

Pulmonary Arterial Hypertension

Evangelos D. Michelakis and Stephen L. Archer

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Introduction and History of the Pulmonary Circulation

The first description of the circulation of blood through the lungs has been attributed to Ibn Nafis (1210–1288).¹ The concept was rediscovered by Michael Servetus, a Spanish physician during the Renaissance (1511–1553) and recorded, oddly enough, in two pages of his religious treatise, *Christianismi Restitutio* (1553).² The definitive exposition of the pulmonary circulation was made by William Harvey in *De Motu Cordis* (1628).³ The first observation of the pulmonary capillaries was first reported by Marcellus Malpighi (1661).⁴ Heart catheterization in humans, driven by a desire to obtain the perfect mixed venous specimen and measure cardiac output, was first performed in 1929 by the German urologist Forssmann,⁵ using a ureteral catheter to access his own right atrium. Over a decade later, Courmand and Richards at Columbia University in New York subsequently used right heart catheterization to record pulmonary artery pressure (PAP) in patients with shock and secondary forms of pulmonary hypertension (PHT). For these accomplishments, which were inspired by an interest in the pulmonary circulation and PHT related to mitral stenosis, Forssmann, Courmand, and Richards received the Nobel Prize in 1956.

Pathologic findings consistent with primary PHT were first noted in autopsy specimens as a form of arterial sclerosis by Romberg⁶ and Monckeberg⁷ over a century ago. However, the first diagnosis of primary PHT in a living human was not made until 1951, by Dresdale et al.⁸ Over the past 50 years it has become clear that primary PHT is largely a disease of the pulmonary circulation, and the pathology is focused in the small pulmonary arteries, which

are characterized by intimal fibrosis, medial hypertrophy, adventitial proliferation, obliteration of small arteries, and, on occasion, vasculitis or changes in the walls of the pulmonary veins.⁹ In addition, there are angioproliferative lesions, called plexiform lesions, which are uniquely found in pulmonary arterial hypertension (PAH) and not in other forms of PHT.⁹

In utero, the pulmonary circulation is largely bypassed, as oxygenation is the responsibility of the placenta. The fetal right ventricle, relative to the adult ventricle, is hypertrophied, and the arteries in this high pressure–low flow circuit have thickened media and adventitia. At birth there is a transition to a high-flow, low-resistance circuit designed for gas exchange, and the right ventricle becomes a thin-walled, afterload-intolerant pump. The adult pulmonary circulation accommodates the entire right heart cardiac output at 20% the pressure and resistance of the systemic vasculature. The pulmonary circulation is composed of large, extrapulmonary, “conduit” arteries, which anatomically and embryologically resemble systemic arteries, and small, muscular intrapulmonary arteries, which control regional distribution of pulmonary blood flow and largely determine pulmonary vascular resistance (PVR). These arteries perfuse an extensive thin-walled, metabolically active, capillary bed where gas exchange occurs. Blood then courses to the left atrium via the venous circulation, which has active tone and which, as it approaches the left atrium, acquires a sleeve of cardiac myocytes.¹⁰ The normal physiologic function of the pulmonary veins is uncertain, although they may be involved in coordinating venous flow with atrial function. In disease, the pulmonary veins can be a source of ectopy, which leads to atrial fibrillation.¹¹

Definition of Pulmonary Hypertension

Pulmonary hypertension is a condition defined as an increase of the mean PAP to more than 25 mmHg at rest or 30 mmHg with exercise. This definition was used in the National Institutes of Health (NIH) registry of patients with primary PHT,¹² a form of PAH in which the etiology is unknown and the pathology is focused in the arterial portion of the pulmonary circulation. Although this chapter focuses on PAH, the most common forms of PHT are “passive,” relating to left ventricular dysfunction with increased left ventricular end-diastolic pressure due to myocardial or valve disease. In this pathology there is usually relatively minor pulmonary vascular pathology, although some patients with left heart failure or mitral stenosis have more severe PHT than would be predicted based on their left atrial pressure, suggesting a reactive form of PAH. The use of PAP as a means to diagnose PAH is flawed because it is not precise in anatomically localizing the cause of the hypertension. For example, the elevated PAP in left heart diseases is due to the elevated pulmonary capillary wedge pressure and the gradient between the PA diastolic pressure and the wedge pressure is minimal. In contrast, in PAH this gradient is more than 10 to 12 mmHg, localizing the problem (obstruction) within the pulmonary circulation, proximal to the left atrium.

Pulmonary artery pressure increases slightly with age and normally increases with conditions that elevate cardiac output (e.g., exercise), even in healthy, young individuals. In healthy older men (ages 61 to 83 years), the mean PAP can increase to more than 40 mmHg during exercise. With exercise, PAP, wedge pressure and cardiac output are all elevated but PVR is relatively unchanged. Consequently, PVR (Table 105.1) is a better parameter with which to define pulmonary arterial pathology. Conversely, PAP may be minimally elevated in a patient with PAH and very low cardiac output; in such a case PVR is usually ele-

vated at rest. In borderline cases, exercise can be used to elicit dramatic increases in PVR. The upper limit for PVR index [(PAP—wedge pressure)/cardiac index] in normal subjects increases from approximately 2.8 mmHg/L/min/m (6 to 10 years) to 3.2 (32 to 45 years) to 4.6 (60 to 83 years).¹³ Pulmonary vascular resistance must be measured in order to diagnose PAH.

The occurrence of PHT, whether as a primary disease or a complication of heart or airway disease (cor pulmonale) is an independent predictor of increased morbidity and mortality. This is because the impact on the function of the afterload-intolerant right ventricle is the same, regardless of the specific etiology of PHT. The function of the thin-walled adult right ventricle decreases abruptly even with small increases in its afterload, resulting in decreases in stroke volume and thus cardiac output. This is in sharp contrast to the left ventricle, which can compensate for much greater increases in afterload (Fig. 105.1).

Classification of Pulmonary Arterial Hypertension and Association with Other Diseases (Table 105.2)

Twenty-five years following the original meeting, the World Health Organization (WHO) sponsored the second International primary PHT meeting in Evian, France, where a new classification of PHT syndromes was adopted.¹⁴ Importantly, primary PHT (both sporadic and familial) was grouped with several other forms of PHT that strongly resembled primary PHT under the rubric of pulmonary arterial hypertension. These “primary PHT-like” cases were associated with identifiable pathogenic stimuli or disease states, such as the use of anorectics, collagen vascular disease, infection with HIV, congenital systemic to pulmonary shunts, and persistent PHT of the newborn. This reclassification reflected the fact that the clinical presentation and the histologic picture

TABLE 105.1. Useful formulas for assessment of pulmonary hypertension

Parameter	Formula	Normal Values
PVR mmHg/L/min/m	$PVR \text{ (Wood units)} = \left[\frac{PA_{mean} - P_{wedge}}{\text{Cardiac output}} \right]$	Age 6–10 years: 2.8; Age 32–45 years: 3.2; Age >60 years: 4.6 ¹³
PVR dynes sec cm ⁻⁵	$PVR \text{ (dyne sec cm}^{-5}\text{)} = \left[\frac{PA_{mean} - P_{wedge}}{\text{Cardiac output}} \right] \times 80$	<60 years: mean PAP: 12 ± 2 mmHg PVR: 70 ± 25 >60 years: mean PAP: 16 ± 3 mmHg PVR: 124 ± 32
Total pulmonary resistance (TPR)	$TPR \text{ (Wood units)} = \left[\frac{PA_{mean}}{\text{Cardiac output}} \right]$	
PAP mean (based on acceleration time, AT)	$PAP_{mean} = 79 - (0.45 \times AT)$ or $90 - (0.62 \times AT)$ Based on pulsed Doppler measurement in the main PA ^{137,246}	121 ± 27 ms ¹³⁵ , 134 ± 20 ms ²⁴⁶
PA Doppler	$PAP = AT/RVET^{247}$ (RVET = right ventricular ejection time)	>0.36 Doppler values in main PA of adults; velocity 70 cm/s and ET of 320 ms
PA systolic pressure (TR velocity, V _{TR}) (modified Bernoulli's equation)	$PA \text{ systolic pressure} = 4 \times V_{TR}^2 + RA \text{ pressure}^*$	

* Estimated from JVP.

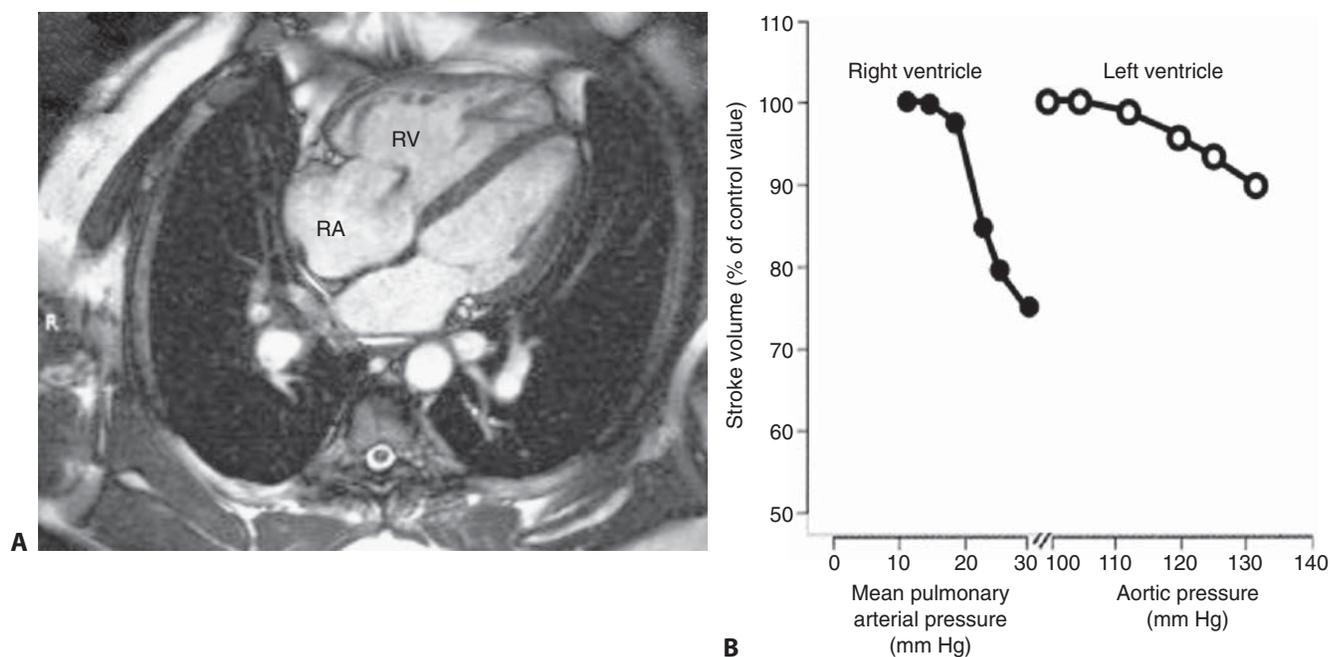


FIGURE 105.1. The right ventricle (RV) in pulmonary arterial hypertension (PAH). (A) A dilated RV is seen in this magnetic resonance (MR) angiography of a 55-year-old man with PAH. A dilated right atrium (RA) is also shown, and a central jet or regurgitation can be seen in the tricuspid valve in systole. The septum is flattened due to the pressure overload in the RV. (B) For the same increase in afterload, the function of the RV decreases much more compared to

that of the left ventricle (LV). The large resulting decrease in cardiac output that results with even small increases in the RV afterload [i.e., the pulmonary vascular resistance (PVR)] is responsible for many of the symptoms in PHT. The rapid deterioration of the RV function in PAH is also responsible for the much worse prognosis in patients with PAH, compared to that of the patients with systemic hypertension.

TABLE 105.2. Revised clinical and classification of pulmonary hypertension (Venice, 2003)

<i>Classification</i>	<i>Specific etiology</i>
Pulmonary arterial hypertension	<ol style="list-style-type: none"> 1. Idiopathic (iPAH) 2. Familial (fPAH) 3. PAH associated with: <ul style="list-style-type: none"> Collagen vascular disease Congenital systemic to pulmonary shunts Portal hypertension HIV infection Drugs and toxins Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy) 4. PAH associated with significant venous or capillary involvement <ul style="list-style-type: none"> Pulmonary veno-occlusive disease (PVOD) Pulmonary capillary hemangiomatosis (PCH) 5. Persistent pulmonary hypertension of the newborn (PPHN)
Pulmonary venous hypertension	<ol style="list-style-type: none"> 1. Left-sided or ventricular heart disease 2. Left-sided valvular disease
PHT associated with hypoxemia	<ol style="list-style-type: none"> 1. Chronic obstructive pulmonary disease 2. Interstitial lung disease 3. Sleep-disordered breathing 4. Alveolar hypoventilation disorders 5. Chronic exposure to high altitude 6. Development abnormalities
Thromboembolic PHT caused by chronic thromboembolism or embolic disease	<ol style="list-style-type: none"> 1. Thromboembolic obstruction of proximal pulmonary arteries 2. Thromboembolic obstruction of distal pulmonary arteries 3. Pulmonary embolism (tumor, parasites, foreign material)
Miscellaneous	Sarcoidosis, histiocytosis x, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

TABLE 105.3. World Health Organization (WHO) functional classification of pulmonary hypertension

Functional class	Defining criteria
I	Patients with PHT but without resulting limitation of physical activity Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or syncope
II	Patients with PHT who are comfortable at rest but in whom ordinary levels of physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
III	Patients with PHT resulting in marked limitation of physical activity with minimal physical activity; they are often comfortable at rest; less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope
IV	Patients with PHT with inability to carry out any physical activity without symptoms; these patients manifest signs of right heart failure; dyspnea and/or fatigue may even be present at rest and increases with physical activity

among different forms of PAH are indistinguishable, suggesting that the syndromes share pathogenetic mechanisms. Minor modifications to the Evian classification were proposed in the Third World Symposium of Pulmonary Arterial Hypertension that was held in Venice, Italy, in 2003. In this latest nomenclature (Table 105.2) the term *primary PHT* was replaced by idiopathic PAH (iPAH), which occurs in sporadic (sPAH) and familial forms (fPAH). The current WHO classification for defining functional class for PAH patients is shown in Table 105.3 (See also Fig. 105.2).

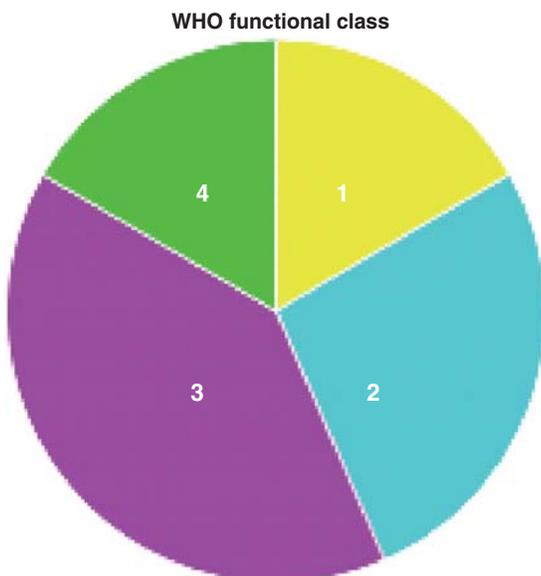


FIGURE 105.2. World Health Organization (WHO) functional classification of pulmonary hypertension.

Prevalence and Natural History of Pulmonary Arterial Hypertension

The prevalence, incidence, and mortality of PAH in the general population remain unknown. Early estimates identified PAH as a rare or “orphan” disease with a prevalence of 1 to 2 per million, based on data from limited cohorts in the United States, France, and Israel.^{15–17} These studies, which did not perform population surveillance, identified a very high mortality in PAH patients, often worse than that of metastatic breast cancer. For reasons discussed below, it is very likely that the prevalence of PAH is underestimated and the mortality overestimated, based on emerging data from centers that have earlier disease detection and offer improved therapies.

The largest primary pulmonary hypertension (PPH) natural history study was based on the NIH primary PHT registry, which followed 187 patients from 1981 to 1987.¹⁸ Primary PHT was defined as mean pulmonary artery (PA) pressure >25 mmHg at rest (or >30 mmHg with exercise) in the absence of secondary causes for PHT, a definition different from the current definition of PAH, which includes PHT due to more common diseases like collagen vascular disease, HIV infection, portal hypertension, congenital heart disease as PAH (Table 105.2). The mean age was ~36 years with a female to male ratio of 1.7:1. The mean right atrial pressure at diagnosis was 10 ± 6 mmHg and mean PA pressure 60 ± 18 mmHg, suggesting that this cohort had very severe PHT. A subsequent survival study of patients from the NIH registry showed a median survival of 2.8 years, with survival rates at 1, 3, and 5 years were 68%, 48%, and 34%, respectively. Mortality increased with advanced New York Heart Association (NYHA) class, elevated right atrial or mean PA pressure, and decreased cardiac index. Similar data were reported from smaller cohorts from Israel,¹⁶ India,¹⁹ and Japan.²⁰

An increase in the number of deaths in the U.S. attributed to iPAH has been reported.²¹ Analysis of cause of death data (based on death certificates) showed an age-adjusted increase in the number of deaths ascribed to iPAH in the U.S. from 1979 to 1996 (Fig. 105.3). The rate

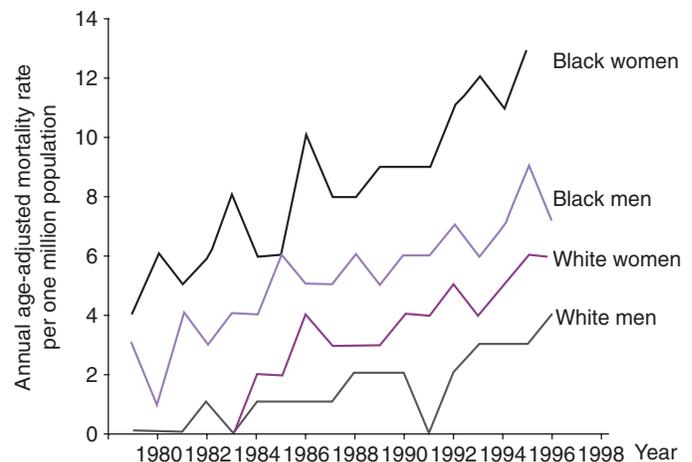


FIGURE 105.3. An increase in the incidence of idiopathic PAH (iPAH) has been documented recently, based on death certificate diagnoses in the United States. The increase has been higher in black men and black women.

of the increase was greatest amongst African-American women.²¹ This increase could be due to a true increase in the incidence of deaths from iPAH (for example, due to the use of anorectic agents, which caused an outbreak of iPAH during that period), better case recognition (due to the increased access to noninvasive means of measuring PA pressure and the increased access to the specialized PAH clinics), or both.

Indeed, widespread access to noninvasive diagnostic techniques (e.g., Doppler echocardiography) has led to an increase in the number of patients who are diagnosed at earlier stages of the disease, sometimes even before the onset of symptoms. However, the isolated measurement of PA pressure without measurement of cardiac output and wedge pressure has led to many misdiagnoses of PHT. In addition, there has recently been a dramatic increase in the awareness of PAH due to a number of factors, including an increase in the interest of the pharmaceutical industry, the medical community (during 2004 there were several publications from the American College of Cardiology (ACC) and the American College of Chest Physicians (ACCP), offering for the first time guidelines and evidence-based recommendations) and public advocacy (with organized Web sites focusing on PAH: <http://www.phassociation.org> and <http://www.phcentral.org/talk/index.html>).

TABLE 105.4. University of Alberta Pulmonary Hypertension (PHT) Program: PAH cases diagnosed (2002–2004)

Women (%)	26 (65)
mean age: 49 y	
Men (%)	14 (35)
mean age: 58 y	
Etiology (%)	
iPAH	24 (60)
Connective tissue disease	11 (28)
Congenital heart disease	2 (5)
Portal hypertension	2 (5)
HIV	

www.phcentral.org/talk/index.html). Patient empowerment has increased the number of self-referrals and referrals from general practitioners to PAH specialists. It is likely that the availability of oral therapies for PAH (such as Bosentan and sildenafil) has also enhanced the interest in making the diagnosis of PAH.

The Changing Epidemiology of Pulmonary Arterial Hypertension

Because of the lack of ongoing national databases and registries since the NIH registry closed, data on the current prevalence and natural history of PAH are lacking. However, anecdotal evidence suggests that the epidemiology has changed. For example, in the University of Alberta Pulmonary Hypertension Program (a tertiary care program serving a catchment population of 1.6 million) there have been 148 referrals for documented PHT over the past 2 years. From these, 40 had PAH, which was a new diagnosis in 75% of cases (Fig. 105.4, see also Table 105.4). The female to male ratio is ~2:1 and the mean age, in years, is 58 for men and 49 for women. Almost half of the patients are NYHA class I or II (Fig. 105.4). Although this is small and predominantly Caucasian cohort, it is consistent with anecdotal evidence that PAH is more common and more prevalent in older ages, and that current PAH cohorts are less sick than the original NIH cohort, which was predominantly young, female, and quite ill. Organized and independent, publicly funded, databases and registries are urgently needed to determine the true prevalence, incidence, and natural history of PAH, much like the NIH registry in the 1980s.

To understand PAH it is essential to review the unique features of the pulmonary circulation and its embryology.

The Mysteries of the Pulmonary Circulation

The pulmonary or “lesser” circulation has fascinated physiologists for over a century. Its many differences from the systemic vascular beds have only recently begun to be understood. For example, the pulmonary circulation is a low-pressure circulation with thin-walled arteries and it accommodates the whole cardiac output at a PA pressure of

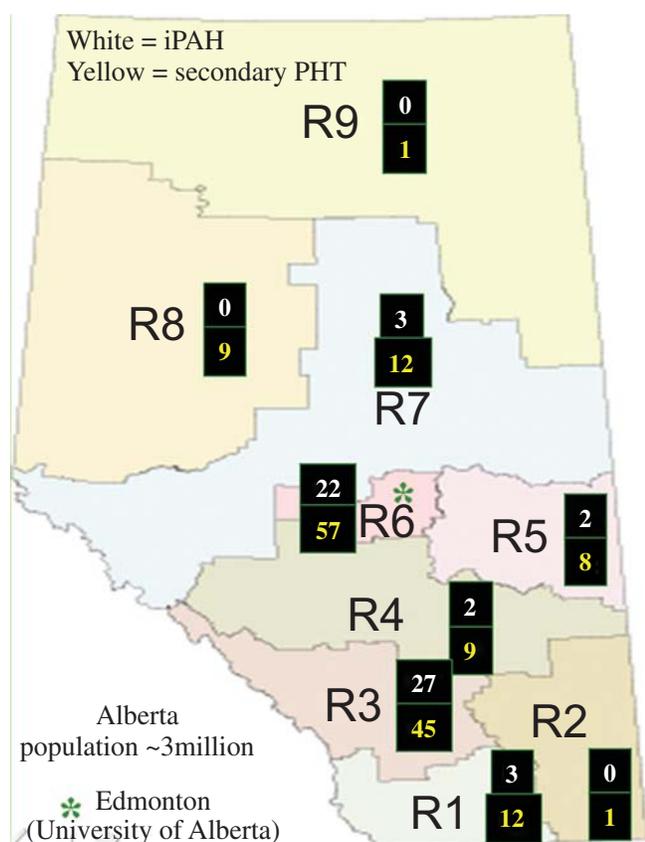


FIGURE 105.4. Pulmonary arterial hypertension in Alberta, Canada. (A) iPAH versus PHT over a 1-year period in Alberta (2002–2003). These numbers are based on hospital discharge diagnoses (each patient was counted once). A cohort of well-characterized consecutive PAH patients in the University of Alberta PAH program over the past 2 years suggests that PAH is more frequent than the National Institutes of Health (NIH) registry suggested and PAH patients are now older and less sick (see Table 105.4).

