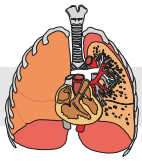

Pulmonary Arterial Hypertension – the Primary Pulmonary Hypertension Syndromes

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There is a broad range of diseases that can cause an elevation in pulmonary pressures. Pulmonary hypertension is the focal point and cause of significant morbidity and mortality in some of these disorders but plays a secondary, less clinically central role in others. Pulmonary arterial hypertension is a subclass of pulmonary hypertension that includes the former type of disorders in which progressive elevation in pulmonary pressures and right heart failure are often the cause of death. The classic example of this group is primary pulmonary hypertension. This review will focus on the various forms of pulmonary arterial hypertension, their pathophysiology, and recent advances in treatment of this life-threatening disorder.

Pulmonary hypertension is a hemodynamic abnormality with multiple causes and clinical presentations. The World Health Organization classification of PH is detailed in Table 1 [1]. This system breaks the classification of PH into five major categories: a) pulmonary arterial hypertension, b) pulmonary venous hypertension, c) PH associated with disorders of the respiratory system and/or hypoxemia, d) embolic disorders, and e) disorders directly affecting the vasculature. It is important to distinguish the various diseases included under the WHO classification because the various forms of PH are quite separate in their natural history and treatment. For example, treatment of PH related to congestive heart failure with pulmonary venous hypertension is aimed at improving the primary abnormalities of left ventricular dysfunction and volume overload rather than attempting to dilate pulmonary vessels. PH due to primary respiratory disease such as emphysema is not treated by vasodilators other than oxygen. These examples are in contrast to the treatment of PAH in which lowering pulmonary vascular resistance is a primary and effective treatment. The current review will focus on the first group in the WHO classification.

Pulmonary arterial hypertension

PAH comprises a collection of disorders characterized by PH without elevated pulmonary venous pressures (usually indicated by

PH = pulmonary hypertension
PAH = pulmonary arterial hypertension

Table 1. World Health Organization Classification of Pulmonary Hypertension

Pulmonary Arterial Hypertension
Primary Pulmonary Hypertension
- Sporadic
- Familial

Related To:
- Collagen Vascular Disease
- Congenital Systemic to Pulmonary Shunts
- Portal Hypertension
- HIV Infection
- Drugs/Toxins
- Persistent Pulmonary Hypertension of the Newborn
- Other

Pulmonary Venous Hypertension
Left-Sided Atrial or Ventricular Heart Disease
Left-Sided Valvular Heart Disease
Extrinsic Compression of Central Pulmonary Veins
Pulmonary Veno-Occlusive Disease
Other

Pulmonary Hypertension Associated with Disorders of the Respiratory System and/or Hypoxemia
Chronic Obstructive Pulmonary Disease
Interstitial Lung Disease
Sleep Disordered Breathing
Alveolar Hypoventilation Disorders
Chronic Exposure to High Altitude
Neonatal Lung Disease
Alveolar-Capillary Dysplasia
Other

Pulmonary Hypertension due to Chronic Thrombotic and/or Embolic Disease
Thromboembolic Obstruction of Proximal Pulmonary Arteries
Obstruction of Distal Pulmonary Arteries
Pulmonary Embolism
In situ Thrombosis
Sickle Cell Disease

Pulmonary Hypertension due to Disorders Directly Affecting the Pulmonary Vasculature
Inflammatory
Pulmonary Capillary Hemangiomatosis

a normal pulmonary capillary wedge pressure), parenchymal lung disease or embolic disease. The prototype disorder is primary pulmonary hypertension, but the group also includes PH secondary to congenital cardiac defects and PH associated with other disease states.

Primary pulmonary hypertension

PPH is a life-threatening, progressive disease that occurs in both sporadic and familial forms. The clinical presentation, ominous natural history and vascular histopathology of PPH were described using a national registry of patients collected in the 1980s [2–4]. The registry data showed that PPH was more common in women and that the mean age at presentation was 36 years. There was possible overlap with the collagen vascular disease spectrum as 29% of patients had a positive antinuclear antibody test [3]. Common presenting symptoms included dyspnea, fatigue and syncope. These were often insidious in onset. Clinical signs of PPH included a loud P2, dilated pulmonary arteries on chest X-ray or computed tomography scan, and little evidence for parenchymal damage or signs of left-sided heart failure. Typical pulmonary function abnormalities included a mild restrictive defect and decreased diffusion capacity. There was often a prolonged period between onset of symptoms and diagnosis, with a median delay of 2 years. The most striking finding was the poor prognosis with estimated median and 5 year survivals of 2.8 years and 34% respectively [4]. A family history of PPH was present in 6% of patients in the registry, suggesting a familial component or a separate genetic form of the disorder. The gene associated with most cases of familial PPH and up to 25% of sporadic PPH has been identified as the bone morphogenetic protein receptor II (*BMPR2*) gene [5].

