George Cherian *
M. Thomas Abraham **
C. Babu Uthaman ***
I. P. Sukumar ****
Krishnaswami ****
A. Bhaktaviziam *****

PRIMARY PULMONARY HYPERTENSION

Primary pulmonary hypertension is not an uncommon condition in tropical countries. In our series of 91 patients the average age was 23.6 years for males and 24.5 years for females. A male predominance was observed unlike in patients from nontropical countries. Dyspnoea on effort was present in all but one patient and effort syncope in 26.4%. Radiologically, the main and right pulmonary arteries were enlarged in over 90% of patients. The height of R or R'-wave in V_1, correlated well with the pulmonary artery pressure, ($P < 0.01$). Cardiac arrhythmias and conduction disturbances were rare. Incomplete right bundle branch block was present in 16.7% and a complete RBBB in only one patient. Pulmonary artery systolic pressure exceeded 90 mm Hg in 69.9% and was suprasystemic in 49.4%. Right ventricular and diastolic pressure was raised in 52.7% and right ventricular alternance was present in 23.1%. Of the 58 patients followed up, 34 died within an average period of 1 year and 8 months. The symptoms, differential diagnosis, possible etiological factors and management are discussed. The reasons for the greater severity and earlier onset of primary pulmonary hypertension in our patients is not known. Ethnic variations in pulmonary vascular disease is one possibility.

Primary pulmonary hypertension (PPH) may be conveniently defined as pulmonary hypertension with no known cause or association[1]. Romberg in 1891 is credited with the first description of the pathological changes in a patient with "pulmonary artery sclerosis and right ventricular hypertrophy without apparent cause"[2].

About 1000 cases have been reported in the literature[3] but with a few exceptions[4-6] most reports have been on single cases or small series, reviews from the literature or on material collected from different centres. Although Brenner in 1935 while reporting om the pathological changes felt that the diagnosis could be made also on clinical grounds, most of the earlier reports have been on the pathological features of PPH[7]. There are later excellent clinical descriptions of PPH[8,9]. In parts of the world where thrombo-embolism is not uncommon and where PPH is rare it is mot surprising that a few cases diagnosed to have PPH were found to have thrombo embolic pulmonary hypertension at autopsy. This, while emphasizing the importance of pulmonary thrombo-embolism in the differential diagnosis, should not overemphasize the difficulty in making a diagnosis of PPH. Thus in a population where PPH is not uncommon and where clinical and autopsy evidence of thrombo-embolism is rare and where parasitic infestation with schistosomiasis does not occur we found that the diagnosis of PPH could be made as confidently as any other cardiac diagnosis, with subsequent confirmation. Our experience and other reports suggest that PPH may be more common in some tropical areas [4,6]. Thus we had 112 patients confirmed to have PPH in 7200 consecutive cardiac catheterizations at the Christian Medical College, Vellore, India.

The present revival of interest in PPH and its clinical recognition can be attributed to three factors. Certain plant alkaloids have been known to be associated with veno-occlusive disease of the liver and others with experimental pulmonary hypertension in rats. In 1968 an 'epidemic' of PPH was reported from several European countries and was ascribed to the use of certain appetite suppressant drugs, mainly Aminonex. Both of these subjects have been reviewed in detail recently [10]. Reports on the drug treatment of this condition have raised

* Professor and Head, Cardiology Department. Christian Medical College Hospital, Vellore, India. ** Formerly Lecturer, Cardiology Department. Christian Medical College Hospital, Vellore, India. *** Lecturer, Cardiology Department. Christian Medical College Hospital, Vellore, India.
**** Professor, Cardiology Department. Christian Medical College Hospital, Vellore, India.
***** Professor and Head, Pathology Department. Christian Medical College Hospital, Vellore, India.

hopes and aroused interest in the management of PPH[11-18].

This paper deals briefly with the pathological changes and etiological factors and attempts to emphasize the clinical diagnosis and differential diagnosis and the present day management of this condition.

Pathological Changes

There have been several reports and reviews on the pathological changes in PPH [19-21] and our own experience has been reported elsewhere [22]. A WHO study group [23] suggested the term plexogenic pulmonary aorteriopathy for the changes found in PH. However, the characteristic medial hypertrophy, intimal fibrosis and plexiform lesions may also be found in other conditions with pulmonary hypertension of diverse etiology like congenital cardiac shunts, liver cirrhosis, following Aminorex therapy and with schistosomiasis.

With PPH there is a progressive decrease in the cross-sectional area of the pulmonary vascular bed with a varying vaso-constrictive element. There is an increase in the right ventricular wall thickness and weight and with right ventricular failure often present at the time of autopsy there is right ventricular dilatation and a widening of the tricuspid valve ring. The main pulmonary artery and its major branches are dilated and the dimensions of the pulmonary artery exceed that of the aorta, and are greater than the sum of the pulmonary veins. The thickness of the media to that of the aorta may be close to or exceed unity (normal 0.4-0.7). Pulmonary arteriosclerosis may extend to the major pulmonary artery branches and cystic medial necrosis May contribute to the development of main pulmonary artery aneurysms. The elastic pattern of the pulmonary artery may occasionally retain its foetal character suggesting congenital or more likely am early onset of pulmonary hypertension during the first year of life[21].

