than less symptomatic patients (functional class II). As already mentioned, low CI and elevated right atrial pressure are prognostic indicators of poor survival. No correlation has been found between hemodynamic data and duration of symptoms.

LUNG BIOPSY

The usefulness of open lung biopsy in patients with PPH is still controversial (94). Lung biopsy allows (1) the differentiation of primary from secondary forms of pulmonary hypertension, (2) definition of the underlying pathologic lesions and their severity and (3) determination of the prognosis of patients. In fact, patients with plexiform lesions and pulmonary veno-occlusive disease in the NIH Registry have been shown to have worse prognosis than patients with thrombotic lesions, even when differences in baseline hemodynamics were taken into account (40). However, even if lung biopsy may be useful in determining prognosis, its usefulness in clinical practice is limited because patients with PPH usually become symptomatic and come to medical attention late in the course of the disease when the vascular changes are advanced and irreversible. Moreover, while it seems reasonable to expect that the presence of isolated medial hypertrophy would reflect the potential for response to vasodilator therapy, and indeed more severe lesions were seen in patients who did not respond to therapy, there is such a variety in the therapeutic response that histologic examination did not predict how individual patients would respond to medical therapy (40).

Open-lung biopsy in patients with pulmonary hypertension is associated with increased risk for complications. One death occurred in the NIH Registry. Because of the risks and because the knowledge of the histologic features has, in most patients with PPH, minimal or no impact on their management, routine lung biopsy is not recommended in the evaluation of patients with PPH. It should be reserved for those patients in whom the diagnosis of primary hypertension is uncertain.

MANAGEMENT OF PATIENTS WITH PPH

1. Changes in Lifestyle

Patients with PPH usually deteriorate during pregnancy because of increased volume load, tachycardia, and decrease in peripheral resistance not associated to a decrease in pulmonary vascular resistance. Both fetal and material mortality are extremely high in patients with pulmonary hypertension (95). Syncope and cardiac arrest have been described (96,97) during delivery in patients with PPH. Therefore, patients with PPH should be strongly advised against pregnancy. Although oral contraceptives have not been demonstrated to cause pulmonary hypertension, since an association has been suggested and their use may increase the risk for thromboemboli,

other means of contraception are indicated. In the event of pregnancy, if a decision is made to terminate it, prostaglandin F2a should not be used since it is known to increase pulmonary arterial pressure even in normal women (98).

Primary pulmonary hypertension worsens at high altitude. Patients may benefit from moving at sea level and should be advised against traveling at high altitude. Smoking should be prohibited. Nicotine inhibits the vascular production of prostacyclin while leaving the synthesis of thromboxane intact (99); therefore, in theory it is likely to exacerbate pulmonary hypertension. Strenuous physical activity and isometric exercise should be avoided. As mentioned before, in patients with fixed pulmonary resistance, exercise produces a marked increase in pulmonary artery pressure, tachycardia and often severe systemic hypotension. These hemodynamic changes may lead to syncope, myocardial ischemia and acute right ventricular failure. For similar reasons, the risk associated with anesthesia and surgical procedure is quite high in patients with PPH (100).

Prostaglandin synthetase inhibitors, such as indomethacin and histamine H_2 blockers, such as cimetidine, should probably be avoided in patients with PPH based on animal data suggesting that these drugs can increase the severity of hypoxic pulmonary vasoconstriction (101) and on the clinical experience showing hemodynamic improvement with administration of prostacyclin.

2. Oxygen Supplementation

An arterial oxygen tension below 70 mmHg is associated with poor survival and a high incidence of sudden death in patients with PPH (24,33). Since hypoxia produces pulmonary vasoconstriction and increases blood viscosity due to secondary polycythemia, oxygen supplementation may be of benefit to patients with PPH. In the few occasional reports on its use in PPH, no benefit, however, has been documented (102). Nevertheless, oxygen supplementation is usually prescribed for patients who exhibit arterial hypoxemia, defined as either an arterial oxygen saturation $< 90\%$ or an arterial oxygen tension < 60 mmHg. The majority of patients with PPH has normal arterial oxygenation at rest but desaturates during exercise. Oxygen supplementation is usually given in an attempt to improve exercise tolerance and to decrease the risk for myocardial ischemia and arrhythmias.

