Primary Pulmonary Hypertension: A Perplexing Plexopathy

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"An impressive feature … was the contrast between the appearance of good health when at rest and the striking discomfort evoked by even mild exertion."

Original clinical description by Dr. David Dresdale, 1951[1]

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In memory of D. G. K. (3/22/76-9/17/99)

Historical Perspective

The term circulation is generally used to refer to the systemic circulation. The unfortunate implication is that the other circulation, the pulmonary circulation, may be less important. However, every breath we take should convince us otherwise. The inequality is rooted in history. In the second century AD the Greek physician Galen of Pergamon wrote scholarly articles claiming blood from the right ventricle percolated through holes in the partition separating the two ventricles. According to Galen the blood entering the left ventricle then combined with the "pneuma" (air) streaming in from the lungs to produce the "life pneuma" (red blood)[2]. Almost a thousand years later Galen's view on the formation of the "life pneuma" was still considered dogma by medical scholars. In the eleventh century the Arab physician Ibn Sina published his famous medical Canon (encyclopedia) which steadfastly supported Galen's theory. However, there was a dissenting voice, Egypt's Prince of Doctors Ibn Nafis[2]. In the middle of the thirteenth century he described a prototype pulmonary circulation.

"After the blood has been rarefied in this cavity (right ventricle) it must ... pass into the left cavity ... Nor, as held by Galen, would an invisible opening be suitable . . . for the pores of the heart there are not patent ... The blood ... passes via the vena-arterialis (pulmonary artery) to the lung for circulation and mixes with air ... The aerated blood gets refined and through the arteria-venalis (pulmonary vein) to reach the left cavity ... after having mixed with the air ..."[3,4].

Unfortunately, while the books and theories of Galen and Ibn Sina were copied and quoted for centuries, the writings of Ibn Nafis were essentially lost[2] only to be rediscovered after the fact in 1922 by an Egyptian medical student[3], Muhyi el din At Tatawi, and published in his Bachelor of Medicine thesis[5].

In the sixteenth century several European scholars took exception to Galen's teachings. Leonardo da Vinci in his extensive studies of human anatomy concluded *"the lung is not capable of sending air to the heart."* However, he did not envision a functional pulmonary circulation.

"it (the lung) does not need to, for air is produced within the heart, which evaporates in the form of perspiration on the skin through the extreme ends of the capillaries"[2].

The theologian and physician Michael Servetus was a man with intellectual courage and the ability to reason outside of traditional views[3,6]. He took direct exception with Galen's teachings.

" ... air mixed with blood, is sent from the lungs to the heart through the pulmonary vein; therefore the mixture occurs in the lungs ... that middle wall (ventricular septum) since it is lacking in vessels and mechanisms, is not suitable for that communication ... a truth which was unknown to Galen"[3,7].

The inquisitiveness of Michael Servetus extended past medicine and into religious matters. Unfortunately, he and his book (*Christianismi Restitutio*) both met an untimely end at the hands of the inquisition. His books were seized and destroyed[3,8].

In 1555, two years after the death of Michael Servetus, Andreas Vesalius, Professor of Anatomy at the school of Padua, published the second edition of his dissertation "*De humanis corporis fabrica.*" He also challenged Galen's dogma.

"not long ago I would not have dared to turn aside even a nail's breadth from the opinion of Galen, the prince of physicians ... But the septum of the heart is as thick, dense, and compact as the rest of the heart"[3].

His assistant, Realdus Columbus in "*De re anatomica*" (1559) went even further.

"Between these ventricles there is placed the septum through which almost all authors think there is a way open ... But these make a great mistake: for the blood is carried by the artery-like vein to the lungs ... brought back thence together with air by the vein-like artery to the left ventricle ..."[3].

Two other sixteenth century anatomists, Juan Valverde and Andreas Caesalpinus, came to similar conclusions, however Galen's theories were not completely dispelled until the seventeenth century by the scientific investigations of William Harvey (*De motu cordis*) and Marcello Malpighi. Harvey basing his theories on multiple animal dissections and perfusion experiments of the heart and lungs was able to definitively demonstrate that the blood "circulated".

"I finally saw that the blood was forced out of the heart and driven by the beating ... through the arteries into the body ... through the arterial vein (pulmonary artery) into the lungs, and then it returns through the veins into the vena cava and so the right ventricle in the same way as it returns from the lungs through the venous artery (pulmonary vein) to the left ventricle."[3,9].

Malpighi's rejection of Galen and Ibn Sina resulted in his doctoral thesis being rejected twice. However, using a new tool, the microscope, he was able to cement Harvey's concept of the circulation. Malpighi discovered the capillaries.

"It is clear to sense that the blood flows away through tortuous vessels, that it is not poured into spaces but always works through tubules and is dispersed by the multiple windings of the vessels ... I can believe that the lungs are made by nature for mixing the mass of blood"[2,3].

Over the next 150 years prominent scientists like Boyle, Hooke, Lower, Priestley, and Lavoisier helped explain respiratory physiology and laid the foundation upon which pulmonary disease processes could be studied. Just as with the discovery of normal pulmonary circulation, the quest to describe the pathophysiology of pulmonary hypertension (HTN) was laden with controversy[10].

In 1891 Romberg reported a case of severe right heart failure and cyanosis that at autopsy showed "unexplainable pulmonary vascular sclerosis." In 1901, Abel Ayerza described a group of patients who exhibited dyspnea, cyanosis, precordial pain and died of right heart failure. The term Ayerza's disease found it's way into the literature. Several authors endorsed the view that syphilitic pulmonary endarteritis was the cause of Ayerza's disease. This view was challenged by several physicians, most notable among them was Oscar Brenner. Brenner reviewed autopsy material from numerous cases of pulmonary HTN[11]. Brenner's criteria for primary pulmonary HTN was the presence of pulmonary vascular sclerosis and right ventricular hypertrophy in the absence of "*All factors commonly ... sought to cause secondary pulmonary vascular sclerosis ...*"[10]. He rebuked many of Ayerza's cases as secondary rather than primary pulmonary HTN and his series of pulmonary HTN cases called into doubt any major role for syphilis in the disease. In addition he described pathological changes found in the lung which included intimal proliferation, and medial hypertrophy and fibrosis. Unfortunately he was unable to discern the cause-effect relationship between pulmonary vascular sclerosis and right ventricular hypertrophy and instead believed they had a common cause.

" it seems unlikely that the hypertrophy of the right ventricle and the heart failure are directly due to the lesions in the pulmonary vessels ... pulmonary vascular lesions and the ventricular hypertrophy and failure are due to some unknown common cause rather than they are related as cause and effect"[10].

The advent of right heart catheterization allowed physiology, in particular pulmonary vascular reactivity, to share the stage with pathology in discerning the pathogenesis of primary pulmonary HTN. The 1940's and 50's brought the description of hypoxic pulmonary vasoconstriction[12,13], and the elucidation of pulmonary vasodilating agents (Priscoline, acetylcholine,)[1,14,15]. David Dresdale[1], Peter Harris[14], and Paul Wood[15] described an acute fall in pulmonary artery pressures in patients with various etiologies of pulmonary HTN given either Priscoline[1] or acetylcholine[14,15]. Paul Wood characterized the ideal pulmonary vasodilator.