Medial hyperthophy of the smooth muscle cells of the muscular pulmonary arteries and arterioles is striking and electron microscope studies suggest that the change is due to cellular hypertrophy and no hyperplasia. The process extends to arterioles less than 70µ which do not normally contain a muscular media. The intimal proliferation generally exceeds that found in secondary forms of pulmonary hypertension. Among the dilatation lesions of the pulmonary arterial bed the characteristic one in PPH is the plexiform lesion, for which many reasons have been postulated. Necrotizing arteritis and fibrinoid necrosis may be present. Thrombo-embolic lesions when present are believed to represent a secondary process[24].

In small repeated thrombo-embolism the initial process is obstruction of the small muscular arteries and arterioles with thrombi of various ages and stages of organization. The intimal changes are eccentric and re-canalization may result in capillary like spaces resembling but different from the plexiform lesions of PPH. The medial hypertrophy in thrombo-embolism is less and patchy being more prominent at the site of thrombo-embolic obstruction.

The pulmonary veins and venules which are not affected in PPH and thrombo-embolism are the primary site of involvement with Pulmonary veno-occlusive disease. In this condition the lung tissue shows patchy pulmonary edema and interstitial pneumonitis and fibrosis and alveolar capillaries show changes characteristic of pulmonary venous hypertension. Secondary changes due to pulmonary hypertension may be found in the small pulmonary arteries and arterioles [25].

Diagnostic criteria - In clinical series the presence of pulmonary arterial hypertension must be confirmed, at cardiac catheterization All other conditions associated with pulmonary hypertension should be excluded by appropriate investigations. Since a normal pulmonary wedge pressure may not be obtained in some patients with severe pulmonary arterial hypertension, direct left atrial pressure recording or echocardiography may be necessary in some. Collagen disease should be excluded.

Age sex distribution - Our patients ranged from 4-51 years with an average age of 24 years(table I). Unlike other reports (table II) there were more males in our series and the male: female ratio was 2:1 in patients under 15 years and 4:3 in those over 15 years. Nome of our patients gave a history of thrombo-phlebitis or the use of contraceptive pills. Two gave a history of Ayurvedic medication. There was no family history of PPH in our series.

Symptoms - The onset of symptoms is generally insidious, but occasionally rapid over a period of weeks. Aggravation occurs particularly during respiratory infections when it is known that the pulmonary vascular resistance increases. When symptomatic, the disease is always well advanced, though occasionally symptoms may be absent for some time despite pulmonary hypertension.

The symptoms found in our patients is outlined in table III - Symptoms had been present for less than 3 years in 70.30% and in over half these for less than a year. Dyspnea on effort was the maim symptom and was present in all but one patient. The pathophysiology of dyspnea in PPH is not clear and cannot be accounted for by the slight right to left shunting of blood that occurs in a few patients. Stimulation of pressoreceptors in the pulmonary circulation has been suggested. The dyspnea is probably related to the low and relatively fixed cardiac output resulting in mild acidosis and a reflex increase in respiration. Pulmonary function tests are relatively normal in patients with PPH. The vital capacity has been reported to be low in some and the diffusion capacity although usually normal is occasionally reduced. The lung compliance may be normal or decreased and

TABLE I - Age and sex distribution.

Age group	Male	Female	Total	Percent
10	3	1	4	4.4
11-20	21	15	36	39.5
21-30	13	14	27	29.7
31-40	11	6	17	18.7
41-50	3	3	6	6.6
50	1	0	1	1.1
Total	52	39	91	100.0

TABLE II - Comparison of age-sex distribution and pulmonary artery pressure.

Author, Country	Number	Age	Sex		Pulmonary
			Male	Female	Artery Pressure
Fuster et al, USA (ref 5)	100	2-70 — 33	26	74	96/43
Wood, U.K. (ref 8)	17	—	3	14	Systolic 65-90
Obeyesekere and de Soysa, Sri Lanka (ref 4)	30	— 27-6	12	18	114/57
Cherian et al, India (ref 1)	91	4 -51 — 24	52	39	107/52

the inspiratory resistence normal or slightly increased.

TABELA III – Symptoms in patients with PPH.

