Primary Pulmonary Hypertension
A Vascular Biology and Translational Research “Work in Progress”

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Abstract—Primary pulmonary hypertension (PPH) is a syndrome of dyspnea, chest pain, and syncope defined by increased pulmonary vascular resistance and the absence of a known cause. It also occurs in a familial form, which is linked to unidentified genes on chromosome 2. This syndrome is characterized by abnormalities of pulmonary vascular biology in each compartment of the blood vessel. The lumen has a prothrombotic diathesis, the endothelium displays an excessive production of vasoconstrictors relative to vasodilators, and the smooth muscle cells are depolarized and calcium-overloaded, which is due in part to reduced expression of voltage-gated potassium channels (Kv). This causes vasoconstriction and may promote cell proliferation. The adventitia displays excessive remodeling, which is associated with exaggerated metalloproteinase and elastase activity. Conceptually, PPH seems to require a permissive genotype, a susceptible phenotype (eg, endothelial dysfunction) and, in many cases, an exogenous trigger (eg, an anorexigen). Although there is not a generally accepted, unifying hypothesis regarding its cause, impaired function and the expression of vascular and platelet Kv channels suggest PPH may be a disease of the ion channels. Abnormal matrix metalloproteinase and elastase activity could also explain the abnormal vascular tone, platelet activation, and remodeling in PPH. Although calcium-channel blockers and prostacyclin, particularly when coadministered with warfarin, improve survival, PPH has a 5-year mortality rate of ≈50%. Pharmacological and gene therapies aimed at enhancing the activity of prostacyclin, nitric oxide synthases, and Kv channels or at inhibiting endothelin and matrix metalloproteinases are promising areas for future development. (Circulation. 2000;102:2781-2791.)

Key Words: hypertension, pulmonary ● ion channels ● potassium ● endothelin ● nitric oxide ● platelets

Pulmonary hypertension (PHT) is an elevation in pulmonary arterial pressure that can be the result of diverse diseases. Primary pulmonary hypertension (PPH) is a term that describes this condition when no cause for the PHT can be found. In secondary PHT, a coexisting disease or stimulus has been identified that presumably explains the PHT. Recently, a new classification was proposed at a World Health Organization–sponsored symposium. It uses terminology that better characterizes our current understanding of the biological mechanisms involved in the various types of PHT. In this nomenclature, pulmonary arterial hypertension (PAH) refers to a disease spectrum with a common pathological picture and shared pathobiological processes that include PPH and PHT which cannot be distinguished from PPH. PAH can occur in association with collagen vascular disease or congenital heart disease, or it may be triggered by an exogenous stimulus such as an anorexigen or the HIV virus. Because of the lack of ideal animal models, most initial clues regarding abnormalities that exist in patients with PAH have come from bedside observations. These observations have then been linked to recent advances in our understanding of endothelial function, smooth muscle cell (SMC) electrophysiology, matrix metalloproteinase (MMP) chemistry, platelet biology, and genetics to provide insights into the cause and pathogenesis of PAH. This, in turn, is leading the development of effective therapies. The first century of progress in understanding PHT is nicely summarized by Weir and Reeves in their classic text.

Pathobiology of PAH

Histopathology
Pathological findings consistent with PPH were first described in autopsy specimens a century ago, although the first antemortem diagnosis was not made until 1951. The pulmonary arteries in PPH are characterized by intimal fibrosis, medial hypertrophy, adventitial proliferation, obliteration of small arteries (Figure 1) and, on occasion, vasculectasis or changes in the walls of the pulmonary veins. A fascinating focal vascular structure, the plexiform lesion, is found in many cases of PPH (Figure 1B). The prevalence of the lesion varies from 20% to 90%, depending on the sample size, the rigor of the examination, and the patient’s biology. Plexiform lesions are not pathognomonic of PPH, because
they are also found in cases of severe PAH associated with other diseases.

The plexiform lesion in PPH resembles the renal glomerulus, and its many channels are lined with endothelial cells rich in type 3 nitric oxide (NO) synthase, factor VIII, vimentin, and the receptor for vascular endothelial growth factor. In the central core of the lesion, the endothelial cells are cyclin-kinase inhibitor p27kip1-negative cells, whereas in peripheral areas adjacent to sites of angiogenesis, p27/kip1-positive cells are present. It has been proposed that plexiform lesions are a form of neoplastic lesion, reflecting a dysregulation of endothelial growth. Alternatively, plexiform lesions may represent an angiogenic response to local ischemia or hypoxia, as occurs with the creation of collateral vessels associated with obstructed arteries in other vascular beds. Computerized 3D reconstructions of vessels in PPH demonstrate that plexogenic lesions occur distal to vascular obstructive lesions (see Figures 1A and 1B for an example).