"*functional pulmonary vasoconstriction plays an important part in initiating and maintaining the high resistance ... administration of a suitable pulmonary vasodilator should result in an appreciable fall in resistance. Ideally the pulmonary vasodilator should be as selective as possible, so that it does not alter pulmonary or systemic venous tone or the systemic peripheral resistance*"[15].

Paul Wood's work would elucidate the cause-effect relationship of "pulmonary vascular sclerosis" and right ventricular hypertrophy that eluded Oscar Brenner. In addition, Paul Wood extensively reviewed cases of Eisenmenger Syndrome and prophetically perceived similarities in the pulmonary histopathology of Eisenmenger Syndrome and primary pulmonary HTN[10,16].

Over the next several decades a familial form of pulmonary HTN (mapped to chromosome 2q31-32) would be characterized[17-21] as well as various conditions

that seemed to increase ones risk for developing pulmonary HTN with pathological lesions similar to that described for the entity primary pulmonary HTN[22-35].

From 1967 to 1972 in Austria, Switzerland, and Germany (FGR) there was an epidemic of pulmonary HTN related to the anorexigen Aminorex (2-amino-5-phenyl-2-oxaxoline)[30,31,34]. In the early 1980's in Spain there was an epidemic of pulmonary HTN related to the ingestion of "toxic" rapeseed oil[29,33]. The pulmonary pathology of these patients revealed the typical lesions of primary pulmonary HTN (ie. intimal proliferation, medial hypertrophy, plexogenic arteriopathy, and *in-situ* thrombosis). Similarly, HIV disease[24-26], congenital heart disease[36], liver disease with portal HTN[32], scleroderma[35], and derivatives of the anorexic agent fenfluramine[22,23,27] are all associated with an increased risk for developing pulmonary HTN with pathological lesions typical of "primary" pulmonary HTN.

The next major event was the convening of an international meeting on primary pulmonary HTN by the World Health Organization (WHO) in Geneva on October 15-17, 1973[37]. The WHO meeting reviewed the classification, pathology, etiologies, clinical features, and epidemiology of the disease and recommended the formation of a central register. In 1981 the National Institutes of Health (NIH) established a National Registry for primary pulmonary HTN[38-40]. Thirty-two medical centers enrolled 194 patients with primary "unexplained" pulmonary HTN. Using uniform diagnostic criteria the NIH registry characterized the natural history of the disease. The registry became a valuable resource for the assessment of the effect of new therapies on mortality, in particular, therapies using the oral calcium channel blockers[41] (nifedipine, diltiazem) and the intravenous vasodilating agent prostacyclin[42,43] (also known as epoprostenol and Flolan).

Histopathology

The lung has a double arterial blood supply consisting of pulmonary and bronchial arteries. The pulmonary arteries accompany the bronchi and divide with them. The pulmonary arteries are categorized as either elastic or muscular based on the amount of elastic tissue or smooth muscle present in the media. As the pulmonary vessels penetrate deeper into the lungs they become less elastic and more muscular. Vessels with a diameter of less than 0.5 mm are muscular pulmonary arteries without any elastic tissue. A normal muscular pulmonary artery (Fig. 1a) consists of a thin intima comprised of a single layer of endothelial cells, a muscular media circumscribed by an internal and external elastic laminae, and an adventitia consisting of dense connective tissue. The design of pulmonary arteries adheres to the structure-function principle. The normal pulmonary circulation is a low pressure and low resistance environment. In comparison with systemic arteries, the pulmonary arteries have a wider lumen

and a thinner media. The pulmonary artery is more compliant then a systemic artery and easily adapts to accommodate large changes in blood volume.

Sustained pulmonary HTN results in a continuum of changes in the muscular pulmonary arteries and arterioles. The histopathology of primary pulmonary HTN is not a single exclusive pathoneumonic finding, but rather a pathologic syndrome consisting of a variety of pulmonary vascular legions. Primary pulmonary HTN affecting the pulmonary arteries results in an arteriopathy characterized by one or more of the following lesions: 1. Isolated medial hypertrophy, 2. plexogenic arteriopathy, 3. thrombotic arteriopathy, and 4. isolated arteritis[44]. A single biopsy or autopsy specimen may simply be a snapshot of a process that is a continuum in evolution.

Isolated Medial Hypertrophy (Thickening): Medial hypertrophy (Fig. 1b) is characterized by an increase in the medial smooth muscle of muscular arteries and the muscularization of non-muscularized arterioles. Medial hypertrophy is nonspecific and represents the general response of an artery to a chronic increase in pressure (chronic vasoconstriction). Isolated medial hypertrophy implies a lack of luminal obstructive or plexogenic legions. The incidence of isolated medial hypertrophy in patients felt to have primary pulmonary HTN ranges from 2 to 4%[45].

Medial thickening is probably a more appropriate term then hypertrophy since various studies suggest it results from not only hypertrophy of preexisting muscle fibers but also proliferation and migration of myofibroblasts that develop into smooth muscle cells[46-48]. Isolated medial thickening may represent an early and potentially reversible form of pulmonary arteriopathy, suggesting that the inciting events in the development of the pathologic lesions of pulmonary HTN contain elements of both chronic vasoconstriction and a disorder of cell growth within the muscular pedigree of cells[46,48]. There is data to suggest that endothelial cell dysfunction may play an important role in the pathogenesis of both chronic vasoconstriction and smooth muscle proliferation[49,50].

Plexogenic Pulmonary Arteriopathy: A plexiform structure is a network or tangle. A plexiform lesion consists of a tangle of thin-walled microvessels situated in the lumen of an aneurysmal dilatation within a muscular artery (Fig. 1c). Distally, the plexiform lesion connects with a network of dilated thin-walled channels known as the dilatation or angiomatoid lesion (Fig. 1d). In addition to plexiform and dilatation lesions, plexogenic pulmonary arteriopathy may also exhibit intimal lesions, medial thickening, arteritis, and thrombotic lesions.

The pathogenesis of the plexiform legion is controversial. One theory is that the legion represents an arterial remodeling process consisting of recanalization and collateralization[45,51]. This would suggest that the pathophysiology of primary pulmonary HTN also involves angiogenesis.

In a subset of patients in the NIH registry who had lung tissue available, 43% were found to have legions consistent with plexogenic pulmonary arteriopathy[44]. However plexogenic pulmonary arteriopathy is not unique to primary pulmonary HTN and is also seen in pulmonary HTN due to congenital heart disease[16], liver disease with portal HTN[32,52], scleroderma[35], certain anorexic agents[30], "toxic" rapeseed oil[53], and HIV disease[24-26].

Thrombotic Pulmonary Arteriopathy: This form of arteriopathy is characterized by thrombotic lesions without the presence of plexiform lesions. Intimal and medial thickening may be present. The thrombotic lesions consist of "fresh thrombus, organizing thrombus and colander-like lesions (recanalized thrombus, Fig. 1d). Since the lesion can be found in the absence of any clinical or pathological evidence of a source of chronic emboli it is assumed to represent *in-situ* thrombosis[44,54,55]. In a subset of patients in the NIH registry who had lung tissue available, 33% were found to have legions consistent with thrombotic pulmonary arteriopathy[44].