Symptom	Patients Number of	Percent
Dyspnoea	90	98.9
Palpitation	60	65.9
Chest pain	36	39.6
Effort syncope	24	26.4
Giddiness	15	16.5
Haemoptysis	15	16.5
Nocturnal dyspnoea	8	8.8
Hoarseness of voice	6	6.6

Characteristically orthopnoea is uncommon but may be present in the late stages and with respiratory infections. Paroxysmal nocturnal dyspnea was present in 8 of our patients. The pathogenesis is not clear but it is known that pulmonary congestion cam result from impaired pulmonary lymphatic drainage related to marked elevation of the systemic venous pressure[26]. The onset of symptoms was abrupt with orthopnoea in one of our patients with PPH who had rupture of one of the papillary muscles on the right side[27].

Effort syncope was present in 26.4% of our patients and is a dramatic and important symptom. No consistent changes are found in the sinus or atrioventricular nodal arteries. Cardiac arrhythmias are frequent in PPH. The low cardiac output and the vaso-dilatation accompanying exercise induces a fall in the systemic blood pressure, cerebral and coronary blood flow. In our patients we could mot correlate the occurrence of syncope with the weight of the heart or degree of vascular changes [22].

Chest pain is a common symptom. At times it is related to am aneurysmal pulmonary artery producing a fairly constant ache at times due to angina which may be present both in children and adults. Ischaemic eletrocardiographic changes have been recorded. At autopsy the coronary arteries are normal and we found that the presence of angina correlated with the weight of the heart, being present in all but one patient when the heart weight was 400 grams or more [22]. Angina in PPH must be related to "fixed" low cardiac output and inadequate argumentation of coronary blood flow.

Hemotysis was present in 16,5% of our patients. It is considered to be infrequent in PPH and attributed to protection of the thin walled pulmonary capillaries and veins by the high pulmonary vascular resistance. Pulmonary infarcts are not found at autopsy in patients with PPH and a history of hemoptysis. The bleeding may be from the dilatation and plexiform lesions[20,21]. By contrast hemoptysis, is more frequent with pulmonary thrombo-embolism.

Central cyanosis which was mild was present in only four of our patients. The mechanisms suggested for central cyanosis include right to left shunting through a patent foramen ovale reversed shunt through broncho-pulmonary anastomoses, pulmonary arterio-venous fistulae, hypoventilation ventilation-perfusion imbalance and defective diffusion[28]. In recumbent patients with a marked elevation of the jugular venous pressure and tricuspid regurgitation the tongue may appear to be cyanosed but this disappears after they stand up for some time.

Weakness, fatigue, and palpitation on exertion are common complaints. Somehow one is always profoundly affected while listening to the symptoms and evaluating patients with PPH partly because most of them are about to be robbed of their life in their prime by a process we know so little about.

Physical findings - The physical findings are those of severe pulmonary hypertension. A low pulse pressure < 30 mm. Hg was present in 53.8 % of our patients and 5l 6% were in congestive cardiac failure. Central cyanosis was rare and was present in only 4 patients (4,4%). The jugular venous pressure was elevated in 73%. A right ventricular heave was present in 94.5% and palpable pulmonary artery pulsations in 81.3% Am ejection click was present in 74.7% and an accentuated pulmonary closure sound in 98.9% with right sided S_3 or S_4 gallops singly or in combination in 52.7%. An ejection systolic murmur was present in 76.9% and the murmur of pulmonary regurgitation in 31.9% and that of tricuspid regurgitation in 37.4%.

Chest X-ray: The chest X-ray can provide valuable information in patients with pulmonary hypertension. None of our patients with PPH had signs of pulmonary venous congestion, left atrial enlargement, pleural thickening or pleural effusion. The lung fields were symmetrically homogenous.

There was evidence of severe pulmonary arterial hypertension in all but five patients, who had normal chest X-rays. The main pulmonary

artery was dilated in 90.1 % with peripheral pruning of the pulmonary vasculature in 86.4 %. The lung vascularity suggested a border lime increase in markings in 5 patients none of whom had a left to right shunt. The right atrium was enlarged in 29.6% and the right descending pulmonary artery could be measured in 40 patients and ranged from 15-26 mm and averaged 20 mm. The size of this branch did not show any significant correlation with the pulmonary artery pressure.

Electrocardiogram - There are several useful diagnostic features in PPH. Sinus rhythm is the rule and was so in 96.7% with only 3 patients in atrial fibrillation. The mean QRS axis in 91.1% of our patients was to the right of 90º. Peaked P waves exceeding 2.5 mm were present in 58.6%. Right ventricular hypertrophy was present in all but 7 patients. The QRS complex in V varied in morphology and the commonest pattern was q R.[1] The height of the R or R' wave correlated well with the pulmonary artery pressure ($P < 0.01$) but there was no significant correlation between the pressure and the mean frontal plane QRS or the QRS-T angle. An incomplete right bundle branch block was seem in only 16 7 % and only 1 patient had a complete right bundle branch block, a point of value in the differential diagnosis of the Eisenmenger syndrome.

