Clinical Insights Into the Pathogenesis of Primary Pulmonary Hypertension*

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Because of the lack of adequate animal models, much of our knowledge of the pathogenesis of primary pulmonary hypertension has come from clinical experiences. The clinical response to vasodilators, prostanoids, and anticoagulants as treatments appear to correlate with the pathologic changes of medial hypertrophy, intimal proliferation, and thrombosis. Endothelial dysfunction, as a primary abnormality in primary pulmonary hypertension, provides an explanation for the pathologic and clinical expression of the disease in its various forms. Other clinical features of the disease, such as age of onset and rapidity of progression, may be influenced by triggers of the disease process and underlying individual genetic susceptibility. As we have been able to correlate the spectrum of clinical observations with advances in vascular biology, newer, more focused and effective therapies should begin to emerge.

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The pathogenesis of primary pulmonary hypertension (PPH) has been elusive. The disease is rare, which makes it difficult to study patients who present with PPH in its various stages. Because there is no comparable animal model, testing clinical hypotheses in the animal laboratory is problematic and forces speculation. Despite these obstacles, a wealth of information has been obtained from the clinical experience in diagnosing and treating patients with PPH that has provided insight into the underlying pathogenesis of the disease. Although the clinical experience tends to raise more questions than answers, this review will focus on advances in our current understanding of the pathogenesis of this disease derived from clinical observations.

PULMONARY HYPERTENSIVE VASCULOPATHY

Medial Hypertrophy

PPH represents a disease that is manifest by a pulmonary hypertensive vasculopathy that has multiple expressions.1 One pathologic feature of PPH is medial hypertrophy of the pulmonary arterioles that appears to represent vasoconstriction.2 Although it is usually seen in conjunction with other lesions, isolated medial hypertrophy has been described in several pathologic series of patients dying with PPH and seems to be more prevalent in children than adults.1,3,4 The vessels are characterized by marked thickening of the media, with only modest amounts of intimal proliferation.5 It was originally postulated that this represented uncontrolled growth and constriction of the smooth muscle cells of the pulmonary arterioles.2 Pulmonary vasoconstriction was believed to be the cause of pulmonary hypertension.5

Clinically, we test for the presence of pulmonary vasoconstriction by challenging the patient with a short-acting vasodilator and measure the response. Observing a substantial fall in pulmonary artery pressure and pulmonary vascular resistance (PVR) characterizes the patient as responsive, and thus implies reversible pulmonary vasoconstriction.6 The unresponsive patients, it is assumed, have advanced vascular changes that preclude the drug from causing smooth muscle cell relaxation. Consistent with this hypothesis, Sitbon and colleagues7 have characterized patients with PPH as responders or nonresponders to nitric oxide based on acute reductions in mean pulmonary artery pressure following inhalation of the gas. However, Palevsky and colleagues8 compared the acute effects of several vasodilators with histology in patients with PPH and were unable to correlate the two. Obviously the mechanisms for pulmonary vasoconstriction and vasodilation are more complex than initially thought.

The monocrotaline rat model has been one of the most widely used animal models to study various aspects of PPH.9 In that model, monocrotaline is injected into the rat; this results in medial hypertrophy of the pulmonary arterioles and pulmonary hypertension after approximately 4 weeks. However, close observation of the development of the medial

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hypertrophy revealed that it is preceded by intense metabolic activity and proliferation of the pulmonary endothelial cell layer. Studies such as those suggest that the development of medial hypertrophy is regulated by the endothelium, and that isolated medial hypertrophy represents an abnormality of endothelial cell control over pulmonary vascular smooth muscle. Nitric oxide has been identified as an endothelial-derived mediator that has important regulatory properties over vascular tone. It is believed that nitric oxide, a powerful vasodilator, keeps the pulmonary vascular bed in a relatively relaxed state. One hypothesis is that the loss of normal endothelial cell production of nitric oxide could result in pulmonary arterial vasoconstriction and smooth muscle cell hypertrophy.

Recently, reduced levels of nitric oxide synthase in the pulmonary vasculature of patients with PPH have been characterized, which implicates inadequate local nitric oxide production as part of this disease process. In addition, the more severe the pulmonary vascular changes, the lower the levels of nitric oxide synthase observed. This may account for the clinical characterization of patients as being responsive or unresponsive to vasodilator challenge. Comparing the effects of vasodilators that are considered to be endothelial dependent, such as acetylcholine, with ones that are endothelial independent, such as nitroglycerine or nitric oxide, has been attempted with the hope of characterizing the degree of endothelial cell dysfunction in a given patient. The studies suggest a progressive loss of vasoreactivity in the pulmonary vascular bed that correlates with the severity of the disease. The response to any pulmonary vasodilator in PPH will likely be a graded one, and the characterization of an individual patient as being a responder or nonresponder an attempt to categorize them for selection of long-term therapy.

