PULMONARY HYPERTENSION

Anthony R. Dal Nogare, M.D.

Medical Grand Rounds
University of Texas
Southwestern Medical Center
October 17, 1996

"Breathing of pure oxygen lowered the pulmonary arterial pressure and oxygen-lack raised it...the experiments seem to warrant the conclusion that the regulation of the pulmonary blood flow is mainly mediated by a local action of the blood and alveolar gases leading to an adequate distribution of the blood through the various parts of the lungs according to the efficiency of aeration"

U.S. V. Euler, G. Liljestrand
Acta Phys. Scand. 12:22-41, 1946

BIOGRAPHICAL INFORMATION

Name: Anthony R. Dal Nogare, M.D.

Rank: Associate Professor of Medicine

Division: Pulmonary and Critical Care Medicine

Particular Interests: Infectious Diseases of the lung, glycoproteins, critical care medicine.

INTRODUCTION

The normal pulmonary circulation consists of a low resistance, high compliance vascular bed in which relatively low pressure suffices to move blood to the left ventricle. The pulmonary circulations' major function is to arterialize venous blood for distribution to the systemic circulation. Pulmonay hypertension results from one of three hemodynamic events-increased resistance, increased flow, or increased pulmonary venous pressure. Alveolar hypoxia, one of the commonest causes of hypertension, increases vascular resistance due to both acute vasoconstriction and induction of structural changes in vessel walls. Pulmonary arteries are unique in their response to hypoxia, and a major focus will be on recent advances in the pathogenesis of hypoxia-induced pulmonary vascular disease.

DEFINITIONS

An expert committee of the World Health Organization has developed the following commonly used definitions (1).

Pulmonary hypertension - A mean pulmonary artery pressure $\geq$ 25 mmHg.
Elevated pulmonary vascular resistance (PVR) - A PVR > 300 dynes sec cm -5.
Cor pulmonale - Hypertrophy of the right ventricle resulting from diseases affecting the function and/or the structure of the lung, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart or of congenital heart disease. Thus, cor pulmonale represents a subset of right heart failure.

DETECTION OF PULMONARY HYPERTENSION

Unlike systemic arteries there is no simple, non-invasive way to measure pulmonary arterial pressure. An elevated pulmonary artery pressure (PAP) per se is not associated with symptoms and the only manifestation on physical examination may be a loud P_2. Over time the right ventricle hypertrophies and then dilates, resulting in the signs and symptoms of right heart failure including jugular venous distention, a right ventricular S3, and tricupsid regurgitation. Although these physical findings frequently indicate the presence of pulmonary hypertension, their sensitivity and specificity are not known, detection of these findings is operator-dependant, and precise measurement of pulmonary pressure by physical examination is impossible.

Laboratory tests for pulmonary hypertension can be divided into two groups - those which directly measure pulmonary arterial pressure, and those measuring the effect hypertension has on the right ventricle (Table 1). Criteria for right ventricular hypertrophy are shown on Table 2. These ECG criteria are highly specific for anatomic right ventricular hypertrophy but are insensitive; several clinical-pathologic correlative studies, largely performed in COPD patients, have shown a sensitivity of only 15-60% (2-4). Both hyper-inflation of the lung, with its confounding effect on voltage and axis, and the dominant effect of the left ventricle on ECG patterns likely account for the low sensitivity.

Table 1

Diagnostic Tests

Indirect

- Electrocardiograhy
- Right ventricular ejection fraction

Direct

- Right heart catheterization
- Chest radiograph
- Doppler echocardiography

Table 2

Electrocardiographic Criteria of Right Ventricular Hypertrophy

- Right axis >90°
- Ratio of R/S voltage > 1.0 in V1, <1.0 in V6
- S1,S2,S3 pattern in leads I,II,III
- Incomplete RBBB pattern V1

Multiple gated acquistion (MUGA) scans, commonly performed to measure a left ventricular ejection fraction, can also measure right ventricular ejection fraction with the first pass technique. The normal resting right ventricular ejection fraction (RVEF) is >45%, and the RVEF normally increases by >5% during low level exercise (5). Many COPD patients have either a low resting RVEF or fail to increase RVEF with exercise. In one study of 20 COPD patients, who had both a RVEF and direct measurement of PAP by catheterization, there was a good inverse correlation between RVEF and pulmonary artery systolic pressure (Figure 1). All of the 14 subjects with pulmonary hypertension had an RVEF <45% (6). Presumably, the effect of pulmonary hypertension on RVEF reflects the sensitivity of the relatively thin-walled right ventricle to the afterload imposed by an elevated PAP. An accurate RVEF cannot be obtained if tricupsid regurgitation is present, but otherwise a low resting RVEF is a reasonable indication of pulmonary hypertension.

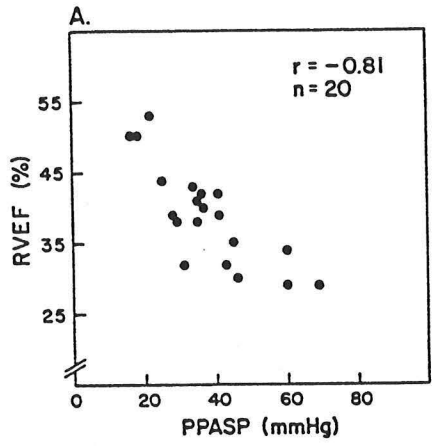

FIGURE 1: Relationship between peak pulmonary artery systolic pressure (PPASP) and RVEF

The definitive, gold standard test remains right heart catheterization with direct measurement of the PAP. In addition to pressure measurement, left to right shunts can be detected and pulmonary angiography can be performed. Angiograms were thought to be contraindicated in pulmonary hypertension, due to the frequent occurrence of procedure-related cardiac arrest reported in the older literature. More recent experience, in which angiograms were performed cautiously with injection of small volumes of contrast material, have shown the procedure to be safe even in patients with extremely elevated PAP (7).

The chest radiograph, a simple, widely available test, may also be useful for detecting pulmonary hypertension because the central pulmonary arteries are often dilated and the diameter of the right descending pulmonary artery can be measured on most chest radiographs. The data shown on Table 3 came from a study of 34 COPD patients who had chest radiographs and right heart catheterization. A right descending pulmonary artery diameter >2 cm was 95% sensitive and 81% specific for the presence of pulmonary hypertension (8). However, it is unknown if an enlarged right descending artery predicts hypertension equally well in patients without COPD.

Table 3

The Chest Radiograph and Pulmonary Hypertension in 34 COPD Patients

	PAP	
Diameter right Descending pulmonary Artery	>25 mmHg	<25 mmHg
>2 cm	19	3
<2 cm	1	11

Doppler echocardiography is able to measure the systolic pressure gradient between the right ventricle and right atrium, if regurgitant flow across the tricupsid valve can be detected. Since most patients, even if no ascultatory evidence of tricupsid regurgitation is present, have regurgitation by echo, the test is widely applicable and can be performed even on COPD patients. In practice, the right ventricular - right atrial pressure gradient is added to an estimated right atrial pressure to obtain right ventricular systolic pressure, which should be equal to pulmonary arterial systolic pressure if no pulmonic stenosis exists. Figure 2 shows the excellent correlation between measured right ventricular systolic pressure and doppler estimated pressure in 127 patients (9). Thus, duplex echocardiography is an accurate method capable of detecting and quantifying pulmonary hypertension and it is the preferred non-invasive test for confirming the diagnosis.

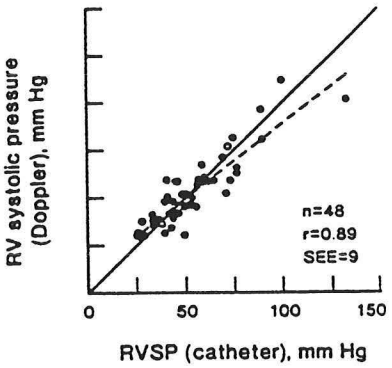

FIGURE 2

DIFFERENTIAL DIAGNOSIS OF PULMONARY HYPERTENSION

Table 4 orders the diverse conditions causing pulmonary hypertension into three groups. Cardiac diseases causing increased pulmonary venous pressure, such as congestive heart failure or mitral valve disease, typically cause mild increases in PAP which correct when the underlying cardiac problem is treated. Large volume, left to right shunts due to atrial/ventricular septal defects or a patent ductus arteriosus cause reversible pulmonary hypertension initially, but if closure is unduly delayed persistent pulmonary hypertension occurs due to fixed structural alterations in pulmonary arteries (Eisenmengers syndrome).

Table 4

Classification of Pulmonary Hypertension

- Secondary to cardiac disease

  Congestive heart failure
  Congenital disease with left to right shunt
  Valvular disease

- Secondary to chronic hypoxia

  Obstructive/restrictive lung disease
  Chest wall - kyphoscoliosis
  Chronic hypoventilation
  Sleep apnea
  High altitude

- Pulmonary vascular disease

  Infections - Schistosomiasis mansoni, HIV
  Hemoglobinopathies - HgSS, HgSC
  Drugs
  Peripheral pulmonic stenosis
  Pulmonary artery sarcoma
  Extrinsic compression - mediastinal tumors, fibrosis
  Cirrhosis
  Vasculitis - Rheumatoid arthritis, PSS, Takayasus arteritis
  Pulmonary emboli
  Primary pulmonary hypertension
  Veno-occlusive disease

Chronic hypoxia is a common cause of pulmonary hypertension. Patients with chronic obstructive pulmonary disease (COPD) typically develop pulmonay hypertension once their FEV1 falls below 1.0 liters. The degree of hypertension is modest and progression is slow, with an average increase in mean PAP of 1 mmHg/year (10). For individual COPD patients the rate of increase is inversely correlated with the degree of hypoxemia. Pulmonary hypertension is a poor prognostic marker for COPD, and survival beyond three years is rare when the PVR exceeds 500 dynes.sec.cm^{-5} (11). Hypertension complicates interstitial lung disease when hypoxemia occurs, usually when the vital capacity falls to <50% of predicted (12). Patients with severe kyphoscoliosis, chronic hypoventilatory disorders, the sleep apnea syndrome, and people living at high altitude may also develop hypertension. Experience with sleep apnea patients has shown that intermittent periods of hypoxia, which occur during apneas, can cause hypertension; most sleep apnea patients are normoxic during the day and remain well oxygenated during sleep except when apneic (13,14). Based on results with animal models, only two hours of hypoxia per 24 hours will cause an elevated PAP (15).