**Epidemiology**

PPH is a rare disease, with an annual incidence of approximately 1 per million population. Most cases of PPH seem to be sporadic, but 6% to 12% of cases are inherited in an autosomal-dominant manner with reduced penetrance. Another clue to the genetic basis of PPH, which has yet to be deciphered, is the consistent finding that PAH occurs in women 3 times more frequently than men. This basis for this imbalance between the sexes is unknown. Female predominance in PAH is not evident before puberty, nor is it overtly explained by oral contraceptive use or childbirth.

**Genetics**

Although clinical and pathological features are the same in both sporadic and familial PAH, familial PPH displays genetic anticipation (i.e., the onset of the disease occurs at progressively younger ages in subsequent generations). The occurrence of genetic anticipation suggests that the molecular basis of familial PPH may be trinucleotide-repeat expansion. After a genome-wide search on specimens from patients with familial PPH using a panel of polymorphic, short tandem, repeat markers, 2 groups have provided evidence for the linkage of PPH with markers on chromosome 2q. Several candidate genes, including those coding for the integrins, reside in the 2q region. The integrins are the receptors for important mitogens, such as tenascin, which are
produced by elastases and metalloproteinases during vascular remodeling in PHT.17

Recently, Morse et al18 and Deng et al19 refined the mapping for familial PPH and showed that the PPH gene(s) lie within chromosome 2q33. This interval contains 7 known genes, including CD28 and apoptotic cysteine protease, and 73 cDNA markers.18,19 In light of the hypothesis that PPH is a “neoplastic” disease,10 it is intriguing that Deng et al19 note that allelic losses of chromosome 2q33 have been reported in some lung cancers, suggesting this region contains a tumor-suppressor gene. Because all 17 PPH pedigrees they studied showed linkage to chromosome 2q33, Deng et al19 conclude that familial PPH is genetically homogeneous (with variable penetrance). The responsible gene(s) still await discovery.

PAH in children is associated with the major histocompatibility complex alleles HLA-DR3, DRw52, and DQw2, indicating that it has some features in common with the DR3+ group of autoimmune diseases.20 Children with severe PHT due to cardiac shunts lack these associations. However, PAH does not occur in the majority of people with these human leukocyte antigen (HLA) types, nor does it recur in those with the abnormal HLA type after lung transplantation. This suggests that other stimuli may be necessary to elicit PAH. For example, there are intriguing links between HLA type and susceptibility to toxic oil syndrome, an outbreak in which rapeseed oil contaminated with an aniline dye caused one of the largest epidemics of PAH in history.21

Coagulation
In PAH, platelet activity is enhanced; levels of serotonin, plasminogen activator inhibitor, and fibrinopeptide A are elevated; and thrombomodulin levels are decreased.22,23 Thrombosis in situ is often found in the pulmonary arterioles of patients with PAH. A different pattern of prothrombotic abnormalities is seen in secondary PHT, including increased levels of von Willebrand factor and fibrinogen and decreased fibrinolytic activity.23 Whether hypercoagulability occurs in response to PAH or can actually initiate PAH is unclear, but it likely contributes to disease progression.

The role of serotonin in the development of PAH has been an enigma.24–26 The major source of serotonin storage is the platelet dense granule. In platelet delta storage pool disease, the number and content of the dense granules is reduced. A case of PAH has been reported in a patient with this platelet disorder.27 Plasma serotonin levels are increased in PPH patients compared with control subjects, and PPH platelets have decreased serotonin concentrations.28 Elevated levels of serotonin are released during in vitro platelet aggregation in PPH, and these abnormalities persist after heart-lung transplantation, suggesting that this platelet abnormality is not secondary to the PAH. Plasma serotonin levels are also elevated in patients who use anorexigenes (K. Weir, MD, personal communication, 2000). Herve et al25 hypothesized that PPH may be associated with impaired handling of serotonin by platelets, resulting in increased plasma serotonin levels. The fawn-hooded rat, so called because of its brown mantle of fur, has an inherited platelet serotonin storage defect and spontaneously develops PHT with aging (particularly in the presence of mild hypoxia). Like humans with PAH, the fawn-hooded rat has endothelial dysfunction.28–30 Conversely, patients with carcinoid syndrome, in which serotonin levels are markedly elevated, do not develop PAH, possibly because they have a healthy endothelium. It is likely that disordered serotonin handling in PAH is a marker for a more fundamental abnormality, as is discussed subsequently.