<30/20 mmHg, in contrast to the higher-pressure systemic circulation (120/80 mmHg) with its thick, muscular arteries. The purpose of the two circulations is also different: O₂ uptake for the pulmonary circulation, and O₂ delivery for the systemic circulation. In this regard, the pulmonary circulation constricts in response to acute hypoxia (hypoxic pulmonary vasoconstriction, HPV²²), which is the major mechanism to optimize ventilation-perfusion matching and thus O₂ uptake; in contrast, the systemic circulation dilates in response to hypoxia, which optimizes O₂ delivery. In addition, the pulmonary circulation develops in utero in a relatively hypoxic environment, compared to the systemic circulation. In utero, the uninflated lungs are bypassed by oxygenated blood coming from the placenta, which is preferentially shunted to the systemic vasculature through the fossa ovalis and the ductus arteriosus. The diseases that afflict the pulmonary circulation are also relatively unique. In adult life, systemic hypertension and atherosclerosis spare the pulmonary circulation, and, conversely, PAH usually occurs without substantial systemic vascular disease. However, systemic arterial vasospasm in the digits, which is a response to cold (Raynaud's phenomenon), is not uncommon in PAH (particularly in association with ingestion of anorexigens or collagen vascular diseases). The relative contribution of genetic versus environmental differences to these pulmonary-systemic arterial differences is unclear and perhaps both contribute. The systemic arteries and pulmonary arteries have different embryologic origins, but also experience markedly different local environments. For example, the small pulmonary arteries that control PVR are adjacent to the alveoli and experience much higher levels of ambient oxygen and much less shear stress than systemic arteries.

Understanding these differences will explain several important mechanisms in health and disease. For example, why is the pathology of PAH restricted to the pulmonary vessels, leaving all the systemic vessels intact? The answer to this question has important clinical implications since currently a major challenge in the therapy of PAH is the lack of selective treatments that lower PAP without causing systemic vasodilatation. The PAH patients tolerate systemic vasodilatation poorly because fixed and elevated levels of right ventricular afterload prevent compensatory increases in cardiac output in response to vasovagal stimuli or vasodilator therapies, promoting a vicious cycle of hypotension. Therapeutic targets unique to the pulmonary circulations have not yet been identified. However, accessing the pulmonary vasculature via the airway permits selective therapy of the pulmonary circulation for compounds that are not systemically absorbed [e.g., Iloprost®, inhaled nitric oxide (iNO)].

The lung has two parallel circulations: the pulmonary arteries and the bronchial arteries. The bronchial arteries are thick-walled and muscular, and they supply blood to the bronchi and the wall of the large pulmonary arteries. In other words, they are vessels made to *supply* oxygen to support the lung's relatively minimal metabolic functions. In this regard bronchial arteries resemble systemic vessels. In contrast, the pulmonary arteries are involved in the central *uptake* of oxygen from the lungs. Hypoxic pulmonary vasoconstriction is a homeostatic response, intrinsic to the pulmonary arteries, that optimizes oxygenation by matching ventilation to

perfusion. In HPV, the small (<300 μM) arteries “sense” even small decreases in the local alveolar PO₂ and constrict to divert the blood to better ventilated areas, preventing the delivery of suboptimally oxygenated blood to the body; conversely, all systemic arteries vasodilate, thereby optimizing systemic O₂ transport. The resistance pulmonary arteries, together with carotid body and airway neuroepithelial bodies, constitute the body's specialized O₂ sensing system, the function of which is optimization of O₂ uptake. Interestingly, these tissues share common mechanisms to transduce changes in PO₂ into changes in arterial tone, ventilation, and airflow.²²

The Development of the Pulmonary Circulation

Hypoxic pulmonary vasoconstriction is strongest in the small, fourth- to seventh-division pulmonary arteries that are surrounded by alveoli; conversely proximal, extrapulmonary arteries do not contract, and may even dilate in response to hypoxia (Fig. 105.5C). These differences may be genetically programmed because the proximal pulmonary arteries have a different embryologic origin from the small intrapulmonary arteries.²³ The proximal pulmonary arteries are derived from the truncus arteriosus, which divides into the aorta and pulmonary trunk by 8 weeks of human gestation, by growth of the spiral aorticopulmonary septum. This occurs via *angiogenesis*, which is the branching of new vessels from preexisting ones.²⁴ In contrast, the small intraparenchymal pulmonary arteries are derived from the sixth branchial arch arteries, the most caudal of the brachial arteries, by 7 weeks' gestation in humans.²⁴ This occurs via *vasculogenesis*, which is the development of blood lakes in the mesenchyme. Recent evidence suggests that these arteries originate from a strand of endothelial precursors that connect the ventral wall of the dorsal aortae to the pulmonary trunk.²⁵ Distinct endothelial precursor cells have recently been identified in human embryos²⁶ (Fig. 105.5A). A survival advantage to these endothelial cells is offered by a variety of survival and antiapoptotic factors, and it appears that insulin growth factor plays a central role very early in the process.²⁶ Both the angiogenesis (for the proximal pulmonary arteries) and the vasculogenesis (for the distal pulmonary arteries) are elegantly coordinated, and finally the two developing vascular segments are connected by a fusion process²⁴ (Fig. 105.5).

Vascular Diversity Within the Pulmonary Circulation

The different embryonic origins of vascular cells within the fetal lung may account for some of the endothelial and smooth muscle heterogeneity that characterizes the adult lung. For example, endothelial cells from the proximal arteries have a different phenotype compared to endothelial cells from distal pulmonary arteries.²⁷ The differences between these two types of endothelial cells are maintained even in culture, emphasizing their genetic basis.²⁷ Similarly, smooth muscle cells (SMCs) from the distal and proximal pulmonary arteries have different phenotypes and functional properties.

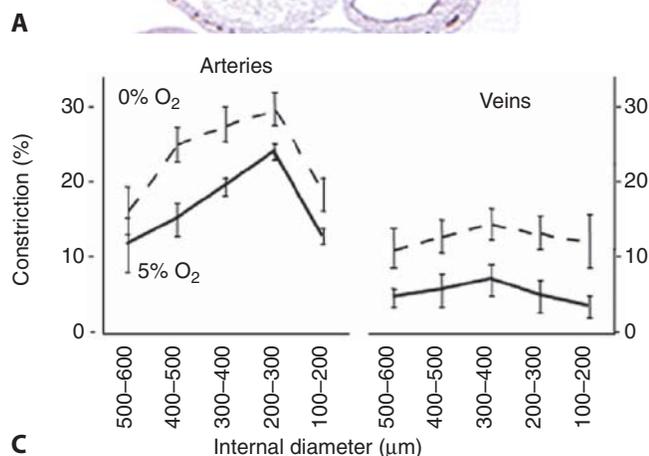
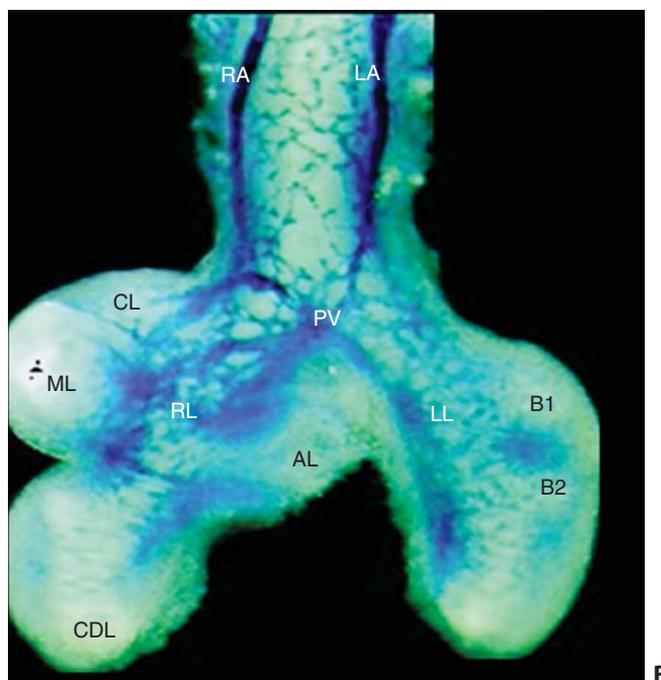
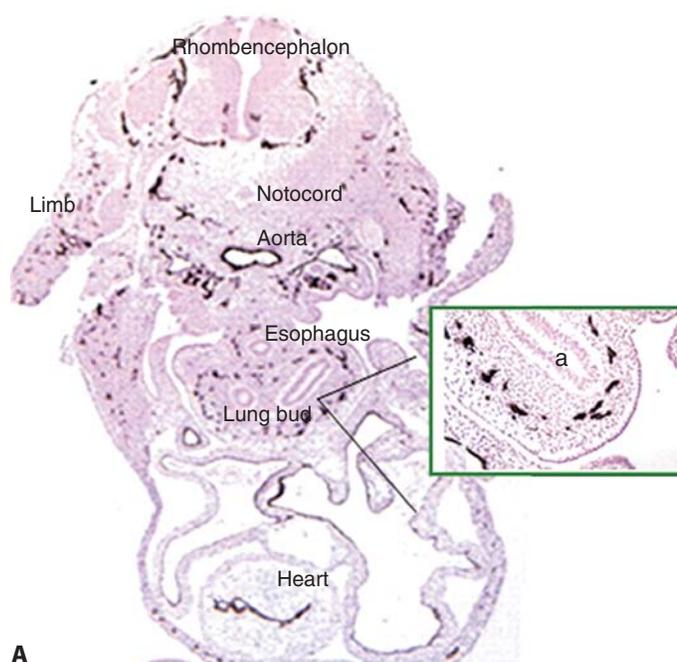


FIGURE 105.5. Embryology might explain the diversity within the pulmonary circulation in response to hypoxia (see text). (A) Horizontal section of a 4-week embryo demonstrates precursor endothelial cells (ECs) (black) as inner linings of the heart and great vessels and in and around several developing organs. Higher magnification of a lung bud demonstrates a single layer of EC organized around the developing airway [a]. (B) Tie-1-Lac Z transgenic mice embryo (11.5 days) shows that the left and right pulmonary arteries are now completed (via a fusion process) and run as a unit, alongside the trachea. (C) Most of the constrictor response to acute hypoxia within the pulmonary circulation occurs in the small and medium-sized pulmonary arteries.

First, distal pulmonary artery SMCs (PASMCs) contract in response to hypoxia *in vitro*, whereas the cells from proximal pulmonary arteries dilate, like the SMCs from systemic arteries.²⁸ Perhaps this reflects the fact that the SMCs of small pulmonary arteries express relatively more oxygen-sensitive Kv channels (particularly Kv1.5 and Kv2.1), whereas proximal PASMCs express more calcium-activated K⁺ channels (KCa).^{29,30} This finding is important because these redox- and oxygen-sensitive Kv channels, such as Kv1.5, have been directly implicated in the initiation of HPV.³¹ Inhibition of these channels leads to depolarization of the SMCs, opening of the voltage-gated L-type calcium channels, influx of calcium, and contraction. The full manifestation of HPV is supported by calcium release from intracellular stores as well as by calcium sensitization of the contractile apparatus by rho kinase.²²

Hypoxic pulmonary vasoconstriction occurs even at mild levels of alveolar hypoxia, and at these levels of physiologic hypoxia, animals and patients do not develop seizures or arrhythmias (which would be expected if these channels were similarly inhibited in the brain and the heart, where they are also expressed). The restriction of HPV to certain

portions of the pulmonary circulation thus might be due to tissue heterogeneity among expressed K⁺ channels between pulmonary and systemic vascular beds (e.g., splice variants). This restricted localization of the hypoxic vascular response could also be due to the presence of unique sensors for hypoxia in the distal pulmonary arteries. It is the sensor, which, in response to hypoxia, alters the production of a mediator that regulates the function of O₂-sensitive K⁺ channels. The sensor of hypoxia in the pulmonary arteries appears to be the SMCs' mitochondrial electron transport chain,^{22,32,33} or possibly another vascular redox enzyme, reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.³⁴ This sensor changes the production of reactive oxygen species (ROSs) in response to mild hypoxia, and these ROSs serve as diffusible second messengers, changing the gating and opening of certain Kv channels, such as Kv1.5 and Kv2.1²² (Fig. 105.6). In hypoxia, altered mitochondrial-derived ROS production leads to Kv channel inhibition and vasoconstriction. Although the identity of the pulmonary oxygen sensor remains controversial, and there is disagreement as to whether hypoxia increases or decreases ROS, mitochondria are vascular O₂ sensors in the pulmonary arteries, as

well as in a variety of other oxygen-sensitive vascular tissues, including the ductus arteriosus and the carotid body.²² The mitochondria of the small pulmonary arteries are functionally distinctly different from the mitochondria of the systemic vessels³⁵ (Fig. 105.7).

Clinical Implications

Although some of these concepts have been introduced only during the past few years, their clinical implications have already become apparent. Kv1.5, which is involved in the initiation of HPV, is selectively downregulated in both animal models of PAH and humans with PPH.^{36–38} This downregulation leads to depolarization and the activation of the voltage-gated calcium channels in the PSMCs. This likely explains the beneficial effects of L-type calcium channel blockers (such as nifedipine) in some patients with PAH.³⁹ These mechanisms can also explain why drugs that open K⁺ channels (e.g., inhaled NO and sildenafil) are beneficial in PAH. In the future, perhaps therapeutic strategies can be devised to exploit mitochondrial diversity to create therapies that are selective for the pulmonary circulation. The mitochondria are promising targets for PAH therapy because they not only regulate vascular tone but also are major determinants of rates of apoptosis in the vascular wall. Induction of apoptosis in the media of remodeled pulmonary arteries in PAH might be an effective and selective therapeutic strategy. In experimental PAH, it appears that mitochondrial function is abnormal (as manifest by a hyperpolarized mitochondrial membrane potential and altered ROS production), and this leads to inappropriately low rates of apoptosis and enhanced SMC proliferation.³⁸ Strategies that induce mitochondria-dependent apoptosis may prove to be effective and selective treatments. Dichloroacetate (an inhibitor of the

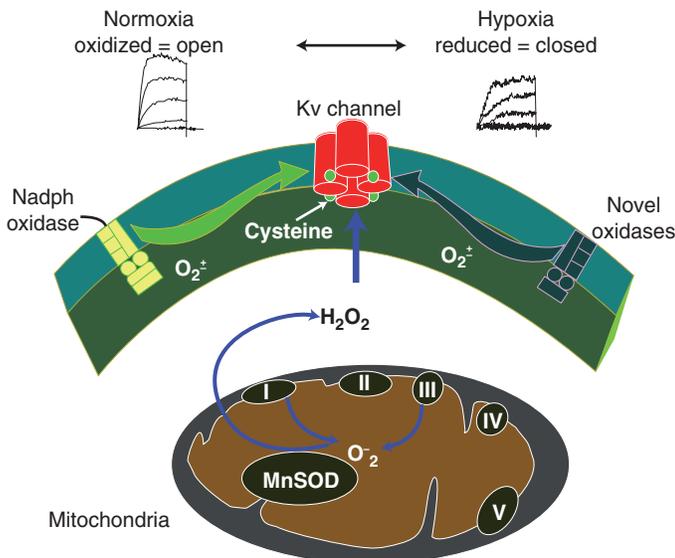
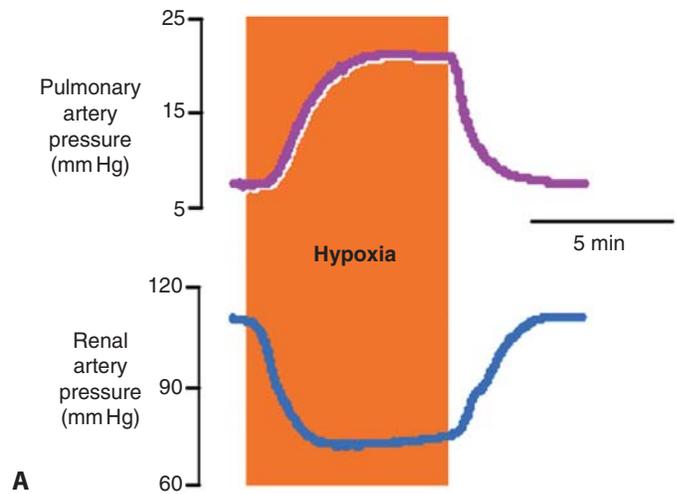
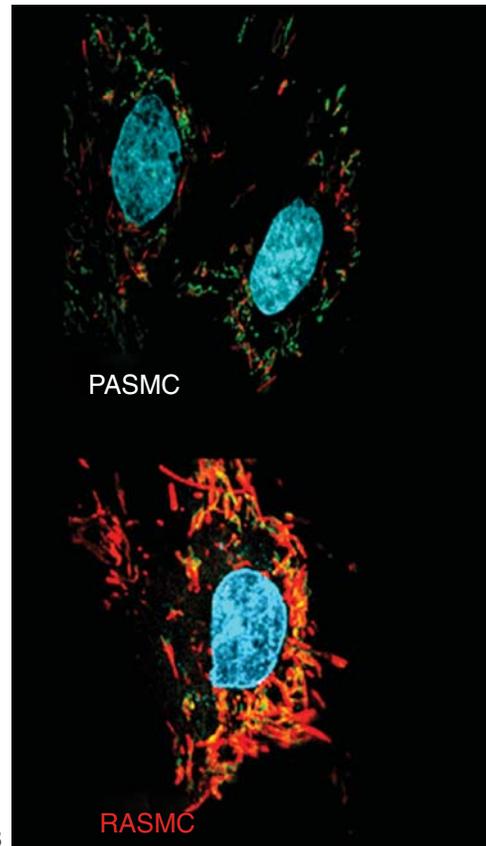


FIGURE 105.6. A model for oxygen sensing in the pulmonary circulation. In hypoxia the sensors (mitochondria) change the production of the mediator (activated oxygen species, AOS) and regulate the function of the effectors (K⁺ channels). Alternate sensors include the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and novel oxidases.



A



B

FIGURE 105.7. Mitochondrial diversity in the vasculature. (A) The opposing effects of the pulmonary and the renal circulation to hypoxia are at least in part due to differences in the oxygen sensor, that is, the mitochondria. The traces shown here are from isolated rat lungs and kidney perfused in series. (B) The pulmonary artery smooth muscle cell (PASMC) mitochondria are more depolarized (as shown by the TMRM fluorescence and confocal microscopy) compared to the renal artery smooth muscle cell (RASMC) mitochondria, although they are imaged under identical condition.

mitochondrial pyruvate dehydrogenase kinase, which has been used orally in human with congenital lactic acidosis) induces vascular apoptosis and reverses PAH in rats, without affecting the systemic vessels.³⁸ Inhaled gene therapy with a

dominant-negative construct that inhibits the inhibitor of apoptosis protein survivin also induces mitochondria-dependent apoptosis and reverses PHT in animals.⁴⁰

Vascular Biology of Pulmonary Arterial Hypertension

Histopathology

Pulmonary arteries in PAH are characterized by intimal fibrosis, medial hypertrophy, adventitial proliferation, obliteration of small arteries, in situ thrombosis, and, on occasion, vasculitis or changes in the walls of the pulmonary veins⁴¹ (Fig. 105.8). A fascinating, focal vascular structure, the plexiform lesion, is found in many cases of PAH and is typically absent in secondary forms of PHT, due to hypoxia, cor pulmonale, left heart disease, and thromboembolism. Plexiform lesions are somewhat reminiscent of renal glomeruli, their many vascular channels being lined with endothelial cells rich in type-3 nitric oxide synthase (eNOS),⁴² factor VIII, vimentin,⁴³ and the receptor for vascular endothelial growth factor (VEGF).⁴⁴ 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. Certainly, computerized three-dimensional reconstruction of vessels in PAH demonstrate that plexogenic lesions occur distal to obstructive vascular lesions.⁴⁴

Studying PAH pulmonary arteries with either a plexiform lesion or intimal or medial hypertrophy, one is impressed by the increased cellularity in the vascular wall. The increased cellularity may represent infiltrating inflammatory cells (in some cases), but in most cases it reflects excessive cell proliferation or suppressed apoptosis. The therapeutic potential of reversing the imbalance between proliferation and apoptosis within the pulmonary artery wall is a very new area of research in PAH and has already produced some attractive experimental treatments for PAH, as will be discussed below.

Mechanisms of Pulmonary Arterial Hypertension

The challenge for any pathogenetic theory of PAH is to account for the entire spectrum of the disease, that is, pulmonary artery vasoconstriction, obstructive vascular remodeling, and thrombosis in situ. However, PAH is likely a syndrome, not a disease, consisting of several conditions that share similar features but result from diverse etiologic stimuli. It is also likely that classic PAH is the end stage of multiple mechanisms and phenotypes, one or more of which might be an initiating mechanism, whereas others follow and exacerbate the condition. A "multiple hit hypothesis" is increasingly being accepted as the leading theory to explain the complexity, relative rarity, and pulmonary vascular selectivity of PAH. Much like cancer, a susceptible patient with a genetic predisposition [e.g., due to mutations of the bone morphogenetic protein receptor-2 (BMPR-2) or gene polymorphisms] appears to require additional environmental insults (like an anorectic drug or a viral infection) before PAH is manifested.⁹

The many abnormalities that have been described in PAH can be grouped into two large thematic categories: (1) abnormalities that contribute to an imbalance between vasoconstrictors and vasodilators and thus promote vasoconstriction, and (2) abnormalities that contribute to an imbalance between proliferation and apoptosis and thereby promote proliferative remodeling. Specific cellular and biochemical abnormalities have been described in PAH at all levels of the vasculature, from the blood (e.g., platelets) and endothelial cells through the SMCs, fibroblasts, and inflammatory cells. In this discussion we emphasize the studies that have used patients or human tissues.

While the mechanisms that we discuss below, alone or in combination, can explain most of the features of PAH, no mechanisms so far can adequately explain perhaps the biggest mystery of this challenging disease: Why are the vascular abnormalities in PAH restricted to the pulmonary circulation? What is it that predisposes the pulmonary arteries or protects the systemic arteries from this disease?

THE ENDOTHELIUM

At the late stages of PAH the pulmonary artery endothelium is highly abnormal.⁴⁵ Because PAH is usually detected only in the late stages of the disease, studies of the endothelial function in patients with early PAH are lacking. The final result of the endothelial dysfunction is an imbalance of endothelial-derived vasoactive factors, with an increase in the vasoconstrictors/vasodilator balance.

Both iPAH and secondary PHT patients excrete elevated levels of a thromboxane A₂ metabolite and reduced amounts of a prostacyclin metabolite.⁴⁶ Thromboxane A₂ is a potent vasoconstrictor and stimulus for platelet aggregation, whereas prostacyclin is an antiproliferative, antiaggregatory, vasodilator endothelial product. The fact that this platelet-endothelial abnormality occurs in both iPAH and secondary PHT suggests it is not the cause of iPAH. Nonetheless, this observation has had rich therapeutic value, as is discussed later.