3. Pharmacological Treatment

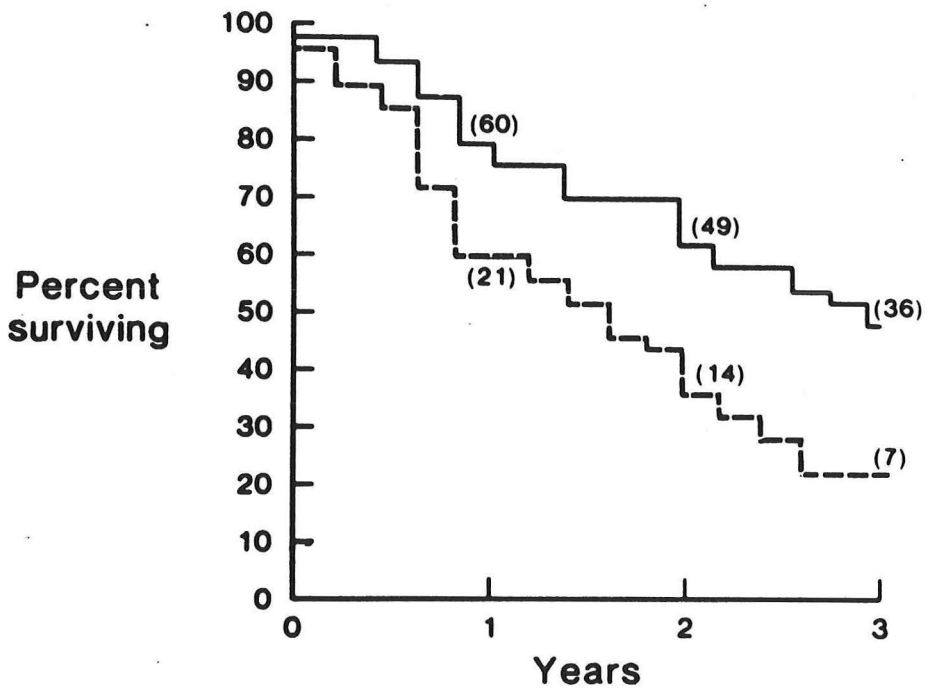
A. *Anticoagulant Therapy:*

Although no prospective study has been performed to assess whether anticoagulant therapy improves clinical course in patients with PPH, anticoagulants are routinely prescribed based on the following justifications:

i. Thrombi have been found in the majority of patients with PPH at biopsy or autopsy. Even if thrombosis is not the cause of PPH but probably the consequence of an endothelial injury, the use of anticoagulants has been advocated in an attempt to halt the progression of the disease.

ii. In a retrospective study (33), from the Mayo Clinic, patients who received anticoagulant therapy had a better survival than patients who did not, 50% vs 25%, respectively at 3 years (Figure 17). A case could also be made for the routine administration of antiplatelet agents such as dipyridamole. Abnormalities of platelet function have been found in patients with PPH and could be relevant to its pathogenesis (103).

FIGURE 17



Observed survival with and without anticoagulant treatment in patients with primary pulmonary hypertension

B. *Digitalis*

There is no data on the effectiveness of digitalis in patients with PPH. Its use should be limited to treatment of right ventricular failure.

C. *Diuretic Agents*

While diuretic agents, such as furosemide, produce systemic arteriolar vasodilation and venodilation, they do not exert any appreciable pulmonary vasodilation. Their use could be deleterious in patients with PPH. In fact, by decreasing blood volume and venous return, they reduce cardiac output with potential for severe hypotension and syncopal episode. Their use in PPH should be limited to (1) patients with right ventricular failure and systemic venous congestion and (2) patients with pulmonary veno-occlusive disease to reduce pulmonary congestion.

D. *Vasodilator Agents*

The use of vasodilator agents for the treatment of PPH has been advocated since the early 50s by Wood (17), who first formulated the hypothesis that PPH was caused by abnormal vasoconstriction of the pulmonary arteries. During the last 10-15 years, treatment of PPH has been primarily focused on the use of different vasodilators. Practically all the available vasodilator agents have been tried in patients with PPH. However, in spite of this enormous interest, we still do not know whether vasodilator therapy is effective in patients with PPH in improving long-term hemodynamics and survival.

Our knowledge is limited due to the lack of prospective, placebo-controlled trials in patients with this disease. The disease is so rare and its natural course so variable that it has been impossible to conduct prospective trials.

There are several additional major problems to be considered when assessing the effect of vasodilator therapy in patients with PPH.

1. There is still no general agreement on what should be considered a satisfactory hemodynamic response of the pulmonary circulation to a vasodilator agent. Theoretically, the "ideal" vasodilator agent should be selective for the pulmonary vessels and not produce systemic vasodilation. Moreover, it should decrease both pulmonary resistance and pressure while increasing cardiac output. More often, however, an increase in cardiac output and a fall in pulmonary resistance are associated with little or no reduction in pulmonary artery pressure. Should such a response be considered satisfactory? I doubt it. In fact, even if clinical improvement has been shown in patients in whom CO increased while pulmonary pressure remained unchanged, such hemodynamic response will increase right ventricular work and wall stress and may increase RV failure and myocardial ischemia.

2. A vasodilator may not produce any hemodynamic change at rest but might improve hemodynamics during exercise and thus be effective in improving exercise tolerance and dyspnea. Unfortunately, vasodilator agents have been assessed during exercise in only a few studies so far.

3. Even when vasodilator drugs produce a satisfactory hemodynamic response, they may exacerbate arterial hypoxemia if they vasodilate vessels supplying poorly ventilated areas of the lungs. This potential negative effect has been overlooked in vasodilator trials in patients with PPH. In our opinion, arterial oxygen content should be monitored during acute drug administration to screen for this potential adverse effect.

4. The question of whether an acute response to a vasodilator agent guarantees a similar long-term response is still unanswered.