A large number of diseases cause pulmonary hypertension by directly affecting pulmonary vessels. Schistosomiasis mansoni infection, a common cause of hypertension in certain parts of the Mideast, causes peri-vascular fibrosis when ova deposited in the bloodstream lodge in pulmonary arteries, and patients infected with HIV may present with pulmonary hypertension which resembles primary pulmonary hypertension (16). Hemoglobinopathies cause hypertension due to obstruction of lung vessels by clumped red blood cells. Both oral and intravenous drugs can cause hypertension. In addition to its numerous effects on systemic vessels, intravenous cocaine can cause pulmonary hypertension (17). In 1967 a large number of European patients treated with the anorexic drug aminorex fumarate developed pulmonary hypertension. Aminorex was never approved in the United States but a similar compound, dexfenfluramine, has recently been approved and has already been linked to pulmonary hypertension (18). Intravenous drug addicts who inject crushed tablets develop hypertension due to talc and other tablet filler material which induces a foreign body granulomatous reaction in lung vessels. Peripheral pulmonic stenosis, primary sarcomas of main pulmonary arteries, and extrinsic compression due to mediastinal fibrosis (a complication of histoplasmosis) or mediastinal tumors are rare causes.

Pulmonary hypertension is an unusual complication of cirrhosis which usually occurs after surgical creation of a portal-systemic shunt. Because of this temporal relationship it has been speculated that the liver normally removes a substance, which is vasoconstrictive/toxic to pulmonary arteries, from the portal blood (19). Significant pulmonary arteritis has been described in rheumatoid arthritis, Takayasu's arteritis, and progressive systemic sclerosis (PSS). In one series of PSS patients who had right heart catheterization, 30% had elevated PAP, and patients with the CREST variant had a 50% prevalence of pulmonary hypertension (20).

The last three disorders listed on Table 4 - pulmonary emboli, primary pulmonary hypertension, and veno-occlusive disease - comprise the differential diagnosis for what has been called unexplained pulmonary hypertension, i.e. patients presenting solely with hypertension which is not secondary to any of the previously mentioned conditions. Most pulmonary emboli, if diagnosed and appropriately treated, do not result in hypertension (21). In one series of 76 patients who had emboli and were followed with right heart catheterization 5 years later, none of the patients with single emboli developed hypertension (22). However, tumor cell emboli, which are usually due to stomach/breast adenocarcinoma or trophoblastic tumors, can cause rapidly progressive hypertension (23). Also, a syndrome known as chronic thromboembolic pulmonary hypertension has been described (Table 5). Patients with this condition present with right heart failure, dyspnea, mild hypoxemia, and have no history of prior emboli. Laboratory examination shows large pulmonary arteries on chest radiographs, normal spirometry but a low diffusion capacity for carbon monoxide (DLCO), and a decreased PaO_2 with exercise. There is no evidence of either hypercoagulability or impaired fibrinolysis. Typically these patients have large, organized, bilateral emboli obstructing main and lobar arteries (24). As will be reviewed in a subsequent section, surgical thromboendarterectomy is lifesaving and results in dramatic functional improvement.

Table 5

Features of Chronic Thromboembolic Pulmonary Hypertension

- No history of prior pulmonary emboli
- Patients present with dyspnea and right ventricular failure
- Perfusion lung scans positive
- Pulmonary angiograms show large clots in central pulmonary arteries
- Surgical thromboendarterectomy treatment of choice

Primary pulmonary hypertension (PPH) is an idiopathic condition usually affecting young females (Table 6) (25). Based on data from the NIH PPH registry of 194 patients, PPH patients typically present with some combination of dyspnea (98%), fatigue (73%), chest pain (47%), and syncope (36%). Physical examination reveals a loud P_2 (93%) and evidence of right ventricular failure. Large pulmonary arteries are present on chest radiographs, pulmonary function tests show normal spirometry with a reduced DLCO, and perfusion lung scans are normal (26). PPH patients typically have extremely elevated PAP, averaging 60 mmHg. PPH is usually fatal, with a median survival of 2.8 years; factors associated with poor survival in individual patients include PAP >85 mmHg and a low cardiac index (<2.0 L/min/m^2) (27).

Table 6

Primary Pulmonary Hypertension

- 1.7:1 Female:Male, average age 36
- Dyspnea, fatigue, chest pain, syncope common complaints
- Normal spirometry, reduced DLCO, normal perfusion lung scan
- Markedly elevated PAP
- Median survival 2.8 years

Veno-occlusive disease is a rare condition usually affecting young males and characterized pathologically by a bland intimal fibrosis of large pulmonary veins. Patients present with dyspnea. The chest radiograph typically shows evidence of interstitial edema (Kerley B lines) with large pulmonary arteries and a normal sized left ventricle. Interestingly, the pulmonary capillary wedge pressure is usually normal. Veno-occlusive disease is idiopathic, although a few cases have occurred following chemotherapy with carmustine or bleomycin (28,29).

Because the clinical features of PPH, chronic thromboembolic disease, and veno-occlusive disease are so similar it is often difficult to distinguish the three. A comparison of two readily available tests, the chest radiograph and perfusion lung scan, will usually allow a rapid presumptive diagnosis and serve as a guide for additional diagnostic studies. (Table 7) (30).

Table 7

Radiographic/Lung Scan Abnormalities in Unexplained Pulmonary Hypertension

Diagnosis	Chest Radiograph	Perfusion Scan
Chronic Thromboembolic	Large PA	Segmental Defects
PPH	Large PA	Normal
Veno-occlusive	Kerley B lines	Patchy Defects

PATHOLOGY OF PULMONARY HYPERTENSION

Normal pulmonary arteries are divided by size into three types - elastic (diameter > 1 mm), muscular (<1 mm, > 0.1 mm), and arterioles (diameter <0.1 mm). Only the media of muscular arteries normally has identifiable smooth muscle cells, accounting for the normal low resistance and high compliance of the pulmonary circulation.

In 1958 two pathologists, Heath and Edwards, developed a widely used grading system for pulmonary vascular disease. Although the scheme was developed to describe vascular changes secondary to congenital heart disease, it is applicable to all types of pulmonary hypertension (Figure 3). In brief, the changes of pulmonary vascular disease can be graded from I to VI. The smaller, muscular arteries and arterioles - which account for most of the normally low pulmonary vascular resistance - are the vessels most affected by disease. Basically, the scheme describes a continuum marked by increasing numbers of smooth muscle cells and connective tissue in the media and intima for grades I-III. Higher grade, IV-VI lesions are characterized by intimal proliferation (plexiform lesions), dilated vessels, and vascular wall necrosis. Grades I-III are reversible, present in all types of pulmonary hypertension, and are generally associated with less severe hypertension. Grades IV-VI are irreversible, present only in primary pulmonary hypertension, chronic thromboembolic disease, congenital cardiac disease with left to right shunt, cirrhosis, and anorexic drug ingestion, and are associated with extremely elevated PAP (31).

GRADE OF HPVD	1	2	3	4	5	6
Medial hypertrophy	+	+	+	+	+	+
Intimal proliferation	O	+ C	+ F	+ FE	+ FE	+ FE
Generalized dilatation	O	O	O	+	+	+
Plexiform and other dilatation lesions	O	O	O	+	+	+
Pulmonary haemosiderosis	O	O	O	O	+	+
Fibrinoid necrosis	O	O	O	O	O	+

C = Cellular F = Fibrous FE = Fibroelastic

FIGURE 3: Heath and Edwards classification of hypertensive pulmonary vascular disease (HPVD)

ACUTE HYPOXIC VASOCONSTRICTION

Hypoxia-induced vasoconstriction of pulmonary arterioles was first described in 1946 (32), but only recently has the basis of this important physiologic response been elucidated. To ensure adequate gas exchange the lung must closely match ventilation (V) and perfusion (Q); when perfusion occurs to areas of poorly-ventilated lung, hypoxemia results due to the presence of ventilation/perfusion (V/Q) inequality, defined as a V/Q ratio <0.1. If perfusion occurs to completely unventilated lung, then severe hypoxemia results due to the presence of an intra-pulmonary shunt (V/Q ratio = 0). Acute hypoxic vasoconstriction occurs in response to low levels of alveolar (not blood) PO_2 and acts to promote V/Q matching by decreasing perfusion to poorly ventilated, hypoxic lung, thus increasing perfusion to other normally ventilated areas (Figure 4) (33). Failure of hypoxic vasoconstriction, which has been shown to occur in animal models of pneumonia (34) and the adult respiratory distress syndrome (35), results in severe hypoxemia.

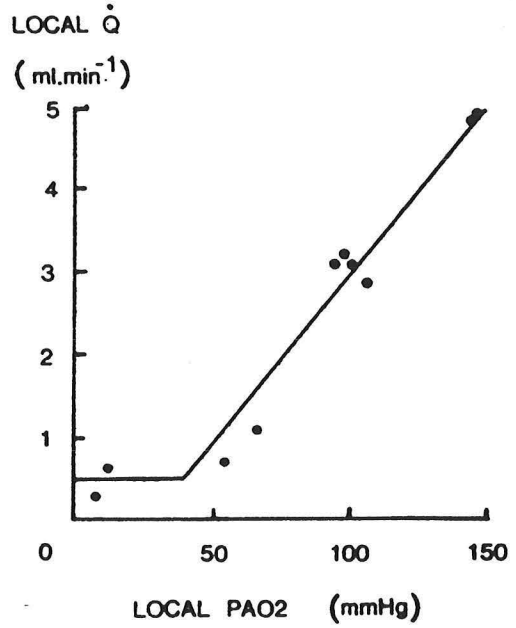

FIGURE 4: Effect of alveolar hypoxia on perfusion (Q)

Some pertinent characteristics of acute hypoxic vasoconstriction are shown on Table 8. For many years it was thought that separate sensor cells respond to hypoxia by releasing a vasoconstrictive mediator, but it is now clear that pulmonary vascular smooth muscle cells by themselves can sense and respond to hypoxia. Vasoconstriction is a unique property of pulmonary arterial muscle cells, because vascular smooth muscle from other sites (cerebral, renal, mesenteric) relax in response to hypoxia (Figure 5) (36). In humans hypoxic vasoconstriction occurs within a physiologic range of oxygen tensions, beginning at a PO_2 of 60 and reaching maximal constriction at 40 mmHg.

