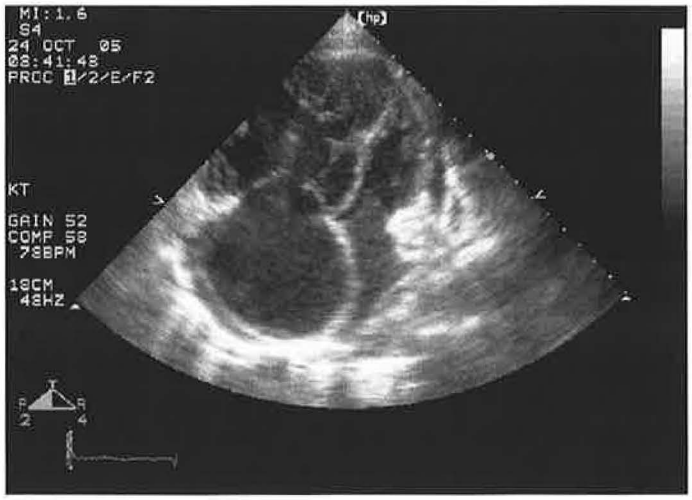
Pulmonary hypertension – a cardiologist's perspective

Beth Brickner, MD



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Beth Brickner, MD
Associate Professor, Internal Medicine
UT Southwestern Medical Center
Division of Cardiology
Internal Medicine Grand Rounds
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Definition of pulmonary hypertension:

Pulmonary hypertension is defined as an elevation in pulmonary arterial pressure above normal. Pulmonary hypertension is a generic term for a common cardiovascular condition, seen in a variety of different disorders. Normal pulmonary artery systolic pressure at rest is between 18-25mmHg and pulmonary artery pressure increases minimally with exercise as pulmonary blood flow increases. Normal mean pulmonary artery pressure at rest is between 12-16mmHg. Pulmonary vascular resistance is calculated as the pressure drop across the lungs divided by the flow across the lungs (cardiac output).

$$PVR = \frac{\text{pressure drop}}{\text{flow}} = \frac{\text{meanPAP - meanPCWP}}{\text{cardiac output}}$$

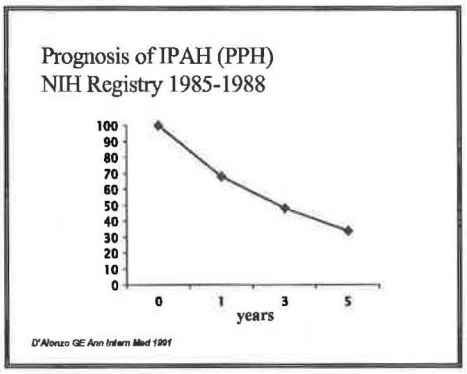
Normal PVR is 80-120 dynes-sec/cm-5 or 1-2 Wood units (divide dynes by 80). The large cross-sectional area of the pulmonary vascular bed results in a very low resistance circulation. Pulmonary vascular resistance is normally quite low, less than one-tenth of systemic vascular resistance.

Pulmonary hypertension is defined by mean pulmonary artery pressure > 25mmHg at rest or > 30mmHg with exercise, pulmonary artery systolic pressure > 36mmHg, or PVR > 3 Wood units (>240dynse-sec/cm-5). Pulmonary hypertension is a hemodynamic observation, not a diagnosis. An increase in pulmonary vascular resistance and/or an increase in pulmonary blood flow may both result in pulmonary hypertension. When the hemodynamic observation of pulmonary hypertension has been made, it is imperative to search for the underlying cause.

Classification of pulmonary hypertension:

There has been an increasing interest in pulmonary hypertension as our ability to understand the disease and its causes, and our ability to provide effective treatment has increased. Formerly, pulmonary hypertension was classified as primary or secondary. Secondary pulmonary hypertension was defined as pulmonary hypertension resulting from a specific disorder while primary pulmonary hypertension was a diagnosis of exclusion. Primary pulmonary hypertension was known as a rare, deadly disease where pulmonary pressures and pulmonary vascular resistance were elevated without a definable cause. This disease was characterized by a relentless disease progression that was

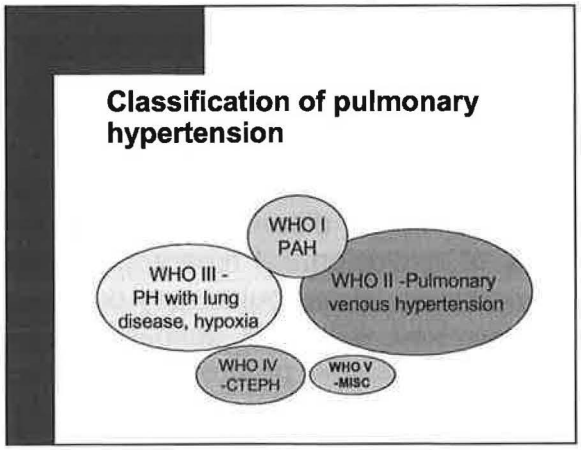
universally fatal. In the 1980's, the median survival was 2.8 years from the time of diagnosis.



Ref 1.

In 1998, during the Second World Symposium on Pulmonary Hypertension, a new classification of pulmonary hypertension was proposed, the Evian classification.(2) In this classification, the clinical conditions associated with pulmonary hypertension were grouped into five categories, based on similar pathologic, pathophysiologic, and therapeutic characteristics. The Third World Symposium on PAH was held in Venice, Italy in 2003 and further modifications were made in the Evian classification of pulmonary hypertension. This revised classification has come to be known as the World Health Organization classification.(3) According to the WHO classification, there are five classes of pulmonary hypertension, with multiple causes listed in each class. Within each class, multiple potential causes are listed. (See table 1)

WHO class I are patients with pulmonary arterial hypertension, a specific disease of the pulmonary vasculature that is either primary (idiopathic) or secondary to a known cause. WHO class II are those with pulmonary venous hypertension, class III those with pulmonary hypertension secondary to hypoxemia or lung disease, class IV those with pulmonary hypertension secondary to chronic thromboembolic disease, and class IV those with miscellaneous disorders with direct pulmonary artery involvement. The relative frequency of the different classes is shown schematically below.



The full classification scheme is shown below.

Table I.