5. The individual response to vasodilator agents cannot be predicted on the basis of clinical characteristics and baseline hemodynamic data.

Patients with POVD usually do not respond to vasodilatory agents and, in fact, vasodilators can precipitate acute pulmonary edema in such patients since dilation of

the pulmonary arterioles in the presence of venular obstruction will increase capillary pressure. Since a vasodilator drug can produce severe systemic hypotension, hypoxemia and may even precipitate pulmonary edema, initiation of vasodilator therapy in patients with PPH should always be done in the hospital and possibly during hemodynamic monitoring.

Several vasodilators have been tested during the last 2 decades with controversial results. For every published paper that describes the beneficial effect of a given drug, another paper describing its adverse effects has been published.

Tolazoline and acetylcholine are seldom used now in the management of patients with PPH, but are mentioned here for their historical value. Both agents were used in the early 1950s to test the vasomotor responsiveness of the pulmonary vasculature in patients with pulmonary hypertension. Both drugs have been shown to acutely decrease pulmonary artery pressure and resistance (48,104-105), but they do not have any role in the chronic management of patients with PPH because of the short half life (tolazoline) or inavailability of an oral form (acetylcholine).

The vasodilators which have been or are currently used can be divided in 6 categories:

1. β-adrenergic agonists
2. α-adrenegic blockers
3. Agents acting directly on vascular smooth muscles
4. Converting enzyme inhibitors
5. Calcium channel-blockers
6. Prostaglandins

β-ADRENERGIC AGONISTS

Isoproterenol, both intravenously and sublingually, increases cardiac output, and decreases systemic and pulmonary resistances. However, it usually increases pulmonary artery pressure. While prolonged hemodynamic and symptomatic improvement has been reported in a few patients during several months of sublingual administration (106-108), no impact on survival has been documented and long-term treatment has been complicated by severe side effects (palpitation, hypotension, angina) requiring discontinuation of the drug (109).

Terbutaline, a relatively selective oral β_2 agonist, has been tried with scarce results (110). Currently, β agonists are not used in the management of patients with primary hypertension except for the use of isoproterenol in emergency situations.

α-ADRENERGIC BLOCKERS

The demonstration in animals of α-receptor-mediated pulmonary vasoconstriction and in man of pulmonary vasodilation by tolazoline, which among other properties causes competitive α blockade, stimulated the use of α-adrenergic blockers for the

treatment of patients with PPH. The published experience with phentolamine and prazosin, however, is limited to few cases and is controversial (111-114).

In the first report on the use of phentolamine, this drug, when given IV to 1 patient at a dose of 5 mg caused a reduction in pulmonary pressure and resistance at rest and during exercise (111). The hemodynamic improvement continued in this patient during chronic administration. Similar acute hemodynamic responses were obtained in few other patients (113). However, during chronic administration even if patients reported subjective clinical improvement, no hemodynamic improvement was documented. Similar results have been reported in a few patients with prazosin (114). Moreover, α-blocking agents have many side effects, most important of which is orthostatic hypotension, which has limited their clinical use. Although α-adrenergic receptors regulate pulmonary resistance of the normal pulmonary vasculature, it seems from these small series that their effect on the severely diseased pulmonary vessels of patients with PPH is minimal and their use at the present should probably be limited to the few patients who present in the very early phases of the disease.

DIRECT-ACTING VASODILATORS

Diazoxide, a thiazide derivative with vasodilator but no diuretic properties, has been widely used in the treatment of systemic hypertensive crises. In 1979 (115), it was reported to reduce pulmonary artery pressure and resistance when given intravenously to 3 patients with PPH. In 2 of them, the symptomatic and hemodynamic improvement persisted for several months during oral administration. Similar results were reported in 2 other cases but were not confirmed in other studies (116-119). The intravenous administration of diazoxide can cause dramatic systemic hypotension which in 2 cases was directly related to the patient's death (120). Because of the risk of severe systemic hypotension, diazoxide is not used any longer as a test drug to assess the potential for reversible pulmonary vasoconstriction in patients with PPH. Chronic administration of diazoxide in a series of 9 patients (116) has been complicated by severe side effects (diabetes, peripheral edema, postural hypotension) which led to discontinuation of therapy.

However, in fairness, it should be added that the only reported case of persistent clinical and hemodynamic improvement for 6 years was in a patient who had chronic treatment with diazoxide (121).

HYDRALAZINE

Hydralazine was widely used in the early 80s since it was reported by Rubin and Peter (122) that when administered orally at 50-75 mg every 6 hours, it reduced PVR in 4 patients at rest and during exercise, both acutely and long-term. The results of Rubin were confirmed by Lupi-Herrera and colleagues (123). These authors however, found that the patients who responded to the chronic administration of hydralazine had less severe pulmonary HTN (36 ± 3) than those who did not respond (80 ± 6) and

response to chronic administration could be identified at the time of cardiac cath by infusing hydralazine (0.33 μg/kg over 3 minutes) into the pulmonary artery (Tables 8 and 9).

