Primary pulmonary hypertension: An overview of epidemiology and pathogenesis

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■ ABSTRACT

Pulmonary arterial hypertension (PAH) refers to a group of diseases characterized by high pulmonary artery pressure of unknown mechanism. Primary pulmonary hypertension (PPH) is the idiopathic subset of PAH that affects a mostly young population and is more common in females than in males. A familial form of PPH accounts for about 6% of cases, and its autosomal dominant gene was recently identified. Pulmonary arterial hypertension is histologically characterized by endothelial and smooth muscle cell proliferation, medial hypertrophy, and thrombosis in situ. The pathogenesis of PAH remains unclear. Elevated pulmonary vascular resistance seems to result from an imbalance between locally produced vasodilators and vasoconstrictors, in addition to vascular wall remodeling. Nitric oxide, a locally produced selective pulmonary vasodilator, appears to play a central role in the pathobiology of PAH.

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Better understanding of the pathogenesis of primary pulmonary hypertension (PPH) over the last decade has led to new treatments that have changed the course of this once uniformly fatal condition. This progress is especially welcome because PPH affects a predominantly young and productive population. This article reviews recent advances in our understanding of the pathogenesis, epidemiology, and genetics of PPH.

■ DEFINITION AND CLASSIFICATION

Primary pulmonary hypertension is defined by an elevation in mean pulmonary artery pressure to greater than 25 mm Hg at rest or greater than 30 mm Hg during exercise in the absence of an identifiable etiology. In 1998 the second World Health Organization (WHO) conference on pulmonary hypertension[1] classified PPH with other pulmonary hypertensive conditions under the grouping of *pulmonary arterial hypertension* (PAH). Under this so-called Evian classification (the WHO conference was held in Evian, France), which was based on similarities in clinical features, PAH refers to a vasculopathy of unknown mechanism that involves the small muscular arteries and arterioles. Pulmonary arterial hypertension can be associated with known diseases, such as connective tissue diseases and human immunodeficiency virus (HIV) infection, in addition to classic idiopathic PPH **(Table 1)**.

■ HISTOPATHOLOGY

The hypertensive pulmonary arteriopathy seen in patients with PPH affects the muscular arteries and

arterioles and probably represents a combination of injury and repair. Several histopathologic patterns can be seen, although none is pathognomonic, since the diagnosis of PPH still relies on the exclusion of secondary causes.[2,3]

Plexogenic pulmonary arteriopathy (Figure 1) is the most common lesion seen in PPH. It is characterized by medial hypertrophy, fibrotic intimal lesions that may comprise organized thrombi, and destructive lesions involving the entire arterial wall. **Thrombotic pulmonary arteriopathy** is defined by the presence of organized mural thrombi resulting from thrombosis in situ in the setting of an intact arterial wall and a nondilated vessel. These two lesion types, though distinct histologically, appear to be the product of the same disease process, since different members of kindreds with familial PPH had evidence of both lesions.[4]

Isolated medial hypertrophy, the third type of histopathologic lesion in PPH, consists of a pattern of increased thickness of the medial smooth muscle wall, duplication of the elastic laminae in muscular arteries, and muscularization of the arterioles. This rare pattern may actually precede the formation of the plexogenic lesions and is thought to be reversible with treatment.[5]

■ EPIDEMIOLOGY

A few case series of elevated pulmonary artery pressures in otherwise healthy young people in the 1950s and 1960s,[6,7] along with the epidemic of anorexigenic-associated PPH in Europe, led to the first WHO conference on PPH in 1973. As part of an ensuing international effort to better understand this rare condition, the National Heart, Lung, and Blood Institute's Division of Lung Disease in 1981 initiated the national Primary Pulmonary Hypertension Patient Registry. The registry prospectively enrolled 187 patients from 32 referral centers nationwide through 1985.[8] These patients' demographic characteristics constitute the best available data to date on the epidemiology of PPH.

The mean age of this population was 36.4 years (± 15 SD; range 1–81). A 1.7:1.0 female-to-male preponderance was noted. Nearly one tenth of patients were older than 60 years of age. No racial predilection was found.