It is also postulated that there is an excess of the constrictor endothelin-1 (ET-1) and a deficiency of the vasodilator NO in iPAH. The idea of a NO deficiency in PAH, the conventional wisdom, relates to the observed decrease in expression of endothelial nitric oxide synthase (eNOS) in the lungs of a few iPAH subjects.⁴⁷ However, NOS function was not measured in this immunohistochemistry study. Conversely, lung NO production, which admittedly may not reflect only pulmonary vascular NO production, is actually enhanced⁴⁸ or preserved in PAH.⁴⁹ Similarly, iPAH patients have higher urinary cyclic guanosine monophosphate (cGMP) concentrations than asthmatic patients or healthy controls.⁵⁰ Since most blood vessels respond to elevation of tone with a homeostatic increase in NO production, NO deficiency in PAH might represent a failure of this pathway in the late stages of the disease. Alternatively, certain patients with endothelial dysfunction or an abnormal eNOS variant may be predisposed to certain forms of PAH. Depressed NO production may contribute to the susceptibility to anorexigen-induced PAH.⁵¹

Endothelin-1 (ET-1) is a potent peptide vasoconstrictor and mitogen. ET-1 levels are increased in experimental⁵² and human PAH.^{53,54} The high levels of ET-1 in arterial compared

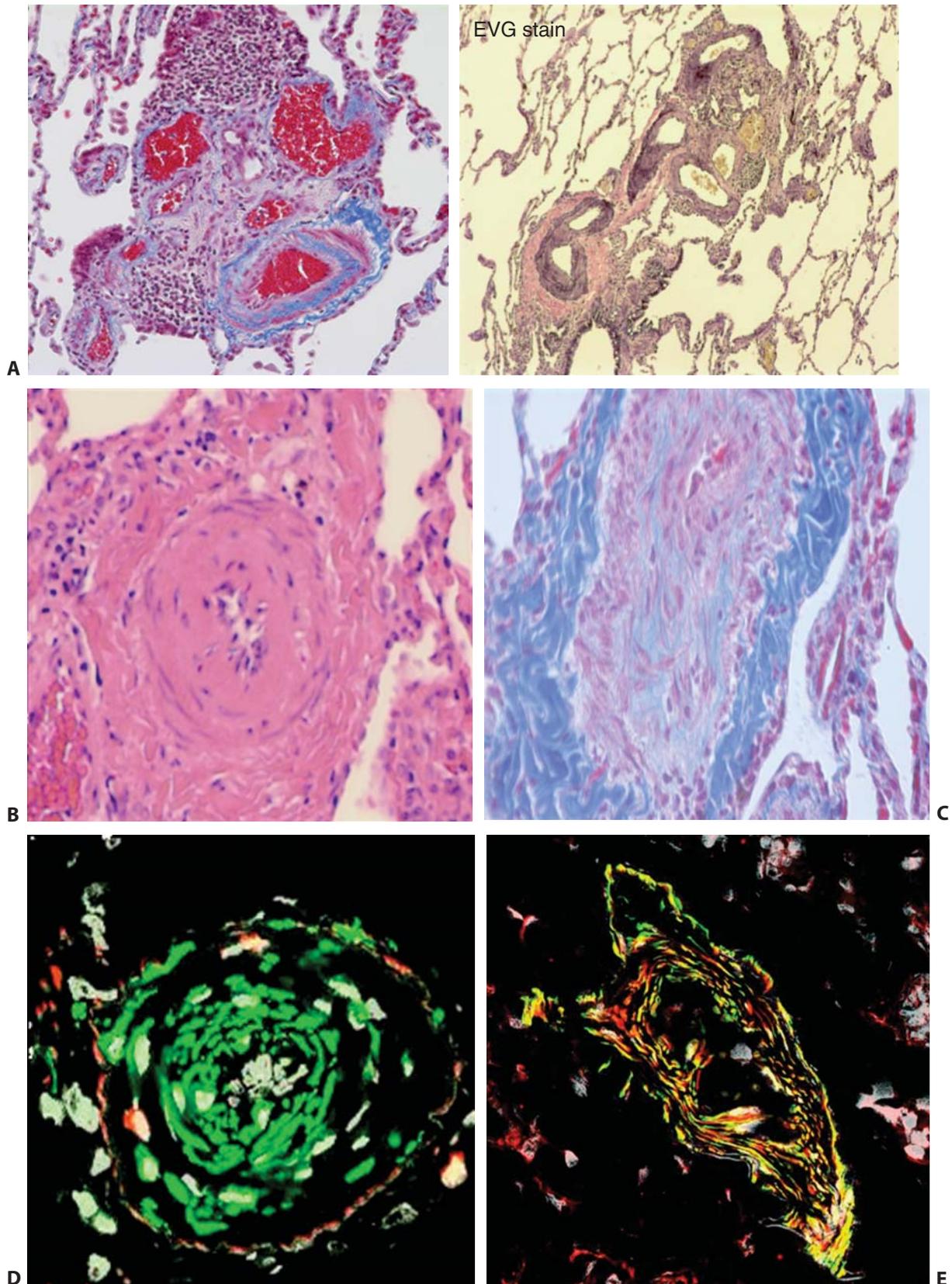


FIGURE 105.8. Idiopathic PAH pathology. All of these sections are obtained from the lungs of a 34-year-old man with iPAH who underwent transplantation. The characteristic plexogenic (A), medial (B), and intimal (C) hypertrophy lesions are shown (EVG, elastic van Giessen stain). Fluorescence immunohistochemistry (D) and confocal

microscopy (E) show medial hypertrophy (smooth muscle actin—green) and survivin or phosphodiesterase 5 (red) expression in the media and adventitia of the remodeled small pulmonary arteries.

with venous plasma in PAH and the increased expression in pulmonary arteries suggest that ET-1 contributes to the increased PVR in iPAH. Increased ET-1 levels also occur in other diseases, such as congestive heart failure. However, elevation of ET-1 levels does not necessarily mean that antagonism of the pathway is beneficial. In congestive heart failure the endothelin receptor antagonists have been ineffective.^{55,56} The mitogenic action of ET-1 in the PSMCs occurs via the endothelin A (ETA) receptor, whereas the endothelin B (ETB) receptor is thought to mediate the clearance of ET-1 from the pulmonary circulation and cause NO-mediated vasodilatation.

Another vasodilator that has more recently been proposed to play a significant role in PAH is the neurotransmitter vasoactive intestinal peptide (VIP), which is a potent pulmonary vasodilator that also inhibits the proliferation of SMCs and decreases platelet aggregation. The VIP receptors are linked to adenylate cyclase and eventually lead to activation of both cyclic adenosine monophosphate (cAMP) and cGMP. Both low serum concentration and low expression of VIP have been reported in iPAH pulmonary arteries, and inhalation of VIP in eight iPAH patients resulted in acute improvement in hemodynamics.⁵⁷

Disordered production of vasoactive mediators is not the only endothelial abnormality in PAH. The endothelial cells also form plexiform lesions. These plexiform lesions, which are seen in several types of PAH (but not in secondary forms of PHT), have an abnormal proliferative phenotype. Lee et al.⁵⁸ assessed whether the proliferation of endothelial cells in plexiform lesions in iPAH is the result of a monoclonal expansion, as occurs in neoplasia, or is polyclonal, typical of normal proliferation. They studied the methylation pattern of the human androgen receptor gene in endothelial cells microdissected from plexiform lesions, and showed that 77% of endothelial lesions were monoclonal, whereas in secondary PHT 100% of the endothelial lesions (not plexiform lesions) were polyclonal. This intriguing hypothesis, that PAH is somewhat of a "neoplastic" condition, remains controversial but merits further assessment. Recent rodent studies confirm this hypothesis, by the finding that a potent inhibitor of apoptosis that was previously thought to be exclusively found in cancer cells, survivin, is selectively expressed in the PA wall in patients with PAH but not normal controls⁴⁰ (Fig. 105.8).

THE SMOOTH MUSCLE CELL

K⁺ CHANNEL DYSREGULATION

K^+ channels are transmembrane spanning proteins that contain a pore with great selectivity for K^+ .⁵⁹ They are tonically active in vascular SMCs, allowing a slow efflux of K^+ along its intracellular/extracellular concentration gradient of 145/5 mM. There are several K^+ channel types: voltage-gated (K_v), inward rectifier (K_{ir}), and calcium-sensitive (K_{Ca}). K_v channels have a voltage sensor and both respond to and help to establish membrane potential. Inhibition of K_v channels results in accumulation of positively charged K^+ ions within the cell, thereby raising the membrane potential to more positive levels (depolarization), which activates the voltage-gated, L-type calcium channels. Calcium then enters the cell, via the L-type, voltage-gated calcium channels, which

are inhibited by nifedipine, activating the contractile apparatus, thus leading to vasoconstriction. Indeed, acute hypoxia appears to initiate HPV by inhibition of K_v channel in the PSMCs.^{60,61} The intracellular calcium increase also activates a number of mechanisms that result in cell proliferation.⁶² Intracellular K^+ causes a tonic inhibition of several caspases. The decreased intracellular K^+ that follows K^+ channel opening inhibits caspases, thereby activates apoptosis.⁶³ Thus a PAH PSMC that is relatively deficient in K^+ channels, whether the basis is genetic or acquired (K^+ channel inhibition by hypoxia or anorexigens), would be depolarized, with increased levels of intracellular Ca^{2+} and K^+ . This ionic environment places the cell in a contracted, proliferative, antiapoptotic state. In the presence of appropriate stimuli or growth factors, the vasoconstriction and the proliferation within the vascular wall likely contributes to the PA remodeling seen in PAH.

There is currently a search for the molecular identity of the K^+ channels involved in HPV and PAH. There are nine families of K_v families (K_v1-9), each with many members (i.e., $K_v1.1$ to $K_v1.7$).⁵⁹ In humans with iPAH, $K_v1.5$ messenger RNA (mRNA) levels are reduced in PSMCs, and this is circumstantially associated with membrane depolarization and elevation of cytosolic Ca^{2+} .^{36,64} Less is known about $K_v2.1$, although it is involved in setting membrane potential in rat PSMCs.³¹ It is fascinating that the anorexigens that caused several epidemics of PAH during the past 30 years⁶⁵ inhibit K^+ current and depolarize PSMCs, leading to pulmonary vasoconstriction. They appear to do this by inhibiting both $K_v1.5$ and $K_v2.1$.⁶⁶ channels whose expression is also selectively downregulated in experimental PAH.⁶⁷ Interestingly, reversal of this "ionic remodeling," whether indirectly by drugs⁶⁷ or directly by K^+ channel gene therapy,³⁷ improves the hemodynamic and remodeling abnormalities in experimental PHT. Taken together these data suggest that the selective downregulation of K_v channels might play a role in the pathogenesis of PAH; in other words, PAH might be a form of a K_v channelopathy. There is clearly a precedent for ion channelopathies causing human disease, including chloride channel mutations causing cystic fibrosis and mutation of K^+ and Na^+ channels causing the long QT syndrome that results in sudden cardiac death. The K_v channel hypothesis requires further investigation.

SURVIVIN

Survivin, a member of the mammalian "inhibitor of apoptosis" family,⁶⁸ is known to be expressed in most cancers but not in most normal adult cell types.⁶⁹ The cell cycle-dependent expression of the survivin gene in mitosis suggests a role for survivin in promoting cell proliferation. However, recent data point to a more selective role of survivin in antagonizing mitochondrial-dependent apoptosis,⁶⁹ and a mitochondrial pool of survivin has recently been identified in cancer cells.⁷⁰ Survivin is expressed in remodeled resistance PAs, but not normal PAs, from PAH patients and rats with monocrotaline (MCT)-induced PAH, a widely used model of PAH.⁴⁰ Inhaled adenoviral gene therapy with a dominant-negative construct that inhibits endogenous survivin reverses established MCT-PAH. The therapeutic effect of inhibition of survivin is achieved by induction of mitochondria-dependent apoptosis in PSMCs. Interest-

ingly, this mechanism is also associated with activation of Kv channels.⁴⁰

Survivin mutations, similar to those observed in oncogenic transformation,⁷¹ might occur in some patients with PAH, resulting in spontaneous survivin expression, although this is entirely speculative. Voelkel et al.⁷² have exposed fascinating similarities between cancer and PAH, by showing that the proliferating cells in the neointimal plexogenic PAH lesions are monoclonal. Alternatively, survivin expression may be induced following endothelial damage, which is likely a critical early event in the pathogenesis of PAH.^{45,73} Endothelial damage would allow direct exposure of PASMCs to circulating growth factors that are known to induce survivin expression. In addition to facilitating the PASMC transition to a proliferative state, survivin inhibits apoptosis by hyperpolarizing mitochondria. This will result in less cytochrome c and H₂O₂ in the cytoplasm, thereby inhibiting Kv channels. The resultant increase in the intracellular K⁺ further suppresses apoptosis and, by depolarizing the cell membrane, increases the opening of the voltage-gated Ca²⁺ channels, thereby enhancing Ca²⁺ influx, causing vasoconstriction and amplification of proliferative signal pathways.

PLATELETS

Several groups have hypothesized that serotonin (5-hydroxytryptamine, 5-HT) may be important in the development of PAH.^{74–77} The majority of the circulating 5-HT is produced by the gastrointestinal tract chromaffin cells and pulmonary neuroepithelial bodies and is stored in the platelet dense granules. A key piece of evidence for the involvement of serotonin is the finding that plasma serotonin levels are increased in iPAH patients versus controls, whereas platelets from iPAH patients have decreased serotonin concentrations.⁷⁵ Serotonin released during *in vitro* platelet aggregation is also exaggerated in iPAH patients relative to controls. Moreover, these abnormalities persist after heart-lung transplantation, suggesting that this platelet abnormality is not secondary to the PHT.⁷⁵

THE 5-HT TRANSPORTER

The classical action of the anorexigens is to cause serotonin release and prevent the reuptake of serotonin. In addition, anorexigens are actively taken up into the cells by means of the 5-HT transporter (5-HTT). It has been shown that there is overexpression of 5-HTT in PASMCs from patients with PAH, and as a result their PASMCs grow abnormally rapidly in response to serotonin or serum stimulation.⁷⁸ 5-HTT expression is also increased in the platelets and lungs from PAH patients versus controls.⁷⁸ 5-HTT overexpression is predominantly evident in the media of the hypertrophied pulmonary arteries.⁷⁸ 5-HTT is encoded by a single gene in chromosome 17q11.2. The L-allelic variant of the 5-HTT gene promoter, which induces a greater rate of 5-HTT gene transcription than the S allele, has been reported, by one group, to be associated with 5-HTT overexpression and increased PASMC growth. The L allele was present in homozygous form in 65% of French PAH patients but in only 27% of controls. Since this report is from a single country and since ethnicity is important in such polymorphisms, independent confirmation in a different population is needed. Mice over-

expressing the 5-HTT gene exhibit spontaneous PHT in normoxia and exaggerated PHT in hypoxia.⁷⁹ These data suggest that 5-HTT activity might play a key role in the pathogenesis of PASMC proliferation in PAH and that a 5-HTT polymorphism confers susceptibility to PAH.⁷⁸ The serotonin hypothesis provides another genetic basis for a PAH-susceptible genotype, in addition to mutations in *BMPR2*.

THE 5-HT RECEPTORS

Activation of 5-HT 1B receptors elicits vasoconstriction in human small pulmonary arteries⁸⁰ by activating G_i signaling, which inhibits adenylate-cyclase and decreases cAMP levels. In the chronic hypoxic model of PHT, mice lacking 5-HT1B receptors develop less vascular remodeling and have no right ventricular hypertrophy compared to the wild-type controls.⁸¹ Similarly, mice lacking the 5-HT2B receptor, which is the receptor activated by nor-dexfenfluramine, the active metabolite of dexfenfluramine, do not develop chronic hypoxic PHT.⁸² Both 5-HT1B and 5-HT2B receptor expression is also increased in PAH.⁸²

Much of the evidence linking 5-HT and PAH comes from the fact that the anorexigens cause 5-HT release. However, a link among K⁺ channels, anorexigens, and 5-HT has been proposed. The anorexigens block Kv channels in platelet progenitor cells, megakaryocytes.⁸³ Kv channel inhibition in platelets leads to serotonin release.⁸³ Furthermore, fenfluramine reduces Kv1.5 mRNA levels by 50% in PASMCs from normotensive patients,⁸⁴ suggesting that inhibited gene transcription and expression of Kv channels may play an important role in anorexigen-PAH. These data suggest that one of the reasons that 5-HT might be increased in PAH is the lack of Kv channels in platelets or pulmonary endothelial cells.

THE EXTRACELLULAR MATRIX

Vascular remodeling is a prominent feature of PAH with muscularization of normally non- or partially muscularized peripheral arteries. The muscularization relates to differentiation of pericytes, medial hypertrophy, as well as proliferation and distal migration of PASMC. However, in PAH there is also increased production of extracellular matrix (collagen, elastin, fibronectin, and tenascin-c). Like the procoagulant state in PAH, altered mitogenesis in PAH appears to be a secondary response to an initial injury. Rabinovitch^{85,86} has suggested that endothelial abnormalities, early in the course of PAH, permit extravasation of blood factors that stimulate SMC production of a vascular serine elastase. This results in the liberation of matrix-bound mitogens, such as basic fibroblast growth factor (FGF-2), and also enhances matrix degradation by activating other matrix metalloproteinases (MMPs). The MMPs can lead to the production of a mitogenic cofactor, tenascin. Tenascin binds to its α - β_3 integrin receptors, leading to phosphorylation of growth factor receptors and SMC proliferation. When MMPs are inhibited, tenascin levels fall and apoptosis ensues.⁸⁶ Direct inhibition of MMP-2 and serine elastases leads to activation of apoptosis and suppression of proliferation in the media, and thus regression of medial hypertrophy.⁸⁶ Although MMPs were conventionally thought to be solely important in remodeling, we have recently learned they can also affect vascular tone. MMP-2 and MMP-9 can activate platelets,⁸⁷ while intravascular

MMP-2 can enhance formation of vasoconstrictors, including a novel form of endothelin, and inhibit the action of endogenous vasodilators.⁸⁸ The inhibition of MMPs, if selectively targeted, could be an appealing therapeutic target for causing regression of PAH.

INFLAMMATION

Inflammatory mechanisms have been implicated in several animal models of PAH (like the monocrotaline model) and human PAH associated with collagen vascular diseases or HIV infection.⁸⁹ Immunosuppressive therapy, using cyclophosphamide and corticosteroids, has been reported to significantly improve PAH in patients with systemic lupus erythematosus.^{90,91} However, this is just anecdotal evidence from case reports. A potential role of inflammation in PAH is also supported by the prevalence of antinuclear antibodies and increased circulating levels of proinflammatory cytokines [interleukin-1 (IL-1), IL-6] in PAH patients. Furthermore, the presence of a large number of inflammatory cells and expression of chemokines, like RANTES and fractaline, has been described in and around the plexogenic lesions in PAH.⁹²

HYPOXIA INDUCIBLE FACTOR (HIF-1 α)

Hypoxia inducible factor-1 α is a master gene that controls the transcription of many genes that are activated by hypoxia. Rats with haploinsufficiency for HIF-1 α , exposure to chronic hypoxia, manifest-delayed or reduced polycythemia, right ventricular hypertrophy, PHT, and pulmonary vascular remodeling have greater weight loss compared with wild-type littermates.^{93,94} Interestingly, this partial deficiency of HIF-1 α is also sufficient to impair hypoxia-induced depolarization and reduction of K⁺ current,⁹⁴ again tying the PASMC K⁺ channels to PHT. The pathophysiologic role of HIF-1 α in nonhypoxic PAH is unknown, but it is likely that this pathway is important, as discussed next.

ANGIOGENESIS

Hypoxic activation of HIF-1 α also results in increased production of VEGF and increased expression of its receptors, Flk and Flt.⁹⁵ Disordered angiogenesis has been described in PAH and has been implicated in the formation of plexogenic lesions. In this regard, it is noteworthy that most PAH patients have systemic hypoxemia and reduced alveolar diffusion capacity, even though their alveolar PO₂ is normal. Increased levels of VEGF and increased expression of Flt as well as HIF-1 α and -1 β have been described in these lesions; on the other hand, plexogenic lesions have decreased levels of essential factors for angiogenesis including phosphoinositide-3-kinase, AKT, and src.⁹⁶ These findings have led to the hypothesis that the plexogenic lesions are not a primary abnormality in PAH but rather a secondary phenomenon, caused by a disordered angiogenesis in response to local tissue hypoxia, distal to the obliterated pulmonary arteries.⁹⁶

GENETICS

Most cases of PAH appear to be sporadic, but 6% to 12% of cases are inherited in an autosomal dominant manner with

incomplete penetrance.⁹⁷ The disease may skip generations and might affect only a few siblings in a generation. Thus the actual proportion of familial cases may be underestimated. Although clinical and pathologic features are the same in sporadic and familial forms, familial PAH displays genetic anticipation and onset at decreasing ages in subsequent generations. Loyd et al.⁹⁸ reported a successive decrease in age of death from PAH over three generations in one kindred, from 46 \pm 15 to 36 \pm 13 to 24 \pm 11 years. This phenomenon has been observed in fragile X syndrome and several dominantly inherited diseases like myotonic dystrophy and Huntington's disease. The occurrence of genetic anticipation suggests that the molecular basis of familial PAH, similarly to myotonic dystrophy, may involve expansion of a trinucleotide repeat,⁹⁹ although this has not been yet shown in iPAH or fPAH. The gene for familial PAH, previously known as *PPH1*, was localized on 2q33 chromosome using genetic linkage analysis.^{97,100,101} A positional candidate approach led to the identification of *BMPR2* as one of the genes causing familial PPH.^{102,103} Heterogeneous germline mutations in *BMPR2* have been identified in up to 60% of several kindreds with fPAH. Interestingly, mutations in this gene have been observed in a minority of sporadic PAH patients (26%), suggesting *BMPR2* may contribute to the pathogenesis of iPAH occasionally.¹⁰⁴

The BMPs are a family of secreted growth factors that are part of the transforming growth factor- β (TGF- β) superfamily. Originally described as the molecules that induce ectopic bone and cartilage formation when implanted subcutaneously,¹⁰⁵ they are now known to be important regulators of mammalian development.¹⁰⁶ For example, BMP-4 plays a critical role in embryonic lung development.¹⁰⁷ Transforming growth factor- β superfamily members interact with two classes of transmembrane receptor, serine-threonine kinases type I and II receptors.¹⁰⁸ Type II receptors have constitutively active cytoplasmic kinase domains, but they are unable to activate downstream signals in the absence of a type I receptor. Furthermore, several TGF- β family members can use the same receptors as the BMPs, adding significant plasticity to the regulation of the downstream responses.¹⁰⁸ This plasticity is further enhanced by the fact that a variety of downstream signaling pathways, following the binding of BMPs to BMP receptors I and II, are activated in a cell-specific manner.¹⁰⁸ An important signaling system is the Smad system, which includes the BMPR-activated Smads (Smad-1, -5, and -8) and the common mediator Smad (Smad-4).¹⁰⁹ The activated Smad-1, -5, -8-Smad-4 complex enters the nucleus to regulate a number of DNA binding transcription factors and cofactors that are required to initiate specific transcriptional responses.¹⁰⁹ The Smads were originally named after a gene called "mothers against decapentaplegic (*dpp*)",¹¹⁰ an upstream gene that controls the function of *dpp*, a gene of *Drosophila melanogaster* that encodes a growth factor that belongs to the TGF- β superfamily that plays a central role in multiple cell-cell developmental signaling events. Overall, activation of the BMPR-2 pathway leads to suppression of several transcription factors, favoring apoptosis.

Homozygous deletion of the *BMPR2* in vivo is associated with embryonic lethality.¹¹¹ Over 40 different germline mutations in the *BMPR2* gene have been described in both

familial and iPAH cases and include missense and frameshift mutations.¹⁰⁸ Although it is known that at least some of the described mutations result in loss of function of the *BMPR2* gene product,¹¹² it is not known how this loss of function leads to the development of PAH. Recently, PASMCs from patients with iPAH, but not secondary PHT, were shown to exhibit enhanced growth responses to TGF- β_1 and BMPs.¹¹³ Recent work with a conditional knockout of *BMPR2* (using a smooth muscle specific, dominant negative strategy) shows that when the *BMPR2* mutation is activated after birth, mice developed PHT, right ventricular hypertrophy, and have increased medial hypertrophy of the PA, all without increase in systemic arterial pressure.¹¹⁴ Nonetheless many questions remain regarding the “sufficiency” of *BMPR2* mutations to cause PAH. Moreover, the mechanism by which mutations in a ubiquitously expressed receptor might result in the highly restricted pattern of disease pathology seen in patients with PAH is unclear. It remains uncertain whether *BMPR2* mutations result in disease by inhibiting a *normal* rate of apoptosis or whether something else stimulates a need for apoptosis, which cannot be supported when *BMPR2* is dysfunctional. Alternatively, one can speculate that since *BMPR2* mutations alter the function of many transcription factors, they may work by several mechanisms, each relating to altered transcription of relevant genes, such as Kv channels, ET-1 or the 5-HTT.

IS THERE A LINK?

Is there a link between these diverse abnormalities? It is apparent that most of these abnormalities result in enhanced vasoconstriction, impaired apoptosis, or accelerated proliferation of the vascular cells. It is becoming clear that not all mechanisms might be operational at a given stage of the

disease or in a given patient. For example, endothelial damage is likely an early event in PAH, whereas increased proliferation/suppressed apoptosis of the SMC is a late event. Whereas one patient might be prone to increased proliferation in the vascular wall because of a *BMPR* mutation, susceptibility in another might relate to an abnormal 5-HTT or dysfunctional K⁺ channel. A multiple hit hypothesis has been proposed for PAH⁹ (Fig. 105.9). In this theory, one or more environmental insults have to occur on a predisposed genetic background because of one or more gene abnormalities. Perhaps the pathogenesis of PAH is too complex to be explained by a single unifying theory.

While the discovery of *BMPR2* mutations may explain some forms of familial PAH and may predispose to PAH in animals, it appears that the majority of iPAH is not due to these mutations. A mechanism such as the loss or inhibition of K⁺ channels (whether genetically or by anorexigens) could unify the 5-HT and the Kv channel theories and, even if not the initiator of PAH, explain much of the phenotype. Similar “channelopathy” could afflict the platelets or the megakaryocytes. In this scenario the PASMCs would be predisposed to constriction and proliferation and would have impaired apoptosis, whereas the platelets would secrete excess 5-HT, thereby reinforcing SMC contraction and proliferation. The increased expression of the inhibitor of apoptosis survivin significantly suppresses K⁺ current. Moreover, the idea that K⁺ channels might be central to the pathogenesis of PAH is supported by the observation that experimental therapies promoting the function and expression of K⁺ channels have been effective in several animal PAH models. In other words, apoptosis resistance and proliferation in the pulmonary vascular wall may occur due to dysregulation in the *BMPR-2* pathway, 5-HT, survivin, and the Kv channels, alone or in combination.