TABLE 8

CHRONIC TREATMENT WITH HYDRALAZINE IN PPH (n = 4)

		Rest			Exercise		
		PA mmHg	CI l/min/M^2	PVR U/M^2	PA mmHg	CI l/min/M^2	PVR U/M^2
C		36.6±3	3.47±0.34	8.4±1.5	65.3±6	5.68±0.8	10.82±2.18
H	48 hr	32±3	5.24±0.66	5.36±1.3	53.5±5	7.79±1.13	6.81±1.55
	8 mo	25±2	4.96±0.33	3.38±0.82	53.4±4	8.11±0.89	5.57±1.17
p*		NS	<0.01	<0.005	<0.05	<0.01	<0.005
p**		<0.05	<0.05	<0.005	NS	<0.05	<0.01

* Mean control value vs value after 48 hours of hydralazine.
** Mean control value vs value after 8 months of hydralazine.
From Lupi-Herrera, et al: Circulation 1982;65:645.

TABLE 9
ACUTE HEMODYNAMIC RESPONSE TO HYDRALAZINE IN PPH

	Responders (n=6)		Non Responders (n=6)	
	Baseline	Hy	Baseline	Hy
Mean PAP mmHg	36±3	33±4	80±6	87±7
PVR units/M^2	8±1	5±1.0	23±4	20±5
SVR units/M^2	25±4	14±2	25±2	17±1
CI l/min/M^2	3.4±0.3	5.8±0.5	3.0±0.4	4.5±0.7

From data by Lupi-Herrera E, et al: Circulation 1982;65:645.

The initial enthusiasm has been tempered since then by other reports unable to demonstrate any sustained benefical effects (124-126). In addition, more recently, severe clinical and hemodynamic deterioration has been reported during chronic administration (127). Deterioration in all these cases was probably caused by a substantial peripheral vasodilation without any significant change in pulmonary resistance which caused severe hypotension.

NITROGLYCERIN

Nitroglycerin has been tested acutely in both intravenous and sublingual forms, in few patients with PPH (124,128). The effects on pulmonary pressure and resistance have been minimal and cardiac output tended to decline. Because of these results, it appears that nitrates do not play any role in the treatment of PPH. No study has been done during their chronic administration.

CONVERTING-ENZYME INHIBITORS (CEI)

Since angiotensin II has been shown to play a role in the hypoxic pulmonary vasoconstriction in rats (129) and its inhibition prevents the pulmonary vascular changes associated with hypoxia in the same model (130), it was thought that CEI could be of benefit to patients with PPH. Even if few beneficial effects have been reported in isolated patients, the overall experience has been disappointing. Captopril does not decrease pulmonary artery pressure in patients with PPH, it might slightly improve cardiac output, may cause severe systolic hypotension and no long-term benefit has been documented (131-133) (Table 10).

TABLE 10
CAPTOPRIL IN PPH (n=7)

	Baseline		Captopril
Mean PA mmHg	63±13	N.S.	58±6
PVR dynes	1733±655	N.S.	1774±878
CI l/min/M^2	2.0±0.8	N.S.	1.9±0.6
Mean SAP mmHg	118±5	$p<0.01$	97±3

From data by Leier CV, et al: Circulation 1983;67:155.

CALCIUM CHANNEL-BLOCKERS

Theoretically, calcium channel blockers appear to be the most promising drugs for the treatment of PPH. Calcium blockers relax vascular smooth muscles by decreasing the inward movement of calcium. In animals, they have been shown to decrease the pulmonary vasoconstriction induced by hypoxia and thromboxane (4,5). Calcium blockers inhibit the proliferation of vascular smooth muscle cells (134) and the aggregation of platelets (135). These effects may be more important than vasodilation itself in the chronic treatment of PPH. The most widely tested calcium channel blocker has been nifedipine (136-141). When compared to verapamil and diltiazem, nifedipine seems to be more consistent in reducing pulmonary resistance and pressure and improving hemodynamics during exercise (142). We have studied the effects of nifedipine in 7 patients with PPH at rest and during bicycle exercise (141). Nifedipine (20 mg) produced a significant and persistent decrease in mean pulmonary artery pressure (58 ± 14 to 48 ± 16 mmHg, $p<0.01$) and pulmonary vascular resistance (1070 ± 260 to 695 ± 266 dynes/sec/cm^{-5}). Cardiac index increased from 2.5 ± 0.6 to 3.3 ± 0.8 l/min/M^2, $p<0.01$ (Figure 18). In 3 patients tested during exercise, nifedipine resulted in an increase in exercise duration in 2 and a blunting of exercise-induced increase in pulmonary pressure in all 3. All but 1 patient experienced symptomatic improvement during chronic treatment. A persistent hemodynamic improvement was seen in 3 of the 4 patients who underwent recatheterization after chronic treatment (Table 11). Other reports have confirmed that the acute effect of nifedipine are maintained during chronic administration (136,138). However, serious adverse effects have been reported (143-146), including systemic hypotension, right ventricular failure, pulmonary edema, sinus-node arrest and death. Moreover, the hemodynamic and clinical responses cannot, as with other vasodilators, be predicted by baseline characteristics and hemodynamic data and vary widely from patient to patient, underscoring the importance for hemodynamic monitoring when initiating therapy (145,146).