Endothelium
Local vascular tone and function are regulated by the balance between vasodilators, such as prostacyclin and NO, and vasoconstrictors, such as thromboxane A2 and endothelin (ET)-1. Christman et al31 found that both PPH and secondary PHT patients had elevated 24-hour excretion of a thromboxane A2 metabolite (a potent stimulus for platelet aggregation) and reduced excretion of a prostacyclin metabolite. Although endothelial NO synthase expression is reduced in the pulmonary circulation of patients with PPH compared with control subjects,32 lung NO production, which may or may not reflect pulmonary vascular NO production, is enhanced33 or preserved.34 Similarly, PPH patients have higher urinary cGMP concentrations than controls,35 and this parameter is inversely correlated with cardiac index and mixed venous oxygen saturation. These observations suggest that the normal response of the pulmonary circulation to PHT is to increase the synthesis of NO and prostacyclin in an attempt to restore normal tone.

ET-1 is a potent vasoconstrictor and mitogen. ET-1 levels are increased in experimental PHT36,37 and in humans38–44 PAH. The high levels of ET-1 in arterial compared with venous plasma in PPH are consistent with the pulmonary production of ET-1, suggesting ET-1 may contribute to elevated pulmonary vascular resistance (PVR).44 PAH is associated with increased expression of ET-1 in pulmonary vascular endothelial cells, suggesting that the local production of ET-1 may contribute to the pathogenesis of PPH.45 The inhibition of ET receptors reduced PHT in an experimental model of PAH induced by injecting rats with monocrotaline, an alkaloid derived from the plant Crotalaria spectabilis.46

K+ Channel Regulation
K+ channels are transmembrane-spanning proteins that contain a pore with great selectivity for K+.47 They are tonically active in vascular SMCs, allowing a slow efflux of K+ along their intracellular/extracellular concentration gradient of 145/5 mmol/L. There are several types of K+ channels, including voltage-gated (Kv), inward rectifier (Kir), and calcium-sensitive (KCa) channels. Kv channels have a voltage sensor and both respond to and contribute to determining membrane potential in SMCs. The inhibition of Kv channels results in an accumulation of positively charged K+ ions within the cell, raising the membrane potential to more positive levels (depolarization), which activates the voltage-gated, L-type calcium channel.48 Calcium then enters the cell, activating the contractile apparatus, leading to vasoconstriction and possibly initiating cell proliferation. Acute hypoxia seems to initiate hypoxic pulmonary vasoconstriction in part by inhibiting the Kv channel in pulmonary artery (PA) SMCs.48,49
There are 9 families of Kv channels (Kv1 to 9), each with many members (ie, Kv1.1 through Kv1.6). In a PASMC, many channels are active at any time and, thus, determining the molecular origins of a given K+ current is difficult, even when using single-cell electrophysiology such as the patch clamp technique. Archer et al used antibodies directed against Kv channels to show that Kv1.5 and Kv2.1 are important components of the whole-cell K+ current in normal rat PASMCs (Figure 2). In humans with PPH but not those with secondary PHT, Kv1.5 mRNA levels are reduced in PASMCs. This downregulation of Kv1.5 is associated with inhibition of the K+ current, membrane depolarization, and the elevation of cytosolic Ca2+ (Figure 2). Thus, decreased expression or function of K+ channels in PASMCs in PPH patients could initiate and/or maintain pulmonary vasoconstriction and play a role in the pathogenesis of PPH.

Less is known about Kv2.1, although it seems more important than Kv1.5 in setting resting membrane potential in rat PASMCs. It is fascinating that Kv2.1 is also inhibited by the anorexigen dexfenfluramine, a weight-loss drug that is associated with the development of PAH. Weir et al postulated that there could be a causal role for K+ channel deficiency in PAH, but major questions remain, including whether the loss of specific K+ channels is a cause or a response to PAH and which specific K+ channels are involved.

Extracellular Matrix

Vascular remodeling is a prominent feature of PPH. Changes in the intima (fibrosis) and media (hypertrophy and distal extension of muscularization to normally nonmuscular peripheral arteries caused by differentiation of pericytes) are well recognized. However, important changes also occur in the adventitia, where there is increased production of extracellular matrix (collagen, elastin, fibronectin, and tenascin). Some have suggested that endothelial abnormalities early in the course of PAH permit the extravasation of factors that stimulate SMC production of a vascular serine elastase. This results in the liberation of matrix-bound SMC mitogens, such as basic fibroblast growth factor, and enhances matrix degradation by activating other MMPs. The MMPs can stimulate the production of a mitogenic cofactor, tenasin, which binds to its αβ3-integrin receptors, thus leading to the phosphorylation of growth factor receptors and SMC proliferation. When MMPs are inhibited, tenasin levels fall and apoptosis ensues.