PAH associated with human immunodeficiency virus disease

In 1987 Kim and Factor [6] described a case of PH in a patient with AIDS. Many publications have followed and HIV infection has become widely recognized as a cause of PAH. The mechanism for this association is unknown, however the pathologic findings are similar to those found in patients with PPH [7]. Also unknown is whether there is a relationship between PAH and CD4 counts and if PAH responds to antiretroviral therapy.

PAH associated with portal hypertension and cirrhosis

PAH is known to complicate some cases of portal hypertension, though this is relatively rare. The increased pulmonary vascular resistance in these patients is related to pathologic changes that mirror those of PPH [8]. The presence of PAH in patients with cirrhosis is surprising. The more common form of pulmonary abnormality in patients with advanced liver disease and portal hypertension is the hepatopulmonary syndrome. In this disorder pulmonary vessels are actually dilated and create intrapulmonary right to left shunts. The reason some patients develop PAH while others develop hepatopulmonary syndrome is unknown. PAH complicating portal hypertension has been treated with vasodilators including epoprostenol with some success as a bridge to liver transplantation [9].

PAH associated with appetite suppressants

In the 1960s there was an epidemic of PH in Europe associated with the use of the anorexic agent aminorex fumarate. In the 1990s French investigators reported a cluster of cases among patients using derivatives of fenfluramine or dexfenfluramine for treatment of obesity [10]. A number of studies appeared in the mid to late 1990s investigating this phenomenon. One case-control study [11] from Europe demonstrated that the use of anorexic drugs, mainly fenfluramine, was associated with an increased risk of PPH. with odds ratios ranging from 6.3 to 23.1 depending on duration and proximity of their use. These reports led to the withdrawal from the market of several of these agents.

PAH associated with collagen vascular disease

Most of the collagen vascular diseases have been associated with PAH, including scleroderma, systemic lupus erythematosus, and rheumatoid arthritis. Scleroderma is the collagen vascular disease most often associated with PAH, with up to 35% of patients having echocardiographic evidence of PH [12]. PAH is particularly common in patients with the limited form of scleroderma and is a major cause of morbidity and mortality in these patients.

PAH associated with use of miscellaneous substances

As listed in the Executive Summary from the World Symposium on Primary Pulmonary Hypertension in 1998 [1], other definite or likely causes of PAH include toxic rapeseed oil, amphetamine use, and L-tryptophan. Possible causes include amphetamines, cocaine, and anticancer chemotherapeutic agents.

Pathophysiology of PAH

The vascular pathology of PPH is not restricted to one cell type or vessel layer. This has complicated the search for a disease mechanism, with possible targets including the endothelium, smooth muscle cells, and mediators of fibrosis and vascular tone. The dominant pathologic findings include medial smooth muscle hypertrophy, intimal thickening and fibrosis, *in situ* thrombosis and plexiform lesions. Plexiform lesions are areas of vascular dilation filled with a network of endothelial lined channels. The end result of these changes is loss of vascular surface area and compliance, leading to increased vascular resistance. In the early stages of the disease this is most notable during exercise. The normal pulmonary vascular system can dramatically lower resistance through vasodilation and recruitment to accommodate the rise in cardiac output that occurs with exercise. Thus, normally, pulmonary pressure rises only slightly even with the large increase in cardiac output during exercise. In patients with PPH the ability to lower vascular resistance is diminished and pulmonary vascular pressures rise quickly during exercise, even in those patients with normal resting pulmonary pressures. A mean pulmonary artery pressure above 30 mmHg during exercise (compared with 25 mmHg at rest) has been recommended as one of the diagnostic criteria for PH. The multiple

PPH = primary pulmonary hypertension
HIV = immunodeficiency virus

components of vascular pathology found in PPH may be present in the other forms of PAH [7,13,14]. Because of the unique finding of the plexiform lesion, this group of PPH-like diseases is sometimes referred to as the plexogenic arteriopathies. How disparate disease states such as scleroderma and HIV infection lead to the same clinical and pathologic findings as PPH is unclear.