FIGURE 18

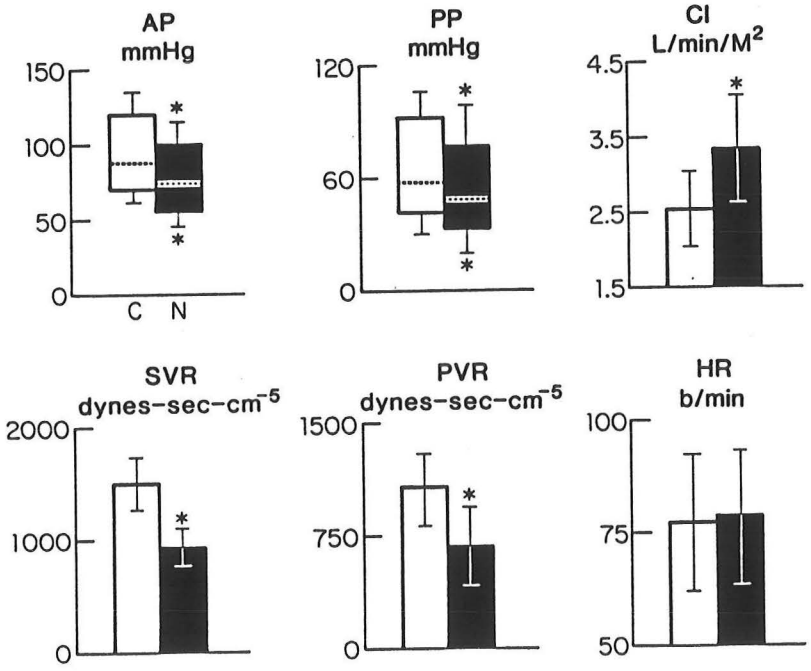


TABLE 11

CHRONIC HEMODYNAMIC EFFECT OF NIFEDIPINE IN PRIMARY PULMONARY HYPERTENSION

Patient	AP mmHg	PP mmHg	CI l/min/m^2	SVR dynes-sec-cm^{-5}	PVR dynes-sec-cm^{-5}
F.B.					
Control	100/57	98/38	2.0	1691	1401
Nifedipine (10 months)	86/62	60/22	3.1	1016	583
B.A.					
Control	120/85	115/65	2.3	1411	1411
Nifedipine (5 months)	108/78	108/60	3.0	1042	1053
S.G.					
Control	110/67	67/33	2.0	1467	800
Nifedipine (3 months)	112/67	60/27	2.1	1327	781
R.B.					
Control	130/70	70/31	2.1	1560	968
Nifedipine (4 months)	120/68	62/24	2.5	1405	728

Similar results have been reported with diltiazem (147) while verapamil in 6 of 9 patients in whom it was given produced adverse hemodynamic effects (increase in resistance, decrease in CO) probably due to its negative inotropic effect (148).

Recently, Rich and colleagues (149) have advocated the use of high dose calcium blockers based on their experience in 8 of 13 patients with PPH who had only minimal reduction in pulmonary resistance and pressure when given the usual standard dose of nifedipine (20 mg) or diltiazem (30 mg) but showed a mean reduction of 48% in PA and 60% in PR when given repeated higher doses of Ca-blockers. No difference in baseline clinical data and hemodynamic was seen between responders and non-responders (Table 12). Six patients were restudied after 1 year of therapy and in 5 of them, the reduction in PA and PR was maintained and associated with regression of right ventricular hypertrophy as evidenced by changes on the EKG and echocardiogram Table 13). Whether this beneficial effect will persist over time and whether treatment with high dose Ca-blockers will improve survival it is unknown at the present time as well as the proportion of patients who will respond to this therapy (8 of 13 in Rich's experience) and how to identify potential responders.

TABLE 12
TREATMENT OF PPH WITH HIGH DOSE CA CHANNEL BLOCKERS

	Responders (n=8)	Non-responders (n=5)
Mean PA mmHg		
Baseline	61 ± 16	60 ± 15
After 1 dose	59 ± 15	60 ± 13
Max dose	35 ± 11	57 ± 15
PVR (Units)		
Baseline	15 ± 8	17 ± 7
After 1 dose	15 ± 6	16 ± 6
Max dose	6 ± 3	14 ± 5
CO (l/min)		
Baseline	3.7 ± 0.9	3.6 ± 1.1
After 1 dose	3.6 ± 0.8	3.6 ± 1.3
Max dose	5.2 ± 0.9	3.4 ± 0.9

PA = pulmonary artery, PVR = pulmonary vascular resistance, CO = cardiac output.
From data by Rich S, et al. Circulation 1987;76:135-141.