Subsequent retrospective reports from France,[9] Israel,[10] and Japan[11] found comparable mean ages among samples of patients with PPH (39.0, 42.8,

TABLE 1
The 1998 WHO Evian classification of pulmonary hypertension

1. Pulmonary arterial hypertension
  1.1 Primary pulmonary hypertension
    a. Sporadic
    b. Familial
  1.2 Related to:
    a. Collagen vascular disease
    b. Congenital systemic to pulmonary shunts
    c. Portal hypertension
    d. HIV infection
    e. Drugs/toxins (anorexigens or others)
    f. Persistent pulmonary hypertension of the newborn
    g. Other

2. Pulmonary venous hypertension
  2.1 Left-sided atrial or ventricular heart disease
  2.2 Left-sided valvular heart disease
  2.3 Extrinsic compression of central pulmonary veins
    a. Fibrosing mediastinitis
    b. Adenopathy/tumors
  2.4 Pulmonary veno-occlusive disease
  2.5 Other

3. Pulmonary hypertension associated with disorders of the respiratory system or hypoxemia
  3.1 Chronic obstructive pulmonary disease
  3.2 Interstitial lung disease
  3.3 Sleep-disordered breathing
  3.4 Alveolar hypoventilation disorders
  3.5 Chronic exposure to high altitude
  3.6 Neonatal lung disease
  3.7 Alveolar-capillary dysplasia
  3.8 Other

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
  4.1 Thromboembolic obstruction of proximal pulmonary arteries
  4.2 Obstruction of distal pulmonary arteries
    a. Pulmonary embolism (thrombus, tumor, ova, parasites, foreign matter)
    b. In situ thrombosis
    c. Sickle cell disease

5. Pulmonary hypertension due to disorders directly affecting the pulmonary vasculature
  5.1 Inflammatory
    a. Schistosomiasis
    b. Sarcoidosis
    c. Other
  5.2 Pulmonary capillary hemangiomatosis

Adapted from reference 1 with permission of the World Health Organization.

and 41.8 years, respectively) and similar female-to-male ratios, indicating an apparent worldwide female preponderance.

No studies on the incidence of PPH have yet been performed, but the incidence has been estimated at 1 to 2 cases per 1 million inhabitants per
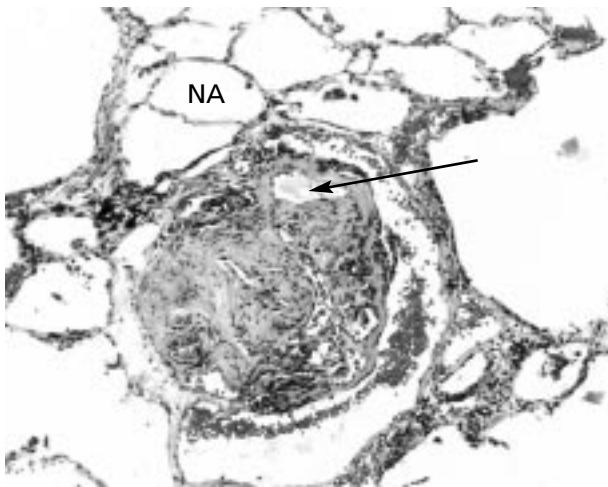
Figure 1. Histopathologic photograph of a plexogenic pulmonary arteriopathy lesion surrounded by normal alveoli (NA). The arrow points to a newly formed vascular lumen. Color versions of this photograph and another photograph of this lesion taken with a different stain appear on the cover of this supplement. Photo courtesy of Carol F. Farver, MD.

year.[8] Considering the rarity and subtle presentation of this disease, underdiagnosis and underreporting are likely widespread, making calculation of a true incidence difficult.

Familial PPH

In the national registry for PPH,[8] 12 (6%) of the 187 enrolled patients had a first-degree relative affected by the same disease process. Familial PPH appears to be inherited as an autosomal dominant trait with a variable but low gene penetrance, with some individuals inheriting the trait without exhibiting the phenotype.[12] Genetic anticipation further affects the gene penetrance, with subsequent generations developing PPH at an earlier age.[13] Interestingly, 160 (57%) of 282 children born to parents who were carriers of the gene for familial PPH were female, suggesting either a selective wastage of male fetuses or a preferential fertilization by an X over a Y male gamete.[13]

In 1997, the gene for familial PPH was mapped to chromosome 2q31–32.[14,15] In 2000, the bone morphogenetic protein receptor type II gene (*BMPR2*) was identified as the actual gene for familial PPH and its product was recognized as a transforming growth factor beta receptor, suggesting a role for this receptor in maintaining pulmonary vascular integrity.[16,17] In fact, mutations in *BMPR2* were also found in 13

(26%) of 50 patients with sporadic or nonfamilial PPH in one series,[18] which suggests that it may soon be possible to identify individuals at risk for PPH.