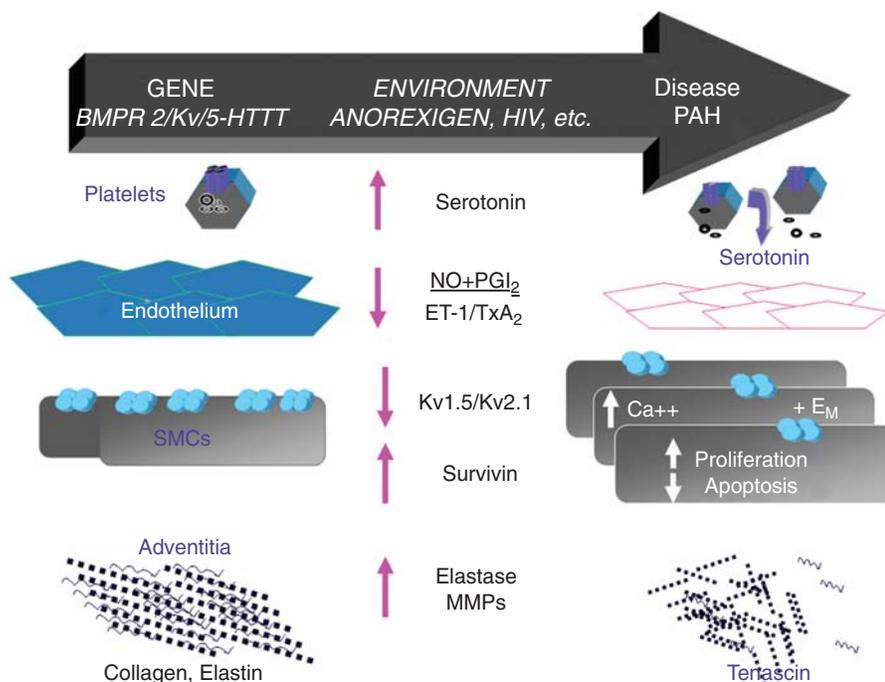


FIGURE 105.9. A schematic for the proposed multiple hit hypothesis in PAH.

Clinical Recognition of Pulmonary Arterial Hypertension

Symptoms (Table 105.5)

Pulmonary arterial hypertension is an uncommon condition, and its symptoms are nonspecific. Therefore, patients often have symptoms for months or years before a correct diagnosis is made, especially in iPAH, where the lack of associated conditions does not provide additional clues. In the NIH registry, the average time from onset of symptoms to diagnosis of PHT was 2.5 years.¹⁸ Although symptoms of PHT do not directly reflect PAP, patients usually remain asymptomatic until PAP has doubled.¹¹⁵

The earliest and most common symptom of PAH is dyspnea. In the NIH registry, 60% of the patients had dyspnea as a presenting symptom, although 98% had dyspnea by the time they were enrolled in the registry.¹⁸ The causes of dyspnea in PAH are diverse, varying somewhat according to the etiology of the syndrome. Dyspnea is found in the majority of pulmonary hypertensive syndromes, with the notable exception of sleep apnea. In most cases, dyspnea appears to relate more to altered lung mechanics and reflex activation than to hypoxemia. In PAH there is often a respiratory alkalosis with mild hypoxemia. In these patients, dyspnea may relate to increased J-receptor activity, possibly a result of decreased vascular and therefore lung compliance. Hypoxemia may also lead to dyspnea in patients with PAH due to intracardiac shunting (e.g., Eisenmenger's syndrome). Interstitial lung disease, with reduced lung compliance and hypoxemia, is another cause of dyspnea and is common in patients with PAH due to connective tissue diseases (e.g., mixed connective tissue disease, scleroderma, CREST syndrome).

Like dyspnea, fatigue is a common and nonspecific symptom in these patients. Fatigue may reflect reduced cardiac output and impaired oxygen delivery to the tissues. In addition, PVR increases dramatically with exercise in patients with PAH, unlike normal individuals. Dyspnea and fatigue occur with similar frequency regardless of the cause of the PHT.

Syncope and near syncope can occur in severe PAH, particularly with exertion. During exercise, the obstructed or obliterated pulmonary vascular bed may be unable to correct for a fall in systemic vascular resistance by accommodating adequate increases in cardiac output, culminating in reduced cerebral blood flow and syncope.

Chest pain is not unusual in PAH and may be described by the patient as sharp and pleuritic or as a dull ache. The dull chest ache noted by some patients with PHT is suggestive of angina. Potential mechanisms include right ventricular ischemia and distention of the pulmonary arteries.

A somewhat unusual symptom of PHT is hoarseness (Ortner's syndrome). Hoarseness results when the left recurrent laryngeal nerve, which passes between the aorta and the pulmonary artery, is compressed by the enlarged pulmonary artery.^{115,116}

Hemoptysis also occurs in many types of PHT. It has been reported that in the capillary bed of patients with PHT there are microaneurysms that may be susceptible to rupture, resulting in hemoptysis.¹¹⁵ Hemoptysis is a frequent cause of morbidity and mortality in Eisenmenger's syndrome, accounting for 15% of deaths in one study.¹¹⁷

Physical Examination

Like the history, the findings on physical examination in PHT are often nonspecific. A number of patients with PHT have an entirely normal physical examination. Furthermore, the physical examination rarely allows quantification of the severity of PHT until the terminal stages of the disease, when right heart failure appears. The physical findings of PHT reflect the presence of an enlarged, noncompliant right ventricle (RV) and insufficiency of the tricuspid or pulmonic valves. The most common clinical signs and their mechanism are shown in Table 105.5.

Although a loud pulmonic component of the second heart sound is common in patients with PHT, as the hypertension becomes more severe the interval between closure of the aortic and pulmonic valves may decrease so that the valves close almost simultaneously, eliminating the value of this sign. However, if a second heart sound is heard at the apex

TABLE 105.5. Signs and symptoms of pulmonary hypertension

<i>Sign</i>	<i>Mechanism</i>
Accentuated component of S ₂	Increased force of P-valve closure
Early systolic click of the pulmonary valve	Sudden interruption of P-valve closure
Midsystolic ejection murmur	Turbulence in P-valve outflow
Diastolic murmur	P-valve regurgitation
Holosystolic murmur increasing with inspiration	Tricuspid regurgitation
Increased jugular a wave	Increased RV filling pressure
Left parasternal lift and right-sided S ₃	RV hypertrophy and failure
Edema, ascites, hepatomegaly	RV failure
<i>Symptom</i>	<i>Mechanism</i>
Dyspnea, fatigue	Decreased cardiac output
Chest pain	RV ischemia, PA dilatation
Syncope	Decreased cardiac output, arrhythmias
Hoarseness (Ortner's syndrome)	Compression of the laryngeal nerve by the dilated PA

(where the aortic component is not audible in normal hearts) it almost always is due to a loud P_2 and suggests severe PAH.

The Graham-Steele murmur of pulmonic valve insufficiency occasionally accompanies severe PHT. This diastolic murmur is usually best heard in the left second or third inner space near the sternum. Pulmonary insufficiency may be distinguished from aortic insufficiency by observing the response to the Valsalva maneuver. The pulmonary regurgitation murmur usually returns to pre-Valsalva intensity within several beats, whereas the aortic regurgitation murmur usually takes longer to return to its intensity. The time delay occurs because the blood excluded from the thorax by the Valsalva maneuver must first traverse the pulmonary circulation before reaching the aorta and augmenting the murmur. In some PHT patients a diastolic murmur that enhances with inspiration occurs. This right-sided "Austin Flint murmur" is due to functional tricuspid stenosis due to valve closure caused by severe pulmonic insufficiency.¹¹⁸ Although echocardiographic evidence of mild tricuspid and pulmonic regurgitation is prevalent even in normal individuals, audible or hemodynamically significant insufficiency is rare. However, pulmonic insufficiency can also occur fairly commonly in patients with fluid overload related to renal failure, which also reflects transient PHT.¹¹⁹

The blowing systolic murmur of tricuspid regurgitation is best heard over the lower right sternal border and may briefly enhance with inspiration (Carvallo's sign). The right-sided third heart sound occurs primarily once the RV has decompensated from chronic pressure overload, and is usually accompanied by a murmur of tricuspid regurgitation.

Clinical and Laboratory Assessment (Table 105.6)

Diagnostic testing in PHT may serve three purposes: (1) documentation and quantification of PHT; (2) defining the

etiology, particularly differentiating between PAH and secondary PHT; and (3) assessment of prognosis. A major emphasis is detecting conditions that have a specific treatable cause of the PHT (notably mitral regurgitation or stenosis and thromboembolic PHT).

Our approach to the patient with presumed PHT is to establish its presence, preferably by a noninvasive test, such as echocardiography. If the pressure is elevated or cannot be accurately measured, then a right heart catheterization is performed. A typical case is presented in Figure 105.10.

Once a diagnosis of PHT is established, the next goal is to determine the etiology. The following tests should be obtained in all patients in whom the cause of PHT is not evident: electrocardiogram (ECG), chest radiograph, arterial blood gases, complete blood count, electrolytes and liver function tests, pulmonary function tests (PFTs), ventilation/perfusion lung scan, serology for rheumatic diseases (e.g., fluorescent antinuclear antibody, FANA), serology for HIV, ventilation perfusion (V/Q) scan, and an echocardiogram with Doppler assessment of PA acceleration time and tricuspid regurgitation velocity as well as an echo-contrast study, to exclude shunting. This relatively inexpensive and safe battery of tests can detect patients with chronic lung disease, valvular heart disease, left ventricular dysfunction, most intracardiac shunts, thromboembolic disease, LV dysfunction, and PAH due to HIV, liver disease/portal hypertension, or connective tissue disease. In patients with abnormal PFTs or inconclusive V/Q scan, a chest computed tomography (CT) is also performed in order to exclude or confirm pulmonary fibrosis or thromboembolic disease.

A right heart catheterization is performed in essentially all patients with evidence for PAH, for the following reasons: (1) to confirm the presence and magnitude of PHT and establish an objective baseline for future therapies; and (2) to determine or confirm the type of PAH (e.g., to make the diagnosis of PAH a gradient between the mean wedge pressure and the pulmonary artery diastolic pressure of more

TABLE 105.6. Comparison of invasive and noninvasive tests in three forms of pulmonary hypertension

	<i>NIH iPAH registry</i> ¹⁸	<i>iPAH</i> ²⁴⁸	<i>Thromboembolic</i> ²⁴⁸	<i>Thromboembolic</i> ^{249,250}	<i>Cor pulmonale</i> ²⁵¹
Pulmonary function tests (% predicted)					
FEV ₁	83 ± 17	79 ± 8	75 ± 9	N/A	33 ± 14
TLC	89	87 ± 12	96 ± 12	N/A	105 ± 15
DLCO	82	59 ± 22	60 ± 19	75–107	
Arterial blood gases (mmHg)					
PO ₂	70 ± 2	65 ± 12	62 ± 8	<80 in 80%	59 ± 8
PCO ₂	30 ± 6	31 ± 5	32 ± 5	24–37	46 ± 8
Mean PAP	61 ± 20	57 ± 15	48 ± 16	49 ± 9	24 ± 5
Wedge pressure	9 ± 4	7 ± 4	7 ± 4	9 ± 3	9 ± 3
Ventilation/perfusion scan					
Low probability or normal	97%	100	0	0	N/A
High probability	0.6%	0	100	100	N/A
Pulmonary angiography (%)					
Positive for proximal thrombi	0	0	100	100	N/A
Deaths from angiography	0	0	0	0	N/A

Values are expressed as the mean (± standard deviation of the mean, if available). DLCO, carbon monoxide diffusing capacity of the lungs; FEV₁, forced expiratory volume in 1 second; PAP, pulmonary artery pressure; TLC, total lung capacity.

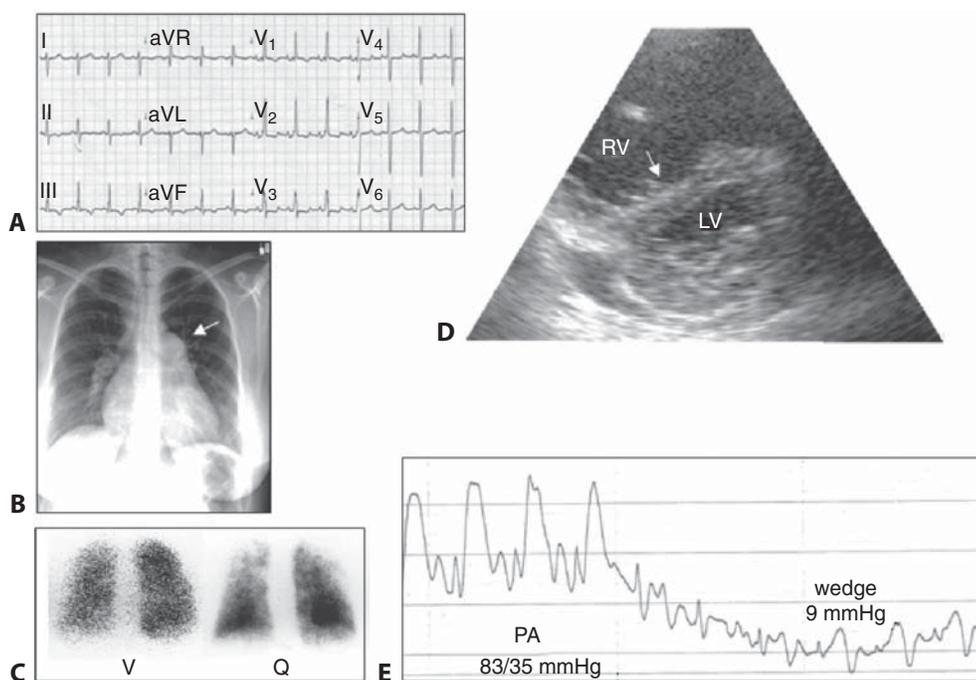


FIGURE 105.10. A classic iPAH case. A 32-year-old woman presents at the University of Alberta with fatigue and dyspnea on exertion of 1 year's duration. Her jugular venous pressure (JVP) is 11 cm H₂O; there is a loud P₂, and pulmonic flow murmur. There is mild peripheral edema. Her electrocardiogram (ECG) (A) shows right axis deviation and right ventricular hypertrophy. Her chest x-ray (B) shows cardiomegaly and no evidence of pulmonary venous hypertension. There is evidence of proximal pulmonary artery dilatation (arrow) and pruning of the peripheral pulmonary arteries. A ventilation/perfusion (V/Q) scan (C) shows low probability of a pulmonary embolism but shows a characteristic "moth-eaten" abnormality in the perfusion image. A transthoracic echocardiogram (D) excludes left ventricular (LV) and valvular disease. A contrast study rules out intracardiac shunts but does show right ventricular dilatation. The systolic flattening of the septum (arrow) is diagnostic of right ventricular (RV) pressure overload. This suggests severe PAH and the estimated systolic PA pressure by Doppler is ~90 mmHg. A right heart catheterization confirms the diagnosis and the severity of PAH. The gradient of 26 mmHg between the diastolic pulmonary artery pressure (PAP) and the wedge pressure confirms that the

problem is intrinsic to the pulmonary arteries, that is, that the patient has PAH (E). There was a 22% decrease in the pulmonary vascular resistance (PVR) by a maximal dose of inhaled nitric oxide (NO) (80 ppm) and a 25% decrease in the PVR, 50 minutes after a single dose of sildenafil (75 mg po). Because the PVR decreased by >20%, this patient is considered a "responder" to pulmonary vasodilators. The patient was started on Ca²⁺ blockers, but she could not tolerate even moderate doses of nifedipine because of peripheral edema, dizziness, and hypotension. Although she responded very well to a single dose of sildenafil, she could not afford to pay for sildenafil (50 mg po t.i.d. = CDN \$500/month). She was started on Bosentan 125 mg po b.i.d. She continued to deteriorate, and 3 months later her 6-minute walk had decreased from 290 m to 250 m. She was started on continuous intravenous epoprostenol and a workup for heart-lung transplantation was initiated. Her condition has been stable for the following 12 months (class II), and her average 6-minute walk performance is 350 m. She has yearly right heart catheterizations and echocardiograms. She attends the multidisciplinary PAH clinic every 3 months where she also sees a dietitian and a psychologist.

than 10 to 12 mmHg has to be established); and (3) to determine the response to acute vasodilators (e.g., iNO), since this is associated with prognosis and might guide choice of therapies (see below).

After the diagnosis of PAH is established and before the initiation of any treatment, a good assessment of the baseline functional class has to be established. The baseline functional class not only predicts prognosis but also guides immediate and future treatments. In addition to the NYHA functional class, quantitative assessment of functional performance can be achieved with maxVO₂ testing, or, if that is not possible, the 6-minute walk test. The 6-minute walk test has emerged as one of the most important end points in clinical trials over the past few years. It is simply the distance

the patient covers during a 6-minute walk period on a standard corridor with standardized supervision. The 6-minute walk is a very strong predictor of survival in PAH.¹²⁰ The ability of this simple test to predict survival likely comes from the fact that it reflects cardiac output and more specifically the ability to increase cardiac output during mild exercise. This in turn reflects the performance of the right ventricle. In clinical practice one is impressed by the frequent dissociation between PVR and functional class and the better correlation with 6-minute walk and functional class. This is because, for reasons that we do not yet understand, the response of the right ventricle to the same increase in its afterload varies significantly among patients. A simple index of the compensation of the right ventricular condition is the

right atrial pressure. The jugular venous pressure and 6-minute walk should be documented at each visit.

More recently, a simple test that is currently available as a point-of-care test is emerging as another index of right ventricular size and function: the brain natriuretic peptide (BNP) levels. Levels of BNP, a peptide released from the ventricles during stretch or ischemia, correlate well with hemodynamics and also predict survival in patients with PAH.¹²¹ There are two assays available, and the advantage of the point of care assay that measures BNP itself (Triage-BNP test®, Biosite, San Diego, CA; normal values are <100pg/mL) over the automated proBNP assay is its convenience (it can be done in the clinic) and its relative independence from confounding effects with age or mild to moderate impairment of renal function. Measurement of BNP may prove a useful means to judge the success of therapy or provide early warning of right ventricular decompensation.

Chest X-Ray

Central pulmonary artery enlargement and enlargement of the right ventricle are important clues to the presence of severe PAH (see case report in Fig. 105.10). “Pruning” of the peripheral pulmonary arteries is a classic sign, which reflects vascular obliteration of the small arteries in the periphery of the lungs. Understanding of this important finding becomes easier if one looks at the MR angiography with gadolinium from the same patient, where the obliteration of the peripheral pulmonary arteries is directly shown (Fig. 105.11). Other radiographic signs of PHT include right heart enlargement (filling in of the retrosternal space on the lateral view) and PA enlargement, measured as the diameter of descending right pulmonary artery (normal values are 12.1 ± 1.2 mm). The absence of signs of secondary hypertension also can be documented with a chest x-ray; for example, the presence of septal thickening or pleural effusions suggests venous hypertension

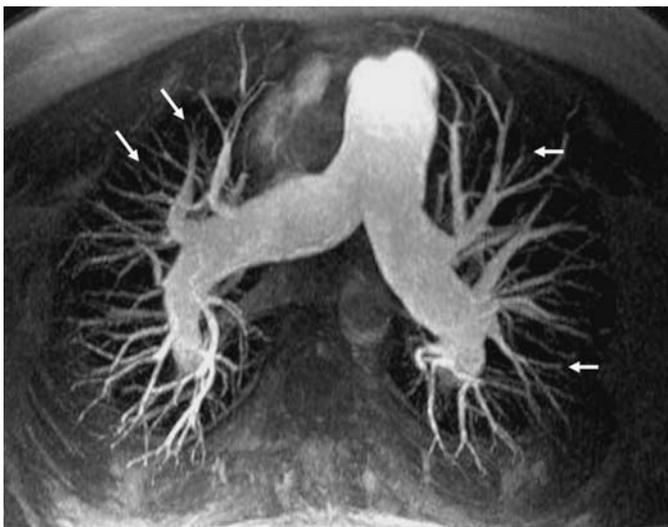


FIGURE 105.11. Noninvasive pulmonary gadolinium MR angiography of a 32-year-old woman with iPAH. Note the obliteration of the distal pulmonary arteries (arrows), a finding that explains the “pruning” seen in the periphery of the lung fields in the x-rays of patients with severe PAH.

to left ventricular dysfunction, veno-occlusive disease, or pulmonary capillary hemangiomatosis.

Electrocardiography

Electrocardiography is a specific but insensitive means of diagnosing RV hypertrophy (RVH), and for this reason, even though it is simple, it is not a good screening test. Nonetheless, by the time they are detected, most PAH patients have clear-cut RVH and right axis deviation (Fig. 105.10). Lehtonen and Sutinen¹²² compared four sets of ECG criteria for diagnosing RVH in patients whose RV thickness was measured at autopsy. Hearts were considered normal if the total weight was less than 250 g, the RV less than 65 g, and the combined LV plus septum (S) weight less than 190 g (ratio of LV + S/RV, 2.3–3.3). By combining aspects of the four sets of ECG criteria, they achieved a diagnostic sensitivity of 63% and a specificity of 96%. These combined criteria included right axis deviation greater than 110, R wave equal to or greater than S wave (in V_1 or V_2), R wave equal to or less than S wave in lead V_6 , and the calculated value $AR:PL$ of 0.7, where A is the maximum R-wave amplitude in leads V_1 or V_2 , R is the maximal S-wave amplitude in leads I or V_6 , and PL is the minimal S-wave amplitude in leads I or V_6 . This set of criteria was quite specific, despite the presence of LV hypertrophy and myocardial infarction in the study population. A limitation of this study is that the autopsy was restricted to patients dying from respiratory failure, and perhaps these criteria might not be applicable in other causes of PHT. For example, the chest size is enlarged in patients with chronic airway disease and influences the voltage and the axis in ECG.

The ECG criteria for RVH become less specific in the presence of right bundle branch block, posterior myocardial infarction, left posterior hemiblock, and Wolff-Parkinson-White syndrome with a posteroseptal accessory pathway. These conditions, rare in PAH except for the right bundle branch block, may cause right axis deviation or a predominant R in lead V_1 , similar to the findings in RVH. Fortunately, there are often clues that permit differentiation of RVH from these conditions. Posterior infarction usually involves associated inferior infarction. One should be cautious in making a diagnosis of RVH in patients with inferior Q waves and dominant R waves in V_1 . Furthermore, patients with RVH typically have right atrial (RA) enlargement (known as P-pulmonale), diagnosed based on the presence of asymmetrical peaked P waves greater than 2.5 mm in amplitude in any lead. Therefore, if one is attempting to distinguish between a posterior hemiblock and RVH, the presence of atrial hypertrophy would militate in favor of the diagnosis of hypertrophy.

Pulmonary Function Tests

Pulmonary function tests are often abnormal in patients with PHT. The abnormality of lung function may be the cause of the PHT, as in chronic obstructive pulmonary disease, or vice versa (see Table 105.6). For example, patients with thromboembolic and iPAH often have mild restrictive or obstructive patterns noted on spirometry. Diffusing capacity for carbon monoxide (DLCO) is typically low in PAH, more so in patients with scleroderma.