Revised Clinical Classification of Pulmonary Hypertension (Venice, 2003)

1. Pulmonary arterial Hypertension (PAH)
   - 1.1 Idiopathic (IPAH)
   - 1.2 Familial (FPAH)
   - 1.3 Associated with (APAH):
     - 1.3.1 Collagen vascular disease
     - 1.3.2 Congenital systemic-to-pulmonary shunts
     - 1.3.3 Portal hypertension
     - 1.3.4 HIV infection
     - 1.3.5 Drugs and toxins
     - 1.3.6 Other (thyroid disorder, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myleoproliferative disorders, splenectomy)
   - 1.4 Associated with significant venous or capillary involvement
     - 1.4.1 Pulmonary veno-occlusive disease (PVOD)
     - 1.4.2 Pulmonary capillary hemangiomatosis (PCAH)
   - 1.5 Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left heart disease
   - 2.1 Left sided atrial or ventricular heart disease
   - 2.2 Left sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Sleep-disordered breathing
   - 3.4 Alveolar hypoventilation disorders
   - 3.5 Chronic exposure to high-altitude
   - 3.6 Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
   - 4.1 Thromboembolic obstruction of proximal pulmonary arteries
   - 4.2 Thromboembolic obstruction of distal pulmonary arteries
   - 4.3 Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous – sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

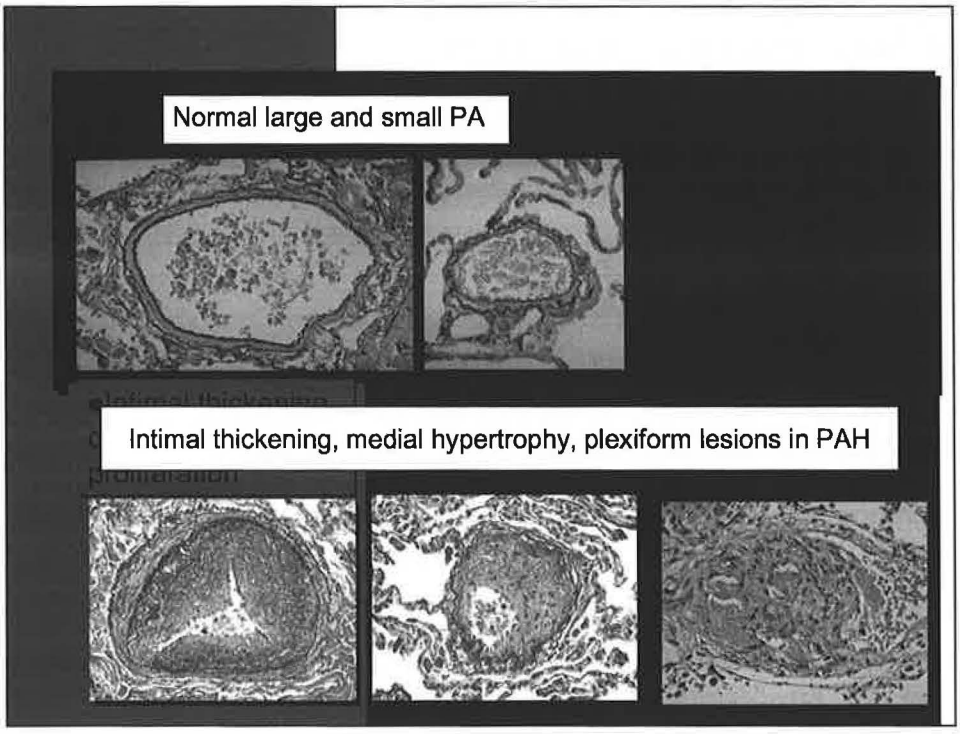
Adapted from Simonneau et al, Clinical Classification of Pulmonary Hypertension. J Am Coll Cardiol 2004;43:5S-12S. (3)

Why is it important to classify the type of pulmonary hypertension? These classifications have been devised and accepted because the underlying mechanisms, diagnostic approaches, prognostic implications, and therapeutic strategies are different for each of the different classes. Although patients in

different classes may have similar elevations in pulmonary pressures, their outcomes are very different.

Specific WHO classes:

WHO class I:
Pulmonary arterial hypertension (PAH)- refers to a pulmonary vascular disease affecting the pulmonary arterioles, resulting in an elevation in pulmonary artery pressure and pulmonary vascular resistance. The diagnosis of pulmonary arterial hypertension requires the exclusion of other causes, most importantly pulmonary venous hypertension. Pulmonary capillary wedge pressure must be < 15mmHg in order to confirm the diagnosis of PAH. The pathophysiological basis of PAH results from an imbalance between vasoconstrictor substances (thromboxane, endothelin) and vasodilator substances (prostacyclin, nitric oxide), between growth inhibitors and mitogenic factors, and between antithrombotic and prothrombotic factors. It is presumed that these homeostatic imbalances are probably consequences of endothelial cell injury or dysfunction. Patient with pulmonary arterial hypertension have a specific histopathology characterized by intimal thickening and fibrosis, increased medial thickness or hypertrophy, and adventitial fibroelastosis with the formation of plexiform lesions that result in pulmonary arteriolar occlusion.



Patients with pulmonary arterial hypertension may have idiopathic pulmonary arterial hypertension (no definable etiology), a familial or genetic form, or may have a secondary disease associated with pulmonary hypertension (see table I).

It is clear that secondary forms of pulmonary arterial hypertension are much more common than idiopathic pulmonary arterial hypertension.

How common is advanced pulmonary arterial hypertension (WHO class I)?

Disease	Prevalence	Percentage w/ pulm htn	Estimated # in North America/Europe
Systemic sclerosis	190/million	33%	37,600
Congenital heart disease	300/million	15-20%	31,500
Cirrhosis	1600/million	0.6%	5,700
HIV	2500/million	0.5%	7,500
Idiopathic PH	7/million	100%	4,200

from Zipes: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed. 2005. (4)

Idiopathic pulmonary arterial hypertension (IAPH) was previously known as primary pulmonary hypertension (PPH). No specific risk factor has been identified. This disease is relentlessly progressive and results in increasing pulmonary vascular resistance, right heart failure, and death without intervention. A rare disease, idiopathic pulmonary hypertension is report to occur in 2-5 persons per million, although higher rates have been reported in autopsy series. Approximately 400 new cases are diagnosed per year in the U.S. Both IAPH and familial forms of PAH are 2.5X more common in women. The average age of onset is in the early to mid thirties.

Patients may have a familial form of PAH which accounts for 6-10% of patients with WHO class I pulmonary arterial hypertension.(5) A gene has been identified on chromosome 2, which encodes for the bone morphometric protein receptor-II which is part of the transforming growth factor (TGF) superfamily.(6) An abnormality of this gene results in changes in the pulmonary vascular endothelium, which ultimately lead to pulmonary arterial hypertension. The gene is inherited in an autosomal dominant fashion with incomplete penetrance. The disease manifests in only 10-20% of patients with the genetic abnormality. This genetic form displays genetic anticipation – the disease manifests earlier and with greater severity in each subsequent generation.

Pulmonary arterial hypertension is commonly associated with connective tissue disorders. In fact, pulmonary arterial hypertension related to connective tissue disorders is actually the most common type of PAH seen in pulmonary hypertension clinics. While pulmonary hypertension can be seen in many types of connective tissue disorders, it is most commonly seen in patients with limited scleroderma, particularly in those patients with CREST syndrome (calcinosis

cutis, Raynaud's phenomenon, esophageal dysmotility, scleroderma, and telangiectasias). (7,8) Pulmonary arterial hypertension is seen in up to 50-60% of patients with CREST syndrome. In diffuse forms of scleroderma, pulmonary hypertension is seen in up to 33%. Pulmonary hypertension is less common in systemic lupus erythematosus (seen in 4-14%), rheumatoid arthritis (up to 21%), and mixed connective disease. In nearly all cases, there is also evidence of Raynaud's phenomenon.(9) The pathology of pulmonary hypertension associated with connective tissue diseases is identical to that seen in idiopathic pulmonary hypertension and the medical treatment that are available are the same that are available for idiopathic pulmonary hypertension. However, the survival benefits seen in these patients appear to be less than seen in patients with IAPH. (10,11)

Pulmonary arterial hypertension can also be seen in association with liver disease. Most of these patients will have a hyperdynamic circulation and a high cardiac output. In patients with advanced liver disease and portal hypertension, pulmonary hypertension has been found in 2-8% with the highest levels seen in those patients being considered for orthotopic liver transplant.(12,13) This is an important diagnosis to since the mortality for transplant is substantially increased for those patients with a mean pulmonary artery pressure greater than 35mmHg. In the population undergoing orthotopic liver transplant, as many as 4% will have elevated pulmonary pressures. For this reason, echocardiographic screening of these patients is routine.