The mechanisms responsible for the elevation of pulmonary vascular resistance in patients with PH are not clear. One area of study for many years has been the mediators of vascular tone. Early studies concentrated on prostenoids, which are agents of inflammation. Prostacyclin is an eicosanoid produced by endothelial cells with vasodilator and platelet inhibitory activities. Thromboxane is also produced by endothelial cells but has opposing actions of platelet activation and vasoconstriction. Prostacyclin was found to be deficient relative to thromboxane in patients with PH [15]. It was theorized that this imbalance could lead to chronic elevations in pulmonary vascular resistance and clinical PH. Prostacyclin was later used to treat the disease.

Research on other possible mediators has followed. Nitric oxide, a gaseous molecule produced by several forms of nitric oxide synthase in the pulmonary and peripheral vasculature, is a potent, locally active vasodilator. Giaid and Saleh [16] found diminished levels of NOS expression in the pulmonary vasculature of patients with pulmonary arterial hypertension and plexogenic vascular lesions. Thus, a relative deficiency in NO production was associated with a rise in pulmonary vascular resistance in PAH. Inhaled NO is an effective pulmonary vasodilator and produces an immediate lowering of pulmonary pressures and rise in cardiac output in patients with PH [17]. NO is routinely used as a test agent for vasodilator response in PPH and for controlling pulmonary hypertension in the neonatal and post-lung transplant settings.

Endothelin-1 is a peptide with predominantly vasoconstrictor properties produced by the endothelium that also plays a role in mediating vascular tone. ET has been implicated in the increased vascular resistance found in PH and congestive heart failure, based on elevated serum levels and local tissue levels [18,19]. These findings have led to the use of ET receptor antagonists in the treatment of PH and congestive heart failure, as will be discussed below.

It is possible that the imbalance of vasoactive mediators found in PH is a consequence of the disease rather than a cause. A different focus of investigation has been the mechanisms of vascular growth. The primary abnormality may lie in the overgrowth of endothelial cells in plexiform lesions or in the hypertrophy of smooth muscle cells. The identification of the *BMPR2* gene as a likely cause of familial PPH supports the idea that an abnormality of endothelial cell growth plays a role in the cause of PPH. BMPR2 is a receptor in the transforming growth factor-beta family and is involved in regulation of endothelial cell proliferation. Further evidence comes from research on clonality of the plexiform lesions. Lee et al. [20] showed that the endothelial cells of plexiform lesions from PPH patients were monoclonal in origin, while lesions from patients with PH related to congenital intracardiac shunts or collagen vascular disease were polyclonal in nature. Monoclonality was also demonstrated in patients with appetite suppressant-related PH, further linking this disorder to PPH [21].

NOS = nitric oxide synthase
NO = nitric oxide
ET = endothelin-1

Treatment of PAH

The treatment of pulmonary arterial hypertension has evolved dramatically in recent years. Traditionally, patients were treated for their clinical presentation of heart failure with the standard approach of diuretics and digoxin as well as oxygen if needed. However, the onset of clinical heart failure and even the elevation of right atrial pressure are now known to herald a poor outcome [4]. Thus treatments directed at the primary vascular abnormalities were needed. Of particular attention were the vascular thrombosis and elevated pulmonary vascular resistance found in these patients.

Anticoagulation

Anticoagulation was often used to prevent further thrombosis and loss of vascular channels in patients with abnormal ventilation/perfusion scans. A retrospective analysis of 120 PPH patients with a 5 year mortality of 79% found anticoagulation to be associated with improved outcome [22]. A prospective trial of calcium channel blockers in PPH patients found anticoagulation to be an independent predictor of improved survival [23]. Thus long-term anticoagulation has become standard care in PPH. No studies of anticoagulants in other forms of PAH have been carried out, but anticoagulation is used in all forms of the disease when feasible.

Vasodilatation

The major advances in the treatment of PPH have involved vasodilators directed at lowering pulmonary vascular resistance and improving right ventricular function. These have included non-specific vasodilators as well as novel agents directed at the pulmonary vasculature. In 1980 Rubin and Peter [24] demonstrated that oral hydralazine could significantly reduce pulmonary vascular resistance in patients with PH and that the effect could be maintained with ongoing therapy. Since that time vasodilators have become standard treatment of pulmonary arterial hypertension and have been evaluated for other forms of PH, including pulmonary venous hypertension and PH associated with disorders of the respiratory system and/or hypoxemia. Here we will briefly review the most commonly used classes of vasodilators.