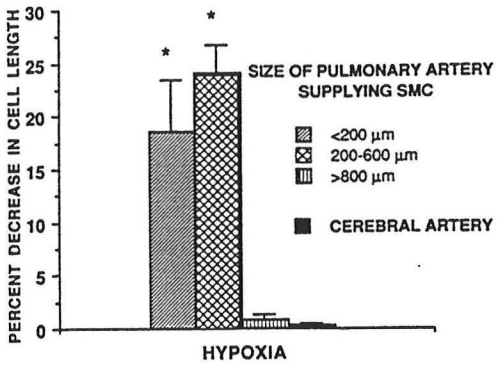

FIGURE 5: Acute hypoxic vasoconstriction

Table 8

Acute Hypoxic Vasoconstriction

- Rapid, reversible response to alveolar hypoxia (37)
- Occurs in small (<300 µm) pulmonary arterioles (38)
- Unique property of pulmonary vascular smooth muscle cells
- Increased by oxidative phosphorylation inhibitors and intra-cellular calcium (39)

In vitro investigation of isolated pulmonary smooth muscle cells showed that the earliest change induced by hypoxia is depolarization of the muscle cell membrane (i.e. The resting membrane potential or EM becomes less negative) (Figure 6) (40). Membrane depolarization opens a voltage-dependant CA^{++} channel, resulting in an increase in intracellular calcium concentration and muscle cell contraction. Subsequently it was shown that normal vascular smooth muscle cell polarization is dependent on an outward efflux of K^+ through a K^+ channel; hypoxia decreases K^+ efflux through the channel, causing membrane depolarization (41,42). Thus, hypoxic vasoconstriction involves two ion channels and begins with decreased K^+ conductance through the K^+ channel (43).

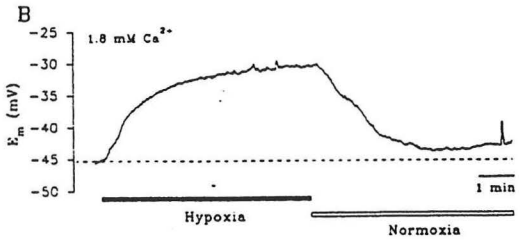

FIGURE 6

How does hypoxia regulate the membrane K^+ channel protein of pulmonary vascular smooth muscle cells? Although currently unproven, two observations suggest the following mechanism. Patch clamp experiments with pulmonary smooth muscle have shown that intracellular reducing compounds such as NADH and GSH inactivate the K^+ channel and depolarize the cells (44). Previous work with cloned rat brain K^+ channel proteins had shown that amino-terminal cysteine residues are critical for channel function. Cysteine reduction apparently frees the amino-terminal portion of the K^+ channel protein, allowing it to move and block K^+ efflux; conversely, cysteine oxidation creates intra-cysteine disulfide bonds, reducing mobility and opening the channel (Figure 7) (45,46). Since even modest levels of hypoxia reduce formation of intracellular oxidants, NADH and GSH quickly accumulate inside hypoxic smooth muscle cells (Figure 8). Such a mechanism is supported by the time required (seconds) for hypoxic vasoconstriction and by the *in vivo* observations that acidosis and reducing agents increase, whereas oxidants decrease, hypoxic vasoconstriction (39). Thus, pulmonary vascular muscle cells possess an elegant mechanism which allows a direct and rapid response to hypoxia (Figure 9) (47).

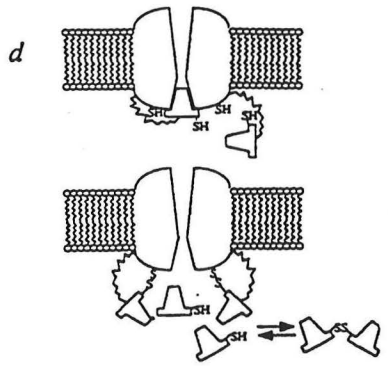

FIGURE 7

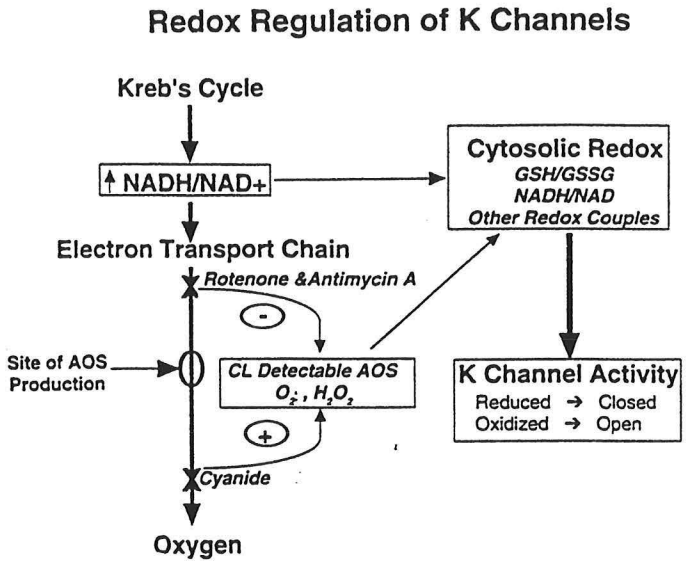

FIGURE 8

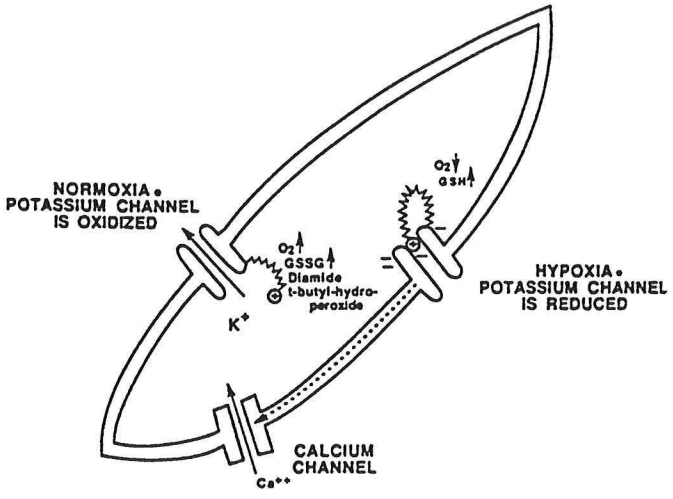

FIGURE 9

PATHOPHYSIOLOGY OF CHRONIC HYPOXIC PULMONARY HYPERTENSION

Acute hypoxic vasoconstriction is fully reversible, and the PAP rapidly normalizes when normoxia is restored. After several weeks of hypoxia structural changes occur in pulmonary arteries which result in a fixed increase of PVR and PAP; although some degree of acute vasoconstriction probably exists, restoration of normoxia initially results in only a small decrease in PAP. This section reviews new information about the mediators responsible for the structural vascular changes which are characteristic of all types of pulmonary hypertension. Most experimental and clinical investigations have used chronic hypoxia to induce hypertension. In the commonly used rat model as few as 10-20 days of hypoxia (10% oxygen corresponding to an alveolar oxygen tension of approximately 50 mmHg) results in increased arteriolar muscularization, right ventricular hypertrophy, and biochemical changes of increased vascular collagen and elastin content (48,49). Physiologically, the pulmonary vessels are less compliant and have an increased resistance, resulting in a doubling of PAP (50). Concomitant treatment with inhibitors of collagen synthesis or low doses of heparin, which inhibit smooth muscle proliferation, decrease pulmonary hypertension (51-52). Although the model uses hypoxia as a stimulus, the resultant vascular structural changes resemble those seen in all types of pulmonary hypertension and thus information derived from the model may be broadly applicable. Three mediators - Nitric oxide (NO), endothelin 1, and platelet derived growth factor (PDGF) - have been implicated in the pathogenesis of pulmonary hypertension.

Nitric Oxide (NO)

Nitric oxide, produced from L-arginine by pulmonary endothelial cells containing the type III isoform of nitric oxide synthase, dilates blood vessels by increasing cGMP in smooth muscle cells. Some relevant characteristics of NO are shown on Table 9. In normal subjects, administration of nitric oxide synthase inhibitors increases pulmonary vascular resistance (54), suggesting that basal NO production maintains the normally low pulmonary vascular resistance. *In vitro*, NO inhibits smooth muscle cell mitogenesis and, under conditions of extreme hypoxia (PO_2 of zero), NO blocks production of a vasoconstrictor (endothelin 1) and a growth factor (PDGF) (54,55). These observations have suggested the possibility that pulmonary hypertension might be caused by a NO deficiency.