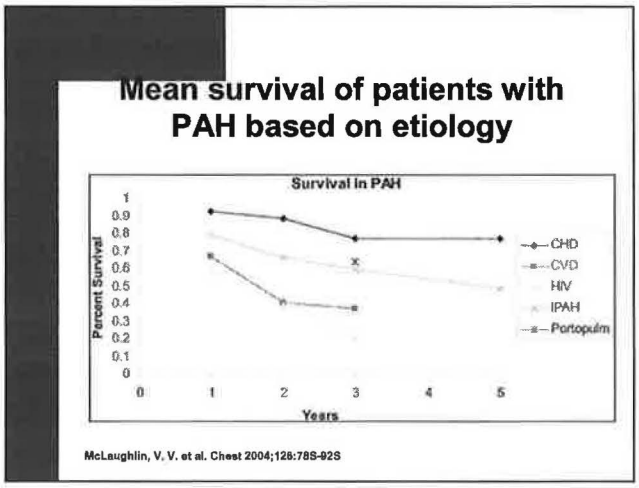
Patients with certain types of congenital heart disease may develop pulmonary arterial hypertension.(14,15) Any congenital defect which results in increased pulmonary blood flow may result in pulmonary vascular disease. Most commonly, large left to right shunts related to ventricular septal defects and patent ductus arteriosus, and occasionally large shunts due to atrial septal defects, result in progressive pulmonary hypertension and ultimately in shunt reversal with development of the Eisenmenger syndrome. In some cases, pulmonary arterial hypertension will persist or even progress despite successful closure of the defect. Patients with pulmonary hypertension due to congenital heart disease (and in particular, the Eisenmenger patients) have a long-term survival that is much better than that for other forms of pulmonary arterial hypertension.(16,17,18) Therefore, treatment decisions should not be based on algorithms for other forms of pulmonary arterial hypertension. To date, there is only limited data about the effectiveness of medical therapy of pulmonary arterial hypertension in patients with congenital heart disease and virtually no long-term outcome data. I personally disagree with including PAH secondary to congenital heart disease in the WHO class I category without specifying that outcomes are different and different treatment algorithms may apply.

Pulmonary arterial hypertension is also seen in associated with HIV infection, seen in 1/200 of patients with HIV.(19) The mechanism of pulmonary hypertension is unclear. When PAH occurs secondary to HIV infection, it is the

most common cause of death. Pulmonary hypertension has been seen with exposure to certain drugs and toxins. One of the most widely recognized drugs associated with the development of pulmonary hypertension are the anorexigenic drugs, including the now notorious fenfluramines (fen-phen), but seen consistently with all types of diet drugs.(20,21) All known anorexigen drugs have been shown to have an association with the development of pulmonary hypertension. Pulmonary hypertension has been seen in patients post-splenectomy, also seen in certain hemoglobinopathies (sickle cell disease) and myeloproliferative disorders.(22-25) Pulmonary hypertension has also been seen in glycogen storage disorders and Gauchers disease (deficiency of beta-galactosidase) and also in patients with hereditary hemorrhagic telangiectasia.

Finally, rare disorders such as pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis are included in the WHO class I. Pulmonary veno-occlusive disease is characterized by obstructive eccentric fibrous intimal pads in the pulmonary veins and venules. Pulmonary capillary hemangiomatosis is characterized by invasion of lung parenchyma by small, nodular foci of thin-walled, capillary sized vessels. Both of these diseases have a clinical presentation that is similar to pulmonary venous hypertension and, in fact, these disorders have been classified as a form of pulmonary venous hypertension in the past. However, these patients have pathologic changes consistent with pulmonary arterial hypertension as well as having pulmonary hemosiderosis, interstitial edema, lymphatic dilatation, and pulmonary interstitial fibrosis.(26,27) Chest CT scans play an important role in making these rare diagnoses. This is an important diagnosis to make since, unlike the other causes in this class, these patients often respond poorly to medical therapy, frequently developing pulmonary edema when treated with vasodilator therapy.(28,29) Lung transplant is the only available treatment and patients should be listed for transplant as soon as the diagnosis is made. .

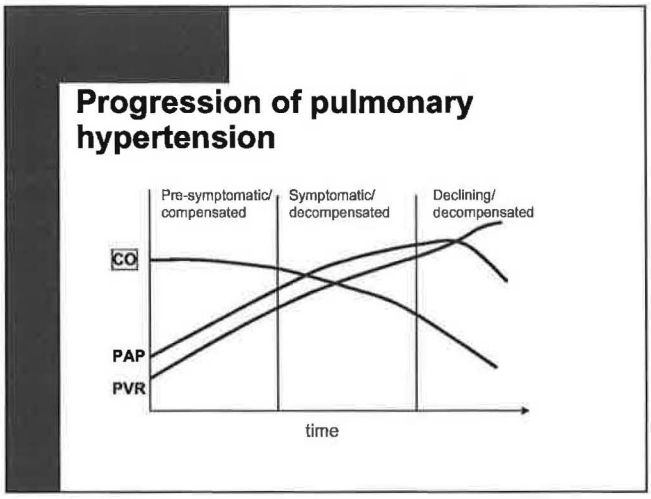
For patients in WHO class I alone, the survival differs depending on the underlying etiology.



Ref 18

This is observational data from the modern treatment era. The congenital heart disease population has a much better survival than other forms of pulmonary arterial hypertension. This slide demonstrates that patients with pulmonary arterial hypertension due to collagen vascular disease and HIV have a worse survival than those with IAPH. There were inadequate numbers of patients with portopulmonary hypertension to plot survival. Clearly, different diagnoses carry a different prognosis, emphasizing the importance of determining a specific diagnosis.

Clinical deterioration and death in these patients results from gradual deterioration in right ventricular function. In the presymptomatic phase, as pulmonary pressures and pulmonary vascular resistance increase, the right ventricle compensates by developing hypertrophy and cardiac output is maintained, at least at rest. With increasing severity of disease, the right ventricle is not able to increase cardiac output adequately with exercise, resulting in exertional symptoms. As patients become more symptomatic, characterized by further right ventricular hypertrophy and enlargement, right ventricular function begins to deteriorate, resulting in a decline in cardiac output. RV dilatation with tricuspid annular dilation and worsening tricuspid regurgitation are hallmarks of deteriorating RV function, which results in a further decline in cardiac output and worsening symptoms. In the decompensated state, cardiac output cannot be maintained and patients are severely symptomatic with congestion, peripheral edema, syncope, and chest pain due to RV ischemia. Without intervention, death is inevitable. RV dysfunction is directly related to prognosis.(30) Therapeutic strategies are designed to decrease pulmonary artery pressure and pulmonary vascular resistance, thereby reversing RV dilatation and dysfunction, leading to decreased symptoms and hopefully prolonging survival.