- *Calcium channel blockers*

Calcium channel blocking agents became the major vasodilators for use in PH in the early 1990s. The most commonly used agents are nifedipine and diltiazem. These medications act as pulmonary vasodilators but also have significant peripheral arterial effects and can lower cardiac output. The clinical effects vary. The majority of patients will not have a significant positive response to acute challenge as measured by pulmonary artery pressure and pulmonary vascular resistance [23]. Those that do respond favorably have prolonged survival and improved hemodynamics resulting from long-term treatment [23,25]. Much of the data on the use of these

drugs for PH involve high doses, often above what would be used for routine systemic hypertension. However, the high doses can increase side effects and complications, thus common practice is to stop at the upper end of the recommended dose range and then use other agents. In the past an acute trial of an escalating dose of a calcium channel blocker during continuous pulmonary and systemic arterial pressure monitoring was used to determine if long-term therapy was indicated. This approach had drawbacks. Dose titration using the oral medication was time consuming. The trials were associated with complications and even death in patients with advanced pulmonary hypertension. In these cases a predominant systemic effect was seen with a fall in systemic blood pressure followed by a fall in cardiac output, resulting in cardiogenic shock. Short-acting, more selective pulmonary vasodilators such as inhaled nitric oxide, inhaled or intravenous prostacyclin and intravenous adenosine have proved to be safer while also highlighting those patients with a reactive vasculature [26]. Patients who respond to a short-acting vasodilator can be treated with long-term calcium channel blockers with a good chance for improvement. However, with the newer agents available, a minority of PH patients are treated with calcium channel blockers alone.

- *Prostacyclin analogues* [Table 2]

Prostacyclin is produced by the vascular endothelium and acts locally as a vasodilator. A possible etiologic role for prostacyclin in PH was suggested by the finding of lower than normal levels of its metabolites in PH patients [15]. Whether this deficiency is the cause or result of the disease is not certain but the finding did suggest the possible use of prostacyclin for treatment. The development of the intravenous form, epoprostenol, revolutionized PH treatment, particularly the treatment of pulmonary arterial hypertension. Epoprostenol is delivered as a continuous intravenous infusion through an indwelling catheter using a battery-operated pump. The effect on pulmonary hemodynamics over time is significant even in patients without an initial vasodilator response [27]. This is in contrast to the calcium channel blockers. In a randomized trial of epoprostenol in the treatment of PPH the drug was shown to improve symptoms, hemodynamics and survival [28]. Epoprostenol is particularly beneficial in advanced cases where the dose can be titrated aggressively to improve right ventricular function. Several limitations should be mentioned. First, the delivery system is cumbersome and the patients are subject to catheter-related complications. Second, when catheter or pump malfunctions do occur and the epoprostenol infusion is halted, there is a significant risk for sudden death related to an acute increase in pulmonary artery pressures. Third, significant side effects including headache, flushing and jaw pain are common. However, epoprostenol is the only treatment thus far to show a clear survival benefit in a randomized trial, and it remains the backbone of therapy for many patients.

An inhaled form of prostacyclin, iloprost, has been developed for PH treatment. Iloprost is delivered using a standard nebulizer and does not require the continuous infusion apparatus of epoprostenol. The acute inhalation of iloprost acts as a pulmonary vasodilator similar to intravenous epoprostenol or inhaled nitric oxide [17]. A protocol using 6–8 inhalations a day has been shown to improve exercise capacity and hemodynamics after 1 year of treatment [29]. A 12 week randomized trial of inhaled iloprost confirmed its benefit with regard to heart failure class, dyspnea and exercise capacity [30]. The drawbacks of iloprost include symptoms of flushing and jaw pain as seen with epoprostenol, and the inconvenience of up to nine nebulized treatments every day.

Table 2. Prostacyclin analogues

Formulation	Route	Delivery system	Advantages	Drawbacks
Epoprostenol*	IV	Continuous pump	Easily titratable Proven survival benefit	Drug mixing
			Vast experience	Central access
Iloprost	Inhaled	Nebulizer	Non-invasive Simple system	Frequent dosing Syncope reported
Treprostinil*	s.c.	Continuous pump	Easily titratable No central access	Insertion site pain Frequent site changes
Beraprost	Oral	Tablet	Simple delivery	No randomized data

* Currently FDA approved

Treprostinil is a prostacyclin analogue recently approved by the Food and Drug Administration for treatment of PPH. Treprostinil is delivered subcutaneously using a pump. The dose is titratable as it is with epoprostenol. The infusion catheter is placed in the abdominal wall with a change in site every 1–3 days. This is a less invasive system than the indwelling catheter needed for epoprostenol. A randomized 12 week trial of treprostinil in patients with PPH, PH associated with collagen vascular disease or congenital left to right shunts demonstrated efficacy with improved exercise tolerance, hemodynamics and dyspnea scores [31]. Patients treated with intravenous epoprostenol have been successfully switched to subcutaneous treprostinil [32]. Treprostinil, like other prostacyclin analogues, can cause symptoms of flushing, jaw pain and diarrhea. A more significant problem with this system was infusion site pain, requiring treatment in 85% of patients.