TABLE 13
LONG-TERM RESULTS WITH HIGH-DOSE CA BLOCKERS IN PPH

Patient	1		2		3		4		5	
	B	1 yr	B	1 yr	B	1 yr	B	1 yr	B	1 yr
mean PA mmHg	77	28	62	55	41	28	60	39	41	35
PVR Units	17	4	14	10	7	2	23	5	8	4
CO l/min	4.1	5.4	4.1	4.7	4.9	8.8	2.3	7.5	3.7	6.1
QRS axis (degree)	95	66	115	110	98	76	110	78	125	105
RV_1 mm	2	1	4	2	4	1	7	1	5	3
RVID mm	31	21	32	26	28	16	40	28	34	26

B = Baseline
From data by Rich S, et al. Circulation 1987;76:135-141.

PROSTAGLANDINS

Prostaglandins appear to play an important role in modulating pulmonary vascular tone under usual conditions and during hypoxia (150-152). Although not selective for the pulmonary circulation, PGE_1, and prostacyclin (PGI_2) have been shown to acutely decrease pulmonary resistance and pressure (153-155) (Table 14). In addition, they have the advantage that the dose can be titrated according to the hemodynamic effect and discontinuation of the drug, in the event of adverse effects (e.g., systemic hypotension) is followed by rapid return of hemodynamics to pre-drug values (155). Because of their effectiveness and short duration of action, the use of prostaglandins, mainly prostacyclin, has been suggested as a substitute to tolazoline and diazoxide for determining the potential for pulmonary vasodilation in patients with PPH. Prostacyclin is currently the drug of choice to characterize a patient's pulmonary vasodilator potential prior to evaluating other vasodilator drugs. It has been suggested that it is not worthwhile to start any vasodilator agent in patients who did not have a favorable hemodynamic response to prostacyclin because the changes of a response to a different vasodilator are practically nonexistent. In addition to its hemodynamic effects, other potential advantages of prostacyclin include inhibition of platelet aggregation and DNA synthesis in muscular cells stimulated with platelet-derived growth factor (156-157).

TABLE 14
MAXIMAL HEMODYNAMIC EFFECT OF PGI_2 INFUSION

	Baseline		$PG1_2$ (5.7±3.1 ng/kg/min)
SAP mmHg	90±12	N.S.	77±4
PAP mmHg	62±15	p<0.05	55±16
CO l/min	4.2±1.6	p<0.01	6.5±2.0
HR b/min	83±13	N.S.	94±11
TPR units	17.1±8.7	p<0.005	9.7±5.9
SVR units	23.6±7.4	p<0.001	13.1±5.4

From data by Rubin LJ, et al: Circulation 1982;66:334.

Jones (158) has given prostacyclin, administered through an implantable IV infusion pump, as chronic therapy to 10 patients with PPH while waiting for heart-lung transplant (Table 15). In this uncontrolled study, symptomatic improvement and

increase in exercise tolerance and in VO_2 max, from a mean pretreatment value of 7 to 15 ml/kg/min, were reported although no significant reduction in pulmonary artery pressure was seen. Recently, the results of a randomized placebo-controlled trial of chronic intravenous prostacyclin have been published (159). Prostacyclin was infused into a central vein by a portable pump at a rate ranging from 2 to 20 ng/kg/min. In patients randomized to prostacyclin, after eight weeks of therapy, pulmonary vascular resistance have decreased from 21 units to 14, pulmonary pressure decreased from a mean value of 58 to 49 mmHg, while no change was observed in the conventional treatment group (Table 16). Six of the 10 prostacyclin-treated patients had a decrease in mean pulmonary artery pressures greater than 10 mmHg and a decrease greater than 30% in pulmonary resistance. Nine patients who received prostacyclin for up to 18 months had persistent clinical and hemodynamic benefits. However, the dose requirements increased over time necessitating periodic adjustment in the infusion rate in order to maintain the effects. The size of the study group was too small to assess the impact of this treatment on survival.

TABLE 15
EFFECT OF IV PROSTACYCLIN IN 10 PATIENTS WITH PPH

	Baseline		Prostacyclin (5.5 ng/kg/min)
Mean PA mmHg	76±6		73±6
CI l/min/M^2	1.8±0.2	p<0.005	2.2±0.2
PVR dynes	1727±202	p<0.02	1401±175
$P_{\alpha}O_2$ mmHg	48±2	p<0.001	57±2
Walking speed (km/hr)	25±0.7	p<0.01	4.3±0.6
Max VO_2 ml/kg/min	7.2±0.7	p<0.01	14.9±1.4

From data by Jones DK, et al: Br Heart J 1987;57:270.

At the present time, since chronic IV administration is troublesome and may be complicated by serious adverse events (infection, malfunction of pump), the use of prostacyclin should be reserved to patients who do not respond or cannot tolerate treatment with high dose oral calcium blockers and are severely symptomatic.

TABLE 16
HEMODYNAMIC VARIABLES AT BASELINE AND AFTER CHRONIC THERAPY WITH PROSTACYCLIN

	Prostacyclin (n=10)			Conventional Therapy (n=9)	
	Baseline		2 months	Baseline	2 months
Heart rate (b/min)	83		87	85	83
CO (l/min)	3.3	p<0.02	3.9	3.5	3.9
Mean PA (mmHg)	58	p<0.05	49	62	62
Mean SAP (mmHg)	88		83	102	95
PVR (units)	21.6	p<0.02	13.9	20.6	20.4
SVR (units)	29.1	p<0.05	22.9	34.1	30.3

CO= cardiac output, PA = pulmonary artery, SAP = systemic arterial pressure, PVR = pulmonary vascular resistance, SVR = systemic vascular resistance.
From data by Rubin LJ, et al. Ann Int Med 1990;112:485.