WHO class II:
Left-sided heart disease is common. Therefore, pulmonary venous hypertension secondary to left-sided heart disease (WHO class II) is common. Multiple left-

sided heart diseases can result in pulmonary venous hypertension, including valvular heart disease (mitral or aortic), and LV myocardial disease of any etiology (hypertensive, ischemic, restrictive, postpartum, idiopathic, etc.). Elevation in pulmonary venous pressure leads to reactive pulmonary artery vasoconstriction, resulting in elevation of pulmonary arterial pressure. The degree of pulmonary vasoconstriction is quite variable among different patients. Thus, patients with similar degrees of left heart disease will have varying degrees of pulmonary hypertension. The hallmark of this type of pulmonary hypertension is the elevated pulmonary capillary wedge pressure, reflecting elevated pulmonary venous pressure. Treatment for pulmonary venous hypertension is to treat the underlying left-sided heart disease, which should result in a decrease in PCWP and a corresponding decrease in pulmonary arterial pressures. Pulmonary hypertension in these patients is usually reversible. However, in some patients with long-standing elevation of pulmonary venous pressure, pulmonary arterial disease develops as well which may not reverse after treatment of the primary disease. Extrinsic compression of the pulmonary veins (mediastinal masses, fibrosis, etc.) also results in pulmonary hypertension, but this type of PH is classified under WHO class I since it shares some pathologic characteristics with PAH.

WHO class III:

Pulmonary hypertension can be seen in a variety of lung diseases resulting in chronic hypoxia (WHO class III). These include COPD, interstitial lung disease, sleep-disorder breathing, hypoventilation disorders, chronic exposure to high altitude, neonatal lung disease, alveolar capillary dysplasia and other developmental disorders. There are multiple potential mechanisms for pulmonary hypertension in patients with lung disease, including pulmonary vasoconstriction due to hypoxia, compression of pulmonary vessels by expanded lung volumes, and loss of small pulmonary vessels due to lung destruction. Pulmonary hypertension associated with lung disease usually progresses slowly, but its presence indicates a poor prognosis.(31) As with pulmonary venous hypertension, the treatment for PH associated with lung disease is to treat the underlying disorder. In most cases, the therapy includes oxygen administration to relieve hypoxia as well as therapy specific to the underlying lung disorder. Pulmonary hypertension associated with obstructive sleep apnea is usually mild at rest, increases with exercise. CPAP therapy has been shown to improve pulmonary hemodynamics.(32) The use of vasodilator therapy other than oxygen in patients with pulmonary hypertension due to lung disease has been disappointing.

WHO class IV:

Chronic thromboembolic pulmonary hypertension (CTEPH) is a fairly uncommon cause of pulmonary hypertension, but is a very important diagnosis to make as its treatment is quite different from other types of pulmonary hypertension. CTEPH occurs in as many as 4% of patients with pulmonary embolism.(33,34) In patients who develop CTEPH, the initial thromboembolic events are usually

asymptomatic (34,35). In acute pulmonary embolism, the pulmonary thrombi are fragile, predominantly red thrombus that is loosely adherent to the vessel wall. In CTEPH, the thrombi are whitish and are firmly attached to the arterial medial layer, replacing the intima. It is unclear why these thrombi persist. In patients with CTEPH, the thrombi form an endothelialized or fibrotic obstruction of the pulmonary arteries. This process evolves over months to years. Most patients with CTEPH do not share the traditional risk factors for deep venous thrombosis or pulmonary embolism and most do not have a definable abnormality of fibrinolysis. The treatment for CTEPH is certainly lifelong anticoagulation for all patients. For those patients who have organized clot in the major pulmonary artery branches, surgical pulmonary endarterectomy has been shown to be beneficial.(35,3), preferably in a center specializing in CTEPH (about 20 such centers world wide). Patients with peripheral emboli can usually be treated with pulmonary vasodilator therapy.

WHO class IV:
There are a variety of miscellaneous disorders, which directly affect the pulmonary vasculature, causing pulmonary hypertension (WHO class V). These include sarcoidosis, histiocytosis X, lymphangiomatosis, schistosomiasis, and extrinsic compression of pulmonary vessels (by adenopathy, tumor, or fibrosing mediastinitis).

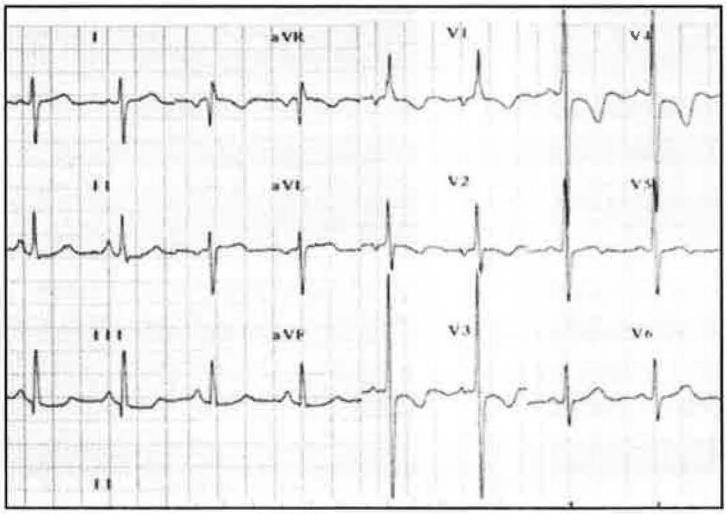
Clinical assessment of patients with pulmonary hypertension:

The symptoms of pulmonary hypertension are fairly vague and often gradual in onset. Dyspnea is the most common symptom, initially present only with exertion. Patients with WHO class II (pulmonary venous hypertension) typically have orthopnea and PND as well. Angina is a common symptom in patients with pulmonary hypertension and usually suggests more advanced disease as it is caused by right ventricular ischemia due to right ventricular hypertrophy. Syncope or near-syncope may occur (often with exertion) due to inability of the RV to increase cardiac output.(36). The presence of edema suggests decompensated right heart failure and is a later symptom. Raynaud's phenomenon is often seen in patients with connective tissue disorders and in up to 20% of patients with IAPH. The clinical diagnosis of pulmonary hypertension can be difficult and misdiagnosis is fairly common.

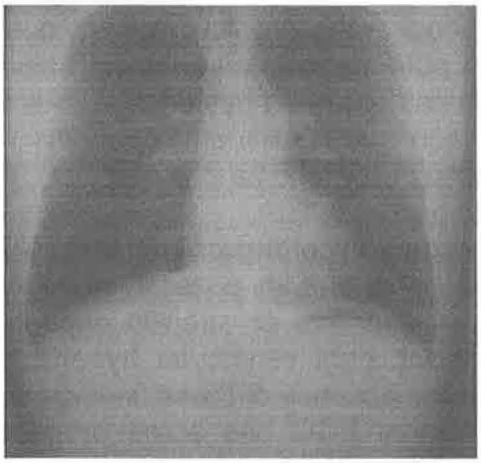
Physical exam findings suggestive of pulmonary hypertension include a loud P2, an RV lift (indicating RV hypertension), a systolic murmur of tricuspid regurgitation, a diastolic murmur of pulmonary regurgitation, and a right-sided S4. Other signs include signs of RV failure, including jugular venous distension (often with a prominent V wave due to tricuspid regurgitation), presence of a right-sided S3, presence of hepatomegaly, peripheral edema, and ascites. Those patients with pulmonary venous hypertension due to left-sided valvular disease or with pulmonary hypertension due to congenital heart disease may have other

murmurs, although patients with the Eisenmenger syndrome commonly have no audible murmurs. Clubbing is seen in patients with chronic cyanosis due to congenital heart disease and is also seen in patients with long-standing severe lung disease. The presence of edema suggests right heart dysfunction. Ascites is a late finding, seen in severe RV dysfunction and also seen in patients with advanced liver disease. Raynaud's phenomenon may also be detected.