Laboratory findings - The hemoglobin may be elevated in response to arterial desaturation. The hemoglobin was above 17 grams in 9 patients, although only 3 had desaturation at rest. Sedimentation is normal, as also the VDRL and antibody tests. Serum protein abnormalities may be present in some and increased levels of alpha, beta and gamma globulin have been reported and also hypo albuminemia and cyoglobulinemia. Coagulation studies performed on a series of our patients did not reveal any abnormality. The results of coagulation studies, caseinolytic determinations of plasminogen and antiplasmin, and fibrinolytic titers of antiurokinase did not differ significantly from those of the control group[29]. Eosinophilia has not been a striking feature in our series and was present in 19 cases. Microfilaria in the peripheral blood was present in only 1 patient.

Cardiac catheterization - In primary hypertension, the pulmonary artery pressure is raised with a normal post capillary pressure. This may be obtained indirectly through the pulmonary wedge, or directly from the left atrium by a transeptal pucture or through a patent foramen ovale. In the presence of severe pulmonary arterial hypertension a satisfactory wedge pressure may not be possible and this was so in about 50% of most series including our own [4,30]. The pulmonary arterial wedge pressure or direct left atrial pressure when obtained was always normal.

In our patients the pulmonary artery systolic pressure ranged from 50 168 mm Hg and averaged 106.8 mm, Hg, being supra systemic in 49.4%. The pulmonary artery diastolic pressure averaged 51.7 mm Hg. With mild supine exercise in 9 patients the pulmonary artery systolic pressure, diastolic and mean increased by 18.8, 10.2 and 12.4 respectively, and while on oxygen fell by an average of 12.0, 8.3 and 8.1 mm Hg. The pulmonary arteriolar resistance averaged 29.4 units/M^2 and the total pulmonary vascular resistance 33.7 units/M^2.

The average mean right atrial pressure was 5.6 mm Hg and the right ventricular and diastolic pressure was above 7 mm Hg in 52.7%. Right ventricular alternans was present in 23.1%. The cardiac index ranged from 1.2 to 4.0 L/min/M^2 and averaged 2.3 L/min/M^2. Cardiac catheterization is not without risk in patients with severe pulmonary hypertension. Patients with severe congestive cardiac failure and particularly those who do not improve with digitalis and diuretics should probably not be catheterized. With a conservative selection of patients the mortality risk would be around 1%[31].

Differential diagnosis - PPH has often been presented as a diagnosis that is difficult to make and one that should be made by a process of exclusion. However, in the clinical setting of centres where PPH is seen not infrequently, the diagnosis can often be confidently suspected at the initial evaluation. Confirmation by cardiac catheterization is essential as also related investigations like pulmonary angiography and echocardiography where indicated to exclude other causes of severe pulmonary hypertension.

Eisenmenger syndrome with a balanced shunt may masquerade as PPH, and such was the case in two of our patients. Patients with the Eisenmenger syndrome when in congestive heart failure are always cyanosed while most patients with PPH in congestive heart failure are not. The chest x-ray, particularly early ones may show a past left to right shunt or the ECG evidence of left ventricular hyperthrophy neither of which are seem in PPH. A complete balanced shunt at the atrial level particularly RBBB is rare in PPH. Some patients with a balanced shunt at the atrial level, particularly when unassociated with a previous large left to right shunt can be separated only at cardiac catheterization.

Left sided disease can result in severe pulmonary hypertension but most often the primary diagnosis is obvious. Left atrial myxoma with severe pulmonary hypertension and syncope may be mistaken for PPH, but unusual auscultatory findings may provide a clue and echocardiography shows pathognomonic changes In cor triatriatum pulmonary venous congestion is present. 'Silent' mitral stenosis with severe pulmonary hypertension is generally easy to distinguish from PPH. Left atrial enlargement and radiological signs of pulmonary venous hypertension are mot seem in PPH. Rarely the presystolic right atrial gallop in PPH may be mistaken for the presystolic murmur of mitral stenosis and with severe pulmonary venous hypertension the characteristic upper pulmonary venous distension may disappear. In such instances, echocardiography is helpful in the diagnosis of mitral stenosis. For as yet unexplained reasons, a right atrial gallop has not been present in any of our several hundred patients with mitral stenosis and pulmonary hypertension.

Pulmonary veno-occlusive disease presents with symptoms of pulmonary venous congestion and the radiological features ate dominated by patchy signs of pulmonary venous congestion

and progressive pulmonary arterial hypertension. At times the radiological features could closely mimic PPH[25].