Recently, Cowan et al showed that direct inhibition of MMP-2 and serine elastases leads to the regression of experimental PHT. Although MMPs were thought to be important only in remodeling, we recently learned that they can also affect vascular tone and platelet function. MMP-2 and MMP-9 can activate platelets, and intravascular MMP-2
can enhance the formation of vasoconstrictors (including a novel form of ET) and inhibit the action of endogenous vasodilators.\(^{57}\)

**Triggers for PHT**

**Anorexigens**

The anorexigens aminorex, fenfluramine, and dexfenfluramine are amphetamine-like drugs that enhance serotonin release and inhibit serotonin reuptake in the brain, resulting in appetite suppression and modest weight loss. Between 1967 and 1972, there was an outbreak of PAH in Europe related to the anorexigen aminorex.\(^ {58}\) Although 61\% of the 582 PAH patients at that time had taken aminorex, only 0.1\% of those who took aminorex manifested PAH. A similar epidemic ensued in the 1980s and 1990s with the use of fenfluramine and dexfenfluramine.\(^ {53}\) Although the use of these appetite suppressants was associated with a 23-fold increase in the risk of developing PAH, the annual incidence of the syndrome in the population remained very low (1.7 per million in Belgium).\(^ {53}\) Thus, both with aminorex and the fenfluramines, only a small proportion of the patients exposed developed PAH, suggesting a requirement for \( \geq 1 \) predisposing conditions.

Many of the anorexigens are also serotonin-transporter substrates\(^ {29}\) and, thus, get translocated into pulmonary vascular cells, where their intrinsic toxicity may become amplified. Depending on individual susceptibility, PAH could develop as a response to high levels of these drugs. It was recently discovered that anorexigens are Kv channel blockers,\(^ {60}\) and one of their targets is Kv2.1.\(^ {52}\) Anorexigen-induced Kv channel inhibition and membrane depolarization can contribute to pulmonary vasoconstriction.\(^ {54,61}\) In addition to its effects on \( \text{Ca}^{2+} \) entry via the \( \text{L-type} \ \text{Ca}^{2+} \) channel, dexfenfluramine also promotes vasoconstriction by enhancing \( \text{Ca}^{2+} \) release from the sarcoplasmic reticulum.\(^ {62}\) The anorexigens also block Kv channels in platelet progenitor cells (megakaryocytes)\(^ {54}\) and can lead to platelet serotonin release (E. Michelakis, MD, et al, unpublished data, 1998). Furthermore, fenfluramine reduces Kv1.5 mRNA levels by 50\% in PASMCs from normotensive patients,\(^ {63}\) suggesting that inhibited gene transcription and expression of Kv channels may play an important role in anorexigen-induced PAH.

The role of both the endothelium and Kv channels in the pathogenesis of anorexigen-associated PAH is suggested by several animal studies. In isolated rat lungs, aminorex, dexfenfluramine, and fenfluramine each caused consistent but small increases in PVR, but only at doses higher than those used in vivo. However, in the presence of both cyclooxygenase and NO synthase inhibitors, these drugs dramatically increased PVR at doses comparable to those achieved clinically.\(^ {60}\)

**Toxic Oil Syndrome**

In 1981, 20,000 people were poisoned by rapeseed oil adulterated with aniline dye, intended for industrial use, that was sold illegally in Spain.\(^ {64,65}\) The early clinical manifestations included respiratory distress syndrome, myalgia, eosinophilia, and widespread vascular and neural lesions. PAH developed in 20\% of the patients and, in many, it regressed spontaneously. In a minority, it progressed to a fatal form of PPH.\(^ {21}\) A careful examination of the contaminated oils suggests the pathogenic products of this dye include fatty acid oleyl anilides and the monoester and diester of 3-phenylamino-1,2-propanediol.\(^ {60,66}\) Toxic oil syndrome PAH, like spontaneous PPH, is characterized by endothelial damage.\(^ {67}\) It also has an associated-genotype HLA profile (excess occurrence of female sex and HLA-A24, DRA-DQ8 genotypes).\(^ {66}\)