One example is the common practice to categorize patients with PPH as being responders or nonresponders to calcium blockers. However, there is no accepted definition of a response to calcium blockers, with investigators arbitrarily choosing an acute change in PVR that varies between 20% and 50%. In the calcium blocker experience, it is clear that there is a subset of patients who seem to be highly responsive, who maintain a sustained fall in pulmonary artery pressure and PVR while receiving long-term therapy indefinitely. As with nitric oxide, one would presume that the difference between these subgroups of patients relates to the severity of the pulmonary vascular disease.

However, the experience with calcium channel blockers has raised more questions than it has answered. If one presumes that the calcium channel blocker is opposing pulmonary vasoconstriction, which occurs as a result of endothelial injury, then one would expect that the long-term effectiveness of the calcium channel blockers would be limited by progressive endothelial dysfunction at some point in time. However, this does not appear to be the case, as we have patients with PPH receiving calcium channel blockers with sustained improvement for >10 years. Whether the calcium channel blockers affect endothelial cell proliferation or injury is unknown. It has also been shown that the vasodilatory response to calcium channel blockers does not represent the maximal extent of pulmonary vasodilator reserve. For example, patients who are responsive to calcium channel blockers will have a further fall in pulmonary artery pressure and PVR when a more potent vasodilator such as IV adenosine is added. Another important question is how to interpret the more common acute hemodynamic response to calcium blockers in patients with PPH, namely a rise in cardiac output and thus a fall in PVR, without any fall in pulmonary artery pressure. The conditions of some patients will improve with long-term therapy, whereas others will deteriorate. Unfortunately, the widespread practice of using calcium blockers in PPH without documenting beneficial effects hemodynamically has probably led to worsening and death in many patients.

From clinical observations, one can conclude that pulmonary vascular smooth muscle cell hypertrophy appears to express marked reactivity early in the disease, and that it loses reactivity as endothelial cell injury progresses. It is possible that pulmonary vasoconstriction and smooth muscle cell hypertrophy are linked to endothelial cell regulation via nitric oxide. It remains unclear, however, what role the calcium channel plays in the regulation of pulmonary vascular tone in normal patients and patients with pulmonary hypertension.

Intimal Proliferation and Fibrosis

Endothelial proliferation leading to obliteration of the pulmonary vascular bed has also been characterized in patients with advanced PPH. Wagenvoort and Wagenvoort have described this as a manifestation of advanced disease that follows medial hypertrophy and pulmonary vasoconstriction. However, severe endothelial proliferation in the absence of medial hypertrophy and demonstrable clinical vasoconstriction has also been described. This suggests a causative role for growth factors, of which endothelin is a strong possibility, leading to intimal proliferation with or without vasoconstriction. There are endothelin receptors in the pulmonary vasculature that interact with G-proteins that regulate intracellular...
calcium and reduce protein kinase C activity.21 Patients with PPH have elevated endothelin levels that appear to be liberated by the pulmonary vascular bed.22 A relationship between endothelin levels and severity of disease has been demonstrated, but it remains unclear whether endothelin is the cause or result of PPH.23 Patients with primary and secondary forms of pulmonary hypertension have markedly elevated levels of endothelin-like activity in the pulmonary vascular endothelium, which raises the possibility that endothelin receptor blockers may be useful as a treatment of pulmonary hypertension.24

Thromboxane, another growth factor that is primarily derived from platelets, has received particular attention in pulmonary hypertension.25 Besides its effects on platelet aggregation, it also causes vasoconstriction and induces intimal proliferation. The action of thromboxane is opposed by prostacyclin, a compound that is produced by normal vascular endothelium and that has vasodilatory and anticoagulant properties.26 Patients with PPH have been characterized as having an imbalance in the ratio of thromboxane to prostacyclin production, suggesting that overproduction of one or underproduction of the other might be a factor in the disease.27 Clinical trials have now shown significant reductions in pulmonary artery pressure and PVR when prostacyclin (epoprostenol [Flolan]; Glaxo-Wellcome; Research Triangle Park, NC) is given to patients with PPH long term.27-30 Prostacyclin is effective even in patients who show no acute vasodilatory response from it, suggesting that it works as an antiproliferative agent as well.31

Angiotensin-converting enzyme (ACE) inhibitors have also been tested in patients with PPH. Short-term studies have been disappointing, as the acute hemodynamic effects of these drugs seem to be minimal.32 However, lessons learned from the effectiveness of ACE inhibitors in heart failure have taught us that they also work beyond vasodilation, as the effect of ACE inhibitors in reducing circulating neurohormones results in improved exercise tolerance and survival.33 Recently, it has been described that patients with PPH have increased expression of ACE in the endothelium and media of the pulmonary vasculature.34 Elevated neurohormonal profiles have also been demonstrated in these patients.23 Thus, it might seem that ACE inhibition would be a logical treatment of PPH, not necessarily with the goal of causing acute pulmonary vasodilatation, but with the goal affecting the disease process by limiting vascular proliferation and by lessening the effects of neurohormonal activation on the pulmonary vasculature and myocardium.