Thrombo-embolic pulmonary hypertension may occur in two forms one of which is due to micro-emboli and thus clinically 'silent'. PPH is a uniform generalized process, not confined to any particular area of the lung. Thrombo-embolism on the other hand is patchy and selective and even micro-emboli are likely to be selective, since blood flow to the lungs is not uniform, being less in the upper zones. At the stage of severe pulmonary hypertension, repeated pulmonary thrombo-embolism is often associated with a history of haemoptysis and episodic aggravation of symptoms. Serial x-rays are likely to show one or a combination of signs like a segmental increase in transradiancy, abrupt termination and irregularities of pulmonary vessels, fissure displacement, sub-pleural shadows and pleural effusion. On the other hand the lung fields are symmetrically homogenous in PFH. When indicated pulmonary angiography and lung scans should be performed to exclude thrombo-embolic pulmonary hypertension. In PPH, the pulmonary arteries are not blocked by thrombi, the fine arborization of the small arteries is not seen and the slow circulation through the lungs results in only a faint outline of the normal sized pulmonary veins and the normal left atrium.

Etiology - Several theories have been advanced and some of the pathogenetic mechanisms suggested are outline in table IV. Where the cause is known as with Aminorex or schistosomiasis the term primary pulmonary hypertension is no longer tenable even though the pathological changes may at times be identical. It is possible that PPH is a heterogenous disorder with an etiology that varies in different geographical situations. It is hoped that more of such 'secondary forms' will be recognized.

It has been suggested that recurrent unrecognized episodes of thromboembolism are responsible for most if not all cases of PPH. A number of known features of PPH make the thrombo embolic theory difficult to accept PPH is not uncommon in childhood when thrombo-embolism is rare and 31 out of our 91 patients were below 18 years. There also appears to be a higher incidence of PPH in Asian countries where thrombo-embolism is rare. Several families have been reported with PPH and no known pre-disposition for thrombo-embolism. No consistent disorder of coagulation has been reported in PPH. Significant pulmonary hypertension is infrequent in patients followed up after repeated thrombo-embolism and the pulmonary vascular changes in thrombo-embolic pulmonary hypertension are quite distinct from those of PPH [21].

TABLE IV - Pathogenesis of PPPH - Suggested Mechanisms.

1.	Thrombo embolism and thrombosis in situ.
2.	Vasoconstrictive factors - Intrinsic hyperreactivity: hypoxia: neurohumoral mechanisms: serotonin: immune process: drugs: dietary factors.
3.	Congenital - Persistence of foetal vessels; hypoplasia or aplasia of media.
4.	Degenerative arteriopathy.
5.	Autoimmune process.
6.	Drugs - Aminorex: Oral contraceptives: Biguanides: ? Indigenous drugs (e.g. Ayurvedic).
7.	Dietary factors - Crotalaria.
8.	Parasitic infestation - Filariasis: Schistosomiasis.
9.	Female reproductive storids.
10.	Aminotic fluid embolism.

An earlier report from Sri Lanka suggested a possible association between filariasis and PPH[4]. Later reports from the same centre mention several patients with PPH who did not come from areas endemic for filariasis nor had positive filarial complement fixation tests[32]. Peripheral blood eosinophilia was no more common in PPH than in patients with other cardiac disorders seen by us.

Several observations support the view that vaso-constriction is the initiating factor. Particularly in the younger age group in a few cases the only histological abnormality has been an increase in the medial muscle mass in the small arteries and arterioles. Pharmacologic agents lower the pulmonary artery pressure in patient s with PPH. Primary pulmonary hypertension is more at high altitudes with a lower oxygen tension and it has also been recorded that patients with PPH deteriorate at higher altitude. Raynaud's phenomenon denoting hyper-reactivity of the digital arteries has been often observed in PPH[24] though not present in any of our patients. What triggers the vasospasm in these patients? Hypoxia, neuro-humoral mechanisms, immune processes, drugs and dietary factors have all been implicated[33].

Species variations have been noted in the development of pulmonary vascular disease. Thus cattle are reported, to be prone, sheep less so with man some where in between with genetic variations in the same species [34]. The number of patients in our series with PPH and the severity of pulmonary vascular disease in young patients in India with secundum atrial septal defects suggest that ethnic variations may well play a role in the development and progression of pulmonary vascular disease. From our data, patients in India with PPH develop more severe pulmonary hypertension with a pulmonary artery mean pressure about 10 mm Hg higher than their western counterparts and almost one decade earlier (table V).

TABLE V - Age at onset, pulmonary artery pressure, survival.

Author country	Number	Age	Pulmonary artery pressure mm Hg	Cardiac index L/min/M^2	Age at onset	Survival after diagnosis
Fuster et al	100	—				
USA		33	96/43	?	30	24 Months
Ref 5						
Abraham et al	91	—		—		
India		24	107/52	2.3	21	20 Months
Ref 6						

Management - Our current understanding of the regulation of the pulmonary circulation and its response to metabolic, neural, hormonal, chemical and pharmacological agents is incomplete. (table VI). Alveolar oxygen tension is a major determinant of pulmonary arteriolar tone. It is not clear if the low oxygen tension in mixed venous blood flowing through the small pulmonary arteries and arterioles can also lead to vaso-constriction. The importance of nervous control in the regulation of the pulmonary circulation in the normal adult is not known. Since beta adrenergic blockade has no significant changes, it is likely that there is no tonic action of the beta receptors.