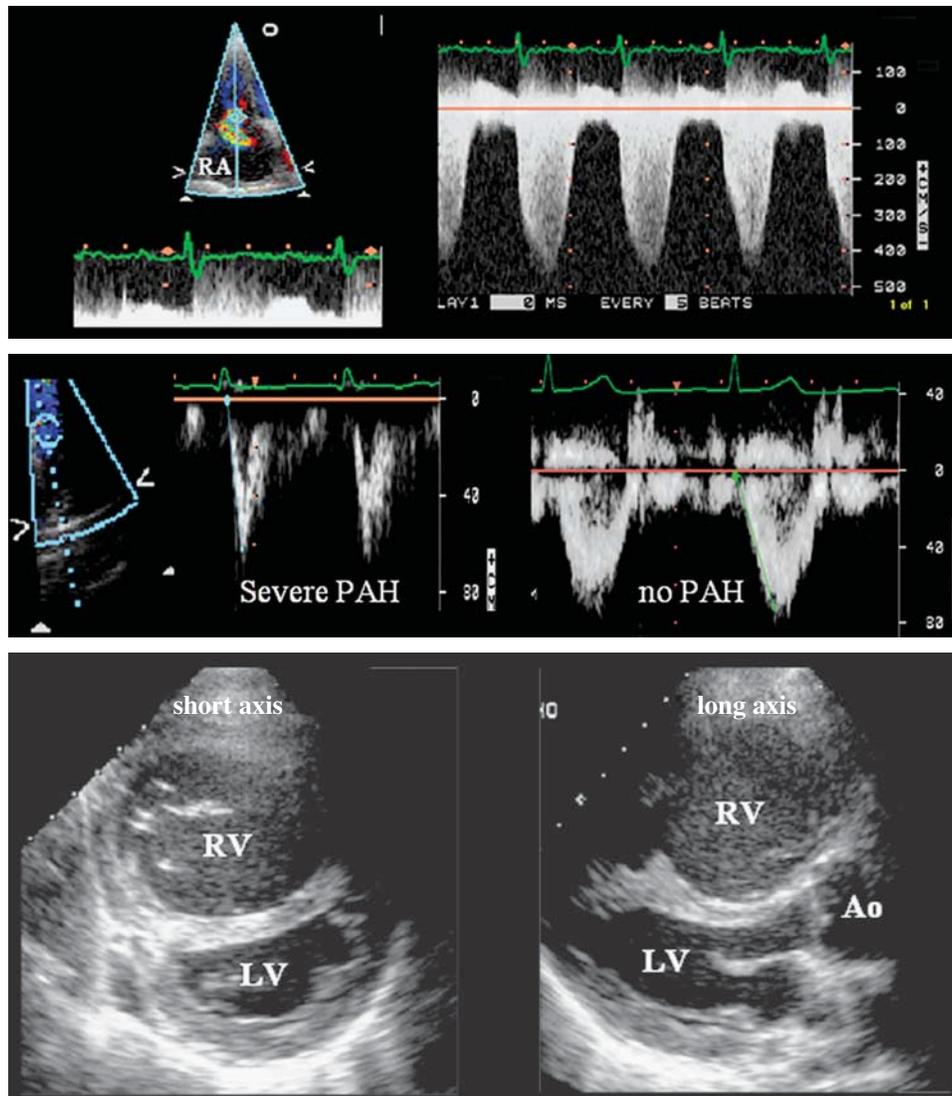


FIGURE 105.12. Echocardiography findings in PAH. Classic examples of continuous and pulsed Doppler as well as 2D imaging are shown.

Echocardiography (Fig. 105.12)

There are a number of excellent articles and chapters reviewing the use of echocardiography in the detection and quantification of PHT.^{123,124} If the image quality is adequate and one integrates anatomic data (RV chamber size and thickness, mitral valve anatomy), physiologic measurements (Doppler measurement of valve insufficiency and shunts), and a few simple calculations of pulmonary artery pressures, the echocardiogram is a reliable test for suggesting the presence of PHT. The likelihood of finding and estimating the severity of PHT is directly proportional to the diligence of the sonographer and the experience of the physician who interprets the study.

M-Mode Echocardiogram

Although the M-mode echocardiogram is less widely used since the advent of two-dimensional echocardiography, it is

occasionally a useful modality in the diagnosis of PHT. The M-mode signs of PHT are indirect measurements that predominantly reflect the rigid, noncompliant nature of the diseased pulmonary vasculature. A characteristic sign of PHT is the absence of an "A" dip on the M mode of the pulmonic valve.¹²⁵ The A dip, which occurs when atrial systole causes a bulging or partial opening of the pulmonic valve, is present only in patients in sinus rhythm. The sensitivity and specificity of this sign are relatively low.¹²⁶

A second sign of PHT is the transient midsystolic closure of the pulmonic valve. The reasons for the premature closure of the pulmonic valve in PHT include the reduced capacitance of the pulmonary vascular bed and a prominent flow reversal within the hypertensive pulmonary artery.¹²⁷ Reflection of the systolic wave front may be enhanced in the hypertensive pulmonary vasculature, resulting in deceleration of midsystolic flow. This M-mode sign of PHT is related to the finding on pulsed Doppler of a transient, early systolic pulmonary arterial flow deceleration. The notched morphology

on M mode is fairly specific but is insensitive as a test for PHT and has been reported in patients with normal PAP who have idiopathic dilatation of the pulmonary artery.¹²⁸

The adult right ventricle is roughly one third the thickness of the LV. Right ventricle hypertrophy can be measured using the M-mode echocardiogram or the electronic calipers on the two-dimensional image. Care must be taken to ensure that the M-mode cursor avoids the papillary muscles and the RV muscular bands. The RV can be measured from many acoustic windows, but it is optimally measured from a medially angulated parasternal or subcostal window at the level of the tips of the tricuspid valve leaflets, using a 5-MHz transducer.¹²⁹ With this technique, Gottdiener et al.¹³⁰ found that normal subjects have an RV wall thickness of ≤ 4 mm.

TWO-DIMENSIONAL ECHOCARDIOGRAPHY

The RV has a complex geometric shape. Unlike the somewhat ellipsoid configuration of the LV, the RV is crescentic and is not readily described by simple geometric equations. Even measurement of wall thickness is difficult owing to the trabeculation, which can result in significant variation in wall thickness within a relatively small sample volume.

Goerke and Carlsson¹³¹ have shown that Simpson's rule can be used to calculate volumes of ventricular casts in a similar model. Starling et al.¹³² showed that RV volume could be calculated as area times length of the right ventricle, but the appropriate subcostal views could be obtained only in 64% of patients.

The end-systolic configuration of the ventricular septum is a useful indirect measurement of the relative pressures in the LV and RV.¹³³ As RV systolic pressure increases, there is a gradual change in septal configuration from convex (bulging toward the right ventricle) to flat, and finally to concave (indented toward the left ventricle) (Fig. 105.12). Two-dimensional estimates of RV mass are difficult, and a three-dimensional technique, specifically magnetic resonance imaging (MRI), is preferred to accurately measure RV mass.

Pericardial effusion is a common but nonspecific finding in chronic severe PHT. In one study, largely comprising patients with thromboembolic PHT, 41% had small or medium-sized effusions, none of which was symptomatic. The likelihood of effusion was increased in those patients with the highest RA pressure or PAP.¹³⁴

PULSED DOPPLER (Fig. 105.12, Table 105.1)

Pulsed Doppler measurement of pulmonary artery flow velocity in the main PA is an extremely useful qualitative and quantitative technique for measuring PA pressure, and, unlike estimates based on tricuspid regurgitation velocity, is available in virtually all patients. In PHT, the peak velocity of the Doppler envelope decreases and the time to peak velocity (measured from the onset of flow) or acceleration time (PAAT) shortens. In severe PHT there may be "notching" or early systolic deceleration, which, like the premature partial closure of the pulmonic valve on M mode, reflects the velocity waves and cancellation by reverse flow. This is due to the noncompliant nature of the distal vascular bed in PHT. The normal pulmonary artery flow velocity is 81 ± 17 cm/s and occurs with a PAAT of 121 ± 27 seconds.¹³⁵ A typical Doppler signal in patients with PHT is often of triangular shape rather than the normal broad shield shape seen in normotensive

patients, and the PAAT is shortened.¹³⁶ Although there is a fair correlation between acceleration time and pulmonary artery systolic pressure, Mahan et al.¹³⁷ found a better correlation between PAAT and mean PAP. They used a regression equation to develop the following formula predictive of mean PAP: mean PA pressure = $79 - 0.45 \times \text{PAAT}$. Other groups have confirmed this relationship, albeit with modified regression equations (Table 105.1). This technique is somewhat heart rate dependent, but it correlates well with mean PAP in patients with heart rates between 60 and 100. It is useful to express the PAAT as a ratio with the systolic ejection time (SET), which also shortens in PHT. A PAAT/SET < 0.36 reliably indicates PHT. These same Doppler parameters are useful in assessment of rodent models of PHT.^{38,40}

CONTINUOUS WAVE DOPPLER (Fig. 105.12)

Continuous wave Doppler measurement of tricuspid regurgitation velocities permits accurate, noninvasive measurement of systolic PAP, even in many normal individuals. Tricuspid regurgitation is extremely common, and increases in prevalence and severity as PAP increases. Berger et al.¹³⁸ found tricuspid regurgitation in 39 of 49 patients with systolic pressures less than 35 mmHg and in 26 of 27 patients with pressures greater than 50 mmHg. They noted an excellent correlation between Doppler and catheter estimates of pulmonary artery systolic pressure ($r = 0.97$).

Guided by color flow Doppler, the continuous wave Doppler must be positioned parallel to the regurgitant jet to accurately measure peak tricuspid regurgitation velocity. However, the jets are often eccentric and small, which results in incomplete envelopes that underestimate PAP; PAP is calculated using the modified Bernoulli equation. Systolic PAP can be estimated as four times the square of the systolic tricuspid valve plus the RA pressure (the pressure into which the tricuspid regurgitation is ejected) (Table 105.1). Yock and Popp¹³⁹ used this modified Bernoulli's equation to estimate RV systolic pressures in patients with clinical signs of PHT. In their study, tricuspid regurgitation velocity could be measured in 54 of 62 patients. There was a good correlation between the pressures obtained by catheter and by Doppler. The utility of the tricuspid regurgitation jet in evaluating pulmonary systolic pressure has been well validated.¹⁴⁰ It is apparent that accurate estimation of PAP relies on knowledge of the RA pressure. RA pressure can be estimated at the bedside by measuring the jugular venous pulse (JVP). Unfortunately, this is difficult in some patients, and sonographers, who perform most studies, are usually not trained to measure JVP. The RA pressure is approximated by the perpendicular height of the JVP above the sternal angle plus the estimated distance from the middle RA to the sternal angle (~ 5 cm in an average-sized adult). This estimated atrial pressure in cm H₂O can be converted to mm Hg by dividing by 1.3.

The diameter of the proximal inferior vena cava is more readily measured by the sonographer and can be used to estimate RA pressure. At normal RA pressures, the vena cava decreases in size 50% with normal inspiration (inspiratory pressures of 0 to 5 mmHg).¹⁴¹ Much higher inspiratory pressures are required to achieve the same degree of collapse in patients with elevated RA pressure. There is a good relationship between RA pressure and the inspiratory pressure required to alter caval size, but this requires the use of

sonospirometry.¹⁴² Measurement of caval diameter 2 cm proximal to the RA junction at rest and with respiratory maneuvers, such as a sniff, permits approximation of right atrial pressure.¹⁴² As a rule, an inferior vena cava that is more than 2 cm in diameter and that collapses by less than 50% when the patient sniffs is "plethoric" and usually reflects an RA pressure >10 mmHg. Conversely, cavae that are under 2 cm that collapse by >50% with spontaneous respiration reflect normal atrial pressures (1 to 6 mmHg).

In clinical practice, due to time constraints on sonographers, jet eccentricity, inaccurate estimation of RA pressure, and poor acoustic windows, the ability to accurately predict PAP using tricuspid regurgitation (TR) velocity is substantially less than the 90% reported in select research cohorts, even if one enhances the tricuspid regurgitation jet with injection of contrast material. Consequently measurement of RVH on a two-dimensional echocardiogram and PAAT, using pulsed Doppler, should also be used in assessing possible PHT.

Computed Tomography

High-resolution CT is a significant aid in excluding occult parenchymal lung disease, pulmonary fibrosis, or chronic pulmonary embolism in possible PAH patients. Of patients with biopsy-proven interstitial fibrosis, 10% may have normal chest radiographs, and for these patients CT scans are a more sensitive technique.¹⁴³ Contrast-enhanced, multislice CT (16 or, more recently, 64 slice), can detect central chronic thromboembolic with a specificity of 85% to 90% and sensitivity of 90%.¹⁴⁴ Computed tomography scanning is also helpful in differentiating PAH due to veno-occlusive disease from iPAH. The presence of ground-glass opacities (particularly with a centrilobular distribution), septal lines, and adenopathy are indicative of pulmonary veno-occlusive disease in PAH patients (Fig. 105.13).

Multislice and electron beam CT was used to compare the pulmonary vascular and parenchymal characteristics of the lung in 31 PAH patients with Eisenmenger's syndrome

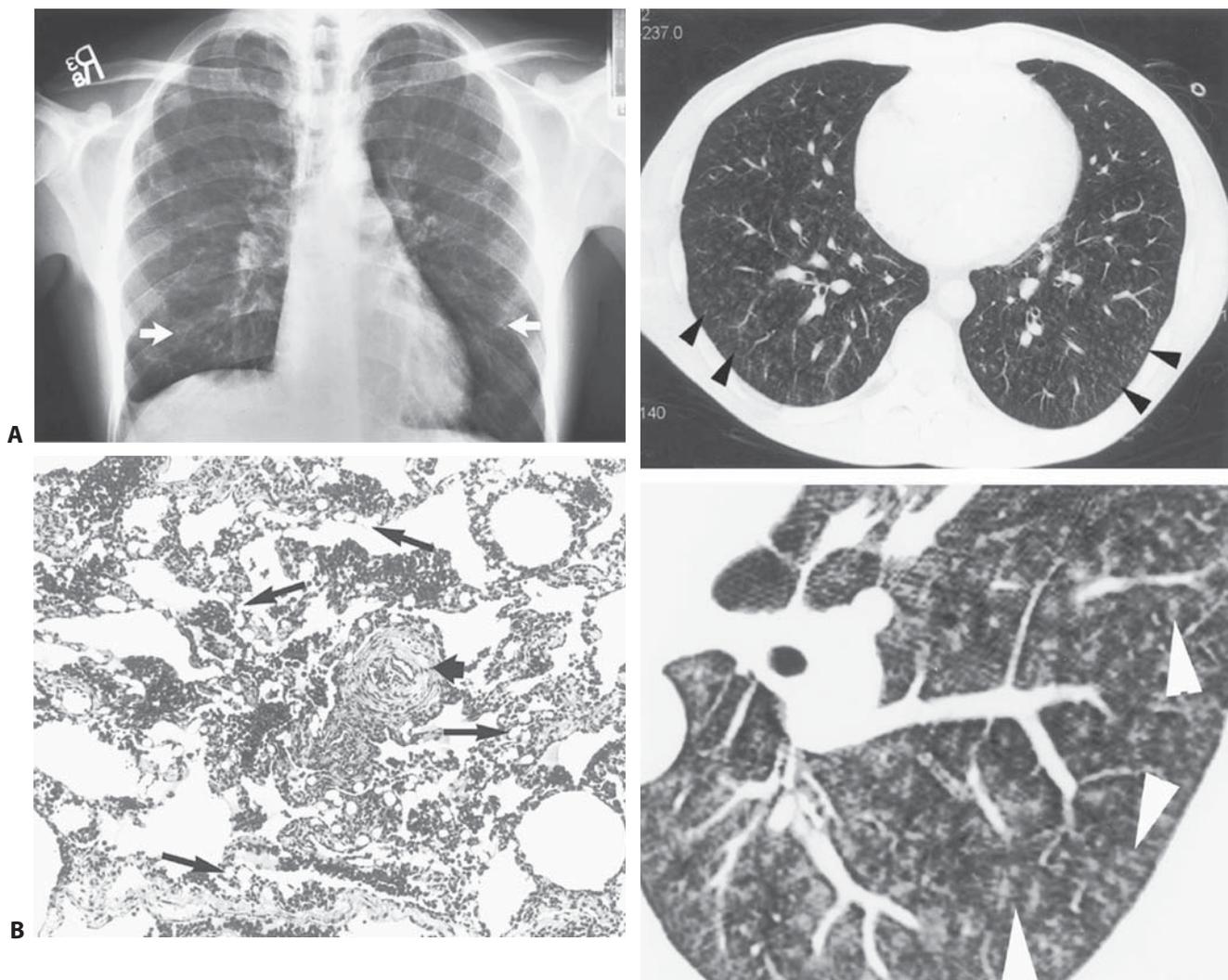


FIGURE 105.13. Pulmonary capillary hemangiomas. (A) Ill-defined nodular irregularities representing the nodular capillary proliferation are shown (arrows) in the chest x-ray. (B) Open lung biopsy shows diffuse alveolar septal involvement by a proliferation of small thin-walled vessels (long arrows). Thickening of the wall and narrowing of the lumen of a pulmonary artery are due to fibro-

plasias (short arrow). (C) Axial computed tomography (CT) shows subtle innumerable micronodular densities in the centrilobular regions (arrowheads) surrounded by normal parenchyma are observed (top). A magnified image of the left lower lung demonstrates the micronodular ill-defined centrilobular densities (arrowheads) separated by relatively spared normal parenchyma (bottom).

versus 13 iPAH patients.¹⁴⁵ In Eisenmenger's patients the proximal PAs were consistently enlarged and 13% of patients were aneurysmal, which caused bronchial compression and atelectasis. Thromboses were uniformly present on CT, although they were large in only 29% of patients. Mural calcific deposits occurred in 26% of these patients. In addition, Eisenmenger's patients often had pulmonary infarction, intrapulmonary hemorrhage, bronchial collateral vessels, and neovascularization. In contrast, iPAH patients had consistent enlargement of proximal PAs on CT, but no aneurysms, thromboses, infarcts, or neovascularity.¹⁴⁵ However, like Eisenmenger's patients, extensive mural calcific deposits were found in 23% of PAH patients and they too had bronchial collaterals.¹⁴⁵

Ventilation Perfusion Scans (Fig. 105.14)

V/Q scans are widely used in assessment of patients with PHT to exclude thromboembolic PHT. Hull et al.¹⁴⁶ compared the relative roles of V/Q scans, objective testing for venous thrombosis, and pulmonary angiography in 305 consecutive patients with suspected acute pulmonary embolism. This classic study proved that a segmental or larger unmatched perfusion defect was associated with an 86% frequency of pulmonary embolism (and thus could be considered "high probability"); however, the common clinical practice of excluding a diagnosis of pulmonary embolism based on the finding of a matched defect (perfusion and ventilation scans abnormal in the same area) was incorrect. Segmental and subsegmental matched low-probability V/Q abnormalities were associated with 36% and 25% incidence of angiographically confirmed embolism, respectively. Fortunately, virtually all patients with chronic thromboembolic PHT have one or more high-probability defects on their V/Q scan.

Patients with iPAH often have diffuse, inhomogeneous, or "moth-eaten" perfusion scans that are interpreted as being low probability. This reflects loss of small arteries in PAH. There have been a handful of reports of death within minutes of injecting the albumin macroaggregates, which are the

small particles (75 μm) that are labeled with technetium.¹⁴⁷ These complications have usually occurred in patients with severe PHT and may represent the inability of a severely obstructed vascular bed to deal with a shower of microemboli. With the advent of 64-slice CT scanning, capable of sub-1-mm resolution, the role of V/Q scans will diminish. In a recent meta-analysis, based on 12 studies of CT and V/Q scanning in suspected pulmonary embolism, CT was found to have a sensitivity and specificity of 86% [95% confidence interval (CI), 80–92%], and 94% (95% CI, 91–96%), respectively.¹⁴⁸ V/Q scanning had a much lower sensitivity of 39.0% (95% CI, 37–41%), although specificity was also high at 97% (95% CI, 96–98%).¹⁴⁸ Thus, CT is the technique of choice to exclude pulmonary embolism, although a positive V/Q scan (high probability) is sufficient to predict pulmonary embolism.

The challenge with "possible PAH" patients is not to exclude acute pulmonary embolism, which can usually be done based on the presentation; rather, it is to actively exclude the diagnosis of chronic thromboembolic PHT because the latter has a specific and often curative surgical therapy—pulmonary thromboendarterectomy. In a center with high volumes, such as University of California–San Diego, results are excellent. In a series of 1100 patients with chronic pulmonary thromboembolism treated with thromboendarterectomy, survival was 94.2% and PVR was decreased by 547 dynes × sec × cm⁻⁵.¹⁴⁹

Pulmonary Angiography

Pulmonary angiography is primarily used to evaluate the possibility that the pulmonary hypertensive patient has chronic pulmonary emboli. In addition, angiography is a useful test to diagnose peripheral pulmonary artery stenoses, arteriovenous fistulas, and obliterative pulmonary vascular disease. In the University of Alberta PAH program, due to the use of V/Q CT scanning and MRI, conventional pulmonary angiography has not been required in characterizing any of the last consecutive 160 PHT patients. In patients

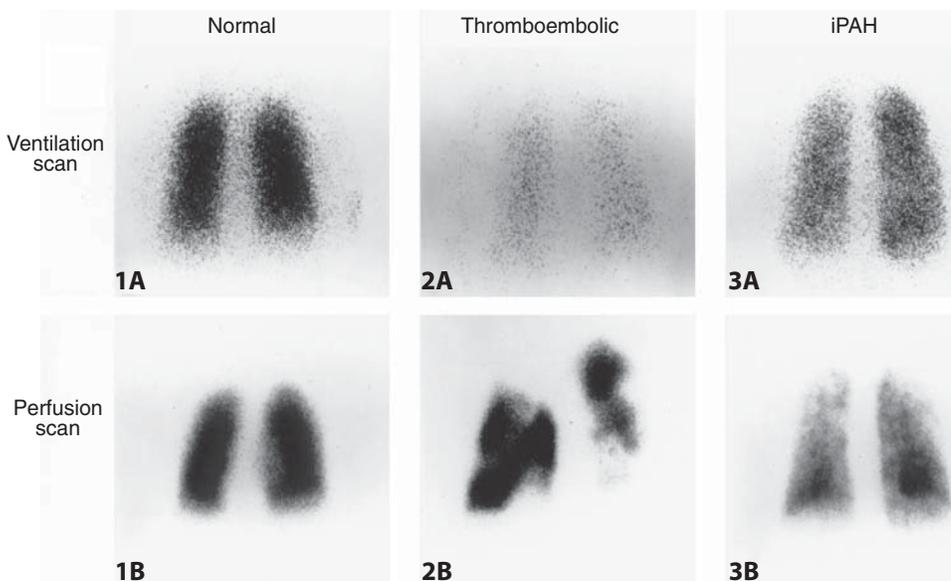


FIGURE 105.14. V/Q scanning in pulmonary hypertension (PHT). Note the "moth-eaten" pattern of perfusion in iPAH.

being assessed for chronic PHT, pulmonary angiography should be reserved for those with equivocal CT scans.

Pulmonary angiography typically involves placement of a catheter in the pulmonary artery using the Seldinger technique. Unless the femoral veins and inferior vena cava are shown to be free of thrombus, it is best to use an antecubital or internal jugular route for vascular access to avoid embolization. Pulmonary angiography can be performed in PHT patients with minimal morbidity and mortality. The incremental risk of injection of contrast beyond the risk of placing a catheter merely to measure pressures is relatively small. The patients most at risk for complications are those with RV end diastolic pressures greater than 20mmHg or those with overt evidence of right heart failure, and in these patients the technique should be used cautiously.

Whereas conventional angiography images the large vessels, an alternative angiographic technique, wedge angiography, can be used to study the microvasculature. This technique is primarily employed to assess the anatomy of the small vessels and capillary bed. Small amounts of contrast are injected distal to the inflated balloon while the catheter is "wedged," and magnified angiograms are obtained. In normal subjects the subsegmental vessel is plump and smooth, and there is a distal blush produced by the microcirculation. Narrowing of the vessel or reduction in the size of the microvascular bed occurs with progressive PAH.¹⁵⁰ Findings on wedge angiography correlate fairly well with histologic assessment of the pulmonary vasculature obtained at lung biopsy.¹⁵¹

The literature contains many reports of deaths caused by pulmonary angiography, especially in patients with PHT. Advances in catheter design, use of nonionic contrast agents, and the advent of selective angiography have all contributed to improved safety. Nicod et al.¹⁵² analyzed the safety of pulmonary angiography in 67 patients with moderate to severe primary or thromboembolic PHT. These authors observed no significant complications but noted occasional transient episodes of hypotension, cough, and flushing. Supplemental oxygen to avoid hypoxemia and careful attention to analgesia are critical to safe pulmonary angiography.

The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) multicenter cooperative trial reported the safety and utility of pulmonary angiography in patients with acute pulmonary embolism.¹⁵³ The 1111 pulmonary angiograms were performed with ionic contrast injected at 20 to 35 mL/s for a total volume of 40 to 50mL. The mortality rate from pulmonary angiography was 0.5%, with major, nonfatal complications in 1% and minor complications in 5% of patients. Mean PAP did not differ in those with major, minor, or no complications. A review of complications of pulmonary angiography revealed several incidents of cardiac perforation, which were attributed to the use of older, rigid catheters.

Cardiac Catheterization

Catheterization of the pulmonary artery remains the gold standard for determination of PAP, and, despite a plethora of available noninvasive techniques, is usually required to firmly establish a diagnosis of PAH. The goals of right heart catheterization include measurement of pressure, flow, and

resistance. In addition, the catheter is used to establish the type of PHT.