An oral form of prostacyclin, beraprost, is also now available. This agent has been used in the treatment of occlusive peripheral arterial disease and has been investigated in patients with PH. In small, non-randomized studies, beraprost was documented to improve exercise tolerance and lower pulmonary artery pressures with chronic treatment [33]. Because of the ease of administration this drug holds great promise, however the results of randomized trial data are not yet available.

- *Endothelin antagonists* [Table 3]

As previously mentioned, ET is an endothelial derived peptide that is a key mediator of vascular tone. It is generated from a pro-peptide, big ET, through the action of endothelin-converting enzyme. There are receptors for ET on vascular smooth muscle and endothelial cells, and both vasoconstrictor and vasodilator properties have been described; however the former predominates

Table 3. Endothelin receptor antagonists

Formulation	Route	Target receptor	Drawbacks
Bosentan*	PO	A&B	Liver toxicity Peripheral edema Drug interactions: Cyclosporine Glyburide
Sitaxsentan	IV, PO	A	Liver toxicity Peripheral edema Drug interactions: Warfarin

* Currently FDA approved

in most systems. Data on ET in pulmonary hypertension suggests it may be a mediator of elevated vascular resistance. There is increased expression of ET in the vasculature of PH patients, possibly related to diminished clearance in the pulmonary vessels [18,34]. Several inhibitors of the major ET receptors, ET-A and ET-B, have been developed and at least two have been used clinically.

Bosentan is an inhibitor of ET-A and ET-B and is currently approved for the treatment of PPH. It is available in an oral formulation. Two randomized trials of bosentan for treatment of PPH and PH related to collagen vascular disease have reported improvement in exercise capacity, dyspnea and functional status [35,36]. The ease of delivery compared to the available prostacyclin analogues is an advantage. The most significant drawback has been hepatotoxicity, thus regular monitoring of liver function is recommended. Peripheral edema has also been seen in patients on bosentan and is usually managed with diuretics. Bosentan has been used in combination with prostacyclin analogues, but controlled trials have not yet been published.

Sitaxsentan is a selective ET-A receptor antagonist that has been used in small, preliminary studies in PH. The theoretical advantage with this medication is that the ET-B receptor may be responsible for vasodilatory properties and clearance of ET. Thus, the ET-A receptor is the preferential target. Acute intravenous administration of sitaxsentan lowers pulmonary vascular resistance and pulmonary artery pressure [37]. An oral form of the medication was also shown to improve hemodynamics and exercise capacity in a 12 week study, however there were some cases of significant hepatotoxicity [38].

- *Sildenafil*

As mentioned previously, NO is a potent vasodilator produced by endothelial cells. The NO effect is mediated intracellularly through cyclic guanosine monophosphate. Phosphodiesterase-5 is responsible for the breakdown of cGMP. Thus, the inhibition of PDE5 would lead to increased intracellular NO levels. Sildenafil, a PDE5 inhibitor, is used in the treatment of erectile dysfunction. By decreasing the breakdown of cGMP activity sildenafil maintains the vasodilatory activity of NO. The pulmonary vasodilating action of sildenafil has now been well documented, as has a synergistic effect with other agents such as iloprost [39,40]. Case reports of its long-term use in PH have appeared and further studies are ongoing.

cGMP = cyclic guanosine monophosphate
PDE5 = phosphodiesterase-5

Heart and lung transplantation

Patients who experience disease progression with available medical treatments are candidates for lung or heart-lung transplantation. The need for transplantation has decreased with the use of epoprostenol, however the option needs to be considered in all patients.

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Capsule

Combating liver disease

Protecting the liver, either naturally or therapeutically, is the focus of two reports. Endothelial cells (ECs) were once thought to function primarily in the delivery of nutrients and oxygen to tissues, but recently ECs were shown also to secrete factors that induce organ development in vertebrate embryos prior to the establishment of blood flow. Studying mouse models, LeCouter et al. (*Science* 2003;299:890) now show that ECs have a protective function in the adult liver that is independent of their role in new blood vessel growth. In response to activation of vascular endothelial growth factor receptor-1 (VEGFR-1), ECs were shown to secrete several proteins, including hepatocyte growth factor, which stimulate hepatocyte proliferation and reduce tissue damage in a liver injury model. In the search for effective drugs in treating chronic cases of hepatitis B virus, it is important to find drug candidates that target novel aspects of virus physiology. Deres et al. (p. 893) describe a compound, Bay 41-4109, that appears to act by inhibiting the maturation of the viral nucleocapsids.