TABLE VI - Effect on pulmonary circulation.

Oxygen	Vasodilatation
Hypoxia	Vasoconstriction
Acidosis	Vasoconstriction
Hypercapnia	Vasoconstriction
Nor-epinephrine	Vasoconstriction ±
Isoproterenol	Vasodilatation
Angiotensin II	Vasoconstriction
Serotonin	No vasoconstriction x in humans
Histamine	Hl Vasoconstriction H2 Vasodilatation
Prostaglandins	I_2 & E Vasodilatation F_2 & A_2 Vasoconstriction

Certain conservative measures should be adopted. High altitude, pregnancy, contraceptive medications, elective surgery and anaesthesia should be avoided. All respiratory infections should be promptly treated. Cardiac failure if present should be treated in the usual manner.

The beneficial effects of O_2 therapy have been reported[35] and we used O_2 therapy for several months and varying from 6-18 hours a day with symptomatic improvement. Administration for about 1 hour before meals and about 2 hours thereafter appears to improve the appetite and lessen post-prandial distress in some.

Long term anticoagulants have been considered useful by some and not by others. The follow-up report from the Mayo Clinic would suggest that it improves the prognosis and should be tried[5].

Some of the surgical procedures suggested are more of historical than practical importance.

Drug treatment - Pathological observations that medial hypertrophy precedes intimal changes implies that vaso-constriction is the dominant initiating factor. There are also instances where at autopsy there were minimal changes despite marked pulmonary hypertension during life.

Unfortunately patients rarely present in the early stages of PPH. The response of the pulmonary vascular bed is variable and also dependent on the extent of anatomical changes. The use of drugs may also be unpredictable in those with a very low cardiac output or severe congestive cardiac failure. The evaluation of a therapeutic response with an acute intervention may also be difficult to interpret. Thus an increase in the cardiac output will result in a calculated decrease in the pulmonary vascular resistance. In the early stages recruitment of additional vessels can result in a fall in the pulmonary artery pressure and resistance. It would be ideal to show the response to exercise at rest and also after drug intervention.

Acute reduction of pulmonary artery pressure has been seen after oxygen administration, acetylcholine, tolazoline hydrochloride, phentolamine hydrochloride. isoproterenol, diazoxide, hydralazine and nefidepine. Some of the results reported are shown in table VII. There is a marked variation in the severity of pulmonary vascular disease between different reports and within the same group. At the present time it would be necessary to titrate the response in individual patients while planning long term treatment and always in those with advanced disease. There is hope that long term lowering of the pulmonary vascular resistance may slow the progression of the disease and in some even halt or reserve the process.

Natural history - The prognosis is uniformly poor, though there are 2 groups of patients, one with a short history and rapid progression and the other with a longer history and slower progression, PPH in childhood has a 'malignant' course. Survival is short after the onset of right heart failure. Survival has also been correlated with the size of the hilar pulmonary arteries. Pregnancy, anaesthesia and surgery are hazardous for patients with PPH. Deaths during cardiac catheterization have been well documented. There is marked pallor and persistent hypotension, suggesting a low cardiac output in those that deteriorate after cardiac catheterization. At times there is bradycardia. We had one patient who complained of feeling very faint about 15 seconds before any fall in her heart rate and blood pressure and who could not be resuscitated.

We did not find that survival was longer in patients with a patent foramen ovale but we feel that the presence of pulmonary regurgitation affords some haemodynamic protection to patients with PPH as for those with the Eisenmenger syndrome. A recent report suggests that long term anticoagulants may prolong survival [5].

Out of the 91 patients 58 were followed up and 34 of them were known to have died. The average period of survival after discharge from hospital was 1 year and 8 months 18 out of the 58 patients survived for more than 7 years after discharge and 3 for more than 15 years. One patient is alive 26 years after the first episode of effort syncope. Table V shows that in the 100 patients seen at the Mayo Clinic[5], there was a female preponderance of 3:1. The average age at the time of diagnosis was almost a decade higher at 33 years, the average period of survival after diagnosis was 2 years.

RESUMO

Os autores apresentam resultados de uma série de 91 pacientes com hipertensão pulmonar primária observada em área tropical. Havia

TABLE VII - Effects of drvig intervention.

