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CARDIOLOGY Rounds™

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Primary Pulmonary Hypertension

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Introduction

Primary pulmonary hypertension (PPH) remains one of medicine's more difficult challenges since it is a rare disease, its causes are obscure, its natural history is unclear, and there are few treatment options. The unifying finding is that of a pulmonary vasculature which undergoes extensive remodeling, leading to elevations in pulmonary artery pressure and pulmonary vascular resistance. Clinically PPH is defined[1] by: (1) the presence of pulmonary hypertension (mean pulmonary artery pressure >25 mm Hg at rest or >30 mm Hg during exercise) (2) normal pulmonary artery wedge pressure (3) absence of secondary causes (see Table 1).

PPH is likely a disease of predisposed individuals, in whom certain stimuli may initiate pulmonary vascular endothelial injury or dysfunction. Possible triggers of pulmonary vascular injury include hypoxia, increased pulmonary blood flow with or without increased pressure and shear stress, drugs and toxins (see later), autoimmune disorders,[2] and increased sympathetic tone.[3]

Pulmonary Vasoconstriction

(a) Vasodilator and Vasoconstrictor Imbalance

Although it is still speculative whether vasoconstriction is the primary event in the pathogenesis of PPH, it is clearly an important component of its pathophysiology. The endothelium elaborates locally active mediators which contribute to the control of vasomotor tone, including the vasodilator, nitric oxide (NO). In addition to vasodilation, the functions of NO in the pulmonary circulation include anti-mitogenic and anti-proliferative effects on vascular smooth cells, and inhibition of platelet aggregation. Both NO and prostacyclin (PGI_2), a vasodilitation and antiplatelet product of cyclooxygenase metabolism of arachidonic acid, likely maintain vascular homeostasis. The responsiveness of the pulmonary circulation to endothelium-dependent vasodilators is impaired in patients with PPH.[4,5] Patients with PPH also have reduced release of prostacyclin and enhanced levels of the vasoconstrictor, thromboxane A_2, whereas normal levels are seen in patients with secondary causes of pulmonary hypertension.[6]

Endothelin-1 (ET-1) is a potent endothelium-derived vasoconstrictor peptide. Low levels are expressed by normal endothelium in situ. Its production is strikingly upregulated in certain pathophysiological states and it may be a marker of endothelial activation.[7] Increased production of ET-1 has been demonstrated in numerous animal models [8-10] of pulmonary hypertension. In humans with pulmonary hypertension, plasma immunoreactive levels of ET-1 are increased[11] and there is increased expression of ET-1 in the pulmonary vascular endothelium.[12]

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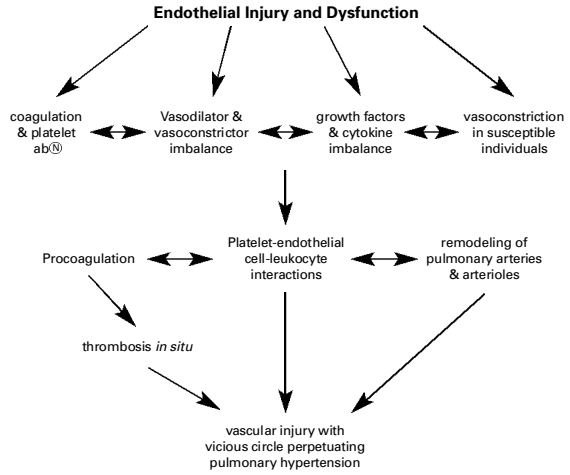
Figure 1: Pathogenesis of Primary Pulmonary Hypertension



(b) Vascular Growth Factor Actions

Intimal proliferation is a striking feature of the pulmonary vasculature in patients with PPH. Growth factors which may play a role in the development of these vascular changes include basic fibroblast growth factor, platelet-derived growth factor,[13] and transforming growth factor-beta.[14] Enhanced growth factor release and intracellular signalling may contribute to smooth muscle cell proliferation and migration, and the elaboration of proteins in the extracellular matrix.[13]