Table 9

Nitric Oxide

- Normally produced by pulmonary endothelium
- Activates smooth muscle guanylate cyclase, thereby increasing cGMP concentration and relaxing vascular smooth muscle
- Inhibits endothelin 1 and platelet derived growth factor production by endothelial cells
- Decreases smooth muscle proliferation

Two recent human studies have supported the concept that NO production is decreased in pulmonary hypertension. Pulmonary artery rings, obtained from severe COPD patients (most of whom actually had cystic fibrosis) undergoing lung transplantation, had decreased dilation in response to acetylcholine (acetylcholine stimulates NO production by NOS) (Figure 10) (57). Decreased endothelial cell NOS, determined by histochemical staining and northern blot, was present in lung tissue obtained at the time of transplantation or open lung biopsy; patients in this study had either primary pulmonary hypertension or severe hypertension (mean PAP 60-70 mmHg) due to COPD, pulmonary fibrosis, or bronchiectasis (58,59). Although these findings are interesting, the patients in these two series had far advanced lung disease and severe hypertension, so it is uncertain whether the reduced endothelial NO production and NOS caused the pulmonary hypertension or whether they were reduced secondary to widespread endothelial injury caused by the severe pulmonary hypertension.

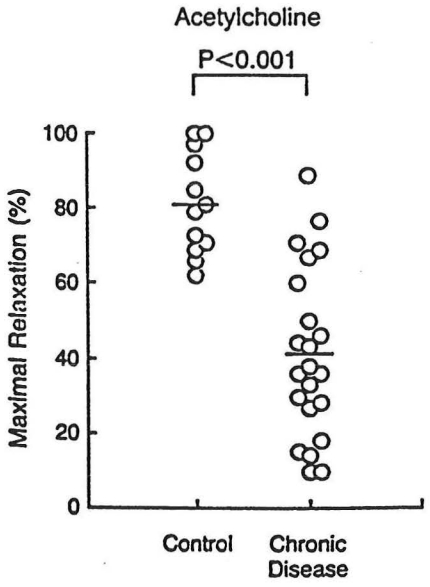

FIGURE 10: Acetylcholine-stinulated relaxation of pulmonary artery rings

Conflicting results regarding NO's role in pulmonary hypertension come from studies done with animal models. Five studies have reported increased levels of either NO production, cGMP (the vasodilator produced by smooth muscle in response to NO), or NOS in rats after 3 weeks hypoxia (Figure 11). These increase are large and are consistent with the observation that shear stress, which would increase secondary to acute hypoxic vasoconstriction, is a known stimulus for endothelial NO production (60-64). Only one study has reported a decreased acetylcholine response in pulmonary arteries of chronically hypoxic rats (65). In vitro, isolated bovine pulmonary artery endothelial cells release less NO under hypoxic conditions, but the degree of hypoxia required (PO_2 15 mmHg) is not physiologically relevant (66). Thus, the majority of animal studies in which early effects of hypoxia on NO have been measured suggest that NO deficiency is not required for the development of hypertension.

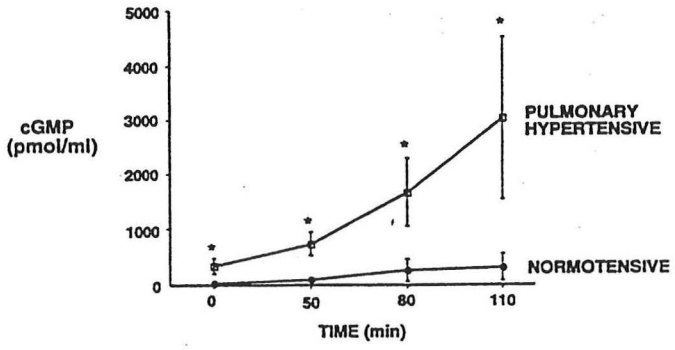

FIGURE 11: cGMP levels in normal and chronically hypoxic rats

Although it is probably not involved in the pathogenesis of hypertension, supplying increased amounts of NO to the pulmonary vasculature will decrease hypoxic hypertension. Rats exposed to hypoxia plus 40 PPM NO had significantly lower PAP and less arteriolar muscularization (67). Rats given NOS via an aerosolized adenoviral vector showed widespread NOS expression and less acute hypoxic vasoconstriction (68). Concentrations of cGMP, the smooth muscle vasodilator produced in response to NO, can be increased by inhibiting the phosphodiesterase which degrades cGMP, and recent experiments have demonstrated lower PAP in hypoxic rats treated with phosphodiesterase inhibitors (61). These results suggest that increasing pulmonary NO might be a useful therapy for pulmonary hypertension.

Endothelin 1

Endothelin 1 is a 21 amino acid peptide with the properties listed on Table 10. Endothelin's pathophysiologic role is complicated by the fact that its effects are receptor-dependent (69). Stimulation of the A receptor causes vasoconstriction, whereas B receptor stimulation causes vasodilation due to prostacyclin production (70). The normal lung removes circulating endothelin, and thus venous levels are higher than arterial.

Table 10

Endothelin 1

- Produced by endothelial cells
- Can cause vasoconstriction, smooth muscle/fibroblast proliferation (71)
- Two endothelin receptors (A and B) mediate different effects
- Pulmonary vessels normally remove endothelin from venous blood

Immunostaining of open lung biopsies obtained from patients with primary pulmonary hypertension and hypertension secondary to hypoxia has demonstrated increased endothelin 1 in pulmonary arteries (Figure 12). Normal controls had very little endothelin (72). Human endothelial cells exposed to Po_2 <30 mmHg express increased amounts of endothelin mRNA (73). Multiple studies of chronically hypoxic animals have shown that treatment with endothelin A receptor antagonists lowers, but does not normalize, the PAP (73-77). However, other investigators have not found increased endothelin 1 in chronically hypoxic animals, and one study reported increased levels of mRNA for the vasodilating B receptor and decreased A receptor mRNA (78,79). Because of these conflicting results no firm conclusions can be reached regarding endothelin 1 and hypoxia-induced hypertension.

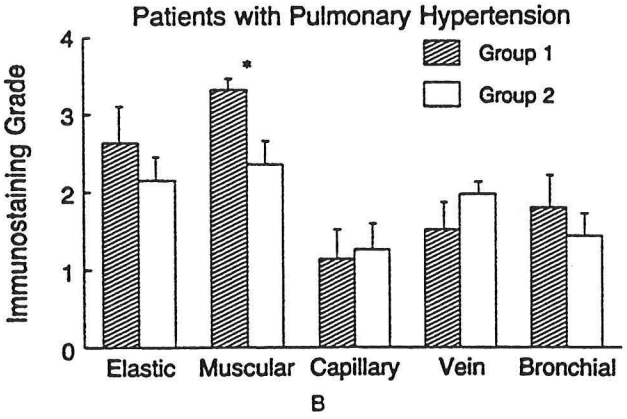

FIGURE 12: Endothelin 1 immunostraining

There is some preliminary data that endothelin 1 is involved in primary pulmonary hypertension. Systemic arterial blood obtained from primary pulmonary hypertension patients contains endothelin 1 in significantly higher concentration than venous blood, suggesting a net production of endothelin by pulmonary arteries (Figure 13) (81). Fawn hooded rats spontaneously develop pulmonary hypertension, thus resembling primary pulmonary hypertension in humans. Lung cell endothelin mRNA levels are three fold increased in these animals, and lung cell nuclei actively transcribe endothelin mRNA (78). These data suggest that excess endothelin 1 production by the lung may initiate primary pulmonary hypertension.

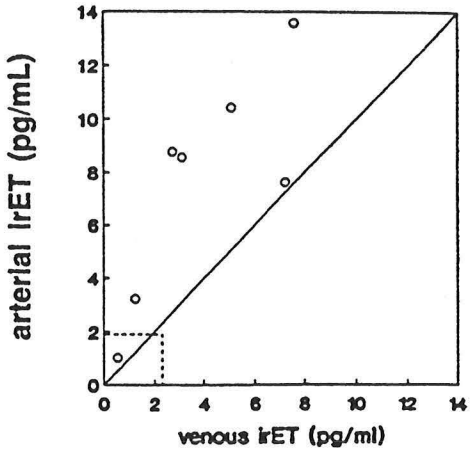

FIGURE 13: Endothelin 1 levels in seven PPH patients

Platelet Derived Growth Factor

Platelet derived growth factor (PDGF) is a dimeric glycoprotein composed of an A and B chain. PDGF is produced by endothelial and smooth muscle cells, is chemotactic and mitogenic for smooth muscle and fibroblasts, and stimulates collagen and elastin production by fibroblasts (82-84). Evidence that PDGF may be an important mediator includes the following:

1. Either pulmonary artery rings or pulmonary endothelial cell monolayers, when exposed to modest pressures of 40-50 mmHg, produce and release PDGF (85,86). PDGF is produced within hours of increased pressure, even under normoxic conditions. Hypoxia (30 mmHg PO_2) by itself also stimulates endothelial PDGF production (87).

2. Isolated vascular smooth muscle cells, exposed to a mechanical strain, produce and release PDGF which acts in an autocrine fasion to rapidly (24 - 48 hrs) stimulate smooth muscle proliferation (Figure 14) (88).

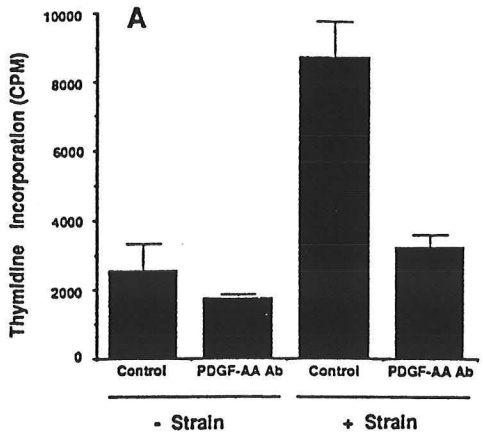

FIGURE 14: PDGF release by smooth muscle cells subjected to mechanical strain

3. Marked increases in collagen and elastin synthesis and cell proliferation occur rapidly in pulmonary arteries under hypoxic conditions, coincident with increased PDGF (85,89). Systemic arteries do not make PDGF in response to increased pressure and do not respond with cellular proliferation and connective tissue production.

4. In the chronic hypoxic rat model total lung PDGF mRNA increases within 24 hours of hypoxia and remains elevated for the entire period of hypoxia (up to 14 days) (Figure 15) (90).