Drug	Author	Route and dose	Number duration	Hemodynamic effect
Diazoxide	Honey et al 1980 ref 15	IV PA	9	Oral PA 68 → 66; PVF
		Oral 400-600 mg a day	7	Cl 5.4 → 6.3; SR 1176
	Klinke and Gilbert, 1980 ref 13	Oral 300 mg a day	1	PA 39 → 27; PVR 430
			6 months	CI 4.8→ 8.3
Hydralazine	Rubin and Peter, 1980 ref 14	Oral 50 mg q6h	4	PA 70 → 69; PVR 131
			6 months	CI 4.7 → 8.7; SR 2092
	Handel et al 1981 ref 36	Oral	15-3PPH	PA 62 → 57; TPR 159
			3 doses	CI 2.2 → 3.2
Isoproterenol	Lupi-Herrera et al 1981	IV 15 mg q 4h.sd	6 Acute	Acute PA 35 → 23; PV
			2 Oral-3yrs .	PA 56 → 57; PVR 112
Nifedepine	Camerini at al 1980 (ref 37)	Oral 100 mg daily	1 3 mths	Acute PA 62 → 46 PVR 1139 → 786; CI 4
Prostaglandins	Watkins et al 1980 (ref 38)	Atrium PGI_2 44 mgkgmin PGE_1 50 mgkgmin	1 Acute	PA 81 → 64 PVR 2240 →1086; CI
Indomethacin	Person and Proctor 1979 (ref 17)	Sublingual 50 mg q 8h	1 1 year	PA 45 → 30 CI 1.9 → 2.4
Captopril	Horowitz at al 1981 (ref 18)	IV 6 mg	1 Acute	PA 60 →56; CI 1.78 – PVR 1210 → 820

IV = Intravenous; PA = Pulmonary artery; CI = Cardiac Index; SR = Systemic ressitance; PVR = Pulmonary vascular resistance; TPR = Total pulmonary resistanc

predominância de doentes do sexo masculino, ao contrário do constatado em regiões não-tropicais. Praticamente, todos os pacientes apresentavam dispnéia de esforço. Alterações eletrocardiográficas com aumento de voltagem de onda R em V1 tinham forte correlação positiva com o nível de pressão arterial pulmonar. Alterações da condução de estímulo elétrico eram pouco freqüentes. Era destacado em 90% dos casos o aumento de tamanho das artérias pulmonares, apreciado sob o aspecto radiológico. Pressão arterial pulmonar sistólica superior a 90 mmHg foi registrada em cerca de 70% dos doentes, sendo que em cerca de 49% ela superava o nível sistêmico. De um total de 58 pacientes seguidos, 34 morreram dentro de um período médio de 20 meses. Não se podem determinar as razões para o maior grau de severidade observado nessa série, sendo possível a participação de um fator étnico.