(c) Coagulation Abnormalities

Patients with PPH have an increased susceptibility for in situ thrombosis. Various defects have been identified, including abnormal platelet function, increased thrombin activity (increased fibrinopeptide A), defective fibrinolysis (increased PAI-1 activity), increased exposure to von Willebrand factor, and exposure of subendothelial cell surface structures due to injury.[15,16]

Histopathology of primary pulmonary vascular disease

Three subsets of PPH have been identified: primary pulmonary arteriopathy, pulmonary veno-occlusive disease (PVOD), and pulmonary capillary hemangiomatosis. Primary pulmonary arteriopathy represents a spectrum of histopathologic lesions: 1) classic plexogenic pulmonary arteriopathy, which is a non-specific pattern of response of the pulmonary vasculature to hemodynamic injury; 2) microthrombotic pulmonary arteriopathy; and 3) medial hypertrophy (with or without associated intimal fibrosis). PVOD (5% of cases of PPH) is characterized by the presence of organized and recanalized thrombi in pulmonary veins and venules, intimal fibrosis, and frequent arterialization of pulmonary veins. Pulmonary capillary hemangiomatosis is the rarest form of PPH and is characterized by the proliferation of thin-walled microvessels that infiltrate the perivascular interstitium and lung parenchyma.

Exogenous causes of pulmonary vasculopathy

Various exogenous agents have been implicated in the development of pulmonary hypertension:

(1) anorexic agents[17-19]
(2) L-tryptophan[20]
(3) crack cocaine inhalation[21]
(4) rapeseed cooking oil (toxic oil syndrome)[22]
(5) HIV infection[23]

A well-recognized epidemic of pulmonary hypertension occurred in Europe in the 1960's in association with the use of the appetite suppressant, aminorex. In a recent case-control study,[19] the newer anorexic agents, dexfenfluramine and fenfluramine, were found to be associated with a significantly increased risk for the development of PPH, with an adjusted odds ratio of 6.3 (95% CI=3.0-13.2) for patients with a history of definite use of these agents and an adjusted odds ratio of 23.1 (95% CI=9.9-77.7) for those with a history of greater than 3 months of use. The exact mechanism of action of these agents is unclear. However a recent study suggests that there is a direct vasoconstrictor effect of the anorexic agents through the blockade of potassium channels.[24]

Table 1: Secondary Causes of Pulmonary Hypertension

Primary Cardiac Disorder
- Cardiomyopathy
- Left ventricular diastolic failure
  - Hypertension
  - Coronary artery disease
  - Aortic stenosis
  - Left ventricular outflow tract obstruction
  - Constrictive pericarditis
- Left atrial hypertension
  - Mitral stenosis
  - Mitral regurgitation
  - Left atrial myxoma or thrombus
  - Cor triatriatum

Pulmonary Vascular Disease
- Increased pulmonary blood flow
  - Congenital heart disease with post-tricuspid left-to-right shunt
  - Atrial septal defect
  - Anomalous pulmonary venous drainage
  - High-output cardiac failure
- Persistent fetal circulation of newborn
- Collagen vascular disease
- Pulmonary vasculitis

Pulmonary Vascular Obstruction
- Chronic pulmonary thromboemboli
- Foreign body embolization
- Tumour embolization
- Schistosomiasis
- Sickle cell anemia
- Peripheral artery stenosis
- Mediastinal fibrosis

Exogenous agents
- Anorexic agents
- Toxic rapeseed oil
- L-tryptophan
- Crack cocaine
- HIV infection

Lung Disease
- Parenchymal lung disease
- Disorders of ventilation
- Congenital anomalies
- Hypoxia-induced (eg altitude)

Clinical Features & Natural History

One of the first natural history studies of PPH highlighted the poor prognosis of these patients. In 120 patients (33 males and 87 females) the most frequent clinical features were exertional dyspnea (75%), a loud second heart sound (98%), CXR abnormalities (95%), and ECG abnormalities (95%). Less frequent clinical features include exertional dizziness or syncope (30%), exertional chest pain (8%), and ankle swelling (8%). The median time interval from diagnosis to death was 1.9 years (range: 0 to 16 years), and greater than 75% of deaths occurred within five years of the diagnosis of PPH.[25] On multivariate analysis the only significant predictors of survival in this study were systemic arterial oxygen saturation and anti-coagulant use. A more recent study of patients in the National Prospective Registry of the National Heart, Lung, and Blood Institute (NHLBI)[26] showed a modest improvement in the prognosis of PPH. Estimated median survival of these patients was 2.8 years (95% CI, 1.9 to 3.7 years).