NON-PHARMACOLOGIC THERAPIES IN PPH

1. Atrial Septostomy

The creation of a small atrial septal defect has been advocated (160) by same authors based on (1) animal data showing that dogs with atrial septal defect and right ventricular pressure overload, from pulmonary artery banding, tolerate exercise better than dogs without septal defect and (2) the suggestion that patients with PPH with patent foramen ovale may live longer than patients without it.

Atrial septostomy has been tried in few patients without any improvement and cannot be recommended.

2. Heart-Lung Transplantation and Single Lung Transplant

Since the first successful heart-lung transplant in 1981, more than 800 heart-lung transplants have been performed worldwide. Approximately one-third of the recipients

had PPH. The survival rate after this procedure is steadily improving. Currently, according to the International Society for Heart Transplant Registry (161), the 1-year survival is in excess of 60% with a 2-year survival of 55%. Early mortality (<30 days from surgery) remains, however, elevated at 20-30% due to intraoperative complications, post surgical multi-organ failure and infections. During the last 2 years, single lung transplant has been advocated to be superior to combined heart and lung transplant in patients with PPH who have normal or near normal right ventricular function because the procedure is technically less complicated and does not require the use of extracorporeal by-pass. The early mortality in patients with PPH has been lower with single lung transplant than with heart and lung transplant. Thus far, approximately 350 single lung transplants have been performed worldwide (161), mainly in patients with pulmonary fibrosis and α_1 antitrypsin deficiency. However, the number of patients with PPH undergoing single lung transplant is steadily increasing. In 1990, approximately 15% of patients who received single lung transplant had PPH. One further potential advantage of single lung transplant over combined heart and lung transplant seems to be the low incidence of chronic obliterative bronchiolitis after single lung transplant. Obliterative bronchiolitis can cause significant impairment in pulmonary function and currently represents the major long-term complication after pulmonary transplantation (162,163). Since its incidence increases over time (10% at 1 year, 33% at 3 years), in my opinion, it is too early to determine if indeed its occurrence is less frequent after single lung transplant than after combined heart and lung transplant.

Both procedures improve survival and function in patients with end-stage PPH (162,164,165). A dramatic decrease in pulmonary artery pressure and resistance associated with an increase in cardiac output occurs within a few hours following single lung transplant. Normalization of right ventricular size on chest x-ray follows in a few days while regression of right ventricular hypertrophy on echocardiogram or EKG usually takes several weeks (Figure 19a,b). The hemodynamic improvement seen with both procedures persist long term and it is associated with normalization of right ventricular ejection fraction in recipients of single lung, as recently shown by Patterson, and near normalization of exercise tolerance (Table 17).

TABLE 17

LONG-TERM HEMODYNAMIC DATA AFTER SINGLE LUNG TRANSPLANT IN PATIENTS WITH PPH

	n = 7	
	Pretransplant	Posttransplant
Mean pulmonary artery pressure (mmHg)	58	16
Mean right atrial pressure (mmHg)	8	1
RV ejection fraction (%)	25	52

From data by Patterson A, et al: Symposium on Lung Transplant, Laguna Niguel, Feb. 20-22, 1991