In summary, intimal proliferation of the pulmonary arterioles appears to parallel increases in endothelin levels, implicating endothelin as important in the pathogenesis of the disease. The severity of the intimal proliferation seems to reflect the severity and chronicity of the disease. It is possible that the intimal proliferation is reversible, which suggests that we should also be evaluating drug therapy by looking at measures of the disease other than hemodynamics as an end point.

Thrombosis In Situ

A third representation of PPH histologically is thrombosis in situ of the pulmonary arterioles.1,3,4 Vessels with eccentric intimal pads that are presumed to be caused by local thrombosis, as well as recanalized thrombi, are randomly scattered throughout the pulmonary vasculature of patients with PPH.4 Although once believed this could represent pulmonary microembolism, to our knowledge, a source of these microemboli in patients with PPH has never been demonstrated.4 The current thinking is that this represents local thrombosis of the pulmonary arteriolar bed. It has been shown that these patients have elevated levels of fibrinopeptide A, which reflects the procoagulant environment within the pulmonary vascular bed.35 Consistent with this hypothesis are the long-term effects of warfarin anticoagulation in improving survival as demonstrated in one retrospective study and one prospective study.16,36 As platelet activation is likely part of thrombosis, it again brings into question the role of the platelet and its associated growth factors in the development of PPH. The National Institutes of Health Registry on Primary Pulmonary Hypertension reported that these thrombotic lesions seem to be equally prevalent between men and women, whereas plexiform lesions seem to be more commonly found in women.4

It is quite possible that in some patients, thrombosis of the pulmonary arterioles may be the only pathologic manifestation of PPH. Warfarin therapy alone has been shown to improve survival and hemodynamics in some cases.37 Another curiosity is the fact that some patients with PPH can develop extensive central thrombi that are nonocclusive in nature, suggesting that the local procoagulant state of the pulmonary vascular bed can be quite intense.38

The basis for the in situ thrombosis of the pulmonary arteriolar bed in PPH is probably endothelial injury. It is likely that platelet activation and vasoadilatory substance release are occurring, and this may serve to either perpetuate or promote the disease process in many patients. In patients in whom in situ thrombosis is the predominant lesion, there may be no demonstration of pulmonary vasoreactivity (since pulmonary vasoconstriction is not underlying). These
patients should benefit substantially from long-term anticoagulant therapy. However, because of the relatively ubiquitous nature of these thrombotic lesions in the lungs of patients with PPH, it is recommended that all patients be treated with anticoagulant therapy.30

**ENDOTHELIAL INJURY—THE COMMON PATHWAY**

So that one does not assume that PPH is three separate distinct diseases, it needs to be underscored that the three pathologic features of PPH that have been reviewed are typically seen throughout the lungs of most patients with PPH. This has been demonstrated in the National Institutes of Health Registry on PPH,4 in patients with familial PPH,40 in patients with pulmonary hypertension secondary to atrial septal defects,41 and from exposure to toxic rapeseed oil.42 It appears that the hypertensive vasculopathy that is seen in PPH represents a spectrum that includes medial hypertrophy, intimal proliferation and fibrosis, and in situ thrombosis, all of which can be explained by injury to the pulmonary vascular endothelium.

The clinical expression of PPH will be influenced by the underlying histologic changes so that patients with predominant medial hypertrophy should have more vasoreactivity than those whose predominant lesions are thrombotic in nature. The distribution of these lesions is likely influenced by the patient’s age at onset, gender and other genetic factors, and triggers to the disease (such as HIV virus or anorexigen). Individual genetic susceptibility, combined with the intensity and duration of exposure to a trigger, probably influences the histologic manifestation of the disease, and hence its clinical expression (Fig 1).

In the coming years, we will be looking to identify the triggers of endothelial injury in these patients and why some people seem to be predisposed whereas others are not. However, as we understand the nature of the vascular abnormality in these patients and the effects of drugs, more progress in drug treatment and improved survival will be forthcoming.

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