Prognostic Evaluation

A prognostic equation has been derived from the NHLBI prospective study. The equation is as follows:

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

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

$$A(x,y,z)=e^{(0.007325x+0.0526y-0.3275z)}$$

Where:

P(t)=patient's chances of survival at t years

t=1,2, or 3 years

x=mean pulmonary arterial pressure

y=mean RAP

z=cardiac index

This prognostic equation has been prospectively validated.[27]

Medical Therapy

(1) Anti-Coagulation

The rationale for chronic anti-coagulation in patients with PPH stems from the importance of in situ thrombosis in the pathophysiology of PPH and from clinical evidence from the natural history study of PPH demonstrating improved survival in patients on anti-coagulation. Therefore, the current ACCP consensus statement[1] advocates long-term warfarin in PPH patients to maintain an INR of 2.0 to 3.0. In addition, in a prospective trial of high-dose calcium blockers[28] there was an observed improved survival in patients on warfarin, in both the groups which were either responsive or unresponsive to calcium channel blockers.

(2) Vasodilators

Multiple vasodilating agents have been evaluated in the management of PPH.[29] Intravenous vasodilators may be of value in the short-term assessment of pulmonary vasodilator reserve in patients with PPH. Experience with tolazoline, nitroprusside, nitroglycerine, adenosine, all classes of calcium-channel blockers, and direct arterial vasodilators have been described.

Calcium-Channel Blockers

There has been one major long-term prospective trial of high-dose calcium-channel blockers for the treatment of PPH.[28] Sixty-four patients were administered either oral nifedipine (20 mg) or diltiazem (60 mg) hourly until a favourable hemodynamic response (≥20% decrease in mean pulmonary artery pressure and the pulmonary vascular resistance, PVR) was achieved. Permitted additional therapy included anti-coagulants, digoxin, and diuretics. Of this cohort, 17 out of 64 patients (26.6%) were responders, with a 39% reduction in mean pulmonary artery pressure and a 53% reduction in the PVR. The mean dose of nifedipine was 172 +/- 41 mg/day (range, 120-240 mg/d) and of diltiazem was 720 +/- 208 mg/day (range, 540-900 mg/day). Long-term response showed an improved functional capacity, electrocardiographic regression of RVH, and maintained hemodynamic response (in 15 out of 17 patients) at serial annual hemodynamic evaluation. Overall survival at follow-up was significantly improved in the responder group when compared with the non-responders (94% vs 55%, respectively, p=0.003), whose survival did not differ greatly with that of historical controls. It is unknown whether a response to calcium-channel blockers identified a different subset of PPH or a different stage of PPH.

(3) Prostacyclin

The use of a continuous prostacyclin infusion represents the strategy of treating an illness characterized by reduced levels of an endothelial cell product with a parenterally administered formulation of that compound. In the last several years three major clinical trials have evaluated the efficacy of continuous prostacyclin (IV Epoprostenol) in patients with PPH.[30-32]

In an uncontrolled trial of 18 patients with PPH, all were treated with continuous IV Epoprostenol. Measurements were exercise capacity, hemodynamics, and overall survival. During four-year follow-up, of the original 18 patients, 6 remained on prostacyclin, 8 received heart-lung or single-lung transplants (with 3 subsequent deaths), and 4 died prior to transplantation. Major complications of IV Epoprostenol use included two deaths attributable to the drug or its delivery system, 7 episodes of non-fatal sepsis (in 3 patients), 9 episodes of

clotting of the system (in 5 patients), and mechanical problems or catheter replacements in 8 patients. Minor but clearly non-trivial adverse effects included loose stools, jaw pain, flushing, photosensitivity, and headaches.