These landmark discoveries in the genetics of familial PPH have opened the way to a better understanding of the pathogenesis of PPH and may have important therapeutic implications as more of the molecular pathways are revealed.

■ PATHOGENESIS

Pulmonary arterial hypertension, although associated with some disease entities, has a still-unknown mechanism that probably results from multiple noxious stimuli targeting a predisposed pulmonary vasculature. The most obvious predisposing factors are the mutations in the *BMPR2* gene[16,17] that result in familial PPH and in some cases of sporadic PPH, as discussed above.[18]

The epidemic of PAH that developed in users of appetite-suppressant drugs,[19,20] probably through these drugs' serotonergic effects,[20,21] is an example of a noxious stimulus causing PAH. However, because only 0.1% of aminorex users were affected, possible polymorphism at the level of the vascular smooth muscle serotonin transporter was recently hypothesized as a predisposing factor for PPH in these individuals.[21] The mechanism of injury leading to PAH associated with HIV infection is less clear,[22] although some evidence points to stimulation of endothelial cell growth by infected T lymphocytes.[23] Pulmonary arterial hypertension is also associated with connective tissue diseases without any obvious pathophysiologic link.[24] Some have proposed the possibility of an autoimmune injury leading to the vasculopathy.[25,26] Deficiency of thyroid hormone, either through a shared autoimmune insult to the thyroid gland and the pulmonary vasculature, or through loss of the thyroid hormone's vasomotor role, has also been associated with PPH.[27] Moreover, the paracrine actions of the vascular endothelium appear dysfunctional in PAH, resulting in abnormal proliferation of vascular smooth muscle and endothelial cells, which may contribute to the increased pulmonary vascular resistance observed in this disease.

Many advances have been made in unraveling the pathogenesis of PAH. In many instances, however, any cause-and-effect explanation for the observed abnormalities remains blurred, as most abnormalities are found in advanced stages of pulmonary hypertension.

Endothelial dysfunction/vasoconstriction

An injured endothelium probably represents the response to a variety of stimuli that lead to secondary pulmonary hypertension, but the endothelial dysfunction seen in PPH seems to be idiopathic, or of yet unknown etiology. It remains uncertain whether this constitutes one of the triggers for the vasculopathy of PPH or whether it is in response to a variety of noxious mechanical and chemical stimuli. The endothelial malfunction is manifested by an imbalance between locally produced vasoconstrictors and vasodilators, resulting in abnormal vascular tone. Of those local mediators, nitric oxide, prostacyclin, and endothelin-1 are among the best studied and carry several therapeutic implications.

Nitric oxide. The endothelium-derived relaxing factor nitric oxide (NO) has been shown to play a pivotal role in the pathobiology of PPH.[28–33] Nitric oxide is a potent pulmonary vasodilator that is produced locally in the lung and has profound effects on smooth muscle relaxation and proliferation. Normal pulmonary vascular tone is maintained in part by local production of the vasodilator NO, and NO exerts an inhibitory effect on vascular smooth muscle cell proliferation and migration.[34] Anatomic sources of NO in the lung include the pulmonary circulation, the lower airways, and the upper airways and paranasal sinuses.[35]

Nitric oxide is endogenously synthesized by NO synthases, which convert L-arginine to L-citrulline and NO in the presence of oxygen and several cofactors.[36,37] Three NO synthases (types I, II, and III) have been identified and are widely expressed in various tissues, including the lungs.[38] Nitric oxide also can be detected in the exhaled breath of humans.[35,39]

Once produced, NO is freely diffusible and enters pulmonary smooth muscle cells to activate soluble guanylate cyclase and produce guanosine 3′,5′-cyclic monophosphate (cGMP).[36] Increased cGMP activates a kinase that phosphorylates a calcium-dependent potassium channel, leading to hyperpolarization and pulmonary vascular smooth muscle relaxation. The close proximity of the airways to the blood vessels allows the NO produced in high levels in the upper[40] and lower airways by NO synthase II[35] to affect the pulmonary vascular tone in concert with the low NO levels produced by NO synthase III in the vascular endothelium. As soon as this potent vasodilator's job is done in the lung, it binds to hemoglobin and has virtually no effect on systemic hemodynamics, making it a truly selective pulmonary vasodilator.