One can generally consider PHT as being the result of vascular obstruction, as in thromboembolic and iPAH, or a passive response to elevated LV end-diastolic pressure, as in congestive cardiomyopathy. In patients with PAH, there is a large gradient between the pulmonary diastolic pressure and the wedge pressure (>12 mmHg). This may be due to fixed vascular obstruction in a narrowed and partially obliterated vascular bed or may be due, in part, to increased pulmonary vascular tone. Based on studies of vasodilator therapy in patients with iPAH, which consistently show only <20% of them responding to vasodilators (defined as a 20% or greater fall in PAP in response to inhaled NO or IV prostacyclin), it appears that the majority of PAH patients have fixed anatomic vascular disease as the sole cause of their transpulmonary gradient. Even responders have a significant component of their PVR elevation as a consequence of vascular remodeling.

In patients with left ventricular failure, pulmonary artery diastolic and wedge pressures are elevated to similar levels. In these patients, the total pulmonary resistance, which does not take into account the left atrial pressure, may be elevated but PVR is not increased (Table 105.1). The right heart catheterization readily distinguishes these forms of hypertension, and thus aids in achieving a specific mechanistic diagnosis.

Additional studies may be necessary if there is a suspicion of intracardiac shunting or valvular disease. In any patient with a question of shunting, we perform oximetry in all right heart chambers to localize and quantify the shunt.

Right heart catheterization carries some risks in patients with PHT. The risks of right heart catheterization can be divided into three categories: (1) risks related to obtaining vascular access (e.g., vasovagal reactions); (2) risks of having a catheter in the heart (pulmonary artery rupture, arrhythmia); and (3) risks of administering medications (e.g., negative inotropic effects, systemic vasodilatation with hypotension). Pulmonary hypertensive patients may be intolerant to vasovagal reactions that may occur during attempted vascular access. When systemic vasodilatation occurs, whether due to a drug or reflex, the dysfunctional RV and obstructed pulmonary vascular bed may not support the normal increase in left heart output that accompanies systemic vasodilatation. Therefore, a simple vasovagal reaction may lead to a fatal cycle of bradycardia, hypotension, acidosis, and death. However, it is noteworthy that there were no deaths during diagnostic catheterization in the NIH registry study, in which 187 patients, mostly class III and IV, underwent right heart catheterization.¹²

ACUTE VASODILATOR TESTING—INO

Since the observation that patients who respond to acute pulmonary vasodilators with a >20% decrease in their PVR have better prognosis and a high chance of responding to high doses of oral calcium channel blockers chronically,³⁹ acute vasodilator testing has become a critical part of the PAH patient management. Although earlier studies used intravenous epoprostenol (2mg/kg/min, increase by this amount every 30 minutes, until effect is observed or adverse effects occur) or adenosine (50mg/kg/min, increase by this

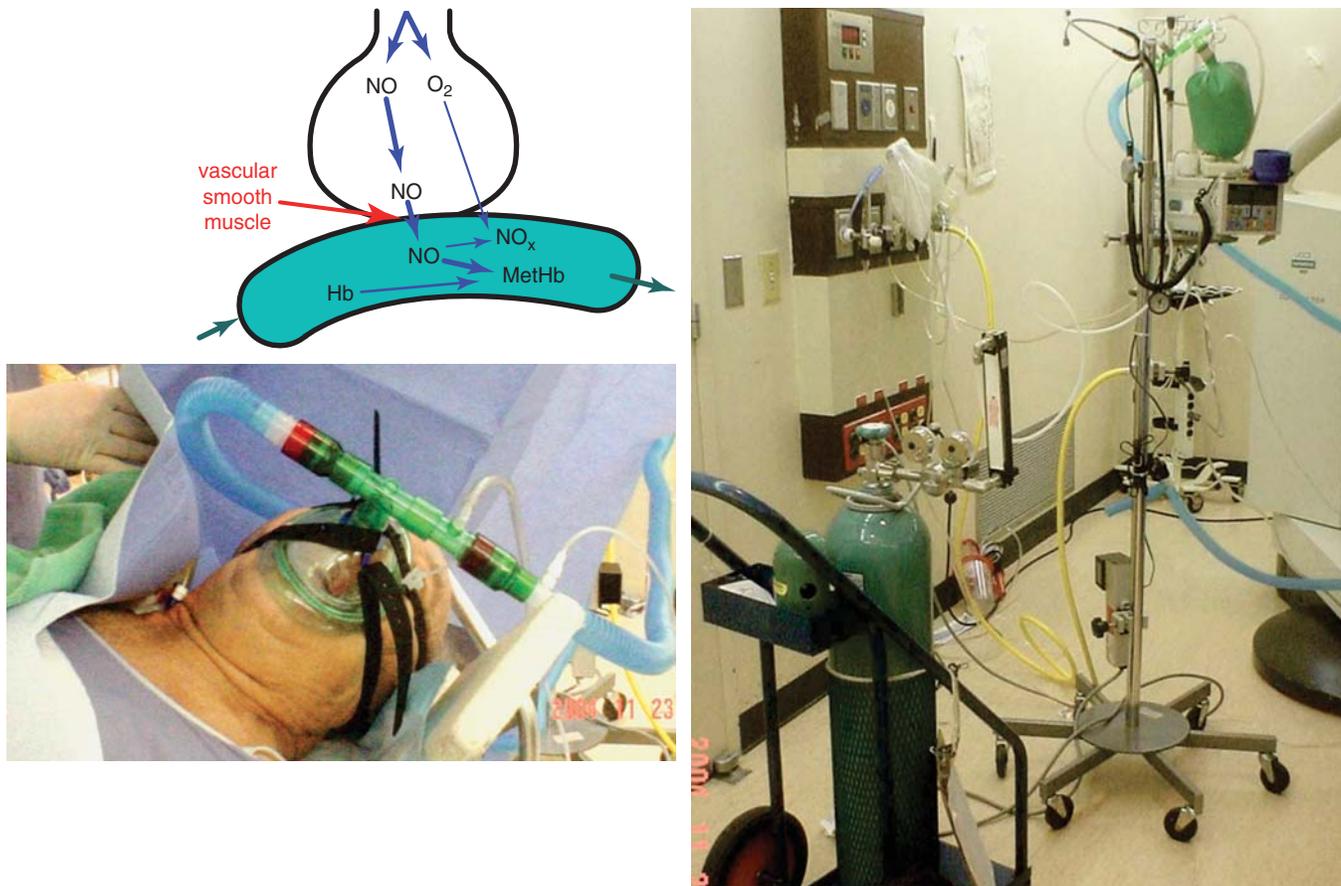


FIGURE 105.15. iNO delivery setup in the University of Alberta catheterization laboratory. Due to the almost immediate reaction with hemoglobin, the systemic effects of iNO are minimal.

amount every 2 to 3 minutes until effect is observed or adverse effects occur), iNO has recently become the vasodilator of choice. The inhaled route of administration offers a high degree of selectivity, and the effect disappears almost instantaneously with cessation of inhalation. A special mask and a device for the controlled delivery of the gas are required (Fig. 105.15), although iNO is not hard to administer. Unfortunately, the recent increases in its price make iNO relatively expensive. In our center, we begin the delivery of iNO at 5ppm and then we increase to 10, 20, 40, and 80ppm (maximal dose) every 5 minutes. Calculation of the PVR before and after the maximal dose is important. With the recent introduction of therapies that, in addition to vasodilator effects, have antiproliferative properties as well (epoprostenol, endothelin receptor antagonists, sildenafil), the usefulness of vasodilator testing in terms of selecting future therapy has become less clear. For example, in scleroderma, prognosis and response to epoprostenol are not associated with acute vasodilator response.¹⁵⁴ Nevertheless, the response to acute vasodilator testing remains an important means by which to determine the prognosis of PAH patients, even before treatments are initiated.

Magnetic Resonance Imaging

Magnetic resonance imaging facilitates reproducible, noninvasive volumetric flow measurement in the major pulmo-

nary arteries and RV. There are many advantages of MRI, including the avoidance of intravenous contrast, its entirely noninvasive nature, and the high probability of obtaining an adequate image, even in patients with lung disease. Although scan times remain significantly longer than those for CT scanning, the technique facilitates measurement of chamber dimension, RV mass, and increasingly of pressure and flow in the right heart. Bogren et al.¹⁵⁵ used MRI to evaluate pulmonary arterial compliance (vascular distensibility) in normal individuals and patients with PHT. Compliance, measured as the change in pulmonary artery volume resulting from an observed change in pressure, was considerably less in patients with PHT (8%) than in controls (23%). Furthermore, patients with PHT had a larger retrograde flow volume (26%) than normals (2%). This exaggerated reversal of pulmonary flow may explain the systolic closure ("notching") of the pulmonic valve in PHT. Recently, MRI has been used to track regression of RV hypertrophy in two small trials of the phosphodiesterase-5 inhibitor sildenafil and the endothelin receptor inhibitor Bosentan for PAH.^{156,157} Magnetic resonance imaging can also be used to generate pressure volume relationships to define RV contractility. These techniques reveal that chronic RV pressure overload is associated with reduced RV pump function despite enhanced RV myocardial contractility in PHT patients.¹⁵⁸ The interesting approach of simultaneous catheterization, using special catheters and MRI, holds clinical promise. Three-

dimensional ultrafast dynamic contrast-enhanced MRI has been used to quantify regional lung perfusion in PHT and normal individuals on a pixel-by-pixel basis.¹⁵⁹ This may be helpful, when coupled with gadolinium-enhanced MRI angiography, in assessing regression of pulmonary vascular disease (Fig. 105.11). Gadolinium-enhanced pulmonary MRI can reliably detect chronic PHT (based on the combination of dilated central PAs (diameter >28 mm) and abnormal proximal-to-distal tapering of the PAs).¹⁶⁰ In addition, MRI can be used noninvasively to measure PA systolic and diastolic pressures. It is likely that the comprehensive “one-stop” MRI facilitating serial anatomic and functional assessment will become the gold standard for PAH patients.¹⁶¹

Lung Biopsy

Biopsy of the lung parenchyma, either transbronchially via the fiberoptic bronchoscope or by open thoracotomy, is a critically important diagnostic tool in the approach to patients with a variety of diffuse lung diseases. However, lung biopsy plays a less important role in the diagnosis of PHT in most clinical settings. A clinical diagnosis of iPAH can be established with reasonable certainty clinically. Indeed, pathology data from the NIH registry demonstrated that no other diagnosis was made pathologically in patients entered into the registry when lung tissue became available for review. In cases where the etiology is less certain, such as patients with significant elevations in PAP associated with moderately abnormal lung function tests or evidence of interstitial disease by chest radiograph or high-resolution computerized scans of the chest, or patients with serologic abnormalities or other clinical signs that are suggestive of a vasculitis, lung biopsy may be highly useful in establishing a diagnosis and guiding therapy. Transbronchial lung biopsy is not advocated in patients with PHT, since the small size of the specimen generally precludes establishing a definitive diagnosis, and the risk of hemorrhage from hypertensive pulmonary vessels is increased. Open lung biopsy via a mini-thoracotomy had been considered the approach of choice; however, the risks of this procedure are increased in patients with pulmonary vascular disease, and such cases should be performed by experienced surgeons supported by a cardiovascular anesthetist. Thoracoscopic lung biopsy, which is less invasive and provides adequate tissue for diagnosis, is the preferred approach when a histologic diagnosis is deemed necessary.

To recap, evaluation of PAH can be accurately accomplished by noninvasive techniques (echocardiography, multislice CT, and MRI). Consequently, lung biopsy and pulmonary angiography are rarely required and even V/Q scanning is becoming less necessary; however, the role of right heart catheterization remains critical.

Comorbidities with Pulmonary Arterial Hypertension

Connective Tissue Disease

Several connective tissue disease (CTDs) are complicated by PAH and they include systemic sclerosis, mixed connective

tissue disease, systemic lupus erythematosus, and, rarely, rheumatoid arthritis, dermatomyositis, and Sjögren's syndrome. The strongest association is with scleroderma,^{162,163} and PAH is the leading cause of mortality in patients with scleroderma.¹⁶⁴ In a prospective study using a catheterization-based diagnosis of PAH, ~12% of the patients with scleroderma ($n = 722$) were found to have PAH.¹⁵⁴ The mean age of the patients with PAH in this study was 66 years and the female-to-male ratio was 4:1. Because patients with scleroderma also suffer from pulmonary fibrosis, the assessment of dyspnea and the cause of PHT (hypoxic PHT due to lung disease versus PAH) can be very difficult. A significant decrease in DLCO (<55%) usually suggests the presence of PAH in these patients. It is also important to make sure that their PHT is not secondary to left ventricular dysfunction, particularly diastolic dysfunction, which may complicate scleroderma. For all these reasons the threshold for right heart catheterization should be relatively low, since this is often the only test that will definitively determine the extent and the cause of PHT.

Despite the fact that their histology and hemodynamics are similar to that of iPAH in recent trials, patients with PAH and scleroderma have worse prognosis compared with iPAH patients. In a study conducted between 1998 and 2002, their 3-year mortality was 56%,¹⁵⁴ illustrating that the prognosis remains poor despite modern treatments, and perhaps challenging the notion that mechanisms of disease are homogeneous among the various forms of PAH. Interestingly, in contrast to the patients with iPAH, the response to acute vasodilators in patients with scleroderma is not associated with improved survival.¹⁵⁴

Congenital Heart Disease

The high flow and the increased shear stress through the pulmonary circulation in congenital heart disease syndromes with significant left to right shunts, particularly if the shunt is at high pressure, causes endothelial damage and initiates proliferative remodeling in the pulmonary vessels. The histology, which can be graded using the validated Heath-Edwards classification, is indistinguishable from that of iPAH and includes medial and intimal hypertrophy, small vessel obliteration, thrombosis, and plexiform lesions. As the PA pressure rises and exceeds systemic arterial pressure, the shunt reverses and Eisenmenger's syndrome is established. The development of PAH is much more common in ventricular septal defects than atrial septal defects.^{165,166} If the ventricular septal defect is bigger than 1.5 cm, there is a 50% chance for PAH, while fewer than 3% of patients with small defects develop PAH.¹⁶⁷ The lower pressure shunts of atrial septal defect are less likely to cause PAH, but even here there is diversity. Sinus venosus atrial septal defects are associated with a 16% chance for PAH, whereas with ostium secundum defects the chance is less than 4%.¹⁶⁸ Patients with congenital heart disease and PAH have better prognosis than patients with iPAH.¹⁶⁹ Nonetheless, these patients are more prone to manifest significant desaturation with exercise and to have polycythemia than are iPAH patients. They also may develop hemoptysis, due to the rupture of bronchial arteries.

Portal Hypertension

While cirrhosis without portal hypertension is not associated with PAH, patients referred for liver transplant with portal hypertension have a 3% to 4% incidence of PAH.^{170,171} However, increased PA pressures, without elevated PVR, are found in up to 20% of this population.¹⁷⁰ In most patients with cirrhosis, the associated increase in the cardiac output can cause elevated PAP, simply due to the increased flow in the pulmonary circulation. Thus, it is very important not to rely on indirect estimations of the PA pressures with tests like echocardiography, but proceed with right heart catheterization in patients with hepatic disease in whom PAH is suspected. The prognosis of patients with PAH and untreated portopulmonary hypertension is very poor, with an average survival of only 15 months after diagnosis.¹⁷² In a small cohort of 15 patients, significant improvement was reported with epoprostenol.¹⁷³ The recognition and possible treatment of patients with portopulmonary hypertension prior to transplantation is critical because the perioperative mortality is very high. In a recent meta-analysis of patients undergoing liver transplantation, a mean PA pressure of more than 50 mm Hg was associated with 100% perioperative mortality; for mean PA pressure of 35 to 50 mm Hg, the mortality was 50%; the mortality was 0% for mean PA pressure of less than 35 mm Hg.¹⁷⁴ In selected patients, liver transplantation has reversed the PAH.¹⁷⁴ The role of the liver in the pathogenesis of PAH is intriguing. One of the common animal models of PAH is created by injecting rats with the toxin monocrotaline, derived from the plant *Crotalaria spectabilis*. Monocrotaline requires hepatic activation before the alkaloid is active and can induce PAH.

Human Immunodeficiency Virus Infection

The first case of PAH in a patient with AIDS was reported in 1987,¹⁷⁵ and the association between infection with HIV and PAH was recognized a few years later.^{176,177} In a cohort of ~1200 HIV-infected patients, a 0.5% incidence of PAH was reported. The largest case control study so far has come from the Swiss HIV Cohort (3349 HIV patients followed over 5.5 years), which reported a cumulative incidence of 0.57%.¹⁷⁸ Patients with HIV infection have a rate for PAH 6 to 12 times higher than the general population. With the introduction of highly active antiretroviral therapy over the past few years and the improved prognosis, the incidence of noninfectious complications in this population has been increasing. The mechanism of PAH in patients with HIV infection remains unknown. The virus, to date, has not been isolated for the pulmonary arteries,¹⁷⁹ leading to the unconfirmed hypothesis that the disease is caused by activated mediators or cytokines that result from the infection or the immune reaction to the infection.¹⁸⁰ The mortality of HIV-infected patients is significantly higher compared to the HIV-infected patients without PAH, although it is similar to that of iPAH patients.^{181,182} Univariate analysis indicates that a CD4 lymphocyte count of more than 212 cells mm³ and the use of combination antiretroviral therapy and epoprostenol infusion were associated with better survival.¹⁸²

Interestingly, another retrovirus, human herpes virus 8 (HHV8), was isolated from 10 out of 16 patients with iPAH.¹⁸³

This is intriguing because HHV8 causes Kaposi's sarcoma, a tumor with endothelial abnormalities that show impressive similarities with the plexogenic lesions in iPAH.

The Impact of Anorexigens

The anorexigens aminorex, fenfluramine, and dexfenfluramine are modified amphetamines that enhance serotonin release and inhibit serotonin reuptake in the brain, resulting in appetite suppression and a 5% to 10% weight loss. Between 1967 and 1972, there was an outbreak of PAH in Europe related to the anorectic agent aminorex that resolved with withdrawal of the drug.¹⁸⁴ A similar PAH epidemic ensued in the 1980s and 1990s with the use of fenfluramine and dexfenfluramine. Although use of these appetite suppressants for 3 months was associated with a 23-fold increase in the risk of developing PAH, the annual incidence of PAH in the population as a whole remained very low (1.7 per million).¹⁸⁵ Only a small proportion of the patients exposed to anorexigen developed PAH, suggesting a requirement for one or more predisposing conditions. Endothelial dysfunction, acquired or genetic, is almost certainly a predisposing factor. Patients with anorexigen-induced PAH tended to be older and frequently had known risk factors for endothelial dysfunction (cigarette use or obesity).¹⁸⁶ Indeed, compared with iPAH patients, those with anorexigen-associated PAH have decreased lung NO production, and their PVR is inversely related to NO production.¹⁸⁶ Despite repeated attempts, it was not possible to create an animal model of PAH by feeding different species with large amounts of the various anorexigens, again suggesting the need for genetic or other predisposing factors.

The conventional view of the toxicity related to these agents is that it relates to elevation of serotonin, and certainly the "carcinoid-like" valve disease, which ultimately led to their withdrawal,¹⁸⁷ may relate to disordered serotonin metabolism. However, it has been shown that potassium channel inhibition and membrane depolarization partially accounts for the pulmonary⁸³ and systemic vasoconstriction that these agents induce.¹⁸⁸ Although only weak pulmonary vasoconstrictors are seen in normal lungs, inhibition of NO synthase exposes the constrictor potency of the anorexigens,⁸³ which supports the notion that endothelial dysfunction predisposes to this form of PAH. It has been proposed that the anorexigens are in reality Kv channel blockers that cause their intended (appetite suppression) and their unintended (altered platelet function and increased vascular tone) effects through their control of membrane potential and cytosolic Ca²⁺ levels.^{83,188} Indeed, the anorexigens do inhibit heterologously expressed Kv1.5¹⁸⁹ and Kv2.1 channels,¹⁹⁰ channels that control the membrane potential of PSMCs and whose expression is decreased in PAH.

Veno-Occlusive Disease

In this rare disease, obliterative fibrotic lesions are seen in pulmonary veins and venules. These lesions are characteristically patchy and result in focal increase in the wedge pressure. Because of the patchy nature of the disease, the wedge pressure might be increased in one pulmonary artery branch but not in another. When this disease is suspected, wedging

the catheter in several pulmonary artery branches is recommended during right heart catheterization.

A CT scan may be helpful, showing septal thickening, ground glass opacities and a mosaic pattern of lung attenuation¹⁹¹ (Fig. 105.13). The prognosis is poor, and early referral for lung transplantation is suggested. It is also important to identify pulmonary veno-occlusive disease early in the assessment of PAH because administration of prostacyclin can cause acute pulmonary edema in this syndrome (as is the case in patients with impaired pulmonary venous drainage, whether due to pulmonary capillary hemangiomatosis or anomalous pulmonary venous drainage).¹⁹²

Pulmonary Capillary Hemangiomatosis

Pulmonary capillary hemangiomatosis (PCH) is a rare cause of PAH that occurs predominantly in young adults. It was first recognized in 1978 by Wagenvoort et al.¹⁹³ The condition is characterized by invasion of the lung with cytologically normal capillaries, and it clinically manifests as PHT and impaired gas exchange. Histologically, there is a proliferation of capillary-like vessels on and within the alveolar wall. Pulmonary capillary hemangiomatosis can occur in familial forms,¹⁹⁴ and its complications include hemothorax or clubbing. It is difficult to distinguish (without histology) from pulmonary veno-occlusive disease (PVOD). A typical bilateral diffuse reticular nodular pattern is seen in the chest x-ray. The CT findings (bilateral diffuse, centrilobular, poorly defined nodular opacities reflecting the capillary proliferation) are similar to those of veno-occlusive disease and help differentiate these two conditions from iPAH¹⁹⁵ (Fig. 105.13).

As of 1996, only 18 cases had been reported in the literature.¹⁹⁶ A more recent review noted 35 cases, but the prognosis remained dismal (median survival was 3 years from the first clinical manifestation).¹⁹⁷ Interestingly, there have been reports of improvement using interferon.¹⁹⁷ Early recognition of pulmonary capillary hemangiomatosis is important because there are anecdotal reports of pulmonary edema occurring in response to epoprostenol.¹⁹² Early referral for lung transplantation is recommended.

Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn (PPHN) is a complex syndrome with multiple causes, with an incidence of 0.43 to 6.8/1000 live births. It occurs in both idiopathic and secondary forms (associated with meconium aspiration, respiratory distress syndrome, pulmonary hypoplasia, and congenital diaphragmatic hernia). It causes severe hypoxemia and has a 10% to 20% mortality. Survivors have high morbidity in the forms of neurodevelopmental impairment, cognitive delays, hearing loss, and a high rate of rehospitalization. Persistent pulmonary hypertension of the newborn is characterized by a failure of transition of the hypoxic fetal pulmonary circulation from a high resistance-low flow bed to a low resistance-high flow neonatal circulation. It results in heart failure and persistent hypoxemia due to impaired maturation, vasoconstriction, and obstruction of the pulmonary vascular bed. The mechanisms that cause

PPHN are uncertain, and it is likely that there are many etiologic factors, including impaired angiogenesis, down-regulation of smooth muscle cell potassium channels, and elevated shear stress.^{198,199}

Persistent pulmonary hypertension of the newborn can be fatal, and in severe cases mechanical ventilation/extracorporeal ventilation is required. In a landmark trial, 58 full-term infants with PPHN were prospectively randomized to inhaled nitric oxide (80ppm) versus a control gas (nitrogen), mixed with oxygen from a ventilator.²⁰⁰ Inhaled nitric oxide increased oxygenation in only 7% (two of 28). Long-term therapy with inhaled nitric oxide sustained systemic iNO successfully and doubled systemic oxygenation in 16 of 30 PPHN infants (53%), whereas with conventional therapy without oxygenation, 75% of the infants had initial improvement. Extracorporeal membrane oxygenation was required in 71% of the control group and 40% of the nitric oxide group ($p = .02$).²⁰⁰ Although iNO has not been shown to decrease mortality in PPH, the use of extracorporeal membrane oxygenation has continued to decline since this new standard of care has been accepted. Abrupt discontinuation of inhaled NO can cause a rebound PHT, which may be more severe than prior to treatment. Sildenafil is useful to facilitate weaning of iNO in some PPHN patients, and it avoids rebound PHT. Sildenafil may also be useful as an alternative therapy for PPHN; clinical trials to evaluate this potential therapy are ongoing.

Hereditary Hemorrhagic Telangiectasia (Rendu-Osler-Weber Syndrome)

Patients with Rendu-Osler-Weber syndrome may develop PAH that is histologically indistinguishable from iPAH.²⁰¹ Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular dysplasia caused by mutations in two genes that encode the TGF- β receptors endoglin and activin-receptor-like kinase 1 (ALK1).²⁰¹ These patients have arteriovenous malformations (mostly nasal, hepatic, cerebral, and pulmonary) and sometimes these lesions result in significant shunts. In addition, these patients are anemic due to the nasal bleeds that are often very difficult to manage. The shunts and the anemia result in higher cardiac outputs and an increase in the pulmonary pressures, due to high flow. For this reason right heart catheterization should be performed in patients with HHT and suspected PHT in order to measure cardiac output and calculate PVR.