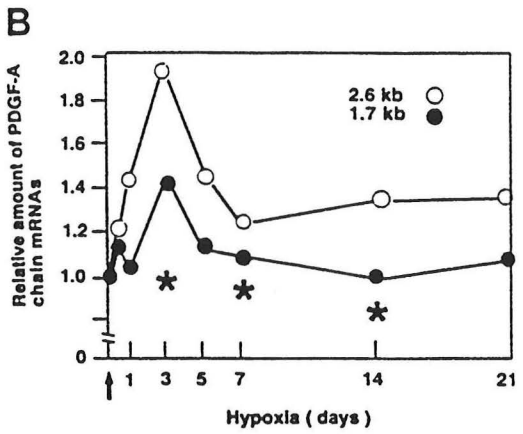

FIGURE 15: Pulmonary PDGF mRNA production during hypoxia

It is important to note that hypoxia per se is not necessary for PDGF production. Instead it is the increase in PAP secondary to acute hypoxic vasoconstriction that stimulates PDGF production. Several observations support this concept. Administration of calcium channel blocking drugs, which prevents acute hypoxic vasoconstriction, prevents structural changes in pulmonary vessels of chronically hypoxic animals (91,92). Banding of the left main pulmonary artery prior to chronic hypoxia prevents structural changes in pulmonary arteries distal to the band even though both sides are subject to the same degree of hypoxia. There is no hypoxia induced rise in vascular pressure on the banded side (Figure 16) (93). Patients with congenital heart disease and left to right shunts develop advanced structural changes in vessels subjected to high pressure/flow conditions. Pulmonary hypertension may thus represent the product of a positive feedback loop involving PDGF. An initial rise in PAP due to acute hypoxic vasoconstriction causes PDGF release, increasing arterial smooth muscle and connective tissue and thereby increasing vascular resistance. The increased resistance maintains or increases hypertension, thus maintaining an ongoing stimulus for continued PDGF release. Although I have focused on acute hypoxic vasoconstriction as the initial event, any cause of acute pulmonary hypertension (vasoactive prostaglandin release during acute inflammation, endothelin 1) could initiate PDGF release, causing structural changes in pulmonary vessels by a common final pathway.

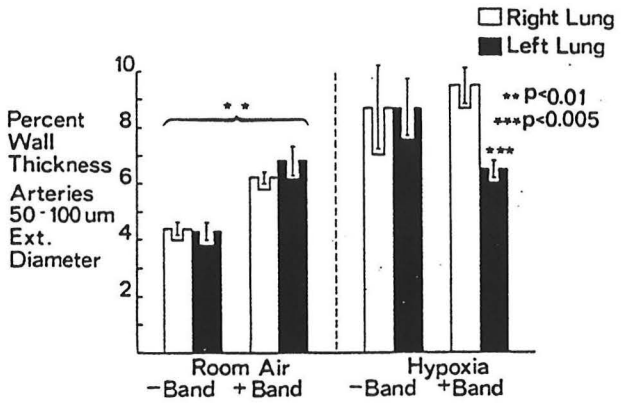

FIGURE 16: Banding reduces muscularization during hypoxia

TREATMENT OF PULMONARY HYPERTENSION

In general, treatment of the underlying disease will improve secondary pulmonary hypertension. For example, aggressive treatment of congestive heart failure normalizes pulmonary pressure, as does prevention of recurrent emboli by anticoagulation therapy. Three specific treatments - thromboendarterectomy, oxygen therapy, and vasodilators for PPH - will be reviewed in detail.

Patients with chronic thromboembolic hypertension have a poor prognosis and should have surgical thromboendarterectomy if possible. As mentioned previously these patients have large, central organized emboli and surgical removal requires a median sternotomy with bypass so that both sides can be cleared. Operative mortality tends to be high at inexperienced centers, is around 5% at experienced hospitals, and the functional improvement seen in patients is dramatic; most improve to NYHA class I or class II (Figure 17) (24).

NYHA Class	Preoperative	Postoperative
IV	63	0
III	49	6
II	5	26
I	0	85
Total	117	117

FIGURE 17: Effect of thromboendarterectomy on functional status

The Nocturnal Oxygen Therapy (NOTS) trial was the first large scale, prospective trial in the US to conclusively show that oxygen benefited hypoxemic COPD patients. 203 hypoxemic patients received either nocturnal or continuous oxygen and were followed for two years. Mortality at year two was 41% for the nocturnal oxygen group and 22% for continuous oxygen patients (94). 118 patients in the trial had both baseline and follow-up right heart catheterization after six months of oxygen, and their hemodynamic data are shown on Table 11. Patients treated with continuous oxygen had significant decreases in PAP and PVR (95). Although six months of continuous oxygen improved pulmonary hypertension, PAP remained elevated, and there are two possible explanations why PAP did not normalize. Patients in the continuous oxygen group actually only averaged about 17 hours oxygen use/day. Experience with animal models of hypoxic hypertension has shown that to reverse the structural changes in pulmonary vessels and normalize PAP 24 hours/day normoxia is necessary (Figure 18) (96). Another explanation is that sleeping COPD patients can develop profound hypoxia. In 15 COPD patients whose arterial blood gases were monitored during sleep, mean PaO_2 went from 65 mmHg (awake) to 55 in stage II-III sleep and fell to 50 during REM sleep (Figure 19). Sleep-induced hypoxia in COPD is due to both hypoventilation and the development of V/Q inequality (97).

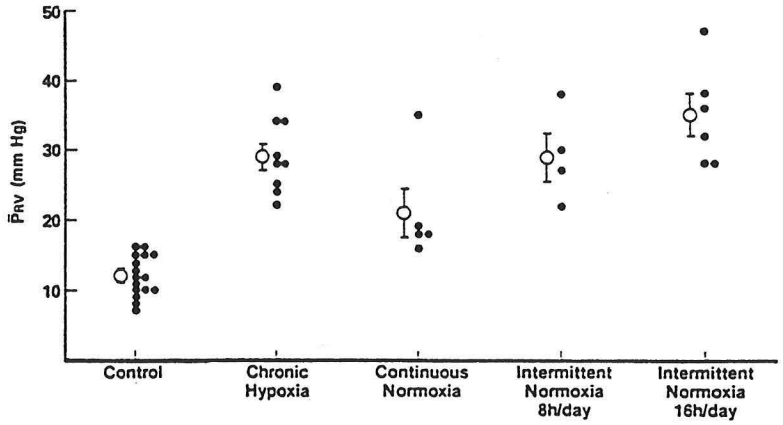

FIGURE 18: Effect of varying periods of normoxia on chronic hypoxic pulmonary hypertension

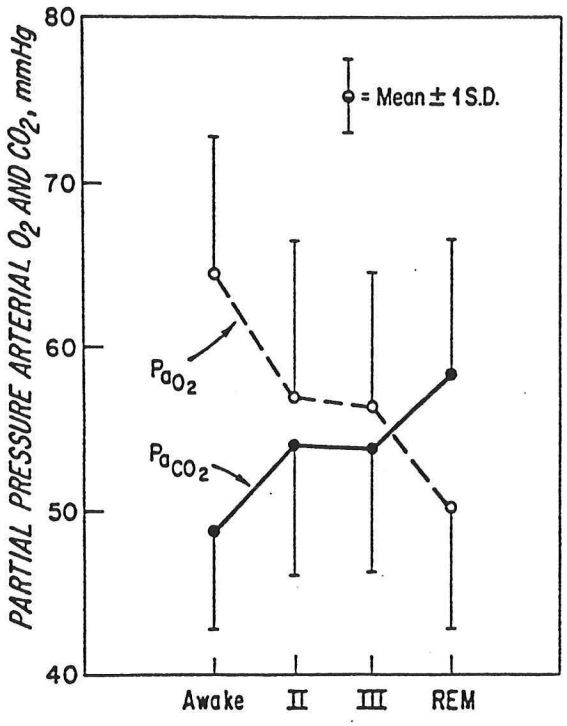

FIGURE 19: Hypoxemia during sleep in COPD

Table 11

Hemodynamic Data From the NOTS Trial

		6 Month	
	Study Entry	**Nocturnal O_2**	**Continuous O_2**
		(Change)	
PAP (mmHg)	29 ± 10	0 ± 7	-3 ± 11
PVR (Dynes)	330 ± 164	-15 ± 116	-68 ± 174
Stroke Vol. Index	34 ± 7	0.4 ± 8.4	+2.4 ± 8.1

In light of these observations, it is clear that we usually do a poor job of treating patients with long-term oxygen. Clinical guidelines for using oxygen are listed on Table 12. It is hoped that following these principles will lead to maximal hemodynamic improvement and survival. In addition to oxygen, cor pulmonale patients are commonly treated with digitalis and diuretics. Most patients have normal left ventricular function and require an increased systemic venous pressure to maintain right ventricular output. Thus, treatment with digitalis and diuretics is not beneficial but is associated with side effects (98,99).

Table 12

Guidelines for Oxygen Therapy

- Give the correct dose
- Adjust for nocturnal hypoxia
- Achieve 24 hour/day normoxia

PPH patients are usually treated with vasodilator drugs in an attempt to lower PAP. A large number of such drugs have been administered to PPH patients, with variable degrees of success; the major problem is that all of the commonly used drugs dilate systemic and pulmonary arteries, leading to complications such as systemic hypotension and death (100). Recently, encouraging results were reported in trials of prostacyclin (PGI2, a vasodilating prostaglandin) and calcium channel blockers. PGI2, which has to be administered by a continuous intravenous infusion, improved functional status, hemodynamics, and survival during a short (12 week) treatment period (101). Similar results were reported in 18 patients treated with long-term PGI2 infusion (102). Complications noted with intravenous PGI2 included sepsis, emboli, and death. Oral therapy with the calcium channel blockers nifedipine or diltiazem was studied in 64 PPH patients. Patients responding to a test dose of either drug with a >20% decrease in PVR were kept on the drug and followed for five years. Only seventeen (27%) of the 64 responded to the test dose with a decrease in PVR. These 17 patients had large, sustained decreases in PVR and PAP, significant functional improvement, and a 95% five year survival. Survival in the 47 non-responders was 55% (Figure 20) (10). One interpretation of these results is that the responders had less severe and irreversible pulmonary vascular disease than did the non-responders, and so might have had a better prognosis regardless of therapy (104). Most experts treat PPH patients with oral anticoagulants due to the frequent presence of in situ thrombi in their pulmonary arteries, and female patients should be counseled to avoid pregnancy (105,106). Heart-lung and single lung transplantation can also be performed in selected patients (107,108).