**HIV**

Approximately 90 cases of HIV-PAH have been reported.\(^ {59}\) In 83\% of the patients, no additional factors were identified that would predispose to PPH. HIV-PAH seems to progress more rapidly than spontaneous PPH,\(^ {70}\) and the prognosis may be worse (1-year survival, 51\% with HIV-PAH versus 68\% for patients with PPH).\(^ {70}\) However, the pathological manifestation of the disease is similar to that of spontaneous PPH, with plexiform lesions noted in 85\% of cases.\(^ {70}\) Interestingly, the expression of Kv1.3, an important molecular target for immunosuppressive agents in T lymphocytes, is inhibited in HIV-PAH via a protein kinase C–dependent mechanism,\(^ {71}\) suggesting a link between cellular electrophysiology, immunity, and PHT.\(^ {72}\)

**Linking Pathobiological Observations**

What is the link between these etiological theories (Table 1)? There is a potential unifying connection between the abnormalities observed in platelets, the endothelium, serotonin handling, and vascular tone in PPH (Figure 3). That link may be the common role of K+ channels in controlling membrane potential and, thus, activity in platelets, SMCs and, possibly, endothelial cells.

Spontaneous PPH and anorexigen-induced PAH both involve a decrease in Kv current in PASMCs and, possibly, platelets. Dexfenfluramine inhibits Kv channels in megakaryocytes, the platelet progenitor cell.\(^ {54}\) Furthermore, the Kv channel inhibitor 4-aminopyridine mimics dexfenfluramine in causing the release of serotonin from platelets and markedly reducing serotonin reuptake (E. Michelakis, MD, unpublished data, 2000). Thus, the loss or inhibition of Kv channels that occur in PAH may also account for the observed decrease in platelet serotonin stores and the rise in plasma serotonin levels. The elevated serotonin level in the presence of endothelial dysfunction would act as a vasoconstrictor,\(^ {65}\) particularly when combined with PASMC membrane depolarization and increased cytosolic \( \text{Ca}^{2+} \). In anorexigen-induced PAH, the Kv channel inhibition may be a direct effect of the drug blocking the Kv channel. In spontaneous PPH, there may be a predisposing genetic channel disease or acquired loss of Kv channels that similarly leads to membrane depolarization. It is uncertain how this K+ channel hypothesis relates to the MMP and prothrombotic theories. Once initiated, PAH is sustained and exacerbated by elastase and MMP-induced matrix remodeling and a prothrombotic diathesis. Perhaps in some individuals, MMP abnormalities are causal, resulting in PAH with a secondary downregulation of Kv channel expression.
TABLE 1. Theories for Cause of PPH

<table>
<thead>
<tr>
<th>Theory</th>
<th>Evidence</th>
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<tr>
<td>Excess endothelial production of constrictor versus dilator prostaglandins</td>
<td>PAH patients have excess thromboxane levels relative to their prostacyclin levels.</td>
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<tr>
<td>Excess ET-1 vs NO</td>
<td>Excess of ET-1 relative to NO. Inhaled NO and ET-1 antagonists reduce PHT.</td>
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<tr>
<td>Excessive thrombosis in situ</td>
<td>PPH patients have increased platelet activation, plasminogen activator inhibitor levels, and decreased thrombomodulin.</td>
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<tr>
<td>Serotonin excess</td>
<td>Anorexigen-induced PAH. Patients with PPH have increased serotonin levels, even after undergoing successful transplantation.</td>
</tr>
<tr>
<td>K+ channelopathy of PASMCs and platelets</td>
<td>Inhibition or downregulation of certain Kv channels (e.g., Kv1.5) occurs in PASMCs from patients with PPH and anorexigen PAH. This leads to membrane depolarization, activation of the L-type Ca2+ channels, and vasoconstriction. The same channel inhibition could lead to platelet depolarization and serotonin release.</td>
</tr>
<tr>
<td>Dysregulated elastase and MMPs</td>
<td>Activation of elastase and MMPs enhances production of mitogens (e.g., tenascin) which promotes cell proliferation. In addition, vascular MMPs may promote vasoconstriction. Inhibition of MMPs is beneficial in experimental PHT.</td>
</tr>
<tr>
<td>Monoclonal proliferation of endothelial cells</td>
<td>Endothelial cells in plexiform lesions in PPH but not secondary PHT display a monoclonality typically found in neoplastic tumors.</td>
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Prognosis of PAH

The NIH Registry (1981 to 1987) established the natural history and prognosis of PPH at a time before the use of current “conventional therapy.” The median survival of enrolled patients was 2.8 years from diagnosis. Independent predictors of poor prognosis (namely, elevated mean right atrial pressure and mean pulmonary artery pressure and reduced cardiac output) reflect aspects of right ventricular function. Thus, it is reasonable to conclude that the prognosis of a patient with PPH is linked to the adequacy of the adaptive response of the right ventricle to the chronic pressure-overload state.