Interestingly, patients with PPH have low levels of NO in their exhaled breath.[30] In fact, the severity of pulmonary hypertension correlates inversely with NO levels estimated by measurement of NO reaction products in bronchoalveolar lavage fluid **(Figure 2)**.[30] Although this is a more complex issue than simple lack of a vasodilator, replacement of NO seems to work well in treating the problem.[41] Exogenous administration of NO gas by inhalation is a highly effective and specific therapy for PPH.[33,41,42] Although cost and unresolved technical difficulties in the delivery of inhaled NO have prevented its widespread use to date,[41] recent evidence suggests that other therapies for PPH may exert their benefits at least partially through endogenous NO.[28,31] Nitric oxide levels were found to be increased in the exhaled breath of patients with PPH after therapeutic infusion of epoprostenol, a prostacyclin analogue.[31]

Endothelin-1 is a peptide produced by the vascular endothelium that has potent vasoconstrictive and proliferative paracrine actions on vascular smooth muscle cells.[43] The pulmonary circulation plays an important role in the production and clearance of endothelin-1, and this physiologic balance is reflected in circulating levels of endothelin-1.[44] Patients with pulmonary hypertension, PPH in particular, have an increased expression of endothelin-1 in pulmonary vascular endothelial cells.[45] Similarly, serum endothelin-1 levels are increased in patients with pulmonary hypertension.[46]

Prostacyclin. The endothelium also produces prostacyclin (PGI_2) by cyclooxygenase metabolism of arachidonic acid. Prostacyclin causes vasodilation throughout the human circulation[47] and is an inhibitor of platelet aggregation by its action on platelet adenylate cyclase.[48]

The final enzyme in the production of PGI_2 is prostacyclin synthase. Transgenic mice overexpressing this enzyme in their respiratory epithelial cells are protected against the development of hypoxic pulmonary hypertension,[49] and the remodeled pulmonary vasculature in lung tissue obtained from patients with severe PPH expresses low levels of prostacyclin synthase when compared with normal lung tissue.[50] In addition, a PGI_2 metabolite, 2,3-dinor-6-keto-PGF, is diminished in the urine of patients with pulmonary hypertension, further underscoring the role of endothelial dysfunction in the pathobiology of PPH.[51]
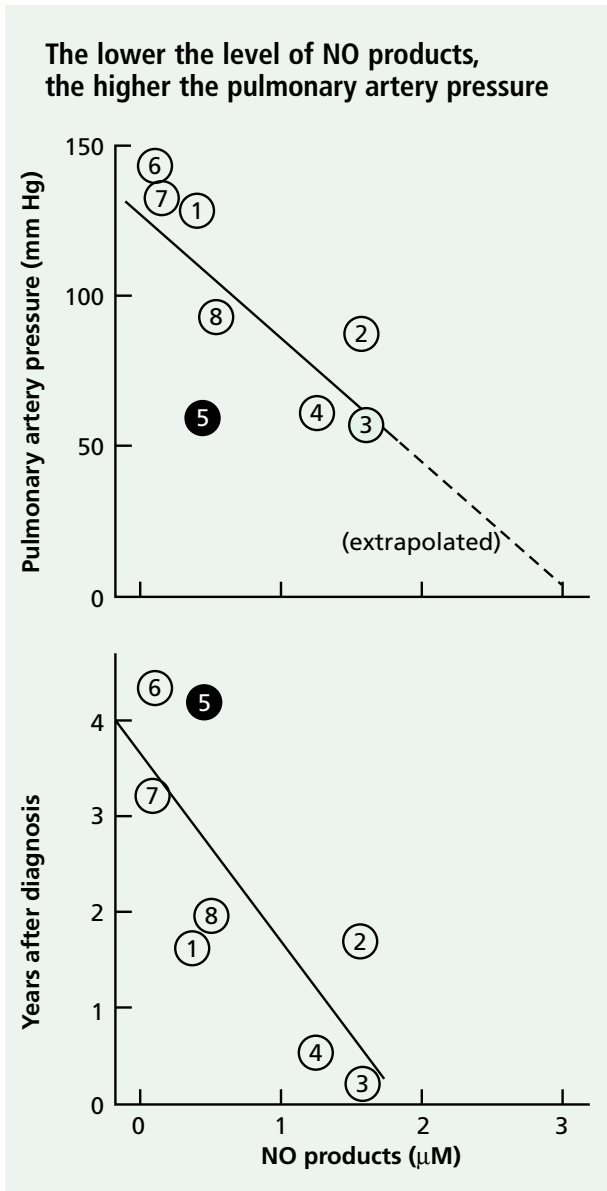
The lower the level of NO products, the higher the pulmonary artery pressure