ECG abnormalities are quite common in pulmonary hypertension and the ECG is recommended in the initial evaluation of all patients with possible pulmonary hypertension. However, the findings are not sensitive or specific enough to confirm the diagnosis. Right atrial enlargement, right ventricular hypertrophy, and right axis deviation are quite common but the absence of these findings does not exclude the diagnosis.(37,38) An abnormal ECG has some prognostic significance. In one study, the presence of right atrial enlargement was associated with a 2.8 times increase in mortality over 6 years.(39)

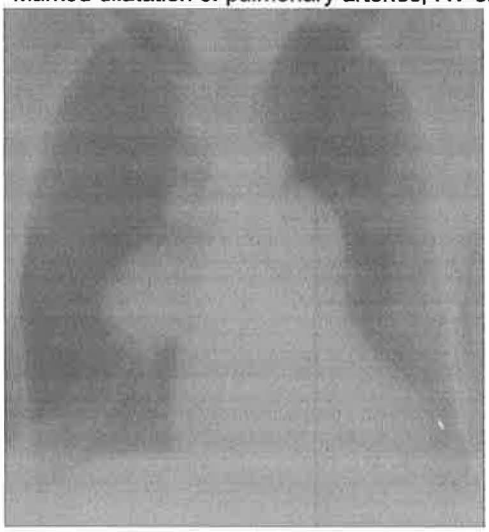


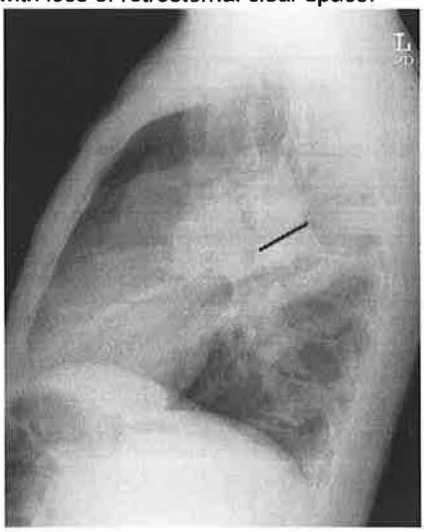
The CXR is also a routine part of the evaluation of patients with pulmonary hypertension. In fact, the presence of pulmonary hypertension may first be suggested by abnormal findings on CXR. Attenuated peripheral lung markings, enlarged main and hilar pulmonary arteries, and obscuration of the retrosternal clear space on lateral chest x-ray (caused by right ventricular enlargement) are all clues to the presence of pulmonary hypertension. The CXR is also important to define concomitant parenchymal disease. Unfortunately, the radiologic abnormalities do not correlate well with the severity of the pulmonary hypertension. Although the test is routinely done, it is not very specific.(39)



Mild enlargement of main pulmonary artery and branch pulmonary arteries.

Marked dilatation of pulmonary arteries, RV enlargement with loss of retrosternal clear space.



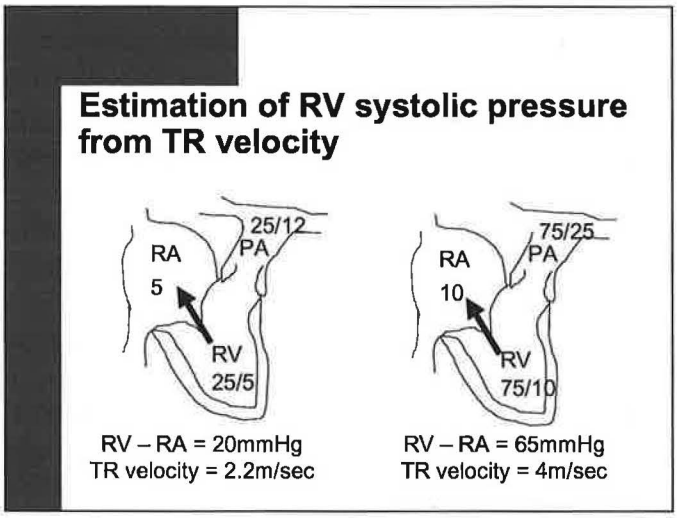


What is an appropriate work-up for a patient with suspected pulmonary hypertension?

Echocardiography: Echocardiography plays a critical role in the evaluation of patients with suspected or known pulmonary hypertension. Left-sided heart disease causing pulmonary venous hypertension can be detected and evaluated. Congenital heart defects can be detected as well. A bubble study to rule out intracardiac shunting should be part of the initial evaluation of all patients with possible pulmonary hypertension. Two-dimensional clues to the presence and severity of pulmonary hypertension include right-sided chamber enlargement, dilatation of the pulmonary arteries, and septal flattening consistent with RV pressure overload.

Assessment of tricuspid regurgitation velocity is a major component of the assessment for these patients. The magnitude of the pressure gradient between the right ventricle and the right atrium can be estimated from the velocity of the

tricuspid regurgitant jet. With increasing RV pressure (as seen in pulmonary hypertension), the TR velocity will increase. In the absence of RV outflow tract obstruction, the RV systolic pressure is equal to the pulmonary artery systolic pressure. Other Doppler techniques can be used to estimate PA diastolic and mean pressure. A good TR signal that can be used to estimate RV systolic pressure is seen in 40-86% of patients with pulmonary hypertension.(40,41) There is a good correlation between Doppler estimated RV/PA systolic pressure and pressures measured at cardiac catheterization, although in some series the difference between the echo-estimated and cath-measured mean PA systolic pressure varied between 2-38mmHg.(42-44) Thus, careful echo technique is critical to obtain reliable data.



MRI/CT: Cardiac MRI has a rapidly evolving role in pulmonary hypertension. It allows precise measurement of right atrial and ventricular volumes, calculation of RV mass and ejection fraction. MRI can also define underlying left-heart disease or congenital heart defects. Flow velocity mapping can also be used to measure PA pressure from TR velocity (although not as well validated as echo methods).(45,46) A high-resolution CT scan of the chest is the most accurate means of diagnosing emphysema and other parenchymal lung disease as well as identifying pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis.(45)

PFTS: Pulmonary function testing are routinely performed in the initial evaluation of all patients with suspected pulmonary hypertension and can help to diagnose underlying lung disease.(39) Restrictive defects and a mildly decreased DLCO are seen in about 20% of patient with IAPH and 20% of patients with CTEPH. An isolated decrease in DLCO may be seen in patients with scleroderma prior to the development of clinical pulmonary hypertension. If there is any suggestion that the patient may have sleep-disordered breathing, a sleep study should be performed.