Isolated Pulmonary Arteritis: Arteritis is an inflammatory process involving an artery or arteriole. Fibrinoid necrosis is a necrotizing arteritis (Fig. 1e) and reveals partial destruction of the arterial wall with fibrin deposition and an inflammatory infiltrate. In isolated pulmonary arteritis thrombotic lesions and varying degrees of medial and intimal lesions may be present, but not plexogenic lesions. It is possible that necrotizing arteritis may be a precursor event to arterial aneurysmal dilatation and formation of a plexiform lesion. The reports of isolated arteritis are very few and mainly in children with pulmonary HTN[55,56].

Pulmonary Occlusive Venopathy: In a subset of patients from the NIH registry, 12% were found to have lesions involving primarily the pulmonary veins[44]. Pulmonary veno-occlusive disease is probably a variant of pulmonary hypertensive vasculopathy that affects the pulmonary veins. The lesions are characterized by the development of a muscular media within pulmonary veins (arterialization of the pulmonary veins, Fig. 1f), obstructive intimal fibrosis, recanalized thrombi, and tortuous sinusoidal channels filling the lumens of lobular and lobar pulmonary veins (Fig. 1g)[57]. The increased venous pressure results in dilatation of alveolar capillaries and pulmonary lymphatics and eventual interstitial and alveolar hemorrhages and edema.

Pulmonary Microangiopathy: A very rare variant of pulmonary hypertensive vasculopathy is known as pulmonary capillary hemangiomatosis. The lesions consist of angiomatous growth of thin-walled microvessels throughout the pulmonary parenchyma (Fig. 1h)[58-60]. There may also be coexisting intimal and medial thickening of muscular pulmonary arteries and arterioles.

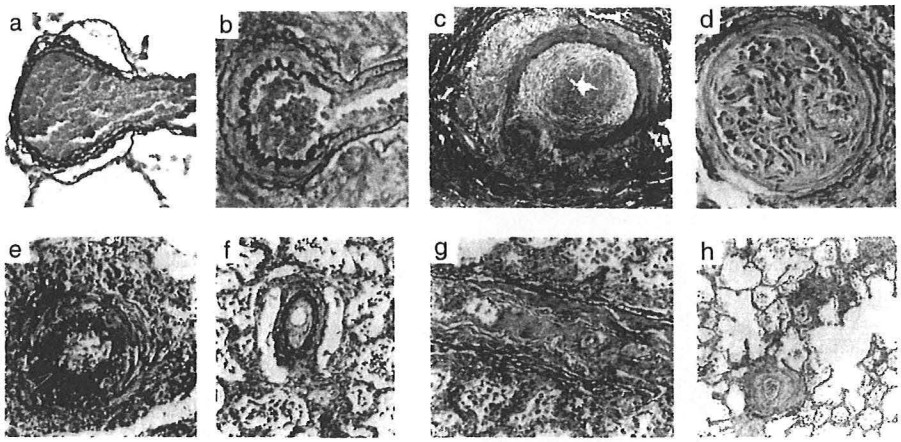

Figure 1. **a.** Normal pulmonary artery[61]; **b.** Medial hypertrophy of muscular pulmonary artery[61]; **c.** Plexiform lesion[45]; **d.** Colander-like lesion[45]; **e.** Arteritis[45]; **f.** Arterialized pulmonary vein[61]; **g.** Pulmonary veno-oclusive disease[45]; **h.** Pulmonary capillary hemangiomatosis[45]. (Verhoeff-van-Gieson a-d, f-h; Hematoxylin-eosin e; x360 a,b; x250 c; x80 d,h; x100 e; x140 f; x120 g)

Pathophysiology

Hemodynamic studies in individuals with pulmonary HTN reveal a high pulmonary artery pressure and a high resistance to pulmonary blood flow. As described above, primary pulmonary HTN is easily visualized and classified as a disease of the pulmonary vasculature. A better term to describe the disease should incorporate the hemodynamic and pathologic abnormalities. "Pulmonary hypertensive angiopathy" is probably a more inclusive and accurate description of the disease.

The elucidation of the pathogenesis of the disease process is complicated by the presentation of patients in the stage of advanced disease and the lack of validated markers of disease activity. Information concerning the early stages of the disease process is lacking. However, knowledge of vascular biology can be used to fill in some of the gaps.

If we accept that pulmonary hypertensive angiopathy has many etiologies some of which remain unexplained then our explanation of the pathophysiology must focus on a common final pathologic pathway that can be triggered by diverse inciting events. The development of clinical disease is probably contingent on an individual susceptibility which is most likely genetically determined.

A schematic of the pathophysiology of pulmonary hypertensive vasculopathy (angiopathy) is presented in Figure 2. The disease process is probably initiated by one or more inciting events probably occurring in an individual with a genetic predisposition to developing the disease[62]. There is evidence that toxic substances, immune disorders, and vasoactive processes resulting in chronic vasoconstriction may represent inciting events[22-27,29-34,36,63,64]. In addition, familial cases exist which are associated with expression of HLA loci DRw52, DR3, and DQw2[65]. Vessels are active systems undergoing a continuous process of remodeling in response to oxidant and shear stress. The inciting events probably cause a state of recurrent or chronic pulmonary vascular injury and repair resulting in an exuberant vascular remodeling process and alterations in gene expression. Vascular remodeling involves endothelial activation, and release of various growth factors, cytokines, and vasoactive agents (Table 1).

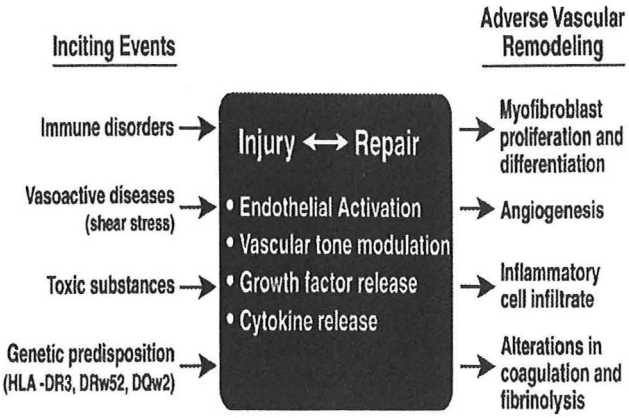

Figure 2. Pathophysiology: Schematic of possible interactions involved in the development of pulmonary hypertensive vasculopathy.

Table 1: Adverse vascular remodeling:
Growth factors, cytokines, and vasoactive agents

➢ Interleukin-1α[66]	➢ Eicosanoids [73-75]
➢ Transforming growth factor-β[67-69]	➢ Endothelin[76]
➢ Platelet derived growth factor[70,71]	➢ Nitric oxide[77,78]
➢ Vascular endothelial growth factor[35]	➢ Serotonin[79,80]
➢ Insulin like growth factor[72]	➢ Ion channels[81,82]

A continuous cycle of vascular injury and repair may eventually lead to deleterious vascular remodeling. This process could be considered analogous to the maladaptive cardiac remodeling that occurs with inciting events leading to cardiomyopathy. In pulmonary vascular adverse remodeling a central role is ascribed to a deficiency in endogenous prostacyclin (PGI_2) synthesis[74,75] and a diminished expression of endothelial nitric oxide synthase[78]. Recent therapeutic

strategies are based on the paradigm of restoring pulmonary vasodilatation by administering prostacyclin or nitric oxide.