Hemoglobinopathies

Pulmonary hypertension of some degree has been reported in up to 75% of patients with β -thalassemia, but the diagnosis was made with echocardiography and not right heart catheterization.²⁰² The high cardiac output that complicates anemia could, by causing high flow, elevate PA pressures without truly causing PAH (i.e., without increasing PVR). In a study of 34 patients with sickle cell anemia who underwent catheterization, 20 were found to have increased PA pressures. However, several of these patients had increased wedge pressures due to left ventricular diastolic dysfunction. In a study of 195 consecutive patients with sickle cell disease, PHT (defined as tricuspid regurgitant jet velocity of >2.5 m/

sec) was found to be an independent and strong index of mortality.²⁰³ The destruction of circulating NO by the free hemoglobin in the blood of patients with hemolytic anemias has been proposed to contribute to the development of PAH in these patients.²⁰⁴

Thyroid Disease

Both hyperthyroidism and hypothyroidism have been associated with PHT. In patients with severe hyperthyroidism, the large increases in cardiac output can cause PHT due to high flow in the pulmonary circulation. There are several reports in the literature in which treatment of the hyperthyroid crisis completely reversed the PHT.^{205,206}

However, the association with hypothyroidism is more interesting than high-flow PHT, which explains most of the apparent hyperthyroid PHT. In a single-center cohort of 41 patients with iPAH, nine patients were found to have hypothyroidism, which is significantly higher than the expected incidence in the general population.²⁰⁷ An autoimmune pathogenetic link between hypothyroidism and iPAH has been proposed.²⁰⁸ In this regard, the lung and the thyroid gland have the same embryologic origins.²⁵ Moreover, it is very interesting that the thyroid hormone has been shown to regulate the expression of Kv1.5 in the myocardium. Hypothyroid rats have decreased expression of Kv1.5 in their hearts. Exogenous triiodothyronine (T₃) restores channel expression within 1 hour of treatment, a reflection of the very short half-life of Kv1.5,²⁰⁹ the K⁺ channel that is down-regulated and potentially involved in the pathogenesis of experimental and human PAH. The possibility that hypothyroid patients might also be deficient in pulmonary artery Kv1.5, predisposing them to develop PAH is an intriguing, but untested, hypothesis.

Management of Pulmonary Arterial Hypertension

It was not until 2004 that the first evidence-based practice guidelines were published and endorsed by the ACCP (see the July 2004 supplement of *Chest*, volume 126). Randomized controlled trials (RCTs) have only recently been performed for PAH treatments (Table 105.7), and still a number of recommended treatments lack support from RCTs. These treatments are discussed in General Measures, below. Following the discussion of specific Food and Drug Administration (FDA)-approved and experimental treatments currently in use, we discuss the approach to the patient with PAH and the treatment options according to the stage of the disease.

General Measures

Conditions that can exacerbate the pathophysiologic process, such as pregnancy, high altitude, and air travel, should be avoided if possible. Similarly, medications that can potentiate pulmonary vasoconstriction, such as sympathomimetics used for allergic symptoms, or vasoconstrictor prostaglandins used as abortifacients, should not be used. Since oral contraceptives may exacerbate PHT in susceptible patients by increasing their risk for a thromboembolic event, other

methods of birth control should be utilized. Lastly, all patients with PAH should be immunized against influenza and pneumococcal pneumonia and evolving respiratory tract infections should be treated aggressively.

OXYGEN THERAPY

In addition to maximizing oxygen delivery, supplemental oxygen therapy reduces the component of PHT that is due to active HPV. Patients with an arterial PO₂ of less than 55 torr at rest or an arterial oxygen saturation of less than 90% with ambulation, measured while breathing ambient air, are candidates for continuous home oxygen therapy. Oxygen is most effective in this setting when it is used continuously.²¹⁰ However, despite mild hypoxemia, most PAH patients do not usually manifest hemodynamic improvement with supplemental oxygen therapy. In patients with PAH due to congenital heart disease and right-to-left shunting, arterial oxygenation does not usually improve with supplemental oxygen, although patients may experience some symptomatic relief with its use. In a recent controlled study of patients with Eisenmenger's syndrome, oxygen therapy did not alter hematologic parameters, quality of life, or survival.²¹¹

Diuretics are useful for the treatment of right heart failure, but aggressive diuresis should be avoided because it can compromise cardiac output by excessively reducing preload. Furosemide in doses of 40 to 160mg per day is usually sufficient for patients with mild to moderate degrees of right heart failure. Patients refractory to furosemide may require the addition of more potent diuretics, such as metolazone or bumetanide. The potassium-sparing aldosterone antagonists, such as spironolactone, are a useful adjunct to loop diuretics for patients with refractory edema or ascites. Serum potassium and sodium levels should be monitored frequently when these agents are used.

CARDIAC GLYCOSIDES

The effectiveness of digitalis in patients with PAH has not been studied. Digitalis is sometimes used in the treatment of refractory right ventricular failure, particularly when this is associated with left ventricular dysfunction or atrial arrhythmias.

ANTICOAGULANTS

The role of anticoagulants in nonthromboembolic PHT is controversial. Patients with pulmonary vascular disease appear to be at increased risk for thromboembolic events because of their physical inactivity, right heart dilatation, and sluggish pulmonary blood flow. In addition, they develop small thrombi in situ within their diseased arteries. Sudden death due to pulmonary thromboembolism can occur and large thrombi are particularly common in patients with Eisenmenger's physiology. In both a retrospective²¹² and a prospective study,³⁹ survival in iPAH was significantly enhanced in patients who received anticoagulant therapy. The prospective study showed that the patients who benefit the most from warfarin are the ones who do not respond to Ca²⁺ channel blockers. However, this study was not designed to assess the effects of anticoagulation, and the therapy was not randomly assigned nor assessed in a blinded manner.

TABLE 105.7. Randomized controlled trials in pulmonary arterial hypertension (PAH)

	<i>Epoprostenol</i> <i>iPAH</i> ²⁵²	<i>Epoprostenol</i> <i>iPAH</i> ²¹³	<i>Epoprostenol</i> <i>Scl-PAH</i> ²¹⁴	<i>Treprostinil</i> ²²⁴	<i>Beraprost</i> ²²⁹	<i>Iloprost</i> ²²⁸	<i>Bosentan</i> ²³¹	<i>Bosentan</i> ²³²	<i>Sitaxsentan</i> ²³³
No. of patients	23	81	111	469	130	203	32	213	178
Months	2	3	3	3	3	3	3	4	3
Primary end point	Hemodynamics	Hemodynamics	6-min walk	6-min walk	6-min walk	6-min walk & f. class	6-min walk	6-min walk	mVO ₂
NYHA (%)									
II	9	—	5	11	49	—	—	—	33
III	65	75	78	82	51	59	100	91	66
IV	26	25	17	7	—	41	—	9	1
Etiology (%)									
iPAH	100	100	—	58	48	54	85	70	53
CTD	—	—	100	19	7	17	15	30	24
CHD	—	—	—	24	21	—	—	—	24
Thromb	—	—	—	—	—	28	—	—	—
HIV	—	—	—	—	7	—	—	—	—
Port-PAH	—	—	—	—	16	—	—	—	—
6-minute walk (m)	+45	+47	+94	+16	+25	+36	+76	+44	+34
Hemodynamics	Improved	Improved	Improved	Improved	No change	Improved	Improved	—	Improved
Clinical events	Reduced	Reduced	No change	Reduced	No change	Reduced	Reduced	Reduced	Reduced
Survival	N/A	Improved	N/A	N/A	N/A	N/A	N/A	N/A	N/A

CTD, coronary heart disease; CTD, connective tissue disease; NYHA, New York Heart Association; —, not assessed.

Thus, this study provides nondefinitive support only for the prescription of warfarin. Warfarin was used only in the presence of an abnormal V/Q scan, and it is therefore possible that these patients had simply a higher likelihood of survival. Adjusting anticoagulant medications may be particularly difficult in patients prone to altered drug metabolism due to hepatic congestion, and bleeding complications can occur even in the face of therapeutic degrees of anticoagulation. Some of the drugs currently completing phase III RCTs, like sitaxsentan, have a significant interaction with warfarin, requiring a significant decrease in the warfarin dose. Warfarin is the preferred drug, with the dose adjusted to achieve an INR of 1.5 to 2. At this time, warfarin therapy is indicated in all patients with iPAH (recommendation: evidence level B). Some centers extrapolate the iPAH data on other subsets of PAH, while others do not. The risk/benefit ratio for each patient has to be carefully considered. For example, some patients with PAH due to scleroderma or portal hypertension might be at increased risk of gastrointestinal bleeding due to esophagitis or varices, respectively. The role of low molecular weight heparin and new oral direct thrombin inhibitors (e.g., melagatran) in PAH is unknown.

Calcium Channel Blockers

Until recently, calcium channel blockers (CCBs) were the only option in the treatment of PAH. Rich et al.³⁹ used high doses of CCBs in 64 patients with iPAH and followed them for 5 years. Seventeen patients (27%) responded initially with an acute decrease in the PVR of >20%. After 5 years, 97% of these responders were alive, whereas only 55% of the nonresponders were alive (Fig. 105.16). Although this prospective trial was not placebo controlled, it remains one of the longest follow-up trials in PAH so far. Unfortunately, less than 20% of PAH patients respond to vasodilators acutely, and are therefore candidates for long-term CCB therapy.⁹ Furthermore, a number of these patients are unable to tolerate the

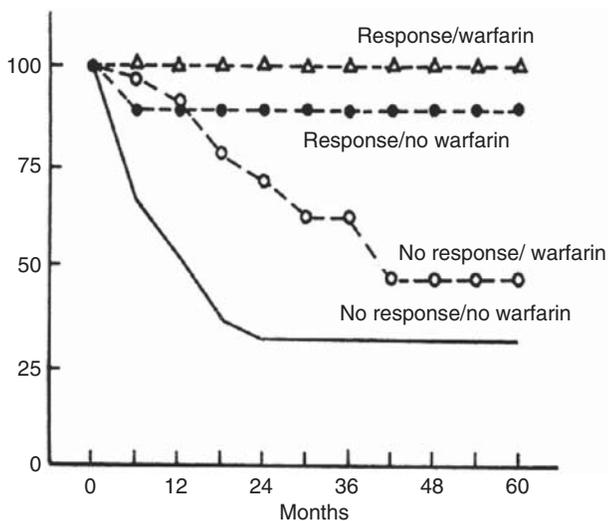
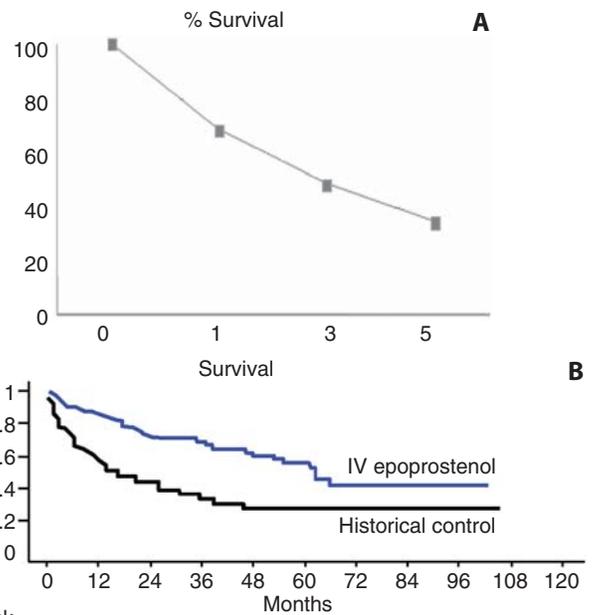


FIGURE 105.16. Response to acute vasodilators with >20% decrease in the PVR at the time of diagnosis (i.e., “responders”) and the use of warfarin are associated with much improved survival in a cohort of patients with iPAH, followed prospectively over 5 years.



No. at risk
 IV epo: 178 129 85 57 36 21 7 3 1
 Hist. control: 135 59 34 20 11 4 2 2 1

FIGURE 105.17. Survival in PAH. (A) Very poor 5-year survival in iPAH patients (NIH registry). (B) Compared to historical controls (from the NIH registry), patients on epoprostenol have a significant increase in survival.

high doses required (e.g., nifedipine 180 to 240 mg per day or an equivalent dose of a dihydropyridine), mainly because of systemic hypotension and peripheral edema.

Prostanoids

EPOPROSTENOL

Flolan® is the first treatment to show a substantial improvement in hemodynamics, functional capacity, and survival in patients with PAH (Fig. 105.17). In a landmark 3-month prospective open-label RCT, Flolan and conventional therapy ($n = 41$) was compared to conventional therapy alone ($n = 40$) in patients with iPAH NYHA class III or IV.²¹³ The Flolan group showed greater improvement: mean pulmonary arterial pressure (mPAP) -8% vs. $+3\%$, PVR -21% vs. $+9\%$, and 6-minute walk $+47\text{m}$ vs. -64m . While eight patients died in the conventional treatment arm, there were no deaths in the Flolan group ($p < .003$). A weakness of this study was that the baseline 6-minute walk performance in the Flolan group (315 m) was significantly better than that of the conventional treatment arm (270 m). The fact that the conventional group patients were sicker than the Flolan treatment group might have contributed to both the survival and the 6-minute walk differences. There were four episodes of sepsis and one of thrombosis attributed to the catheter in the Flolan group. In a similar RCT in PAH due to scleroderma, Flolan was shown to have similar beneficial effects in hemodynamics and functional capacity, but it did not improve survival.²¹⁴

Several studies have shown that the beneficial effects of Flolan on both hemodynamics and functional class can be

sustained for years.^{215–218} Survival with Flolan treatment at 1, 2, and 3 years was shown to be 88%, 76%, and 63%, respectively, significantly higher than the 59%, 46%, and 35% reported from historical survival data²¹⁸ (Fig. 105.15). Flolan was originally used as a bridge to transplantation, but it was soon realized that due to the substantial improvement, most patients were removed from transplant lists. Recently, four cases were reported in which long-term Flolan treatment was successfully tapered off and discontinued, replaced by the newly introduced oral therapies Bosentan and sildenafil.²¹⁹ Although at this point these are exceptions, as combination therapies become more common it is likely that more patients might be able to be weaned off Flolan and maintained on oral therapies. On the other hand, some patients do not respond to Flolan and some criteria have been proposed to identify these patients early on and refer them for transplantation. Multivariate analysis in a long-term (>5 years) follow-up study of 178 patients with iPAH NYHA class III or IV showed that poor long-term outcome is predicted by baseline NYHA class IV, baseline 6-minute walk <250m, baseline right atrial pressure >12mmHg, and, paradoxically, with mPAP <65 mmHg.²²⁰ In addition, poor outcome could be predicted if at 3 months after initiation of Flolan, the functional class had not improved and the total PVR had not increased by 30% or more.²²⁰

Due to its very short half life (<6 minutes) and its instability in acidic pH and in room temperature, the drug has to be given intravenously via a pump and kept cold at all times with ice packs. Also, due to its effects on small veins, it can only be given through central venous, tunneled catheters. A dose is initiated at low levels (1–2 ng/kg/min) and is slowly increased to a level just below the threshold for the many dose-dependent side effects; these include jaw pain, flushing, headache, diarrhea, an erythematous rash, and leg pains. The maximum dose tolerable varies significantly among patients. Excessive doses can lead acutely to hypotension and chronically to high-output cardiac failure.²²¹

Interruption of the Flolan infusion may cause a rebound increase in PAP and systemic blood pressure. In experimental models this rebound hypertension is due to activation of the renin-angiotensin system and can be prevented by angiotensin II receptor blockade.²²² Deaths have occurred when infusion catheters become disconnected or crimped. Patients having problems with the pump need to visit the emergency room immediately and be monitored until a new pump or a new access is established. Most patients carry an extra pump at all times. Lastly, perhaps the most serious side effect with long-term use is the catheter-related infections, from cellulitis to fatal sepsis. The cost of Flolan (over \$100,000/year) and the intrusive nature of administration have restricted its use to class IV patients and this leaves room for development of oral or inhaled therapies. In addition, the demands of Flolan therapy require a compliant patient. It is also noteworthy that this drug is not curative.

In patients with conventional congestive heart failure due to left heart disease, Flolan appears to be harmful. The Flolan International Randomized Survival Trial (FIRST), which assessed the effects of Flolan in 471 patients with class IIIb and IV congestive heart failure trial was terminated early because of a strong trend toward decreased survival in the patients treated with epoprostenol.²²³ In addition, chronic

intravenous epoprostenol therapy did not improve in distance walked, quality of life, or morbid events. By extrapolation Flolan should not be used in forms of PHT associated with left ventricular dysfunction.

TREPROSTINIL

Treprostinil is a prostacyclin analogue with a half-life of 3 hours, which is stable at room temperature. It has recently been introduced as an alternate to Flolan, and is delivered subcutaneously continuously via a pump. This pump is much smaller than the Flolan pump (like an insulin infusion pump—roughly the size of a pager) and there is no need for ice packs. The drug is offered premixed in a syringe and the patient does not have to prepare it sterilely every day as with Flolan. Because of the longer half-life, acute discontinuation of the drug is much less dangerous than it is with Flolan. Unfortunately, the efficacy of treprostinil is at best modest, and its use is limited by the often severe pain at the site of injection.

A large multicenter RCT trial on the use of treprostinil was recently reported, in which 470 patients were randomized to either treprostinil plus conventional therapy or placebo (continuous subcutaneous infusion of vehicle) plus conventional therapy for 12 weeks.²²⁴ There were significant differences in the design of this trial compared to the previous trial on epoprostenol. For the first time, class II patients were enrolled ($n = 53$), and patients with congenital heart disease and scleroderma were also enrolled. The primary end point was the 6-minute walk, which improved in the treprostinil group and did not change in the placebo arm (difference of 16m, $p < .006$). The iPAH group improved by 19m. Several secondary end points including hemodynamics and quality of life indices improved. However, 85% of the patients reported infusion site pain. The 16-m improvement in the 6-minute walk, although statistically significant, is likely to be clinically insignificant. This poor efficacy, at least compared to epoprostenol, might be explained by differences in the disease severity and PAH types enrolled. For example, the class II patients improved only by 2m (whereas the patients in class III improved by 17m and in class IV by 54m), and the patients with congenital heart disease did not improve at all.

ILOPROST

Iloprost is a prostacyclin analogue with a half-life of 25 minutes, available for IV, oral, and inhaled administration (Fig. 105.18). Iloprost is used in the treatment of PAH in Europe, and was approved in April 2005 in the United States. It is mostly delivered via the inhaled route, since this mode of delivery allows for selective effects on the resistance pulmonary arteries. These small PAs are surrounded by the alveoli, and some drugs, depending on their lung absorbance, can be delivered as an aerosol, with sparing of the systemic circulation, thereby limiting peripheral side effects. Unfortunately, multiple inhalations (six to nine per day) are required to achieve sustained clinical benefit, and each inhalation takes from 5 minutes (using ultrasonic nebulizers) to 15 minutes (using jet nebulizers).²²⁵

Following two promising open-label uncontrolled studies of Iloprost in PAH for 3 months²²⁶ and 1 year,²²⁷ a 3-month

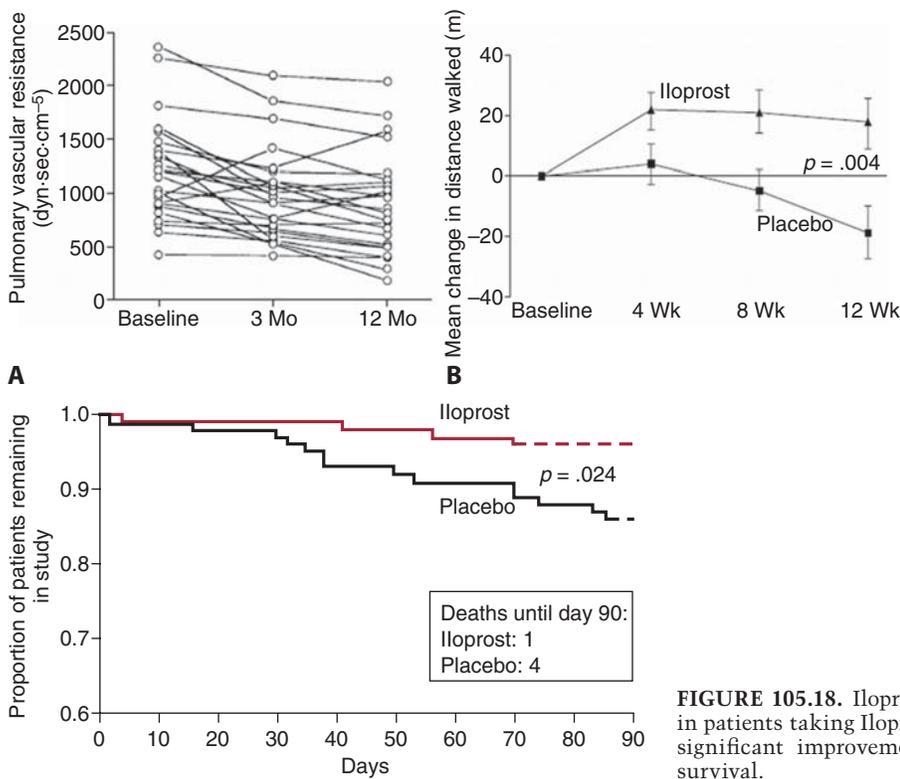


FIGURE 105.18. Iloprost in iPAH. (A) Sustained reduction of the PVR in patients taking Iloprost for 1 year. (B) Iloprost for 3 months leads to a significant improvement in the 6-minute walk and an increase in survival.

double-blind placebo-controlled RCT was reported of 273 patients with class III to IV iPAH as well as PAH due to collagen vascular disease and inoperable thromboembolic disease.²²⁸ Iloprost (2.5 or 5 μ g) six or nine times a day (max dose 45 μ g/day) prolonged the 6-minute walk by 36m in the overall population relative to placebo ($p < .004$). In the iPAH group, the improvement in the 6-minute walk was 59m. There were also statistically significant improvements in NYHA functional class and quality-of-life indices. Importantly, statistically significant improvement was also seen in pulmonary hemodynamics. Interestingly, this improvement was unchanged when measured before and after Iloprost inhalation, suggesting some sustained positive effect on vascular remodeling, rather than reversible effects on pulmonary vascular tone. Iloprost did not improve survival (one death in the Iloprost group, four deaths on placebo, $p = \text{NS}$). Only mild and transient side effects were reported.

BERAPROST

Beraprost is the first orally available prostacyclin analogue with a half-life of 40 minutes after oral administration. It has been used since 1995 in Japan for the treatment of iPAH, based on positive effects from several animal and small, open-label uncontrolled studies. To date, two large double-blind, placebo-controlled RCTs have studied beraprost for 12 weeks²²⁹ and for 1 year.²³⁰ In the 12-week trial, 130 patients with NYHA class II and III with the full spectrum of PAH diseases were studied. The overall improvement in 6-minute walk was 25m; however, the iPAH patients improved by 45m. However, the 12-month study showed that the small benefit in the 6-minute walk at 3 and 6 months (+22m and

+31m from baseline) was lost at 12 months.²³⁰ Tolerance was suspected, especially since the significant side effects improved after the early dose titration phase. Neither Beraprost study showed any significant improvement in hemodynamics or survival. Beraprost is now under evaluation at the European Agency for the Evaluation of Medicinal Products, and there are no plans for application to the FDA.

Endothelin Receptor Inhibitors

BOSENTAN

The first trial of Bosentan, a nonselective endothelin antagonist, aimed to study the safety of the drug on patients with severe PAH as well as explore its effects on functional capacity and hemodynamics.²³¹ Eligible patients were those with NYHA class III and IV with iPAH and scleroderma-PAH in a double-blind, placebo-controlled manner. Interestingly, although class IV patients were eligible, they were not enrolled. Inclusion required patients to have been on stable standard treatment for a month prior to inclusion and not on epoprostenol. Thirty-two patients were randomized to Bosentan or placebo (2:1 ratio). Patients received Bosentan 62.5mg b.i.d. \times 4 weeks followed by 125mg b.i.d., for a total of 12 weeks. Bosentan caused a median increase of 50m in the 6-minute walk from baseline, versus -6m in the placebo group. Bosentan increased the cardiac index (mean improvement 1L/min/m² in favor of Bosentan). Pulmonary vascular resistance was decreased in the Bosentan group while it was increased in the placebo group, and functional class improved in the Bosentan group as well. Asymptomatic increases in

aminotransferases occurred in two Bosentan patients, but they normalized subsequently without discontinuing or decreasing the dose.