Evaluation for CTEPH: V/Q scan should be performed in any patients with unexplained pulmonary hypertension to rule out the possibility of chronic thromboembolic disease (CTEPH).(39) For those patients with an abnormal V/Q scan, pulmonary angiography is required for accurate diagnosis and to define the anatomic extent of disease, especially if surgical intervention is contemplated. On V/Q scan, the presence of one segmental or larger perfusion defect is required for the diagnosis of CTEPH but several defects (usually bilateral) are commonly seen.(47) The severity of the abnormalities on V/Q scan correlates poorly with the angiographic extent of disease. Therefore, confirmation by pulmonary angiography is mandatory. A normal V/Q scan virtually excludes the diagnosis. While CT angiography is popular for the evaluation of acute pulmonary embolism, its role in the diagnosis of CTEPH is evolving. Current guidelines specify V/Q scanning as the initial screening tool but in some institutions, CT angiography has replaced V/Q scanning as the initial screening test. Current guidelines specify invasive pulmonary angiography as the gold standard for the diagnosis of CTEPH.(39) If the patient is being considered for surgical intervention, invasive pulmonary angiography is absolutely required, providing better delineation of distal obstruction and identifying candidates for surgical intervention.

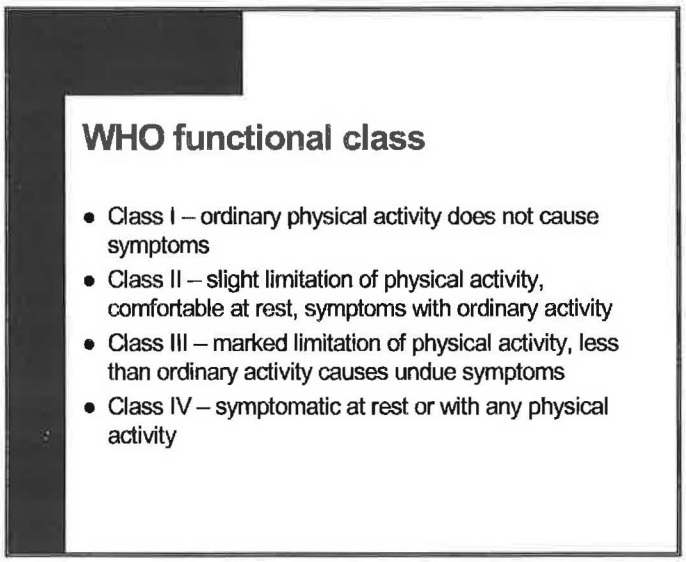
Serologic evaluation: Serologic evaluation in pulmonary hypertension should include serologies for scleroderma, MCTD, lupus, rheumatoid arthritis, polymyositis and other connective tissue disorders, liver disease, HIV testing, and thyroid function testing. BNP levels are often elevated in patients with pulmonary hypertension and the degree of elevation does correlate with the degree of pulmonary pressure elevation. (48-50)

Right heart catheterization: Right heart catheterization is the gold standard, required to confirm the diagnosis of pulmonary hypertension and to assess the severity of disease. Findings at right heart catheterization are a major determinant of prognosis. Right heart catheterization should be performed prior to initiating PAH- specific therapies. A complete right heart catheterization should be performed with pressure measurement in the right atrium, right ventricle, pulmonary artery, and pulmonary capillary wedge position. Systemic arterial pressure and cardiac output should be recorded. An evaluation for intracardiac shunts should be performed using oximetry runs. Assessment of pulmonary vasoreactivity is usually performed as well. For those patients being treated with vasodilator therapy, repeat right heart catheterization is used to follow clinical response and in some cases to help titrate therapy.(51)

Vasodilator testing: Vasodilator testing in the catheterization lab is a very serious undertaking and should be done only with great care. Agents that can be used to assess for vasodilator response include IV epoprostenol, IV adenosine, or inhaled nitric oxide. Before any of the agents are administered, a careful baseline hemodynamic assessment is required and then repeated careful assessment while the agent is being administered. The agent should be stopped

and the test terminated if systolic blood pressure drops by greater than 30%, heart rate increases by greater than 40%, heart rate falls or the patient develops symptomatic hypotension, intolerable side effects, the maximal dose is achieved, or the target response is achieved. Vasodilator testing is important because it does provide prognostic information. A small minority of patients will demonstrate acute vasoreactivity and those patients have been shown to have a good response to chronic calcium channel blocker antagonist therapy. Initiation of calcium channel blocker therapy in these patients should be performed cautiously with graded dosages in patients who have been medically stabilized and with careful hemodynamic monitoring. A vasodilator response is defined as a decrease in mean PAP by at least 10mmHg and/or a mean PAP less than 40mmHg in the presence of a normal or high cardiac output.(52) A recent study demonstrated that a very small percentage of patients demonstrate vasoreactivity at right heart catheterization- only 10% of those with IAPH and anorexigen-induced PAH have a good long-term response to calcium channel blockers.(52)