Figure 2. Relationship of reaction products of nitric oxide (NO) in bronchoalveolar lavage fluid to pulmonary artery pressures (top) and years after diagnosis of PPH (bottom). The circles represent individual patients. The filled circle represents a patient with familial PPH who died during the study. Reprinted, with permission, from reference 30. © American Lung Association

Remodeling

In addition to the pulmonary vasoconstriction that results from dysregulation of the local endothelial mediators as discussed above, pulmonary vascular remodeling seems to play a major role in the increased vascular resistance seen in PPH. An abnormal proliferation of endothelial cells occurs in the irreversible plexogenic lesion.[52] These proliferating endothelial cells are monoclonal in origin, raising the possibility that a random somatic mutation may be one of the initial steps leading to sporadic PPH.[53] The endothelial cells express angiogenic factors (eg, vascular endothelial growth factor), which suggests a role for them in the disordered angiogenesis that may be part of the plexiform lesion formation.[54] In addition, pulmonary vascular smooth muscle cells that normally have a low rate of multiplication undergo proliferation and hypertrophy. Those smooth cell changes arise from the loss of the antimitogenic endothelial substances (eg, PGI_2 and NO)[55,56] and an increase in mitogenic substances (eg, endothelin-1).[57] At the same level, the growth-inhibitory effect of transforming growth factor beta on vascular smooth cells is lost, which may explain the molecular mechanism of the mutation in familial PPH.[18,58]

Other stimuli arise from locally activated platelets that release thromboxane A_2 and serotonin, which act as growth-promoting substances on the vascular smooth muscle cells.[52,59,60] In fact, elevated blood levels of serotonin are found in patients with PPH,[61] perhaps because of an abnormality in the platelet storage pool that is the main source of serotonin in the human circulation.[62] Pulmonary vascular smooth cell hyperplasia also correlates with polymorphism and overexpression of the serotonin transporter, which may constitute an additional factor in an individual's genetic susceptibility to developing PPH.[21,63] On the other hand, the pulmonary artery smooth muscle cells in PPH appear to be in an abnormally depolarized state.[64] This abnormal resting potential results in a heightened state of vasoconstriction secondary to increased levels of cytosolic Ca2+ and seems to relate to a primary dysfunction or downregulation of the voltage-gated K+ channels.[64,65]

In addition to smooth muscle cell proliferation, an increase in extracellular matrix deposition contributes to the medial hypertrophy in PAH.[66] The extracellular matrix is remodeled through a dynamic process of matrix protein degradation and synthesis triggered by the high flow and pressure in the pulmonary vasculature, resulting in the obliterative changes seen in the pulmonary arteries.[66] A perivascular inflammatory cell infiltrate observed in the plexogenic lesion indicates that cytokines may also play a role in its development.[52]

Thrombosis

In a large retrospective series that looked at lung tissue obtained from autopsy specimens of patients with PPH,[67] 22 of 56 pathologic specimens showed evidence of thrombi confined to the small muscular arteries. This was atypical for the classic appearance of venous thromboembolism, and the concept of thrombosis in situ in PPH emerged.

Pulmonary arterial hypertension seems to be associated with a prothrombotic milieu that is a consequence rather than a cause of the vasculopathy, although this remains debatable. The determinants of this increased propensity for thrombosis arise at the level of the microvasculature, where the dysfunctional endothelium loses the anticoagulant properties that usually prevent intravascular clot-ting of blood material.[68] Instead, the procoagulation mediators that are usually inhibited under physiologic conditions seem to be activated. In fact, blood thrombin activity is increased in patients with pulmonary hypertension, indicating activation of intravascular coagulation,[69] whereas soluble thrombomodulin, a cell membrane protein that acts as an important site of thrombin binding and coagulation inactivation, is decreased.[70] In addition, PGI_2 and NO, both inhibitors of platelet aggregation, are decreased at the level of the injured endothelial cell, as discussed above. Circulating platelets in patients with PAH seem to be in a continuous state of activation[51] and contribute to the prothrombotic milieu by aggregating at the level of the injured endothelial cells.[71]

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