In the largest yet long-term prospective trial of IV Epoprostenol reported earlier this year,[32] 81 severely symptomatic patients (all NYHA class III or IV) were randomized to IV Epoprostenol with conventional therapy or to conventional therapy alone. Measured outcomes included exercise tolerance (as assessed by 6-minute walk), functional capacity, hemodynamic measurements (mean PA pressure, PVR), and overall survival. Compared to the conventional therapy arm, the IV Epoprostenol group demonstrated an improvement in 6-minute walk test, improved NYHA class, reduction in mean pulmonary artery pressures and PVR. Eight deaths, all in the conventional therapy arm, occurred. There were five serious complications.

Despite these encouraging results many barriers exist precluding more widespread use of parenteral prostacyclin, including the risks of serious morbidity with the drug delivery system, the significant side effects, and the costs. Recently, newer forms of prostacyclin have been studied, an oral form of prostacyclin, Beraprost,[33] and inhaled aerosolized prostacyclin.[34]

(4) L-Arginine

Intravenous L-arginine, which is catabolized by nitric oxide synthase (NOS) to form nitric oxide and L-citrulline, has been evaluated as a possible form of treatment for pulmonary hypertension.[35] Twenty patients (with either pulmonary hypertension, congestive heart failure without associated secondary pulmonary hypertension, or healthy controls) were given either intravenous L-arginine or prostacyclin. There was a significant reduction in mean PAP and PVR with IV L-arginine. Levels of L-arginine and L-citrulline showed significant relations with peak pulmonary vasodilatory responses (mean PAP, PVR) to L-arginine infusion.

(5) Inhaled Nitric Oxide

Inhaled nitric oxide is a selective pulmonary vasodilator since it is quickly inactivated by hemoglobin (due to its increased affinity). There are no direct systemic effects. In an early small study comparing the effects of inhaled NO and infused prostacyclin,[36] PVR fell significantly with both NO (by between 5 to 68% from baseline) & PGI_2 (by approximately 30%) but SVR was significantly affected only in the PGI_2 group.

Surgical Options

(1) Atrial Septostomy

The rationale for creating an atrial septostomy in patients with pulmonary hypertension stems from the premise that intracardiac (right-to-left) shunting provides protection to the right ventricle in the presence of significant pulmonary hypertension. Atrial septostomy in humans with PPH was initially reported in 1983.[37] More recently a series of 15 patients with severe symptomatic PPH underwent blade balloon atrial septostomy.[38] Immediate post-septostomy hemodynamic assessment showed no significant change in mean pulmonary pressures and right atrial pressures, but there was an increased cardiac index. Two deaths occurred at the time of the procedure. Long-term follow-up showed an improvement in NYHA class in the remaining 13 patients. There was a trend towards increased survival with this procedure when compared to the outcome of a historical control group.

(2) Transplantation

Transplantation options to treat patients with end-stage PPH have evolved. Initially, heart-lung transplantation (HLT) was used to treat all such patients.[39] However, during the past several years, there has been a shift from HLT towards single lung transplantation (SLT)[40] and double lung transplantation (DLT) as alternative procedures. Early post-transplant hemodynamic studies in patients after SLT and DLT have shown an early and sustained reduction in pulmonary artery pressures and vascular resistance[41] and an improvement in right ventricular function.[42,43] There are no prospective randomized data comparing the effectiveness of these three procedures. However, retrospective data have demonstrated similar short- and long-term outcomes in patients undergoing HLT or DLT.[43,44] Earlier data have suggested a two-year survival in the range of 40-50%.[44] A recent series showed a significantly improved prognosis for patients undergoing SLT. Actuarial survival at one-, two-, and three-year follow-up was 78%, 66%, and 61%, respectively.[42]

Conclusion

PPH remains a rare and difficult to manage disorder. Endothelial dysfunction and related vasoconstriction play an important role in its pathophysiology. Management of PPH continues to be difficult with non-uniform success related to vasodilator or surgical intervention. Further work is required in this multifactorial disease with generally extremely poor prognosis.