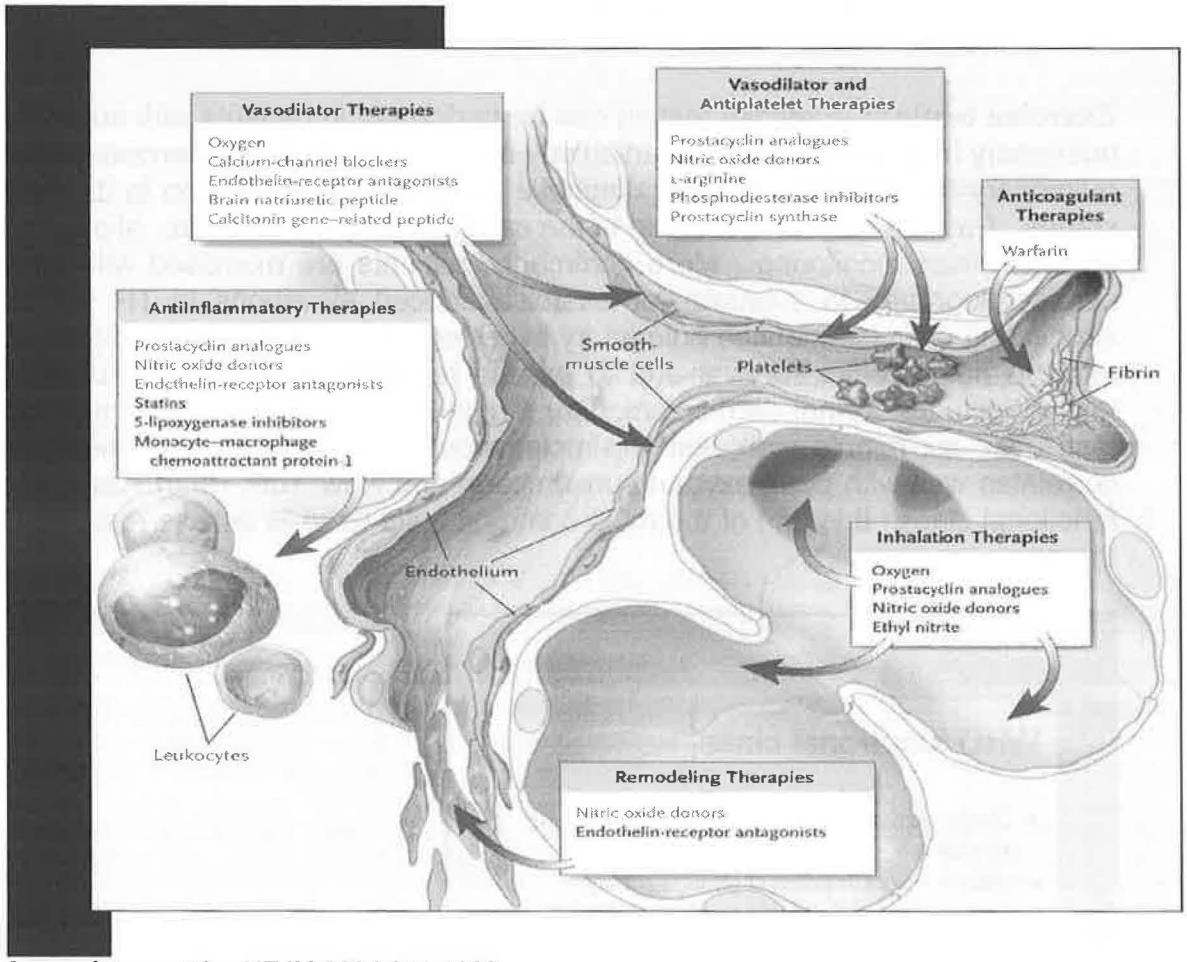
Exercise testing: Exercise testing can be performed in patients with suspected pulmonary hypertension and is particularly helpful in diagnosing exercise-induced pulmonary hypertension, to help diagnose pulmonary hypertension in its earlier stages. Patients can be exercised in the cardiac catheterization lab, allowing for invasive heart monitoring. More commonly, patients are exercised with stress echocardiography to evaluate for exercise-induced elevations in TR velocity, suggesting exercise-induced pulmonary hypertension. Functional testing can be used to help predict survival and to assess response to therapy. Functional testing includes formal cardiopulmonary stress testing and the six minute walk test. The six minute walk test is simple, requires no specific equipment, and correlates well with peak oxygen consumption and New York Heart Association functional class. It is one of the most common tests used to assess response to therapy.



Ref 2

Management of pulmonary hypertension:

A complete review is beyond the scope of this discussion. The most important factor in making the correct treatment decision is to identify the cause of the pulmonary hypertension and the appropriate WHO classification, therefore allowing the practitioner to treat the underlying disease. For those patients with pulmonary vascular disease who are WHO class I, a variety of therapies have been developed which have produced some very exciting results for this formerly rapidly fatal disease. Treatment algorithms are usually based on functional class. The World Health Organization Classification of Functional Class is shown below.(2) Vasodilator treatment has usually been limited to patients in functional class III or IV, although this rationale is being challenged as more clinical trials have begun to enroll patients with class II and even class I disease.



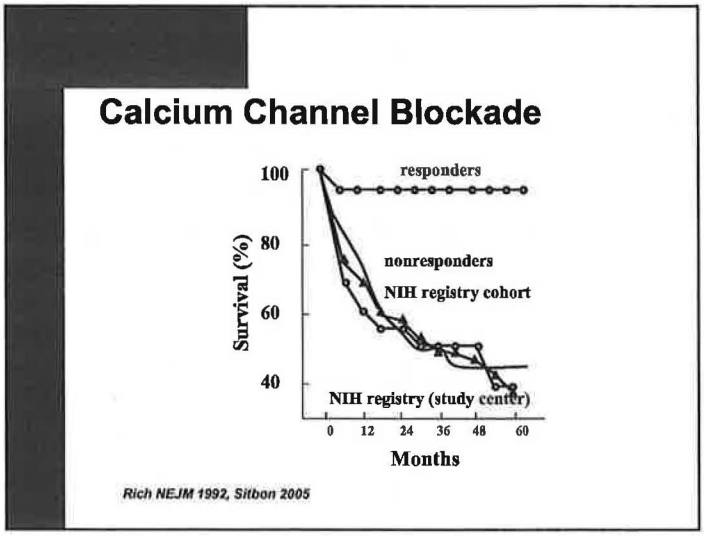
from reference 53 – NEJM 2004;351:1662.

Conventional therapy: Conventional therapy is provided to most patients with pulmonary arterial hypertension and includes oxygen, diuretics, anticoagulation, and digoxin.(54) Warfarin has been recommended based on retrospective data. Pathologic studies in patients with pulmonary hypertension have demonstrated

thrombosis in situ and a variety of clotting abnormalities. Thrombotic lesions, if carefully looked for, can be seen in 20-50% of PAH patients. They tend to have increased procoagulant activity as well as decreased anticoagulant activity. However, the actual data on which the recommendation for chronic anticoagulation is based is only two small studies (one retrospective, one prospective but non-randomized).(55,56) The recommended target range for INR is between 1.5 and 2.5. There is a proposed NIH sponsored study to assess the role of aspirin as an antithrombotic agent in these patients.

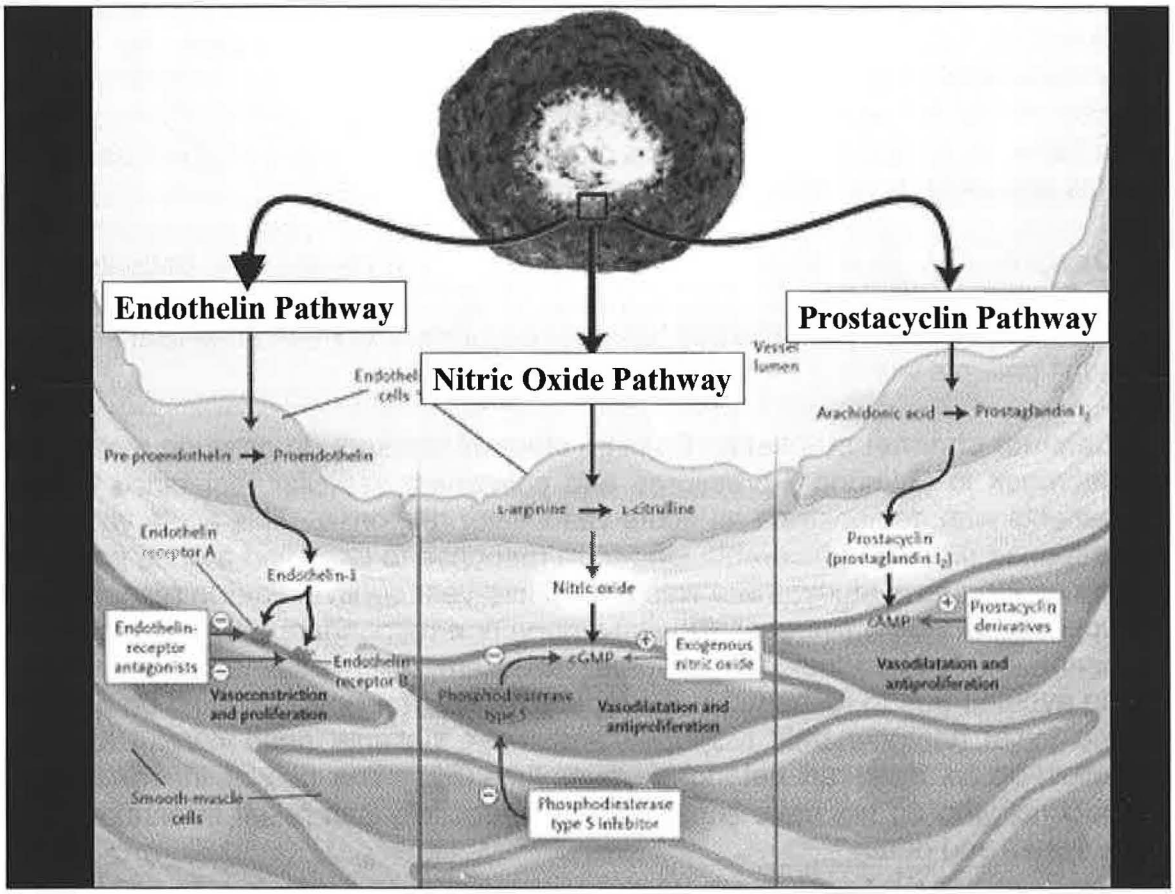
Oxygen: Oxygen is a potent pulmonary vasodilator, especially in patients with hypoxemia and oxygen therapy is recommended for any patient with arterial desaturation. Oxygen therapy has not been shown to have beneficial effects in adult patients with the Eisenmenger syndrome. (57)