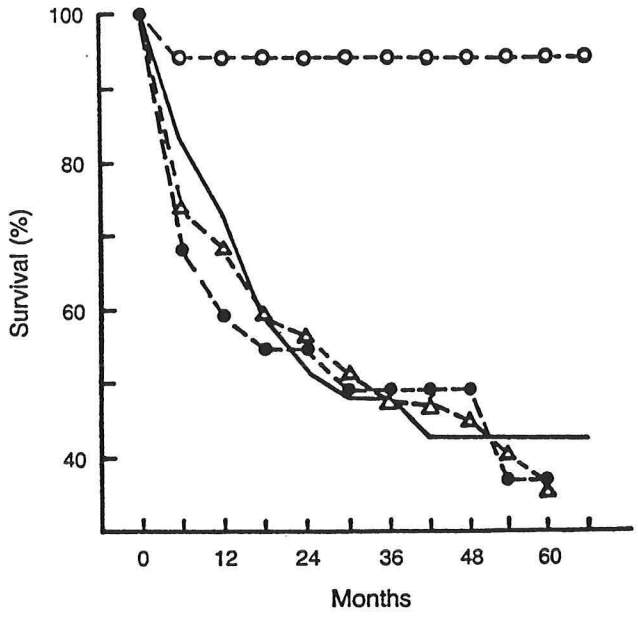

FIGURE 20: Survival of PPH patients treated with calcium channel blockers (open circles)

One selective and potent pulmonary vasodilator with therapeutic potential is inhaled NO. When given in low concentrations (10-40 PPM) as an inhaled gas NO dilates pulmonary vessels but has no systemic effect, because it is rapidly metabolized by red blood cells. Inhaled NO significantly decreases PAP of PPH, COPD, and ARDS patients without toxicity or systemic hypotension (109-111). If a practical delivery system capable of accurately administering NO in the PPM range could be designed, then long-term use of NO as a pulmonary vasodilator might be considered for many types of pulmonary hypertension.

REFERENCES

1. WHO Expert Committee Report on Chronic Cor Pulmonale. Circulation 27:594-600, 1963.

2. Murphy ML, F Hutcheson: The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy in Chronic Obstructive Pulmonary Disease. Chest 65(6):622-627, 1974.

3. Shmock CL, B Pomerantz, RS Mitchell, R Pryor, JC Maisel: The Electrocardiogram in Emphysema With and Without Chronic Airways Obstruction. Chest 60(4):328-334, 1971.

4. Shmock CL, RS Mitchell, B Pomerantz, R Pryor, JC Maisel: The Electrocardiogram in Chronic Airways Obstruction. Chest 60(4):335-340, 1971

5. Matthay RA, HF Berger, RA Davies, J Loke, DA Mahler, A Gottschalk, BL Azret: Right and Left Ventricular Exercise Performance in Chronic Obstructive Pulmonary Disease: Radionuclide Assessment. Ann. Int. Med. 93:234-239, 1980.

6. Brent BR, HF Berger, RA Matthay, D Mahler, L Pytlik, BL Zaret: Physiologic Correlates of Right Ventricular Ejection Fraction in Chronic Obstructive Pulmonary Disease: A Combined Radionuclide and Hemodynamic Study. Am. J. Cardiol. 50:255-261, 1982.

7. Nicod P, K Peterson, M Levine, H Dittrich, M Buchbinder, F Chappuis, K Moser: Pulmonary Angiography in Severe Chronic Pulmonary Hypertension. Ann. Int. Med. 107:565-568, 1987.

8. Chetty KG, SE Brown, RW Light: Identification of Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease From Routine Chest Radiographs. Am. Rev. Respir. Dis. 126:338-341, 1982.

9. Currie PJ, JB Seward, KL Chan, DA Fyfe, DJ Hagler, DDMair, GS Reeder, RA Nishimura, JTajik: Continuous Wave Doppler Determination of Right Ventricular Pressure: A Simultaneous Doppler-Catheterization Study of 127 Patients. J. Am. Coll. Cardiol. 6:750-756, 1985.

10. Weitzenblum E, A Loiseau, C Hirth, R Mirhom, J. Rasaholinjanahary: Course of Pulmonary Hemodynamics in Patients With Chronic Obstructive Pulmonary Disease. Chest 75:656-662, 1979.

11. Burrows B, LJ Kettel, AH Niden, M Gabinowitz, CF Diener: Patterns of Cardiovascular Dysfunction In Chronic Obstructive Lung Disease. New Eng. J. Med. 286:912-918, 1972.

12. Enson Y, HM Thomas, III, CH Bosken, JA Wood, EC Leroy, WA Blanch, HJ Wigger, RM Harvey: Pulmonary Hypertension in Interstitial Lung Disease: Relation of Vascular Resistance to Abnormal Lung Structure. Trans. Assoc. Am. Phys. 88:248-255, 1975.

13. Weitzenblum E, J Krieger, M Apprill, E Vallee, M Ehrhart, J Ratomaharo, M Oswald, D Kurtz: Daytime Pulmonary Hypertension in Patients With Obstructive Sleep Apnea Syndrome. Am. Rev. Respir. Dis. 138:345-349, 1988.

14. Sajkov D, RJ Cowie, AT Thornton, HA Espinoza, RD McEvoy: Pulmonary Hypertension and Hypoxemia in Obstructive Sleep Apnea Syndrome. Am. J. Respir. Crit. Care Med. 149:416-422, 1994.

15. Nattie EE, EA Doble: Threshold of Intermittent Hypoxia-Induced Right Ventricular Hypertrophy in the Rat. Respir. Physiol. 56:253-259, 1984.

16. Petitpretz P, F Brenot, R Azarian, F Parent, B Rain, P Herve, G Simonneau: Pulmonary Hypertension in Patients With Human Immunodeficiency Virus Infection. Circulation 89:2722-2727, 1994.

17. Yakel DL, MJ Eisenberg: Pulmonary Artery Hypertension in Chronic Intravenous Cocaine Users. Am. Heart J. 130(2):398-399, 1995.

18. Abenhaim L, Y Moribe, F Boenot, S Rich, et. al: Appetite-Suppressant Drugs and the Risk of Primary Pulmonary Hypertension. New Eng. J. Med. 335:609-616, 1996.

19. Lebrec D, JP Capron, D Dhumeaux, JP Benhamou: Pulmonary Hypertension Complicating Portal Hypertension. Am. Rev. Respir. Dis. 120:849-856, 1979.

20. Ungerer RG, DP Tashkin, D Furst, PJ Clements, H Gong, Jr., M Bein, JW Smith N Roberts, W Cabeen: Prevalence and Clinical Correlates of Pulmonary Arterial Hypertension in Progressive Systemic Sclerosis. Am. J. Med. 75:65-74, 1983.

21. Dalen JE, JS Banas, Jr., HL Brooks, GL Evans, JA Paraskos, L Dexter: Resolution Rate of Acute Pulmonary Emoblism in Man. New Eng. J. Med. 280(22):1194-1199, 1969

22. Riedel M, V Stanek, J Widimsky, I Perousky: Long Term Follow-up of Patients With Pulmonary Thromboembolism. Chest 81:151-158, 1982.

23. Graham JP, HH Rotman, JG Weg: Tumor Emboli Presenting as Pulmonary Hypertension. Chest 69(2):229-230, 1976.

24. Fedullo PF, WR Auger, RN Channick, KM Moser, SW Jamieson: Chronic Thromboembolic Pulmonary Hypertension. Clinics in Chest Med. 16(2):353-374, 1995.

25. Hughes, JD, LJ Rubin: Primary Pulmonary Hypertension. An Analysis of 28 Cases and A Review of the Literature. Medicine 65(1):56-72, 1986.

26. Rich S, DR Dantzker, SM Ayres, EH Bergofsky, BH Brundage, KM Detre, AP Fishman, RM Goldring, BM Groves, SK Koerner, PC Levy, LM Reid, CE Vreim, GW Williams: Primary Pulmonary Hypertension. A National Prospective Study. Ann. Int. Med. 107:216-223, 1987.

27. D'Alonzo GE, RJ Barst, SM Ayres, EH Bergofsky, BH Brundage, KM Detre, AP Fishman, RM Goldring, BM Groves, JT Kernis, PS Levy, GG Pietra, LM Reid, JT Reeves, S Rich, CE Vreim, GW Williams, M Wu: Survival in Patients With Primary Pulmonary Hypertension. Ann. Int. Med. 115(5):343-349, 1991.

28. Liebow AA, KM Moser MT Southgate: Rapidly Progressive Dyspnea in a Teenage Boy. JAMA 223(11):1243-1253, 1973.

29. Wagenvoort CA, N Wagenvoort, T Takahashi: Pulmonary Veno-Occlusive Disease: Involvement of Pulmonary Arteries and Review of the Literature. Hum. Pathol. 16:1033-1041, 1985.

30. Worsley DF, HI Palevsky, A Alavi: Ventilation-Perfusion Lung Scanning in the Evaluation of Pulmonary Hypertenion. J. Nucl. Med. 35:793-796, 1994.

31. Taylor WE: Pathology of Pulmonary Heart Disease. Pul. Heart Dis. Editor:LJ Rubin, pp. 65-105, 1984. Martinus Nijhoff, Boston, MA.

32. v Euler US, G Liljestrand: Observations on the Pulmonary Arterial Blood Pressure in the Cat. Acta Phys. Scand. 12:301-319.