Adverse vascular remodeling resulting from endothelial cell activation and dysfunction involves myofibroblast proliferation and differentiation, angiogenesis, inflammation, and alterations in coagulation and fibrinolysis[35,48,83-88]. In theory, these processes can result in all the pathologic lesions described in the former section.

Epidemiology and Natural History

"Unexplained" pulmonary HTN is an uncommon disorder. The incidence ranges from 1 to 2 cases per million people[89]. In 1981, the National Institutes of Health (NIH) established *the Patient Registry for the Characterization of Primary Pulmonary Hypertension* to prospectively gather data on "unexplained" pulmonary HTN. The NIH registry defined pulmonary HTN as a mean pulmonary artery pressure (PAP) >25 mm Hg at rest or >30 mm Hg during exercise. Pulmonary HTN was considered "unexplained" if known secondary causes were absent (Table 2). Thirty-two medical centers enrolled 194 patients between July 1, 1981 and December 31, 1985. The patients were followed through August 8, 1988. The registry represents a general population of heterogeneously treated patients. One goal of the registry was to describe the natural history of the disease.

Table 2: NIH Registry Exclusion Criteria[38]

- Congenital or acquired valvular or myocardial disease or pulm. artery stenosis
- Collagen vascular diseases and pulmonary parasitic diseases
- Arterial hypoxemia with hypercapnea
- COPD with hypoxemia and FEV1/FVC > 2 SD from the norm
- Interstitial lung disease with reduced total lung capacity > 2 SD from the norm and infiltrates on chest x-ray
- Pulmonary thromboembolic disease as evidenced by lung perfusion scan or pulmonary angiogram, or diagnosis of sickle cell anemia or IVDA
- Pulmonary HTN within the 1st yr. of life, and congenital abnormalities of the lungs, thorax, and diaphragm
- Pulmonary venous HTN (Pulmonary capillary wedge pressure > 12 mm Hg)

The registry demographics[38-40] revealed the distribution by race to be similar to that of the general population. Women were affected more than men (1.7:1). This discrepancy was amplified among the black population to 4.3:1. The mean age of patients enrolled in the registry was 36.4 years and was similar for both men and women. However, "unexplained" pulmonary HTN can also present late

in life. In the NIH registry 9% of the cases were diagnosed at ≥ 60 years of age. The mean time from onset of symptoms to diagnosis was 2 years.

The NIH registry found no association of "unexplained" pulmonary HTN with pregnancy or oral contraceptives. There was a 29% incidence of a positive ANA (range 1:10 to 1:10,000), and 11% incidence of Raynaud's disease, the majority of whom were women (95% and 69% respectively). Several autoimmune disorders manifest their pulmonary disease as pulmonary HTN (Table 3). In particular, scleroderma has been found to have pulmonary vascular lesions consistent with the arteriopathy of "unexplained" pulmonary HTN[35,90,91]. There are several case reports and series that suggest risk factors exist for developing pulmonary hypertensive vasculopathy probably in individuals with a genetic susceptibility. These factors include high levels of serotonin[92], certain anorexic agents[30], "toxic" rapeseed oil[53], HIV disease[24-26], scleroderma[35], congenital heart disease[16], and liver disease with portal HTN[32,52].

Table 3: Autoimmune disorders complicated by pulmonary HTN

➢ Scleroderma/CREST variant	➢ Polymyositis
➢ Systemic lupus erythematosus	➢ Dermatomyositis
➢ Mixed connective tissue disease	➢ Rheumatoid arthritis

Familial cases exist and are associated with expression of HLA loci DRw52, DR3, and DQw2[65]. HLA-DR3 is also associated with the autoimmune diseases scleroderma[93], systemic lupus erythematosus[94], and Sjögren's syndrome[95]. The gene for familial "unexplained" pulmonary HTN maps to chromosome 2 and shows incomplete penetrance[21]. The disease exhibits genetic anticipation (trinucleotide repeat expansion)[19,20], a phenomenon in which subsequent generations show worsening of disease. This can be manifested by greater severity of symptoms or earlier onset of disease. In the NIH registry familial "unexplained" pulmonary HTN was considered present if a first order relative also had the disease. The incidence was 6.4%. The familial cases had a shorter interval from the onset of symptoms to diagnosis (0.7 vs. 2 years). Otherwise, there was no distinctive difference from non-familial cases. The shorter interval from the onset of symptoms to diagnosis is probably attributable to "heightened awareness". Interestingly, familial "unexplained" pulmonary HTN showed marked heterogeneity concerning the pathological pulmonary lesion within and among families, suggesting the various forms of vascular arteriopathy do not represent different disease processes but rather different pathological representations of the same disease[17].

The estimated median survival of patients in the NIH registry was 2.8 years from the baseline catheterization. The 1-, 3-, and 5-year survivals (Fig. 3) were 68%,

48%, and 34% respectively. Survival was found to vary with New York Heart Association (NYHA) functional class. Patients presenting with NYHA class I-II symptoms had a median survival of 58.6 months, while NYHA class III patients had a median survival of 31.5 months, and NYHA class IV patients had a median survival of 6 months. However, the best correlates of survival were hemodynamic measurements obtained at baseline evaluation. In particular the mean PAP, right atrial pressure (RAP) and cardiac index (CI) were found to be strong predictors of survival (Fig. 4). Cause of death was usually due to right ventricular failure (47%) or sudden cardiac death (26%). Survival time did not correlate with gender, age at diagnosis, symptom duration, tobacco use, seropositive ANA, or family history of "unexplained" pulmonary HTN.

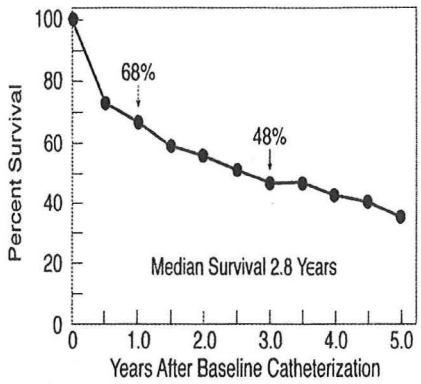

Figure 3: NIH registry (n=194) estimated % survival after baseline catheterization[39].

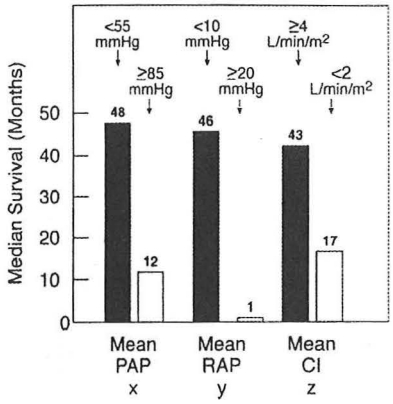

Figure 4: NIH registry (n=194) median survival based on hemodynamic variables from baseline catheterization[39].

Hemodynamic data (mean PAP, RAP, CI) from the baseline right heart catheterization was used to derive a regression equation to predict the individual patient's chances of survival[39]. The equation in Figure 5 uses the patient's mean PAP (x), RAP (y), and CI (z) at baseline catheterization to predict survival at t = 1, 2, 3, 4, and 5 years after diagnosis. Figure 6 illustrates the effect on survival of a decrease in CI (3.3, 2.3, 1.3 L/min/m^2) without a change in mean PAP (60 mm Hg) or RAP (10 mm Hg). The NIH equation has proven useful in assessing the efficacy of treatment modalities. It might also prove to be helpful in allocating scarce resources (donor lungs).