Calcium channel blockers: Calcium channel blockers do produce a consistent decrease in pulmonary pressures and pulmonary vascular resistance in those patients who demonstrate an acute vasodilator response. This acute vasodilator response predicts a favorable long-term response to CCB and a good prognosis. In one long-term study, there was a 94% five-year survival among responders as opposed to a 36% five-year survival among non-responders.(58) Agents that are useful in this class include nifedipine, diltiazem, or amlodipine. Verapamil is to be avoided due to its negative inotropic effects. The dosing should be based on the initial hemodynamic response and these patients need careful long-term follow-up as they can deteriorate over time.(52) The use of these agents in patients who do not have substantial vasoreactivity can result in cardiovascular collapse and death.



In addition to calcium channel blockers, a variety of other vasodilators and vasoactive therapies are available. In addition to producing pulmonary vasodilatation, agents such as prostacyclin analogues and endothelin receptor

antagonists also have antifibrotic effects and may promote beneficial remodeling of the pulmonary vascular endotherlium.



from reference 58. NEJM 2004;351:1425.

Prostacyclin and its analogues: Prostacyclin is a metabolite of arachadonic acid, which is produced by the vascular endothelium. Patients with IAPH and other forms of PAH have reduced levels of prostacyclin synthase and therefore, decreased levels of endogenous prostacyclin. Exogenously administered prostacyclin works as a potent vasodilator in the pulmonary vasculature as well as the systemic circulation and also inhibits platelet aggregation, making it a very favorable agent to be used for the treatment of PAH. Epoprostenol (Flolan) is the IV form of prostacyclin that is given as a continuous infusion, requiring an indwelling catheter and a chronic infusion system. Its use in a variety of types of PAH has been shown to improve functional class, quality of life, 6-minute walk time, and survival.(59-63, 10,11) There are other prostacyclin analogues, including treprostinol (Remodulin) -a prostacyclin analogue given as either a continuous intravenous or subcutaneous infusion (64), beraprost (an oral prostacyclin analogue), and inhaled iloprost (Ventavis) – a prostacyclin analog (65,66) given as repeated aerosolized treatments (6-9/day). As a class, all of these agents do result in significant improvement in symptoms and functional

capacity. Only epoprostenol has been demonstrated conclusively to have a mortality benefit, based on comparison with a historical control population. All of these agents have significant side effect profiles (including nausea, vomiting, headaches, jaw pain, and diarrhea) as well as the risk of complications associated with the delivery systems. There is also a significant risk of a potentially fatal rebound effect for patients who experience interruption of drug delivery. The cost of therapy is not inconsequential.

Endothelin receptor antagonists: The endothelin receptor antagonists are another very important class of drugs in the treatment of pulmonary hypertension. Endothelin is a potent vasoconstrictor and smooth muscle mitogen and plasma endothelin-1 levels have been shown to be increased in PAH and correlate with the severity of hemodynamic derangements.(67,68) Its actions are mediated by 2 receptors, endothelin-A and endothelin-B. Bosentan (Tracleer) is a currently available endothelin-receptor antagonist, which is a dual endothelin-1 and –2 antagonist, approved for use in WHO class III and IV disease. Bosentan has been shown to improve functional capacity and to have mild beneficial hemodynamic effects (decrease in mean RA and pulmonary artery pressures).(69-71) It is teratogenic (pregnancy category X) and cannot be used with sulfonylureas or cyclosporine. Elevation in hepatic transaminases is the primary adverse effect. Primary used for patients with class III symptoms, annual cost $35,000 per year. Sitaxsentan and ambrisentan are oral endothelin-A specific antagonists, not yet available in the U.S.

Phosphodiesterase inhibitors: Phosphodiesterase type 5 (PDE5) is expressed in pulmonary artery smooth muscle cells. Inhibition of PDE5 results in cyclic guanosine monophosphate-mediated vasodilation. In the cath lab, sildenafil (Viagra, marketed as Revatio for pulmonary hypertension) has been shown to have vasodilator properties similar to nitric oxide.(U) Currently, case reports and small, uncontrolled trials with sildenafil have shown improvement in exercise capacity, functional class, and pulmonary hemodynamics. (72-75) While sildenafil is now approved for treatment of PAH, its role has not been well defined.

Surgical treatment: Lung transplant is a very successful treatment for pulmonary hypertension, either single or bilateral lung (most commonly). Despite the marked derangements in RV size and function in patients with pulmonary hypertension, the reduction in PVR results in rapid improvement in RV function. Thus patients do not require combined heart-lung transplant. Lung transplant has many potential complications and only modest long-term survival rates, thus it is the treatment of last resort.

Atrial Septostomy: Atrial septostomy has been used in severe RV decompensation or patients refractory to vasodilator therapy. The aim of this treatment is to decompress the RV and relieve right-sided congestion while augmenting systemic cardiac output. This trades some increase in RV function

for worsening cyanosis, as patients will shunt right to left across the atrial septum. (76)

Summary:

Pulmonary hypertension is a hemodynamic observation, not a diagnosis. Pulmonary hypertension has many causes and is seen in a wide variety of disorders. Effective treatment of pulmonary hypertension involves accurate diagnosis and appropriate classification of the underlying etiology. The diagnostic work-up can be complicated. In most cases, right heart catheterization is indicated to confirm the diagnosis of pulmonary hypertension and its severity, to help differentiate its cause, and to help determine therapy. For patients with pulmonary arterial hypertension, there is a rapidly expanding arsenal of treatments that can improve symptoms and potentially affect survival. However, there therapies are expensive and complex to administer. Diagnostic evaluation (including vaosdilator testing), treatment decisions, monitoring treatment efficacy, and determining suitability and timing of lung transplantation are all complex decisions best suited to a specialized pulmonary hypertension treatment center.

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