33. Capen RL, WW Wagner, Jr.: Intrapulmonary Blood Flow Redistribution During Hypoxia Increases Gas Exchange Surface Area. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 52(6):1575-1581, 1982.

34. Light RB, SN Mink, LDH Wood: Pathophysiology of Gas Exchange and Pulmonary Perfusion in Pneumococcal Lobar Pneumonia in Dogs. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 50(3):524-530, 1981.

35. Hales CA, L Sonne, M Peterson, D Kong, M Miller, WD Watkins: Role of Thromboxane and Prostacyclin in Pulmonary Vasomotor Changes after Endotoxin in Dogs. J. Clin. Inv. 68:497-505, 1981.

36. Madden JA, MS Vadula, VP Kurup: Effects of Hypoxia and Other Vasoactive Agents on Pulmonary and Cerebral Artery Smooth Muscle Cells. Am. J. Physiol. 263:L384-L393, 1992.

37. Jensen KS, AJ Micco, J Czartolomna, LLatham, NF Voelkel: Rapid Onset of Hypoxic Vasoconstriction in Isolated Lungs. J. Appl. Physiol. 72(5):2018-2023, 1992.

38. Nagasaka Y., J Bhattacharya, S Nanjo, MA Gropper, NC Staub: Micropuncture Measurement of Lung Microvascular Pressure Profile During Hypoxia in Cats. Circ. Res. 54:90-95, 1984.

39. Voelkel NF: Mechanisms of Hypoxic Pulmonary Vasoconstriction. Am. Rev. Respir. Dis. 133:1186-1195, 1986.

40. Jin N, CS Packer, RA Rhoades: Pulmonary Arterial Hypoxic Contraction: Signal Transduction. Am. J. Physiol. 263:L73-L78, 1992.

41. Post JM, JR Hume, SL Archer, EK Weir: Direct Role for Potassium Channel Inhibition in Hypoxic Pulmonary Vasoconstriction. Am. J. Physiol. 262:C882-C890, 1992.

42. Yuan X, WF Goldman, ML Tod, LJ Rubin, MP Blaustein: Hypoxia Reduces Potassium Currents in Cultured Rat Pulmonary But Not Mesenteric Arterial Myocytes. Am. J. Physiol. 264:L116-L123, 1993.

43. Weir EK, SL Archer: The Mechanism of Acute Hypoxic Pulmonary Vasoconstriction: The Tale of Two Channels. FASEB J. 9:183-189, 1995.

44. Lee S, M Park, I So, YE Earm: NADH and NAD Modulates Ca^{2+} -Activated K+ Channels in Small Pulmonary Arterial Smooth Muscle Cells of the Rabbit. Pflugers Arch. 427:378-380, 1994.

45. Ruppersberg JP, M Stocker, O Pongs, SH Heinemann, R Frank, M Koenen: Regulation of Fast Inactivation of Cloned Mammalian I_k(A) Channels by Cysteine Oxidation. Nature 352:711-714, 1991.

46. Zagotta WN, T Hoshi, RW Aldrich: Restoration of Inactivation in Mutants of *Shaker* Potassium Channels by a Peptide Derived From ShB. Science 250:568-571, 1990.

47. Barinaga M: Playing Tetherball in the Nervous System. Science 250:506-507, 1990.

48. Poiani GJ, CA Tozzi, SE Yohn, RA Pierce, SA Belsky, RA Berg, SY Yu, SB Deak, DJ Riley: Collagen and Elastin Metabolism in Hypertensive Pulmonary Arteries of Rats. Cir. Res. 66:968-978, 1990.

49. Tozzi CA, DL Christiansen, GJ Poiani, DJ Riley: Excess Collagen in Hypertensive Pulmonary Arteries Decreases Vascular Distensibility. Am. J. Respir. Crit. Care Med. 149:1317-1326, 1994.

50. Emery CJ, D Bee, GR Barer: Mechanical Properties and Reactivity of Vessels in Isolated Perfused Lungs of Chronically Hypoxic Rats. Clin. Sci. 61:569-580, 1981.

51. Kerr JS, DJ Riley, MM Frank, RL Trelstad, HM Frankel: Reduction of Chronic Hypoxic Pulmonary Hypertension in the Rat by β-aminopropionitrile. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 57(6):1760-1766, 1984.

52. Hassoun PM, BT Thompson, D Steigman, CA Hales: Effect of Heaprin and Warfarin on Chronic Hypoxic Pulmonary Hypertension and Vascular Remodeling in the Guinea Pig. Am. Rev. Respir. Dis. 139:763-768, 1989.

53. Poiani GJ, CA Tozzi, JK Choe, SE Yohn, DJ Riley: An Antifibrotic Agent Reduces Blood Pressure in Established Pulmonary Hypertension in the Rat. J. Appl. Physiol. 68(4):1542-1547, 1990.

54. Stamler JS, E Loh, M Roddy, KE Currie, MA Creager: Nitric Oxide Regulates Basal Systemic and Pulmonary Vascular Resistance in Healthy Humans. Circulation 89:2035-2040, 1994.

55. Garg UC, A Hassid: Nitric Oxide-generating Vasodilators and 8-Bromo-Cyclic Guanosine Monophosphate Inhibit Mitogenesis and Proliferation of Cultured Rat Vascular Smooth Muscle Cells. J. Clin. Inv. 83:1774-1777, 1989.

56. Kourembanas S, LP McGuillan, GK Leung, DV Faller: Nitric Oxide Regulates the Expression of Vasoconstrictors and Growth Factors by Vascular Endothelium Unver Both Normoxia and Hypoxia. J. Clin. Inv. 92:99-104, 1993.

57. Dinh-Zuan AT, TW Higenbottam, CA Clelland, J Pepke-Zaba, G Cremona, AY Butt, SR Large, FC Wells, J Wallwork: Impairment of Endothelium-Dependent Pulmonary-Artery Relaxation in Chronic Obstructive Lung Disease. New Eng. J. Med. 324:1539-1947, 1991.

58. Giaid A, D Saleh: Reduced Expression of Endothelial Nitric Oxide Synthase in the Lungs of Patients With Pulmonary Hypertension. New Eng. J. Med. 333(4):214-221, 1995.

59. Roberts JM: Nitric Oxide and Vascular Disease. New Eng. J. Med. 333(4):251, 1995.

60. Shaul PW, AJ North, TS Brannon, K Ujiie, LB Wells, PA Nisen, CJ Lowenstein, SH Snyder, RA Star: Prolonged *In Vivo* Hypoxia Enhances Nitric Oxide Synthase Type I and Type III Gene Expression in Adult Rat Lung. Am. J. Respir. Cell Mol. Biol. 13:167-174, 1995.

61. Cohen AH, K Hanson, K Morris, B Fouty, IF McMurtry, W Clarke, DM Rodman: Inhibition of Cyclic 3'-5'-Guanosine Monophosphate-Specific Phosphodiesterase Selectively Vasodilates the Pulmonary Circulation in Chronically Hypoxic Rats. J. Clin. Inv. 97:172-179, 1996.

62. Xue C, A Rengasamy, TD Le Cras, PA Koberna, GC Dailey, RA Johns: Distribution of NOS in Normoxic vs. Hypoxic Rat Lung: Upregulation of NOS by Chronic Hypoxia. Am. J. Physiol. 267:L667-L678, 1994.

63. Isaacson TC, V Hampl, E K Weir, DP Nelson, SL Archer: Increased Endothelium-Derived NO in Hypertensive Pulmonary Circulation of Chronically Hypoxic Rats. J. Appl. Physiol. 76(2):933-940, 1994.

64. Russ RD, BR Walker: Maintained Endothelium-Dependent Pulmonary Vasodilation Following Chronic Hypoxia in the Rat. J. Appl. Physiol. 74(1):339-344, 1993.

65. Adnot S, B Raffestin, S Eddahibi, P Braquet, P Chabrier: Loss of Endothelium-Dependent Relaxant Activity in the Pulmonary Circulation of Rats Exposed to Chronic Hypoxia. J. Clin. Inv. 87:155-162, 1991.

66. McQuillan LP, GK Leung, PA Marsden, SK Kostyk, S Kourembanas: Hypoxia Inhibits Expression of eNOS Via Transcriptional and Posttranscriptional Mechanisms. Am. J. Physiol. 267:H1921-H1927.

67. Kouyoumdjian C, S Adnot, M Levame, S Eddahibi, H Bousbaa, B Raffestin: Continuous Inhalation of Nitric Oxide Protects Against Development of Pulmonary Hypertension in Chronically Hypoxic Rats. J. Clin. Inv. 94:578-584, 1994.

68. Janssens SP, KD Bloch, Z Nong, RD Gerard, PZoldhelyi, D Collen: Adenoviral-Mediated Transfer of the Human Endothelial Nitric Oxide Synthase Gene Reduces Acute Hypoxic Pulmonary Vasoconstriction in Rats. J. Clin. Inv. 98:317-324, 1996.

69. Levin ER: Endothelins. New Eng. J. Med. 333:356-363, 1995.

70. de Nucci G, R Thomas, P D'Orleans-Juste, E Antunes, C Walder, TD Warner, JR Vane: Pressor Effects of Circulating Endothelin are Limited by its Removal in the Pulmonary Circulation and by the Release of Prostacyclin and Endothelium-Derived Relaxing Factor. Proc. Natl. Acad. Sci. 85:9797-9800, 1988.

71. Muldoon LL, KD Rodland, ML Forsythe, BE Magun: Stimulation of Phosphatidylinositol Hydrolysis, Diacylglycerol Release, and Gene Expression in Response to Endothelin, a Potent New Agonist for Fibroblasts and Smooth Muscle Cells. J. Biol. Chem. 264(15):8529-8536, 1989.

72. Giaid A, M Yanagisawa, D Langleben, RP Michel, R Levy, H Shennib, S Kimura, T Masaki, WP Duguid, DJ Stewart: Expression of Endothelin-1 in the Lungs of Patients With Pulmonary Hypertension. New Eng. J. Med. 328:1732-1739, 1993.