These encouraging results led to a larger RCT, which now enrolled 213 patients, equally randomized into 125 mg b.i.d. or 250 mg b.i.d. for a minimum of 16 weeks.²³² Again patients with class III and IV and iPAH or scleroderma-PAH were eligible. The placebo and Bosentan groups were well matched, and after 16 weeks Bosentan improved the primary end point (the 6-minute walk) by 36 m, versus -8 m deterioration seen in the placebo group. The improvement was more pronounced in the 250 mg b.i.d. group compared to the 125 mg b.i.d. group (+54 vs. +35 m). Abnormal liver function tests, syncope, and flushing were more frequent in the Bosentan group. The increase in the liver function tests was dose dependent (14% vs. 5% in the 250 vs. 125 mg dose, respectively). Two patients in the 125 mg group and five patients in the 250 mg group were found to have increased liver enzymes to more than eight times the normal levels. These abnormalities were not reversible in three of the patients in the 250 mg group, and these patients had to be withdrawn from the study. Three patients died during the study: two in the placebo group and one in the 125 mg Bosentan group.

Based on this trial Bosentan was approved by the FDA for the target dose of 125 mg po b.i.d. However, the FDA requires that liver function tests be performed monthly for patients taking the drug. Strict precautions for pregnancy have to be followed due to the teratogenic effects of Bosentan. Young males have to carefully consider the use of the drug, given the concerns that endothelin blockers as a class cause testicular atrophy with prolonged use.

SITAXSENTAN

In contrast to Bosentan, which is a nonselective ETA and ETB receptor, sitaxsentan is a selective ETA receptor. In theory, this could be advantageous since the vasoconstrictive and mitogenic signaling comes from the ETA receptor in the smooth muscle cells. In contrast the ETB receptor in the endothelial cells is mainly responsible for a NO-mediated vasodilatation and clearance of the circulating ET-1. In 2004, the first placebo-controlled RCT on sitaxsentan was reported,²³³ in which 178 patients with class II, III, and IV and with iPAH, scleroderma PAH, or congenital heart disease-PAH were randomized into placebo versus sitaxsentan 100 mg versus 300 mg po qd for 12 weeks. Sitaxsentan improved the 6-minute walk by 35 m (100 mg group) and 33 m (300 mg group). The NYHA class improved in 29% of the patients in the 100 mg group and in 30% of the patients in the 300 mg group. The PVR and cardiac index improved in a similar manner in both groups. This trial suggested that the 300-mg dose was associated with a saturation of the receptors and, furthermore, was associated with higher incidence of abnormal liver function tests (10% versus 2% for the 100-mg dose). Interestingly, in an earlier pilot study, even higher doses of sitaxsentan (500 mg b.i.d.) were associated with two fatal cases of hepatitis.²³⁴ A significant increase in INR occurs in patients taking sitaxsentan, due to inhibition of the CYP2C9 P-450 enzyme that metabolizes warfarin. A larger double-blind placebo-controlled RCT has just been completed and the results are expected to be announced within a few months.

DISCUSSION

A recent Cochrane review concludes that in the short term (16 weeks) there is evidence that these drugs improve hemodynamics, dyspnea, and exercise capacity in PAH.²³⁵ The endothelin antagonists offer benefits to patients with moderate PAH but are not curative and suffer from a relative lack of efficacy. They have no proven benefit on mortality and have not been adequately studied in class II or class IV PAH. It is noteworthy that hepatotoxicity is a class effect, possibly related to bile salt accumulation, and careful observation is required as the liver toxicity can be fatal.²³⁴ In another cautionary note, these agents were unsuccessful as therapy for congestive heart failure and systemic hypertension, although endothelin levels are increased in these conditions, as they are in PAH.

Phosphodiesterase Inhibitors

In the pulmonary circulation, NO causes vasodilatation in part by the opening of large conductance, Ca²⁺-sensitive K⁺ channels and BK_{Ca} channels via a cGMP-dependent kinase mechanism.²³⁶ At any given time, the cGMP levels in the PASMCs reflect the balance between production (due to the tonic effects of the endothelium-derived or exogenous NO) and breakdown [by phosphodiesterase type 5 (PDE-5), which is relatively specifically expressed in the pulmonary and the penile/clitoral circulation]. Therefore, there is synergism between both endogenous and exogenous NO and the PDE-5 inhibitors. This synergism occurs at all levels of the cGMP pathway, from the electrophysiology (opening of BK_{Ca} channels) to the final vasodilatation.

The oral PDE-5 inhibitor sildenafil (Viagra®, Pfizer) is a very attractive drug to be tested in PAH because of extensive prior clinical use and good safety profile. Sildenafil's most important side effect (systemic hypotension) is largely restricted to patients who ignore the absolute contraindication and concomitantly use systemic nitrates for the treatment of angina. The use of sildenafil for the treatment of conditions other than erectile dysfunction is not complicated by inappropriate erections since it only facilitates erections when arousal increases the levels of NO in the penile tissue.²³⁷ In a cohort of 13 patients with PAH, a single dose of sildenafil (75 mg) decreases PVR to a similar extent as the maximal doses of iNO (80 ppm)²³⁸ (Fig. 105.19). Most importantly, sildenafil significantly increases cardiac output and, in contrast to iNO, decreases pulmonary artery wedge pressure.²³⁸ Like iNO, sildenafil does not decrease systemic arterial pressure. Finally, the combination of iNO and sildenafil is well tolerated acutely and is superior to iNO in reducing PVR. This suggests that PDE-5 inhibitors might be safe alternatives to iNO in the evaluation of patients with PAH.

In a small iPAH cohort, chronic therapy with sildenafil 50 mg po t.i.d. was well tolerated and resulted in improved PVR, right ventricular hypertrophy as well as in a significant increase in the 6-minute walk (+110 m increase from baseline)¹⁵⁶ (Fig. 105.20). We have been following these patients for almost 2 years now. While several have a sustained improvement, some patients slowly returned to their baseline level of hemodynamics, although almost all maintain the improvement in the 6-minute walk that they showed at

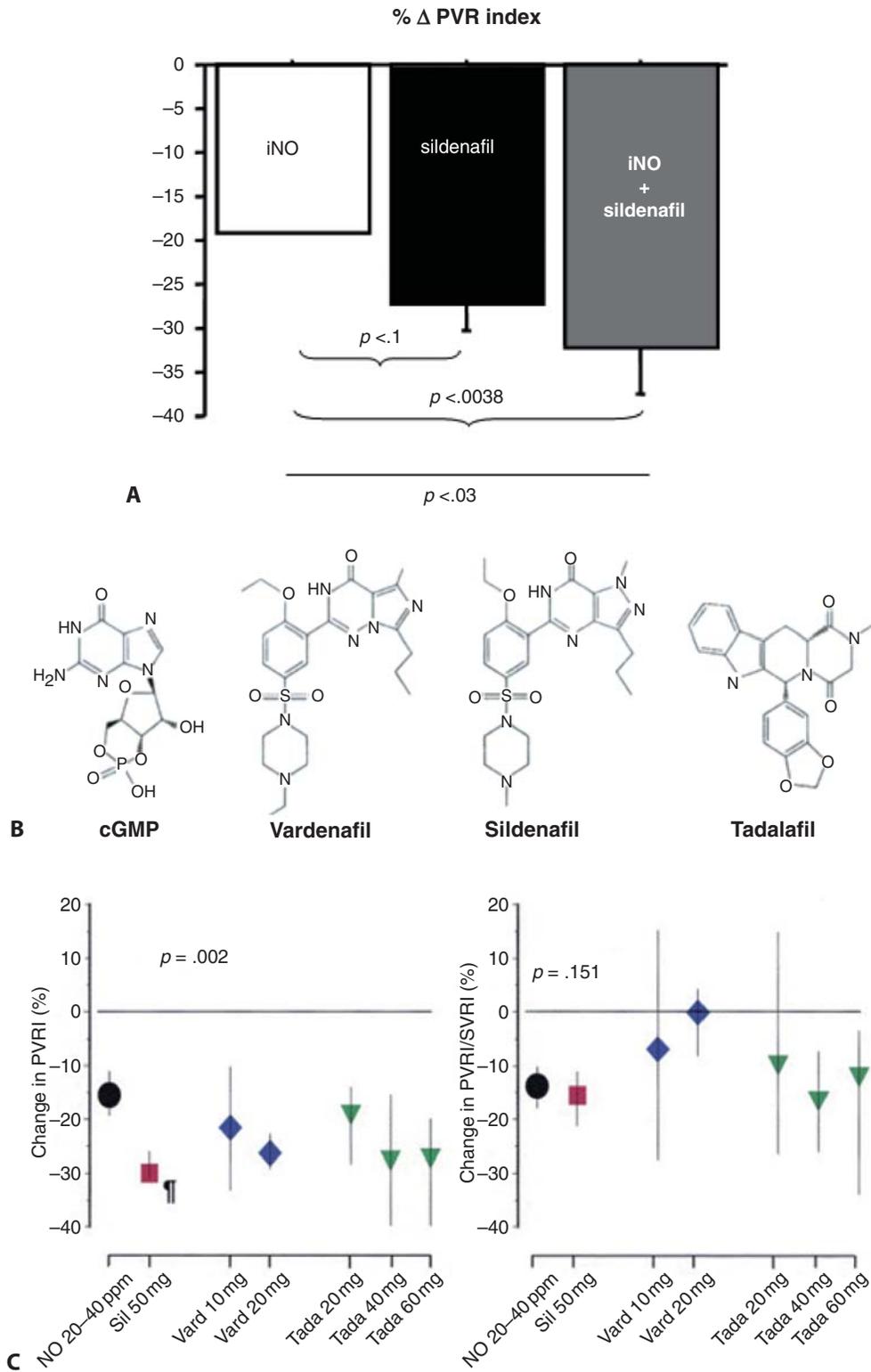


FIGURE 105.19. The acute effects of Phosphodiesterase-5 inhibitors in PAH. (A) A single dose of sildenafil (75 mg po) is as effective as iNO (80ppm) in patients with iPAH. (B) The structures of cyclic guanosine monophosphate (cGMP) and the three currently used

PDE-5 inhibitors. (C) Direct comparison of all the PDE-5 inhibitors in patients with PHT. Note that vardenafil is much less selective than the other inhibitors, since it fails to decrease the PVR/SVR ratio.

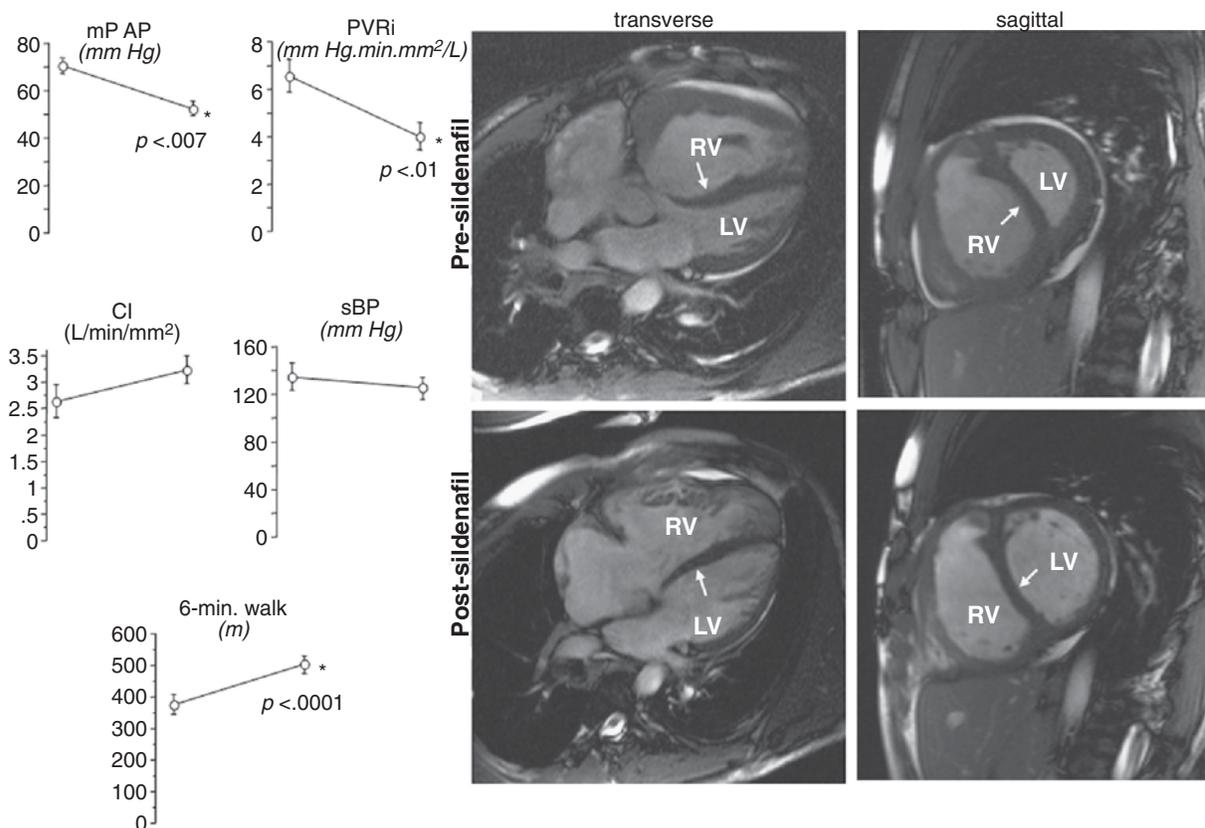


FIGURE 105.20. Chronic (3-month) treatment of iPAH patients with sildenafil (50mg po t.i.d.) leads to improvements in the 6-minute walk and hemodynamics, without affecting system arte-

rial pressure. In the MRI example shown, note that the abnormal septum position due to the RV pressure overload is normalized after sildenafil therapy (arrows).

6 months. The significance of this observation as well as the role of possible tolerance to this drug is unknown at this point. A large industry-sponsored placebo-controlled 3-month trial has been completed and will soon be published. Although this trial will give a more definitive answer on the safety and efficacy of sildenafil, more trials extending to 12 or more months will be needed in the future. Of course, this is true for all RCTs in PAH, most of which have been quite short (3 to 4 months). Sildenafil has already found an "off-license" role in the treatment of patients with PAH. A recent study prospectively compared sildenafil (50mg po t.i.d.) with Bosentan in 26 patients with iPAH and scleroderma-PAH (NYHA class III) in a double-blind fashion.¹⁵⁷ Patients on sildenafil improved their 6-minute walk by 116m while the patients on Bosentan improved only by 59m (Fig. 105.21). Most importantly, sildenafil caused a significant reduction in the RV mass, measured by MRI, while Bosentan failed to improve RV mass¹⁵⁷ (Fig. 105.21). During the study period (16 weeks) there was one death in the sildenafil group that the authors did not associate with sildenafil. This important trial was sponsored by the British Heart Foundation and did not have any industry support.

The newer PDE-5 inhibitors might also prove to be useful in PAH. Ghofrani et al.²³⁹ recently compared the acute hemodynamic effects of sildenafil, tadalafil, and vardenafil in iPAH patients undergoing right heart catheterizations (Fig.

105.19). Their research indicates that not all PDE-5 inhibitors are selective to the pulmonary circulation. For example, vardenafil caused a much higher systemic vasodilatation and, in comparison to sildenafil or tadalafil, failed to decrease the PVR to systemic vascular resistance (SVR) ratio.²³⁹ In small series, sildenafil has also been suggested to be beneficial in preventing rebound in PAH patients treated with inhaled NO,²⁴⁰ PHT associated with pulmonary fibrosis,²⁴¹ PAH due to veno-occlusive disease,²⁴² and PAH in children.²⁴³

Although PDE5 inhibitors have promise in therapy for PAH, further study is required, and there is not currently an FDA-approved PAH indication for this therapy. Nonetheless, the PDE5 inhibitors appear to be well tolerated and, if one excludes patients with connective tissue disease, may offer relatively larger increases in functional class and 6-minute walk than other therapies. In addition, phosphodiesterase inhibitors are significantly less expensive and less toxic than endothelin antagonists, the only other oral therapy available, and are less difficult to administer than Flolan or Iloprost.

Transplantation

Patients with severe PAH may be considered for either combined heart-lung or lung transplantation. Although there is no consensus at present regarding the preferred procedure for

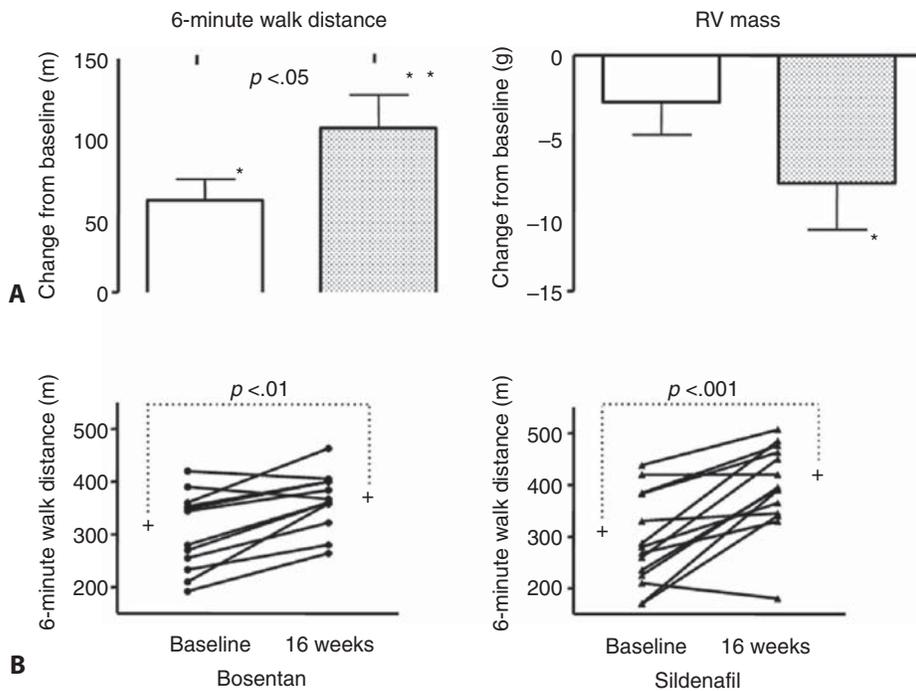


FIGURE 105.21. A head-to-head blinded comparison of sildenafil versus bosentan in iPAH. (A) Following 3 months of treatment the sildenafil groups showed a significant increase in the 6-minute walk and a reduction in RV mass, measured by MRI. The bosentan group had a smaller improvement in the 6-minute walk and did not show any regression of right ventricular hypertrophy. (B) The two group performances in the 6-minute walk are shown.

most patients with pulmonary vascular disease, patients with PAH due to complex congenital heart disease should undergo combined heart-lung transplantation. Single lung transplantation has been performed successfully in patients with iPAH and PHT due to chronic obstructive pulmonary disease and fibrotic lung disease.²⁴⁴ The major complications of transplantation surgery for pulmonary vascular disease are organ rejection and opportunistic infection. Bronchiolitis obliterans occurs in 25% to 40% of transplant patients, and may result in serious respiratory embarrassment or death. Data from the International Society for Heart and Lung transplantation (1990–2001) show that the 3-year survival for iPAH after transplantation is approximately 54% for lung transplantation (total 691 patients) and 50% for heart-lung transplantation (total 302 patients).²⁴⁵

Access to this therapy is, and will remain, severely limited by the availability of donors. In addition, as therapy for PAH improves, there will be reluctance to transplant patients before all medical options are exhausted, as the 5-year survival for patients following lung transplantation is not substantially better than the prognosis of patients with class II to III PAH on medical treatment.

Multidisciplinary Pulmonary Arterial Hypertension Clinics

Because of the diverse conditions that lead to PAH and the often complicated and expensive therapies, patients with PAH should be referred to multidisciplinary clinics in tertiary care centers. As an example, in our PAH clinic at the University of Alberta (www.pulmonaryhypertension.ca), patients are evaluated by teams that include cardiologists, congenital heart disease specialists, pulmonologists, rheu-

matologists, and endocrinologists. Cases are discussed by teams that include radiologists and pharmacologists, and patients are often also seen by social workers and psychologists. The grim prognosis and the predisposition of young women of reproductive age for this disease explain the often severe social and psychological challenges in the management of these patients. In this model, patient care is coordinated by a highly trained nurse practitioner.

An Evidence-Based Approach to the Patient with Pulmonary Arterial Hypertension

Figure 105.22 is an evidence-based algorithm for the treatment of PAH, based on the discussion above. Since class I or II patients have not been studied in the PAH RCTs, no evidence-based recommendations can be made for these patients. Several RCTs are also currently under way, and within the next 5 years additional short-term as well as long-term trials will be available to strengthen this algorithm.

Although Flolan and Iloprost offer major benefits in PAH and are the current drugs of choice in North America and Europe, respectively, for class IV PAH, they are not curative and have major adverse effects and cost implications. Unfortunately, the new oral and subcutaneous analogues suffer from a relative lack of efficacy. Currently sildenafil and Bosentan are useful for class III patients, although the sildenafil therapy must be viewed as an “off-label” indication at the time of writing. It is likely that as with HIV-AIDs or tuberculosis, combination therapy for PAH will be required. This presumably would be targeted to optimize function, PVR, and BNP levels. All PAH patients should be followed in a multidisciplinary PAH clinic.

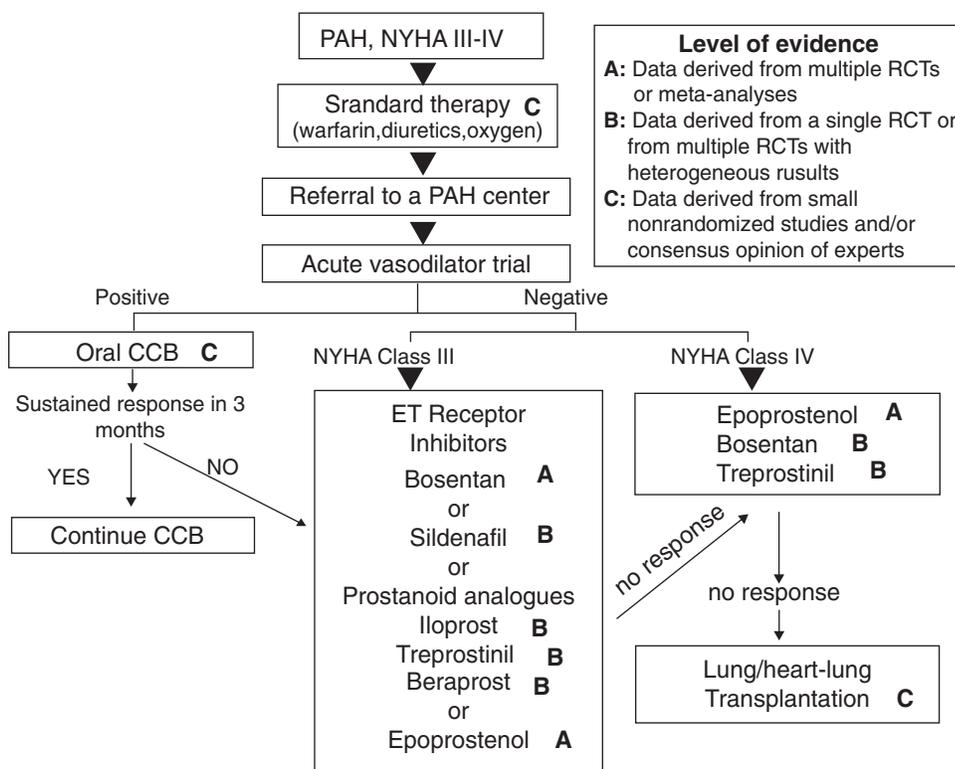


FIGURE 105.22. An evidence-based algorithm for the treatment of patients with New York Heart Association (NYHA) class III and IV PAH. CCB, calcium channel blocker.

Acknowledgments

Drs. Michelakis and Archer are supported by ABACUS, the Alberta Cardiovascular and Stroke Research Centre, Canada Foundation for Innovation, the Canada Research Chair Program, the Alberta Heart and Stroke Foundation, and the Canadian Institutes for Health Research. Dr. Archer is supported by National Institutes of Health grant RO1-HL071115. Dr. Michelakis is supported by the Alberta Heritage Foundation for Medical Research.

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