$P(t)=[H(t)]^{A(x,y,z)}$

$H(t)=[0.88-0.14t+0.01t^2]$

$A(x,y,z)=e^{(0.007325x+0.0526y-0.3725z)}$

$P(1)=0.75^A$
$P(2)=0.65^A$
$P(3)=0.55^A$
$P(4)=0.48^A$
$P(5)=0.43^A$

P(t) = Patient's chances of survival at t ± years
t=1,2,3,4 or 5 years
x=mean PAP, y=mean RAP, z=mean CI

Figure 5: Equation to predict survival at t years[39].

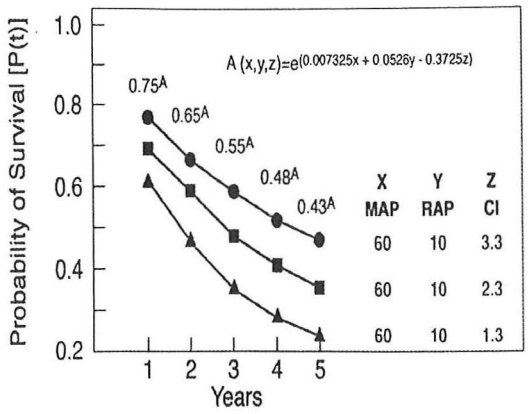

Figure 6: Probability of survival based on baseline mean PAP (x), RAP (y), and CI (z)[89].

Diagnostic Evaluation

Pulmonary HTN should be part of the differential diagnosis in patients presenting with subtle signs of elevated right-sided pressure or exertional dyspnea and fatigue. Unfortunately, patients with pulmonary HTN are usually diagnosed late in their course when they present with overt right–sided heart failure and a low cardiac output state. There is no routine screening test for this disorder and many of the early stage symptoms are nonspecific and mild. Initial evaluation (Fig. 7) should include history, physical examination, chest x–ray (CXray) films and electrocardiogram (EKG).

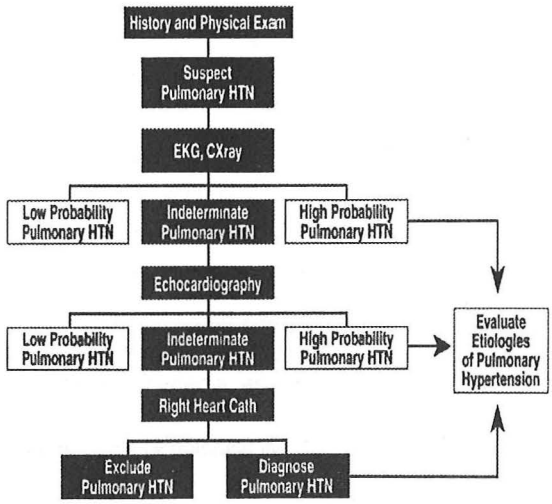

Figure 7: Algorithm for diagnosis of pulmonary HTN. [Adapted from ref[96].]

If the diagnosis remains unclear then one can proceed to further evaluate with an echocardiogram. Right heart catheterization can be used to definitively diagnose or exclude pulmonary HTN.

History: The NIH registry defined the clinical features present in patients with "unexplained" pulmonary HTN upon initial presentation and on enrollment into the registry (Table 4)[40]. The most common complaint on initial presentation was dyspnea. Chest pain, syncope, leg edema and palpitations were very rare on initial presentation. At the time of registry enrollment dyspnea was present in almost everyone and fatigue was also a very common complaint. Hoarseness and hemoptysis have also been reported, but are uncommon[97].

Table 4: "Unexplained" pulmonary HTN: Symptoms[40]

Symptom	Initial %	On enrollment %
➢ Dyspnea	60	98
➢ Fatigue	19	73
➢ Chest pain	7	47
➢ Near syncope	5	41
➢ Syncope	8	36
➢ Leg edema	3	37
➢ Palpitations	5	33

Physical Examination: Table 5 lists physical findings supporting the diagnosis of pulmonary HTN. In the NIH registry 93% had a loud P2, 40% had auscultatory tricuspid regurgitation (TR), 38% had a right-sided S4, 32% had peripheral edema, 23% had a right-sided S3, 20% had cyanosis and 13% had auscultatory pulmonary insufficiency (PI)[38,40]. A right-sided S3 and TR suggest more advanced disease and were associated with an elevated RAP and reduced CI[38].

Table 5: Physical findings supporting the diagnosis of pulmonary HTN[96]

➢ Loud P2	➢ Prominent jugular a and v wave
➢ Right ventricular gallop	➢ Diminished carotid arterial upstroke
➢ Right ventricular lift	➢ Lower extremity edema, ascites
➢ Murmurs of PI or TR	➢ Anasarca
➢ Elevated JVP (± HJR)	➢ Hepatomegaly (± pulsatile liver)

Chest radiograph: The most common abnormalities found in NIH registry patients were an enlarged main pulmonary artery (90%), hilar vessel engorgement (80%) and pruned peripheral vessels (51%). All 3 abnormalities were present in 42% and were associated with a higher mean PAP (66 vs. 53 mm Hg; $p < 0.001$)[38]. A completely normal chest radiograph argues against the diagnosis of pulmonary HTN. However, 6% of NIH registry patients had normal chest radiographs, electrocardiograms, and echocardiograms[38].

Electrocardiogram: The predominant rhythm is sinus. Unlike cor-pulmonale from chronic obstructive lung disease, patients with "unexplained" pulmonary HTN have a notable absence of atrial arrhythmias[96]. Chronic atrial fibrillation has not been reported in the setting of "unexplained" pulmonary HTN. The most common EKG findings among patients in the NIH registry were right ventricular hypertrophy (87%), right axis deviation (79%), and right ventricular strain pattern (74%)[38]. The absence of these EKG findings do not imply the absence of the disorder since mild to moderate degrees of pulmonary HTN may not show EKG changes.

Echocardiogram: The technique can be useful in diagnosing the cause of pulmonary HTN (congenital abnormalities, cardiac valvular disease, myocardial disease). In addition, combined doppler, m-mode and 2-D echocardiography can be used to qualitatively and quantitatively assess hemodynamic abnormalities associated with pulmonary HTN. Table 6 lists echocardiogram findings supportive of pulmonary HTN. The most common echocardiogram findings among patients in the NIH registry were a normal to reduced left ventricular end diastolic internal dimension (100%), right ventricular enlargement (75%), mid-systolic closure of pulmonary valve (60%), and paradoxical septal motion (59%)[38].

Table 6: Echocardiogram findings supporting the diagnosis of Pulmonary HTN.