73. Kourembanas S, PA Marsden, LP McQuillan, DV Faller: Hypoxia Induces Endothelin Gene Expression and Secretion in Cultured Human Endothelium. J. Clin. Inv. 88:1054-1057, 1991.

74. Bonvallet ST, MR Zamora, K Hasunuma, K Sato, N Hanasato, D Anderson, K Sato, TJ Stelzner: BQ123, and ET_A-Receptor Antagonist, Attenuates Hypoxic Pulmonary Hypertension in Rats. Am. J. Physiol. 266:1327-H1331, 1994.

75. S Eddahibi, B Raffestin, M Clozel, M Levame, S Adnot: Protection From Pulmonary Hypertension With an Orally Active Endothelin Receptor Antagonist in Hypoxic Rats. Am. J. Physiol. 268:H828-H835, 1995.

76. Oparil S, S Chen, QC Meng, TS Elton, M Yano, Y Chen: Endothelin-A Receptor Antagonist Prevents Acute Hypoxia-Induced Pulmonary Hypertension in the Rat. Am. J. Appl. Physiol. 268:L95-L100, 1995.

77. Okada M, C Yamashita, M Okada, K Okada: Endothelin Receptor Antagonists in a Beagle Model of Pulmonary Hypertension: Contribution to Possible Potential Therapy? J. Am. Col. Cardiol. 25:1213-1217, 1995.

78. Li H, S Chen, Y Chen, QC Meng, J Durand, S Oparil, TS Elton: Enhanced Endothelin-1 and Endothelin Receptor Gene Expression in Chronic Hypoxia. J. Appl. Physiol. 77(3):1451-1459, 1994.

79. Ono S, JY Westcott, NF Coelkel: PAF Antagonists Inhibit Pulmonary Vascular Remodeling Induced by Hypobaric Hypoxia in Rats. J. App. Physiol. 73:1084-1092, 1992.

80. Stewart DJ, RD Levy, P Cernaced, D Langleben: Increase Plasma Endothelin-1 in Pulmonary Hypertension: Marker or Mediator of Disease? Ann. Int. Med. 114:464-469, 1991.

81. Kentera D, D Susic, V Veljkovic, G Tucakovic, V Koko: Pulmonary Artery Pressure in Rats With Hereditary Platelet Function Defect. Respiration 54:110-114, 1988.

82. Deuel TF, JS Huang: Platelet-Derived Growth Factor Structure, Function, and Roles in Normal and Transformed Cells. J. Clin. Inv. 74:669-676, 1984.

83. Collins T, D Ginsburg, JM Boss, SH Orkins, JS Pober: Cultured Human Endothelial Cells Express Platelet-Derived Growth Factor B Chain: cDNA Cloning and Structural Analysis. Nature 316:748-750, 1985.

84. DiCorleto PE, DF Bowen-Pope: Cultured Endothelial Cells Produce a Platelet-Derived Growth Factor-like Protein. Proc. Natl. Acad. Sci. 80:1919-1923, 1983.

85. Tozzi, CA, GJ Poiani, AM Harangozo, CD boyd, DJ Riley: Pressure-Induced Connective Tissue Synthesis in Pulmonary Artery Segments is Dependent on Intact Endothelium. J. Clin. Inv. 84:1005-1012, 1989.

86. Riley D, J Gullo: Pressure Applied to Cultured Pulmonary Artery Endothelial Cells Causes Release of a Fibroblast Mitogen and Induces A Proto-Oncogene. FASEB J. 2:300, 1988.

87. Kourembanas S, RL Hannan, DV Faller: Oxygen Tension Regulates the Expression of the Platelet-Derived Growth Factor-B Chain Gene in Human Endothelial Cells. J. Clin Inv. 86:670-674, 1990.

88. Wilson E, Q Mai, K Sudhir, RH Weiss, HE Ives: Mechanical Strain Induces Growth of Vascular Smooth Muscle Cells via Autocrine Action of PDGF. J. Cell Biol. 123(3):741-747, 1993.

89. Mecham RP, LA Whitehouse, DS Wrenn, WC Parks, GL Griffin, RM Senior, EC Crouch, KR Stenmark, NF Voelkel: Smooth Muscle-Mediated Connective Tissue Remodeling in Pulmonary Hypertension. Science 237:423-426, 1987.

90. Katayose D, M Ohe, K Yamauchi, M Ogata, K Shirato, H Fujita, S Shibahara, T Takishima: Increase Expression of PDGF A-and B-Chain Genes in Rat Lungs With Hypoxic Pulmonary Hypertension. Am. J. Physiol. 264:L100-L106, 1993.

91. Michael JR, TP Kennedy, P Buescher, I Farrukh, R Lodato, PC Rock, J Gottlieb, G Gurtner, SM De La Monte: Nitrendipine Attenuates the Pulmonary Vascular Remodeling and Right Ventricular Hypertrophy Caused by Intermittent Hypoxia in Rats. Am. Rev. Respir. Dis. 133:375-379, 1986.

92. Stanbrook HS, KG Morris, IF McMurtry: Prevention and Reversal of Hypoxic Pulmonary Hypertension by Calcium Antagonists. Am. Rev. Respir. Dis. 130:81-85, 1984.

93. Rabinovitch M, MA Konstam, WJ Gamble, N Papanicolaou, MJ Aronovitz, Streves, L Reid: Changes in Pulmonary Blood Flow Affect Vascular Response to Chronic Hypoxia in Rats. Circ. Res. 52:432-441, 1983.

94. Nocturnal Oxygen Therapy Trial Group: Continuous or Nocturnal Oxygen Therapy in Hypoxemic Chronic Obstructive Lung Disease. Ann. Int. Med. 93:391-398, 1980.

95. Timms RM, FU Khaja, GW Williams, The Nocturnal Oxygen Therapy Trial Group: Hemodynamic Response to Oxygen Therapy in Chronic Obstructive Pulmonary Disease. Ann. Int. Med. 102:29-36, 1985.

96. Kay JM: Effect of Intermittent Normoxia on Chronic Hypoxic Pulmonary Hypertension, Right Ventricular Hypertrophy, and Polycythemia in Rats. Am. Rev. Respir. Dis. 121:993-1001, 1980.

97. Koo KW, DS Sax, GL Snider: Arterial Blood Gases and pH During Sleep in Chronic Obstructive Pulmonary Disease. Am. J. Med. 58:663-670, 1975.

98. Heinemann HO: Right Sided Heart Failure and the Use of Diuretics. Am. J. Med. 64:367-370, 1978.

99. Salvaterra CG, LJ Rubin: Investigation and Management of Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease. Am. Rev. Respir. Dis. 148:1414-1417, 1993.

100. Packer M, B Greenbert, B Massie, H Dash: Deleterious Effects of Hydralazine in Patients With Pulmonary Hypertension. New Eng. J. Med. 306:1326-1331, 1982.

101. Barst RJ, LJ Rubin, WA Long, MD McGoon, S Rich, DB Badesch, BM Groves, VF Tapson, RC Bourge, BH Brundage, SK Koerner, D Langleben, CA Keller, S Murali, BF Uretsky, LM Clayton, MM Jobsis, SD Blackburn, Jr., D Shortino, MS James, W Crow: A Comparison of Continuous Intravenous Epoprostenol (Prostachyclin) With Conventional Therapy For Primary Pulmonary Hypertension. New Eng. J. Med. 334:296-301, 1996.

102. Barst RJ, LJ Rubin, MD McGoon, EJ Caldwell, WA Long, PS Levy: Survival in Primary Pulmonary Hypertension With Long-Term Continuous Intravenous Prostacyclin. Ann. Int. Med. 121:409-415, 1994.

103. Rich S, E Kaufmann, PS Levy: The Effect of High Doses of Calcium-Channel Blockers on Survival in Primary Pulmonary Hypertension. New Eng. J. Med. 327(2):76-81, 1992.

104. Raffy O, R Azarian, F Brenot, F Parent, O Sitbon, P Petitpretz, P Herve, P Duroux, AT Ding-Xuan, G Simonneau: Clinical Significance of the Pulmonary Vasodilator Response During Short-term Infusion of Prostacyclin in Primary Pulmonary Hypertension. Circulation 93:484-488, 1996.

105. Fuster V, PM Steele, WD Edwards, BJ Gersh, MD McGoon, RL Frye: Primary Pulmonary Hypertension: Natural History and the Importance of Thrombosis. Circulation 70(4):580-587, 1984.

106. Bjornsson J, WD Edwards: Primary Pulmonary Hypertension: A Histopathologic Study of 80 Cases. Mayo Clin. Proc. 60:16-25, 1985.

107. Pasque MK, EP Trulock, JD Cooper, AN Triantafillou, CB Huddleston, M Rosenbloom, S Sundaresan, JL Cox, GA Patterson: Single Lung Transplantation for Pulmonary Hypertension. Circulation 92:2252-2258, 1995.

108. Reitz BA, JL Wallwork, SA Hunt, JL Pennock, ME Billingham, PE Oyer, EB Stinson, NE Shumway: Heart-Lung Transplantation: Successful Therapy for Patients With Pulmonary Vascular Disease. New Eng. J. Med. 306(10):557-564, 1982.

109. Adatia I, J Thompson, M Landzberg, DL Wessel:Inhaled Nitric Oxide in Chronic Obstructive Lung Disease. Lancet 341:307-308, 1993.

110. Pepke-Zaba J, TW Higenbottam, AT Dinh-Xuan, D Stone, J. Wallwork: Inhaled Nitric Oxide as a Cause of Selective Pulmonary vasodilatation in Pulmonary Hypertension. Lancet 338:1173-1174, 1991.

111. Sitbon O, F Brenot, A Denjean, A Bergeron, F Parent, R Azarian, P Herve, B Raffestin, G Simonneau: Inhaled Nitric Oxide as a Screening Vasodilator Agent in Primary Pulmonary Hypertension. Am. J. Respir. Crit. Care Med. 151:384-389, 1995.