REFERENCES

1. Cherian, G.; Abraham M. T.; Sukumar I. P.; Krishnaswami, S.; Abraham, K. A. - Indiopathic pulmonary hypertension. VIII World Congress of Cardiology. Abstracts, 272, 1978.
2. Romberg, E. - Zur Frage der Herzgangnien. Zbl. Physiol. 4 601, 1891.
3. Fishman, A. P.; Pietra, G. G. - Primary pulmonary hypertension. Annual Review of Medicine, 31: 421, 1980.
4. Obeyesekere, I.; De Soysa N. - Primary pulmonary hypertension, eosinophilia and filariasis in Ceylon. Br. Heart J. 32: 524, 1970.
5. Fuster, V.; Giuliani, E. R.; Brandenburg R. O.; Weidman, W. H.; Edwards, W. D. - The natural history of idiopathic pulmonary hypertension Am. J. Cardiol.47: 422, 198l.
6. Abraham, M. T.; Cherian, G.; Sukumar, L. P.: Krishnaswami, S. - Primary pulmonary hypertension. Indian J. Chest Dis. Allied Sen. 23: 21,198l.
7. Brenner, O. - Pathology of the vessels of the pulmonary circulation. Arch . Intern. Med. 56: 211, 457,724, 976, 1189 1935.
8. Wood, P. - Pulmonary Hypertension Chap. 18 - The Diseases of Heart and Circulation. 3rd ed- Eyre & Spottiswoode, London, 1968.
9. Perloff, J. K. - Primary Pulmonary Hypertension. Chap. 14 - The clinical recognition of congenital heart disease. 2nd ed. W.B- Saunders Co, Philadelphia, London , Toronto, 1978.
10. Heath, D.; Kay, J. M. - Diet, drugs and pulmonary hypertension In Yu P. N.; Goodwin, J. F- eds. Chap 4 - Progress in Cardiology. vol. 7. Lea & Febiger, Philadelphia.
11. Shettigar, U. R.; Hultgren, H. N.; Specter, M.; Martin, R.; Davies, D. H. - Primary hypertension: Favourable effect of isoproterenol. N. Engl. J. Med. 295: 1414, 1976.
12. Wang S. W. S.; Pohl, J. E. F.; Rowlands, D. J.; Wade, E. G. - Diazoxide in treatment of primary pulmonary hypertension. Br. Heart J. 40: 572 1978.
13. Klinke, W. P.; Gilbert, J. A. L. - Diazoxide in primary pulmonary hypertension. N. Engl. J. Med. 302: 91, 1980.
14. Rubin, L. J.; Peter, R. H. - Oral hydralazine therapy for primary pulmonary hypertension. N. Engl. J. Med. 302: 69, 1980.
15. Honey, M.; Cotter, L.- Davies, N.; Denison, D.- Clinical and haemodynamic effects of diazoxide in primary pulmonary hypertension Thorax, 35: 269, 1980.
16. Lupi-Herrera, E.; Bialostozky, D.; Sobrino, A. - The role of isoproterenol in pulmonary artery hypertension of unknown etiology (primary). Chest, 79: 292, 1981.
17. Person, B.; Proctor, R. J. - Primary pulmonary hypertension. Response to indomethacin, terbutaline and isoproterenol Chest, 76: 601, 1979.
18. Horowitz, J. D.; Brennan, J. B.; Oliver, L. E.; Harding, D.; Goble, A. J.; Louis, W. J. - Effects of captopril in a patient with primary hypertension. Postgrad Med. J. 57: 115, 1981.
19. Gatewoodo R. P., Jr.; Yu, P. N. - Primary pulmonary hypertension. In Yu, P. N.; Goodwin, J. F. (eds) Progress in Cardiology Vol 8- Lea & Febiger, Philadelphia, 1979.
20. Wagenvoort, V. A.; Wagenvoort, N. - Primary pulmonary hypertension. A. pathological study of the lung vessels in 156 clinically diagnosed cases Circulation, 42: 1162 1970.
21. Wagenvoort, C. A.; Wagenvoort, N. - Pathology of pulmonary hypertension. John Wiley and Sons, New York, 1977.
22. Subramanian, N.; Bhaktaviziam, A.; Sukumar L. P.; Cherian G - Primary pulmonary hypertension. A clinico-pathological study of 11 cases. Ind. Heart J. 26: 171, 1974.
23. Hatano, S.; Strasser, T. - Primary pulmonary hypertension. Report on a WHO meeting Geneva, 1975.
24. Walcott, G.; Burchell, H. B.; Brown, A. L. Jr. -Primary hypertension. Am. J. Med. 49: 70. 1970.
25. Thadani, U.; Burrow, C.; Whitaker W.; Heath D. - Pulmonary veno-occlusive disease. Quart J. Med. 44: 133, 1975.
26. Schlant, R. C. - Altered physiology of the cardiovascular system in heart failure. Chap 27. 1974. The Heart (Hurst. J. W.; Logue, R. B.; Schlant, R. C.; Wenger N. K. eds) 3rd McGraw-Hill Kogakusha Ltd. Tokyo.
27. Kunhali, K.; Cherian, G.; Bhaktaviziam, A.; Abraham, M. T.; Krishnaswami, S. - Rupture of a papillary muscle of the tricuspid valve in primary pulmonary hypertension Am. Heart J. 99: 225, 1980.
28. Sleeper, J. C.; Orgain, E. S.; McIntosh, H. D. -Primary pulmonary hypertension. Review of clinical features and pathologic physiology with a report of pulmonary haemodynamics derived from repeated catheterization circulation, 26: 1358, 1962.
29. Tubbs, R. R.; Levin, R. D.; Shirey, E. K.: Hoffman G. C. - Fibrinolysis in familial pulmonary hypertension. Am. J. Clin. Pathol. 71: 384, 1979.
30. Trell, E.; Lindstrom, C. - Primary and thromb-embolic pulmonary hypertension. Clinical and pathoanatomic observations. Acta Med. Scand. Supplement. 534: 1972.
31. Braunwald, E.; Gorlin, R.; McIntosh, H. D.; Ross R. S.; Rudolph, A. M.; Swan H. J. C. - Cooperative study on cardiac catheterization. Circulation 37 (suppl 3): 15 1968.
32. Wijayawardene, U. B. - Personal Communication(1977).
33. Olsen, E. G. J. - Pulmonary hypertension. Chap 18, 1973. The pathology of the heart. New York. Intercontinental Medical Book Corporation.
34. Grover, R. F.; Vogel J. H. K.; Averil, K. H.; Blount, S. G. Pulmonary hypertension. Individual and species variability to vascular reactivity. Am. Heart. J. 66: 1, 1963.
35. Thilenius, O. G.; Nadas, A. S.; Jockin, H. - Primary pulmonary vascular obstruction in children. Paediatrics 36: 75, 1965.
36. Handel F.; Peter, R. H.; Rubin L. J. - Haemodynamic effects of hydralazine in patients with isolated right ventricular failure. Am. J. Cardiol. 47: 390, 1981.
37. Camerini, F.; Alberti, E.; Klugman S.; Salvi, A. -Primary pulmonary hypertension: Effects of nifedipine. Br. Heart J. 44: 352, 1980.
38. Watkins, W. D.; Peterson, M. B.; Crone, R. K.; Shannon, D. C.; Levine, L. - Prostacyclin and prostaglandin E, for severe idiopathic pulmonary artery hypertension. Lancet.: 1083, 1980.