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Abstracts of Interest

Reduced Pulmonary Removal of Circulating Endothelian-1: A New Marker of Human Pulmonary Hypertension

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The pulmonary vascular endothelium is an important site for both clearance and production of endothelin-1 (ET-1). Pulmonary hypertension (PH) is associated with increased circulating ET-1 levels that may contribute to the disease process: it is presently unknown if a reduced clearance, an increased production or a combination of both are responsible. We studied the pulmonary metabolism of ET-1 in 13 controls (C), and 17 patients with PH (12 mitral stenoses, 4 CHF, 1 idiopathic) by combining the indicator dilution technique with measurements of immunoreactive ET-1 levels (IRET-1). We measure percent I^{125}-ET-1 extraction (Ext) as well as net ET-1 production and survival (amount of ET-1 surviving passage through the lungs). The permeability-surface area product (PS) for ET-1 removal was computed using the Renkin model. In controls, aortic IRET-1 levels (0.67 ± 0.10 pg/ml, mean ± SE) were not different from pulmonary artery (0.61 ± 0.08 pg/ml). Levels were higher in PH ($p<0.05$) with a tendency for higher aortic (1.23±0.16 pg/ml) than pulmonary artery levels (1.07±0.19 pg/ml, $p=0.07$) (Table). Both ET-1 Ext and the PS product were reduced in PH explaining and increased ET-1 survival while pulmonary ET-1 production was unchanged. Pulmonary ET-1 Ext was inversely related to the severity of PH ($R=0.524$, $p=0.03$). We conclude that the increase in circulating ET-1 is thus a marker rather than a mediator of PH and reflects pulmonary vascular endothelial dysfunction.

	Ext	PS	Production	Survival
	(%)	(ml/s)	(ng/min)	(ng/min)
C	47±2	199±10	1.10±0.19	0.99±0.15
PH	34±3.6	112±7	1.25±0.22	1.86±0.35
p value	<0.01	<0.001	0.60	0.03

Excerpted from *Circulation*, 1996;Vol 94, No 8:I-412.

Alteration in Human Lung Capillary Endothelial Angiotensin Converting Enzyme Activity in Pulmonary Hypertension is Dependent on Etiology

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The pulmonary microvascular endothelium is a major metabolic organ, converting plasma angiotensin I to angiotensin II via the angiotensin converting ectoenzyme, ACE. All forms of precapillary pulmonary hypertension (PH) result in an underperfused pulmonary vascular bed. However, it is unknown if different pulmonary hypertensive pathologies affect ACE metabolic activity to varying degrees. Therefore, we measured single-pass transpulmonary hydrolysis of the specific ACE substrate 3H-benzoyl-Phe-Ala-Pro, expressed as % metabolism (%M), and calculated Amax/Km an index of functional capillary surface area. In ten normal controls, %M was 69.6 ± 3.8 and Amax/Km = 4185 ± 306ml/min. Patients with autoimmune or scleroderma-induced PH (n=5) had reduced %M (38.1 ± 5.2) and Amax/Km (1097 ± 378). Chronic thromboembolic PH (n=4) caused slightly decreased %M (58.8 ± 6.7) and decreased Amax/Km (1797 ± 206). The range of metabolism in patients with primary pulmonary hypertension (PPH, n=4) was wider (%M = 21 - 67.6), as was Amax/Km (578 - 2820 ml/min), possibly reflecting different underlying PPH pathologies. There were no differences in hemodynamics between the groups. Thus, all patients, regardless of etiology, have a reduced functional capillary surface area. However, some groups are able to maintain first-pass % metabolism. In conclusion, despite increased precapillary resistance sufficient to produce similar degrees of PH and reduced flow, pulmonary capillary ACE metabolism varies with etiology. This may somewhat reflect the degree to which the underlying disease itself affects or injures the pulmonary capillary bed, and may offer insights into pathogenesis.

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