- RV enlargement with reduced LVEDD
- Paradoxical septal motion
- Mid-systolic closure of pulm. Valve
- Right ventricular hypertrophy
- Right atrial enlargement
- Pulmonary artery (PA) enlargement
- Shortened acceleration time in PA
- Distorted/flattened septum
- TR and PI
- Elevated estimated peak RVESP
- Inspiratory collapse of IVC < 50%

Cardiac Catheterization: Right heart catheterization (RHC) is the gold standard for diagnosing or excluding pulmonary HTN. RHC is also useful in assessing the severity of the disease and in diagnosing the cause of pulmonary HTN. Serial oxygen saturation measurements, hydrogen inhalation, or injection of indocyanine green dye can be used to assess for intracardiac shunting. The Fick or thermodilution method can be used to determine cardiac output. In patients with low cardiac output and significant tricuspid regurgitation the Fick method employing direct measurement of oxygen consumption is preferred. Appropriate assessment of PCWP can determine whether the process causing the pulmonary HTN is mixed capillary-precapillary (PCWP <12-15 mm Hg) or post-capillary (Table 7). "Unexplained" pulmonary HTN is traditionally viewed as a precapillary form of pulmonary HTN and thus has a normal or near-normal

PCWP. Variability in the PCWP determinations from various sites within the pulmonary vasculature is characteristic of the pulmonary veno-occlusive variant of the disease. Pulmonary veno-occlusive disease can result in a gradient between the PCWP and the true left ventricular end diastolic pressure. Baseline catheterization data from the NIH registry revealed a mild to moderately elevated mean RAP (9.7±6 mm Hg), severely elevated mean PAP (60±18 mm Hg), mild to moderately reduced mean CI (2.3 ±0.9 L/min/m^2), and a severely elevated mean pulmonary vascular resistance index (PVRI; 26±14 Wood units/m^2)[38].

Table 7: Classification of etiology of pulmonary HTN based on anatomical site of disease. [Adapted from ref[96].]

Postcapillary	Mixed capillary & precapillary	Normal or near-normal lungs
Constrictive pericarditis and mediastinitis	Airway and parenchymal disease (COPD, ILD)	Sleep disordered breathing
Pulm veno-occlusive disease	Chest wall disease (Kyphoscoliosis, Fibrothorax)	Chronic Alveolar Hypoventilation
LV dysfunction(CM, LVH)	Liver disease (porto-pulmonary HTN)	High-altitude sickness
LA myxoma/ thrombus	Pulmonary vascular disease (PE, PS, CVD, PPH)	Neuromuscular disease (ALS, myasthenia, polio)
Cor triatriatum	Congenital heart disease (Intracardiac L-to-R shunts)	
MV disease (MS, MR)		

Cardiopulmonary function testing: Symptom-limited cardiopulmonary stress testing using a Naughton protocol is useful in objectively assessing a patient's functional capacity. Functional capacity provides prognostic information[98]. Pulmonary function tests can discern the presence of restrictive or obstructive lung disease. NIH registry patients had only a mild reduction in mean forced vital capacity (82% predicted), mild-moderate decrease in mean diffusing capacity for carbon monoxide (69% predicted), mild hypoxemia, and a chronic respiratory alkalosis (mean PO_2 71, mean PCO_2 31)[38,40,96,99]. Thus the presence of hypercapnia or more than a mild form of restrictive[100] or obstructive lung disease suggests a profile very different from an NIH registry patient and perhaps an explanation for the pulmonary HTN can be found.

Lung scanning and pulmonary angiography: These tests are useful for distinguishing patients with major vessel or recurrent pulmonary thromboembolic-induced pulmonary HTN from "unexplained " pulmonary HTN. Abnormal lung scans are common in "unexplained" pulmonary HTN and are probably due to the vasculopathy. Diffuse small patchy perfusion defects are thought to suggest thrombotic pulmonary arteriopathy and normal lung scans are thought to suggest the plexogenic form[101]. Lung scans were abnormal in 58% of the NIH registry

patients[38]. A diffuse patchy pattern was seen in the majority of the cases (77%). A lung scan showing one or more segmental or greater ventilation-perfusion mismatches necessitates a pulmonary angiogram[102]. Only one patient in the NIH registry had a high probability scan for pulmonary thromboembolic disease and that patient had a normal pulmonary angiogram[38]. In "unexplained" pulmonary HTN, pulmonary angiography usually reveals dilated proximal and hilar vessels which rapidly taper. The distal vessels show significant bilateral symmetric pruning[103]. Only one adverse event (transient hypotension) occurred among the 50 patients in the NIH registry who had a pulmonary angiogram[38].

Additional testing: The diagnosis of "unexplained" pulmonary HTN remains one of exclusion. History and physical exam should guide the exploration of potential causes of pulmonary HTN. Additional testing may consist of high resolution CT scan (ground glass lesions seen with "unexplained" pulmonary HTN), serologic testing, liver sonogram, testing for infectious agents, and neuromuscular testing. Figure 8 outlines an approach to evaluating the cause of pulmonary HTN.

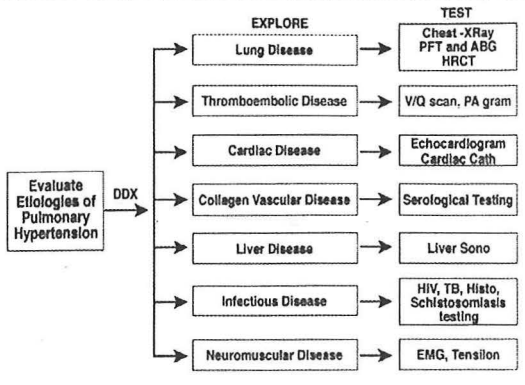

Figure 8: Schematic for assessing the etiology of pulmonary HTN.

Treatment

There remains no cure for "unexplained" pulmonary HTN. Spontaneous remissions are rare[104,105]. Medications that appear to have altered the natural history of the disease are anticoagulation and vasodilator therapy. Surgical therapy consists of heart-lung and more recently lung transplantation alone.

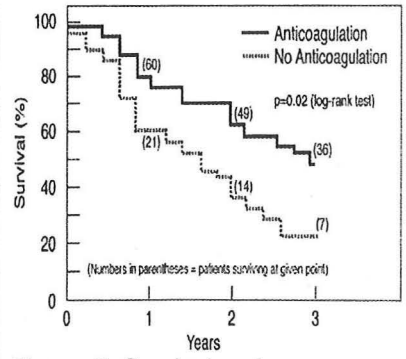

Figure 9: Survival and anticoagulation therapy[54].

Anticoagulation: *In-situ* thrombosis is believed to be an essential element in the pathogenesis of pulmonary vasculopathy. In addition, these patients may have a sedentary lifestyle and venous stasis putting them at risk for deep venous thrombosis. Their pulmonary vascular reserve is minimal and a thromboembolic event would be devastating. The effectiveness of warfarin in "unexplained" pulmonary HTN has not been tested in randomized prospective controlled trials, but a retrospective analysis (Fig. 9)[54]

and a small prospective nonrandomized trial (Fig. 10)[41] suggest warfarin prolongs survival. Warfarin is recommended at a dose sufficient to achieve an INR of 2.0-3.0[89].

Vasodilators: The rationale for vasodilator treatment is based on the predication that vasoconstriction plays a prominent role in the disease process. Unfortunately neither clinical symptoms nor baseline hemodynamic data predict who will respond to vasodilator therapy[106]. The possibility exists not only for therapeutic failure, but also for therapeutic misadventure. It should be emphasized that the majority of the favorable data presented below applies strictly to patients with "unexplained" pulmonary HTN as defined by the NIH registry criteria. Empiric vasodilator therapy for pulmonary HTN should be discouraged. In particular, patients with the pulmonary veno-occlusive[107] and capillary hemangiomatosis[108] variants have developed sudden pulmonary edema during vasodilator therapy. This complication may be related to increased pulmonary perfusion in the setting of downstream fixed vascular obstruction[107].