The natural history of patients who present with secondary forms of PHT, such as congenital heart disease, collagen vascular disease, and so on, is less well characterized. Their prognosis is related both to the severity of the hypertension and to the underlying secondary illness. For example, patients with portopulmonary hypertension will have an outcome that is determined in large part by the status of their underlying liver function. The best-characterized group of patients with secondary PHT are those with congenital heart disease. These patients seem to live longer with severe PHT than their counterparts with PPH. This may relate to more efficient adaptation of the right ventricle by increased expression of embryonic genes that regulate fetal contractile proteins of the right ventricle from the time of birth.

The NIH Registry database was collected at a time when there were relatively few cases of PPH related to exposure to the HIV virus or to anorexigen. The prognosis of patients with HIV infection seems to be unrelated to the duration of the HIV exposure or the viral load. Indeed, HIV has not been recovered from the pulmonary vasculature of these patients. The anorexigen-induced PAH group is unique. Although the risk of developing PAH is clearly related to the duration of exposure, it is likely also influenced by an underlying genetic predisposition. For example, in some patients, the PPH developed slowly and reversed when the anorexigen were withdrawn, but fatal PPH occurred in a woman exposed to diet pills for <30 days.

Current Treatment of PAH

Patients with PHT present with signs and symptoms of right heart failure. Indeed, in most instances, the cause of death is severe right ventricular failure. Consequently, established therapies for patients with left heart failure are often applied to patients with PPH. The use of digitalis has been controversial, but a recent study showed beneficial early hemodynamic and neurohormonal effects. Diuretics are used empirically in patients who present with systemic venous congestion and edema and generally afford symptom relief. In contrast to patients with left heart failure, their use rarely induces systemic hypotension. ACE inhibitors have also been evaluated as pulmonary vasodilators, with little success. However, because the major effect of ACE inhibitors in left heart failure occurs via neurohormonal activation and neuro-
hormonal activation is widespread in patients with PPH, their use seems justified. No prospective studies have evaluated their long-term effectiveness.

**Anticoagulants**

Warfarin has been used in the treatment of patients with PHT for many years. In retrospective and prospective series, the use of long-term warfarin anticoagulation was associated with improved survival (Figure 4). Because histological changes seen in patients with most forms of secondary PHT (ie, congenital heart disease and collagen vascular disease) show similar evidence of in situ thrombosis, it has been suggested that these patients might also benefit from long-term anticoagulation. Warfarin should be used in all PAH patients except those with specific contraindications. The current recommendation has been to target an international normalized ratio of 2 to 2.5 times control, a level that provides effective anticoagulation with a minimal risk of bleeding. The use of unfractionated or low-molecular-weight heparins should provide similar antithrombotic efficacy and potentially offer additional benefits through their inhibitory effects on endothelial and SMC proliferation, but no studies on their long-term use in patients with PPH are available.

**Calcium-Channel Blockers**

Calcium-channel blockers were the first class of drugs shown to have dramatic beneficial long-term effects in selected patients with PPH (Figure 4). The mechanism by which the Ca\(^{2+}\)-channel blockers provide benefit is primarily through vasodilatation, as represented by the fall in mean pulmonary artery pressure that occurs. They do not have positive inotropic effects; thus, the increase in cardiac output that accompanies therapy likely relates to pressure unloading of the right ventricle. There are no clinical features that prospectively identify responsive patients (those with an early 20% fall in PVR), but such patients tend to have less advanced disease and a more recent onset of symptoms. It is estimated that these “responders” represent ~20% of all patients with PPH.

Patients tend to either be responsive or nonresponsive to calcium-channel blockers. Although there are no formal studies, all classes of calcium-channel blockers have been reported to be effective. In patients who are responsive (defined as a 20% fall in PVR), a dose-response relationship seems to exist in terms of the magnitude of effect. In that regard, it has been shown that high doses of calcium-channel blockers seem necessary to achieve the maximum beneficial effects in patients who are responsive. The benefits of high-dose calcium-channel blockers seem to be related both to impaired drug absorption and an increased dose requirement to dilate the pulmonary vasculature in PPH. The duration of the beneficial effect of calcium-channel blockers in responders seems to be indefinite. We recently performed cardiac catheterization in a patient who has taken 720 mg of diltiazem per day for 14 years (Table 2); this demonstrates the remarkable stability of the hemodynamic response to therapy. Conversely, patients who are unresponsive to calcium-channel blockers seem to be unresponsive at any dose.