FIGURE 19a
PREOPERATIVE CHEST X-RAY

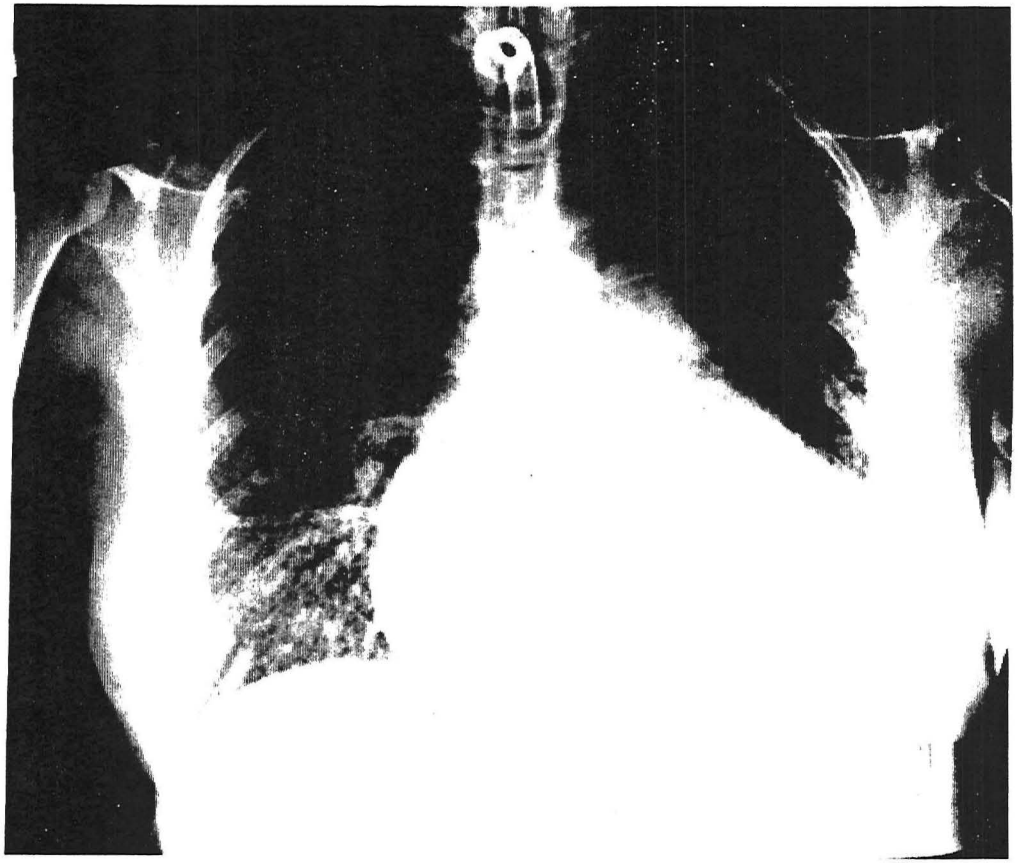
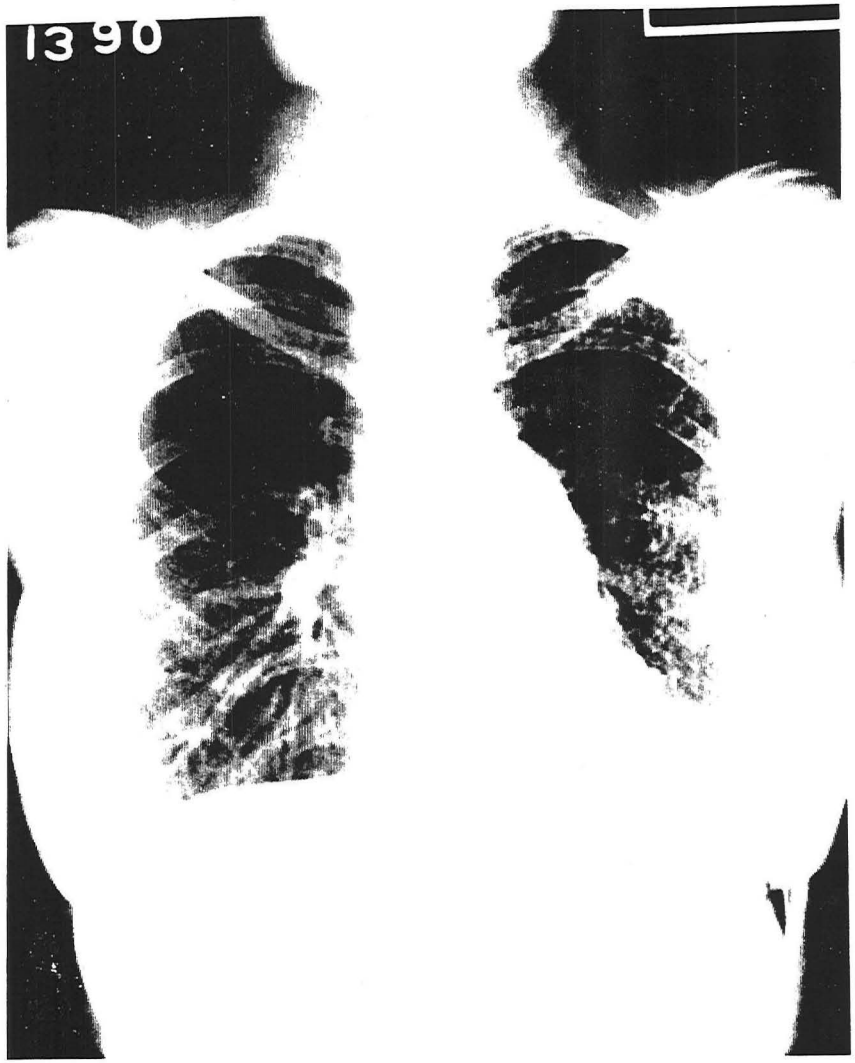


FIGURE 19b
10 WEEKS AFTER SURGERY



SUMMARY

PPH is a rare disease with a poor prognosis which affects mainly young subjects. The cause(s) is (are) unknown. Currently, attention is focused on endothelial cells as the site of initial injury with secondary platelet activation and smooth muscle cell proliferation leading to obstruction of the pulmonary vessels.

The majority of patients is diagnosed very late in the course of the disease when the anatomic changes are irreversible. Current treatment is based on the use of anticoagulant and vasodilator agents. Medical treatment may improve symptoms in several patients but, so far, has not been shown to improve their survival. A better understanding of the pathogenesis of the disease will hopefully enable us to develop better therapeutic regimens.

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