Acute vasodilator challenge involves titration of a potent short acting vasodilator in a controlled setting capable of monitoring arterial saturation, cardiac output and systemic and pulmonary pressures and resistances. The accepted agents are nitric oxide[109], prostacyclin[110] (metabolite of arachidonic acid), and adenosine[111,112]. Of the 3 agents, nitric oxide's action is the most specific for the pulmonary vasculature[109]. However, the necessity for inhalation delivery systems complicates its use. Of the two remaining intravenous agents adenosine is more readily available. The hemodynamic effects of prostacyclin and adenosine on the pulmonary vasculature are similar[112,113]. In addition, there is a significant correlation ($r = 0.714$, $p = 0.01$) between the reduction in PVR that results from adenosine and oral nifedipine[114].

An accepted protocol for acute vasodilator testing involves giving 50 mcg/kg/min of adenosine and increasing every 2 minutes by 50 mcg/kg/min and stopping for adverse symptoms or obtainment of 350 mcg/kg/min[112]. Invasive and noninvasive hemodynamics are obtained at baseline and at peak adenosine dose obtained. There are no accepted standards for defining a successful vasodilator challenge. The ideal response would be a decrease in mean PAP, and PVR with an increase in CI and no significant change in systemic arterial pressure (MAP) or decrease in arterial oxygen saturation[115]. Patients with this response profile are likely to experience sustained hemodynamic benefit, decrement in symptom severity, and prolonged survival[41,115,116]. The efficacy of oral vasodilator therapy is controversial in patients who during vasodilator challenge reduce PVR due to a rise in cardiac output without contribution from a fall in mean PAP[115,117]. These patients may have symptomatic benefit without mortality benefit[41,115]. Patients who experience symptomatic hypotension, arterial oxygen desaturation, decrement in CI, or a rise in mean PAP or RAP are likely to have an adverse risk:benefit profile with oral vasodilator therapy.

Patients responding to acute vasodilator challenge may be treated with oral calcium channel blockers (CCB)[89]. The most widely studied and used drugs are nifedipine and diltiazem[41,115,116,118,119]. A common protocol for administration of CCB challenge is outlined in Table 8. Hourly arterial saturation, cardiac output and systemic and pulmonary pressure and resistance measurements are done. Symptomatic hypotension, rising RAP decreasing CI, arterial desaturation, or heart block warrants immediate discontinuation of the protocol.

Table 8: CCB Challenge [Adapted from ref[118].]

- Agent: Nifedipine 20 mg (HR ≤ 100) or Diltiazem 60 mg (HR > 100)
- Protocol: Hourly Consecutive doses until
  - a. + Effect (↓ MPAP & PVR without further ↓ after 1 additional dose)
  - b. – Effect (Adverse drug effect)
  - c. No Effect (10 consecutive hourly doses without response)
- Characterization of Response:
  - a. Pressure Responders (≥ 20% ↓ MPAP and PVR)
  - b. Resistance Responders (< 20% ↓ MPAP and ≥ 20% ↓ PVR)
  - c. Non-responders (< 20% ↓ MPAP and PVR)

Among 64 patients with "unexplained" pulmonary HTN treated with CCB challenge, 17 (26%) were classified as pressure responders and treated long term with CCB at doses usually higher then conventional doses. Long-term these patients demonstrated sustained improvement in hemodynamics and functional class. Five year survival in these patients compared to patients that did not have a significant decrease in mean PAP was significantly better (Fig. 10; 94% vs. 36%)[41]. Since all patients who responded to initial CCB challenge were treated, it is possible that response to CCB challenge merely selects a subgroup with better prognosis. However, the fact that treatment with CCB substantially prolonged observed 1, 3, and 5-yr. survival over projected survival (Table 9) based on NIH equations (Fig. 5) suggests some treatment effect. Observed and projected survivals of non-responding patients were similar.

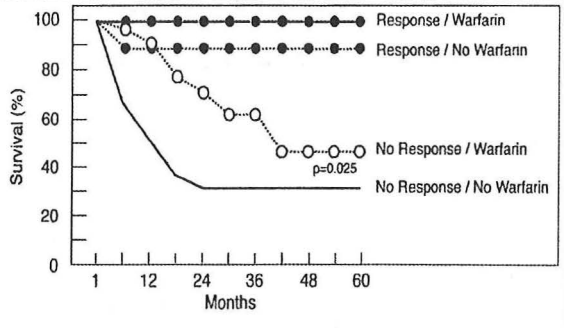

Figure 10: CCB and warfarin treatment vs. survival (n=64)[116].

Table 9: Projected and observed survival in CCB responders and non-responders [Adapted from ref[41].]

	Projected Survival			Observed Survival		
	1 yr.	3 yr.	5 yr.	1 yr.	3 yr.	5 yr.
Responders (n=17)	0.7	0.6	0.4	0.9	0.9	0.9
Non-responders (n=47)	0.7	0.5	0.3	0.7	0.4	0.4

NYHA class III-IV patients with "unexplained" pulmonary HTN, who fail the initial acute vasodilator challenge or the subsequent CCB challenge or decompensate on CCB therapy, should be treated with a continuous infusion of prostacyclin[115]. NYHA class III-IV patients with a poor response to adenosine challenge (mean reduction in PVR 6±13% wood unit, n=7) still demonstrate a significant reduction in PVR on long term continuous prostacyclin therapy (mean reduction PVR 39±14% wood unit; p=0.002)[112]. Similarly, long term treatment with prostacyclin also produces a sustained hemodynamic response in patients with a poor response to acute prostacyclin challenge[42]. This lends support to the notion that prostacyclin possesses other beneficial properties[120] besides vasodilator properties (ie. platelet anti-aggregating properties and inhibitory effects on adverse vascular remodeling).

A suggested starting dose for prostacyclin is 2 ng/kg/min with dose increases in increments of 1.5 ng/kg/min[121]. The average discharge dose after a 3-day initial titration period was 6.5 ng/kg/min. Subsequent increases of 1.5 ng/kg/min are usually based on symptoms, although some centers routinely increase the dose every 3 weeks. Adverse symptoms and outcomes are listed in Table 10.

Table10: Symptoms and adverse outcomes associated with prostacyclin[121].

Early	Chronic	Catheter-related
➢ Jaw pain	➢ Low platelet count	➢ Local Infection
➢ Flushing	➢ Rash	➢ Bacteremia
➢ Headache	➢ Weight loss	➢ Thrombosis
➢ Nausea	➢ Ascites	
➢ Tachycardia	➢ Bone Pain	
➢ Diarrhea	➢ Thyroid Dysfunction	
➢ Hypotension	➢ High cardiac output state	
➢ Joint pain		
➢ Chest Pain		

In NYHA class III-IV "unexplained" pulmonary HTN patients, long-term continuous prostacyclin therapy results in sustained improvements in hemodynamics and functional status[42,112,122]. Survival is improved compared to NIH historical controls[42] (Fig. 11) and among patients randomized to treatment[122]. Prostacyclin experience in NYHA class I-II patients is minimal.