The indiscriminate use of calcium-channel blockers in patients with PPH also has great potential for harm. Systemic hypotension producing reflex, tachycardia, sympathetic stimulation, and right ventricular ischemia are effects of calcium-channel blockers that may worsen survival. The reports of adverse responses to calcium-channel blockers in these patients have been striking, underscoring the fact that these drugs must be used with extraordinary caution. Initiation of therapy should follow a short-term trial of a short-acting vasodilator (NO, adenosine, or prostacyclin) to confirm the
presence of reversible vasoconstriction. Their indiscriminate prescription, without close follow-up and documentation of beneficial effects, is unjustified. We strongly recommend objective assessment of the effectiveness of calcium-channel blockers within the first 6 months of therapy in all patients. This can be done with echocardiography, exercise testing, or cardiac catheterization. It is especially dangerous to increase the dosages of calcium-channel blockers in patients who fail to respond to conventional doses (identifying them as nonresponders), because this will only increase morbidity.

**Prostaglandins**

Sodium epoprostenol (Flolan), the only Food and Drug Administration–approved treatment for PPH, has been studied extensively over the past decade in patients with PPH and secondary PHT. Prostacyclin is a short-lived and, thus, relatively locally acting vasodilator. It is involved in the regulation of vasomotor tone in all vascular beds. It usually does not have a potent vasodilator effect when administered intravenously to PAH patients; it lowers systemic blood pressure minimally and modestly reduces mean pulmonary artery pressure. Prostacyclin’s most potent effect seems to be through positive inotropism, by raising the cardiac output in patients with PAH. In marked distinction to the use of prostacyclin for the treatment of PAH, patients with PAH who lack an acute vasodilator response on initial testing. In addition, the dosages of calcium-channel blockers in patients who fail to respond to conventional doses (identifying them as nonresponders), because this will only increase morbidity.

Like the Ca\(^{2+}\) blockers, the use of long-term intravenous prostacyclin also has potential for harm. The optimal dose is not known but is usually established by dose titration. It was presumed that patients developed tolerance to the effects of prostacyclin, but it now seems that tolerance relates only to the side effects. The long-term use of excessive doses of prostacyclin can be associated with high-output cardiac failure and severe side effects, which include marked flushing, diarrhea, thrombocytopenia, and unremitting foot pain. We have also seen toxic effects, with the development of non-specific alveolitis and the onset of diastolic right ventricular failure, which can be refractory to treatment. In addition, because the continuous infusion of prostacyclin requires the placement of a permanent in-dwelling venous catheter, the risk of potentially life-threatening infections exists. Furthermore, epoprostenol is sufficiently expensive (tens of thousands of dollars per year) that access may be difficult in some countries and for those with inadequate health insurance.

The dramatic success of long-term intravenous prostacyclin is now leading to the development of prostacyclin analogues using newer drug delivery systems. Uniprost, an analogue of prostacyclin that has more stability at room temperature and a longer half-life, is administered subcutaneously through an ambulatory insulin pump delivery system (V. McLaughlin, MD, et al, personal communication of unpublished data, 1999). Preliminary studies have shown that this drug has the same hemodynamic properties as prostacyclin when given intravenously and, when given long-term, it similarly improves exercise tolerance and hemodynamics. Pain, induration, and erythema at the local injection site can be a serious problem in many patients and may prevent some patients from receiving adequate doses. Nonetheless, it offers the potential of the beneficial effects of prostacyclin without the morbidity of central line infection. The results of a large international multicenter trial of Uniprost for PAH should be known this year.

Iloprost, a prostacyclin analogue that can be given by inhalation, is currently being evaluated in an international multicenter trial. The major advantage of this inhalational strategy is that lower doses of the drug, which have minimal systemic side effects, may be used while retaining a reasonable influence on the pulmonary vascular bed. Unfortunately, the short half-life requires frequent inhalations. It remains uncertain whether this type of “pulsed therapy” will yield long-term beneficial effects similar to infusion therapies.