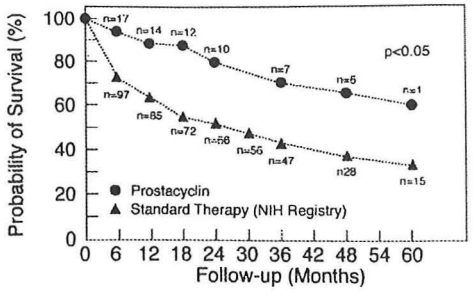

Figure 11: Survival in prostacyclin treated patients vs. historical controls.

Data on prostacyclin is available in a small number of patients with pulmonary HTN due to atrial septal defect, porto-pulmonary HTN, and collagen vascular disease. Significant reductions in mean PAP and PVR were found after 1½ years of therapy. Remember the pathology of these forms of "explained' pulmonary HTN may also demonstrate lesions consistent with pulmonary vasculopathy

Recently, Beraprost sodium (BPS), an oral analogue of prostacyclin, has been shown retrospectively to significantly improve mean PAP, CO and TPR in NYHA class III-IV patients with "unexplained" pulmonary HTN[123]. Patients treated with BPS compared to conventionally treated patients, demonstrated improved 1, 3, and 5 year survivals (96%, 86%, 76% vs. 77%, 47%, 44%; $p<0.05$).

Transplantation: The initial form of transplantation for "unexplained" pulmonary HTN was combined heart-lung[124,125]. It was originally believed that heart-lung transplantation was required due to the combination of pulmonary vascular disease and a failing RV. However, the right heart has a remarkable capacity to reverse remodel. Immediate reduction of PAP and PVR leads to normalization of RV geometry and function even in severely dysfunctional right ventricles[126]. Currently lung transplantation is the preferred method of transplantation for "unexplained" pulmonary HTN. Compared to those who had other indications for lung transplantation, one-year survival rates after lung transplantation for "unexplained" pulmonary HTN (65-70%)[127] are lower[128]. Major long term morbidity and mortality is related to infection, rejection and bronchiolitis obliterans[128]. It is recommended that transplantation be considered for those patients who are NYHA class III-IV and failing prostacyclin therapy[89,115]. Since the wait for a donor lung can be over a year, it is not unreasonable to initiate transplant evaluation while initiating prostacyclin therapy[115]. Patients whose clinical status improves substantially on prostacyclin can defer transplantation.

Adjunctive supportive measures: Patients need to be familiar with factors that can aggravate their illness. They should avoid decongestants with α-adrenergic properties, high altitudes, and non-pressurized airplane cabins[129].

Women of childbearing potential should be counseled on birth control. Pregnancy and parturition are associated with cardiovascular changes that are poorly tolerated by patients with pulmonary HTN[130].

Physical activity can cause an increase in PAP. Patients should avoid isometric exercises and participate in a supervised cardiopulmonary rehabilitation program. In addition to the benefit of conditioning, patients will gain insight into their limitations and become more attentive of early warning symptoms.

Patients with "unexplained" pulmonary HTN develop right-sided heart failure with the resultant salt and water retention. Dietary counseling is beneficial. Symptomatic heart failure can be treated with diuretic agents. These agents lower RV preload and reduce excessive edema. In our practice we frequently use spironolactone alone or combined with furosemide.

The benefit of the cardiac glycoside digoxin in treating right heart dysfunction is controversial. There is no substantial data to suggest that digoxin has either a beneficial or detrimental effect in this disorder. However, adverse neurohormonal activation has been demonstrated in "unexplained" pulmonary HTN[131]. Plasma norepinephrine levels correlated significantly with PAP ($r = 0.66$, p 0.01) and pulmonary vascular resistance ($r = 0.69$, p 0.001). Digoxin therapy may therefore be beneficial in this disorder due to its sympatholytic[132] and inotropic properties.

Supplemental oxygen (O_2) prolongs survival with pulmonary HTN due to hypoxemic chronic obstructive lung disease[133,134]. In "unexplained" pulmonary HTN supplemental O_2 did not produce a significant benefit[135]. Most patients with "unexplained" pulmonary HTN do not exhibit resting hypoxemia until late in their disease[89]. Patients who develop severe right heart failure with markedly and chronically elevated RAP may become hypoxemic due to right to left shunting through a patent foramen ovale (PFO). Hypoxemia due solely to shunting is typically not significantly improved by supplemental O_2. If the hypoxemia is thought to be due to increased O_2 extraction with fixed delivery as may be the case in exercise induced hypoxemia then ambulatory supplemental O_2 (maintain $SaO_2 > 90$-92%) may be reasonable[89].

Atrial septostomy is an investigational strategy. Patients with "unexplained" pulmonary HTN and PFO have been reported to survive longer than those without a PFO[136]. Young patients with severe "unexplained" pulmonary HTN and syncope who survived (13/15) blade balloon atrial septostomy manifested clinical and hemodynamic improvement and improved survival. Atrial septostomy attempts to improve oxygen delivery by "decompressing" the overloaded right heart and improving cardiac output. The degree to which this is counteracted by the decline in oxygen saturation that results from right-to-left shunting is unclear.

Summary

Primary pulmonary HTN is an uncommon disorder for which there is no explainable etiology. Its histopathology is characterized by a vasculopathy and its pathophysiology involves endothelial injury and dysfunction (adverse vascular remodeling). I propose that a better term for the disease is unexplained or idiopathic pulmonary hypertensive vasculopathy. There exist explainable forms of pulmonary hypertensive vasculopathy that are toxin-induced, immune-disorder-induced or shear stress-induced. These processes may represent inciting events (risk factors) for developing pulmonary hypertensive vasculopathy in genetically predisposed individuals. The natural history of the disease is one of high morbidity and mortality in a relatively young population. Vasodilator therapies (CCB, and prostacyclin) and systemic anticoagulation improve survival. Figure 12 presents a management algorithm[115].

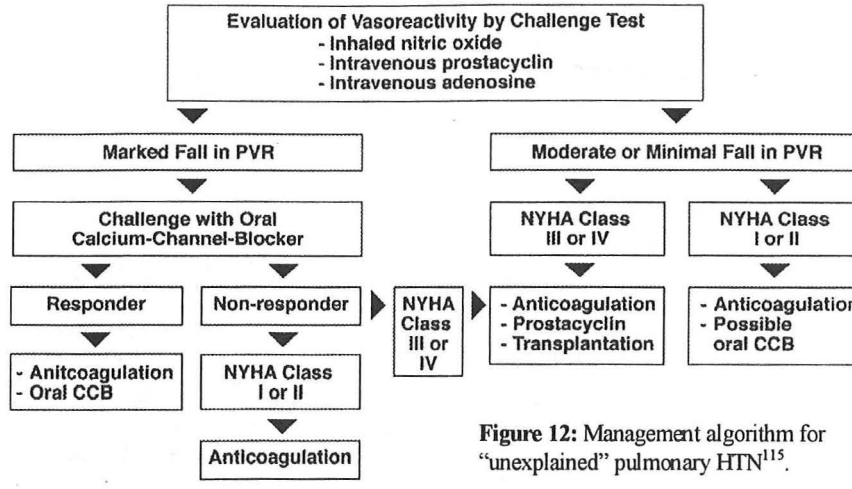

Figure 12: Management algorithm for "unexplained" pulmonary HTN[115].

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