Beraprost is an oral prostacyclin analogue that is reasonably well absorbed and produces both early and short-term beneficial effects in patients with PHT. Although it has not been evaluated in a prospective, randomized fashion, preliminary studies show favorable changes in hemodynamics and exercise tolerance. Beraprost has a relatively short half-life, requiring frequent dosing, and its side effects could limit the ability of a patient to receive adequate doses. A multicenter, prospective, randomized clinical trial of Beraprost in patients with PHT is currently underway.

**Nitric Oxide**

NO is currently approved by the Food and Drug Administration for use in neonates with PAH associated with hypoxia. It has been widely used as an early test of vasodilator response in patients with chronic PAH and in the short-term treatment of patients with PAH resulting from a variety of conditions. The acute responsiveness to inhaled NO seems to predict the subset of patients who might be responsive to oral Ca\(^{2+}\)-channel blockers and, thus, this is a safe and easy test to perform during cardiac catheterization. There is limited experience with the long-term use of inhaled NO as a treatment of PAH. Inhaled NO, however, is cumbersome, expensive, and requires a fairly sophisticated delivery system. Patient mobility is limited by the need for a canister to deliver the gas at all times. Nonetheless, inhaled NO dilates the pulmonary circulation while avoiding unwanted and dangerous systemic vasodilatation, and it has been successful and economical as short-term therapy for critically ill patients, particularly those in intensive care units (eg, after cardiac surgery or transplantation). The possibility that long-term inhaled NO could be of benefit needs to be explored.

**ET Receptor Blockers**

Although it remains unclear whether increased ET-1 production causes PHT, its role as a mediator in PAH seems certain. Antagonists that are nonselective (block both ET-A and B receptors) or are ET-A receptor–selective have been developed and are being evaluated in prospective clinical
It remains debatable whether one class of blocker is preferred. ET-A receptors mediate vasoconstriction and promote SMC hypertrophy and, thus, their blockade should be helpful. The role of the ET-B receptor is less clear. It seems to be involved in the clearance of ET-1 across the pulmonary circulation and, thus, one might argue that leaving it unblocked would be of clinical value. However, other studies suggest that the B-receptor might be involved in vasodilatation and, thus, leaving it unblocked could lead toward more side effects. The actual role that these receptors play in the clinical disease will probably be determined by ongoing trials examining these 2 types of ET receptor blocker therapies.

Gene Therapy
Current exploration into potential gene therapies may hold great promise in patients with pulmonary vascular disease, because proteins have been identified that could be targets for the development of gene therapy. Specifically, researchers have already successfully transfected genes into the airways and small pulmonary arteries by airway nebulization of genes carried in adenoviral vectors. Genes for prostacyclin synthase and NO synthase have been transiently overexpressed in animals. However, enormous hurdles still exist in the successful use of gene therapy in humans, the least of which is the development of a site-specific delivery system that would allow preferential concentration of the virus in the pulmonary circulation. Furthermore, sustained expression is not yet possible, and concerns remain about an inflammatory reaction to the vectors. New vectors, including “gutless” adenoviral vectors, may be useful. Because the vascular pathobiology of pulmonary vascular disease is becoming well characterized, it is likely that specific gene therapies will be developed for its treatment.

Future Perspectives
It remains unclear whether the clinical entities of PAH and secondary PHT represent a multitude of distinct pathobiological processes with a common end point or multiple expressions of pathobiological processes from a common, as-yet-undefined trigger. Nonetheless, it may be reasonable in the future to perform some evaluation of the pathobiology of the patient presenting with PAH (such as measurements of ET, exhaled NO, prostacyclin metabolites, etc) to better characterize the disease process. This may also be done to allow physicians to better select appropriate therapies.

It is likely that some therapies will be applied to all patients (such as long-term anticoagulation), whereas other therapies will be reserved for specific subsets of patients, depending on the biological mechanism involved and their responsiveness to therapeutic challenge. There will always likely be a subset of patients who are highly responsive to long-term oral Ca

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-channel blockers and in need of little other therapy. However, there may be other patients who will benefit from a distinctly different long-term therapeutic approach.

Finally, we may all learn from our oncology colleagues that PPH is a malignant disease process that may respond to multiple therapeutic strategies, which may include combination therapies and staged therapies. The combinations already include warfarin, Ca

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-blockers, and prostacyclins and will likely include newer classes of drugs as they become developed. In addition, it is very possible that staged therapy may be of benefit if there is some way to reverse the disease process. Thus, initial therapy with intravenous prostacyclin and/or an oral ET-1 receptor blocker might induce regression of the disease to a point where the patient would be responsive to either an oral prostacyclin analogue or perhaps a Ca

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-channel blocker.

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