Primary pulmonary hypertension in adults

Clinical features, catheterization findings and long-term follow-up

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Wood[1] first defined primary pulmonary hypertension as a clinical entity in 1950, but considerable controversy exists as to the natural history, etiology, and pathogenesis of the disease. Primary pulmonary hypertension is a progressive disease more commonly seen in women, with death occurring 2 to 10 years after diagnosis. The diagnosis is often one of exclusion. Numerous case reports and small clinical series have been published,[2–6] but there is no large series that describes the clinical and detailed angiographic findings in these patients with long-term follow-up. The purpose of our paper is to report a large clinical series (38 patients) with emphasis on clinical, hemodynamic, and angiographic findings. All but one of our patients were contacted to determine follow-up status. To our knowledge, this is the largest clinical series reported with long-term follow-up.

Patients

Primary pulmonary hypertension was defined as an elevation in mean pulmonary artery pressure greater than 30 mm Hg with exclusion of known secondary causes of pulmonary hypertension. Thirty-eight cases of primary pulmonary hypertension were seen at the Cleveland Clinic from 1962 to 1978. The diagnosis was established by cardiac

catheterization in 37 patients and in one patient was confirmed at autopsy. Written or telephone communication or both on the clinical course and treatment was obtained from referring physicians, the patients, or relatives of the patients. Electrocardiograms were available on all patients. Echocardiograms were performed on 13 of the 38 patients. Eight patients had detailed evaluation for collagen disease, and lung immunofluorescence studies were done on one patient at autopsy. We defined sudden death as death occurring within 24 hours of the onset of symptoms.

Results

Of the 38 patients, 29 women and 9 men, two were younger than age 20; and 11 were older than 50 at the time of diagnosis. In 17 patients (44%) the diagnosis was made between the ages of 41 and 50 years (*Fig. 1*). Clinical signs and symptoms are given in *Table 1.* Dyspnea on exertion was the most common symptom and most common initial complaint. Arthritis was also noted in three patients, but in none was it disabling or the presenting feature. None of the patients had anemia, leukocytosis, leukopenia, or renal or skin disease.

Physical findings are listed in *Table 2.* A loud pulmonic component of the second heart sound (P-2) was the most common auscultatory finding and the P-2 was often palpable. Systolic murmurs were also commonly heard, either ejection type or holosystolic, along the left sternal border suggestive of tricuspid insufficiency. Evidence of right heart failure characterized by peripheral edema, hepatomegaly, and elevated jugular venous pressure was found in 19 patients (50%). Cyanosis was present in 16 patients. A diastolic murmur suggestive of pulmonic insufficiency was heard in eight patients (21%), but appeared unrelated to the degree of pulmonary hypertension.

The electrocardiographic findings are listed in *Table 3.* A permanent pacemaker was inserted in one patient because of complete heart block. Right

Table 1. Clinical signs and symptoms; 38 patients

	Patients	
	Number	Percent
Dyspnea on exertion	37	97
Fatigability/tiredness	30	78
Chest pain	15	39
Cough	15	39
Dizziness	14	34
History of murmur	13	34
Syncope	11	28
Orthopnea	11	28
Hemoptysis	3	8
Raynaud's	3	8
Arthritis	3	8
Psychological symptoms	2	5

Table 2. Physical findings; 38 patients

	Patients	
	Number	Percent
Loud P-2	31	81
Systolic murmur	20	52
Edema	20	52
Right heart failure	19	50
Cyanosis	16	42
Diastolic murmur	8	21

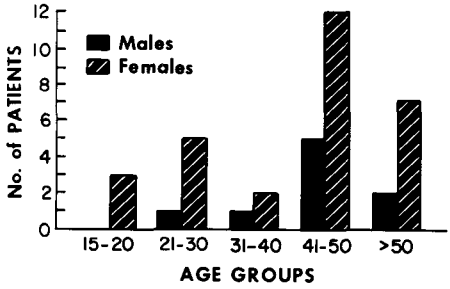

Fig. 1. Population groups (at diagnosis) in patients with primary pulmonary hypertension.

ventricular hypertrophy was the most common finding, and right axis deviation was seen in most patients (*Fig. 2*).

Roentgenograms of the chest showed evidence of right ventricular hypertrophy, a prominent main pulmonary artery trunk, and decreased peripheral pulmonary vascular markings (*Fig. 3*).

Echocardiograms, available for 13 patients (35%), revealed right ventricular dilatation and hypertrophy and echocardiographic evidence of pulmonary hypertension (*Fig. 4A*). Mitral valve prolapse was noted in four of 13 patients (*Fig. 4B*). The echocardiographic criterion used for mitral valve prolapse was abrupt movement in mid-systole of one or both mitral leaflets posteriorly toward the left atrium.[7]

Table 3. Electrocardiographic findings; 38 patients

	Patients	
	Number	Percent
Sinus rhythm	37	97
Right ventricular hypertrophy	28	73
Right axis deviation	27	71
Right atrial enlargement	18	47
Left atrial enlargement	4	10
Normal electrocardiogram	4	10
Complete right bundle branch block	3	8
Pacemaker rhythm	1	...

Cardiac catheterization data revealed elevated pulmonary artery pressures in all patients, with normal pulmonary wedge pressures in all but one patient. Six patients had repeat cardiac catheterization at an interval of 2 weeks to 3 months after diagnosis without any significant change in pulmonary artery pressures. Two patients had a patent foramen ovale without any evidence of significant shunting by oximetry data. Systolic pulmonary artery pressures ranged from 50 to 138 mm Hg and diastolic pressures from 18 to 83 mm Hg. Mean pulmonary artery pressures ranged between 30 and 100 mm Hg.

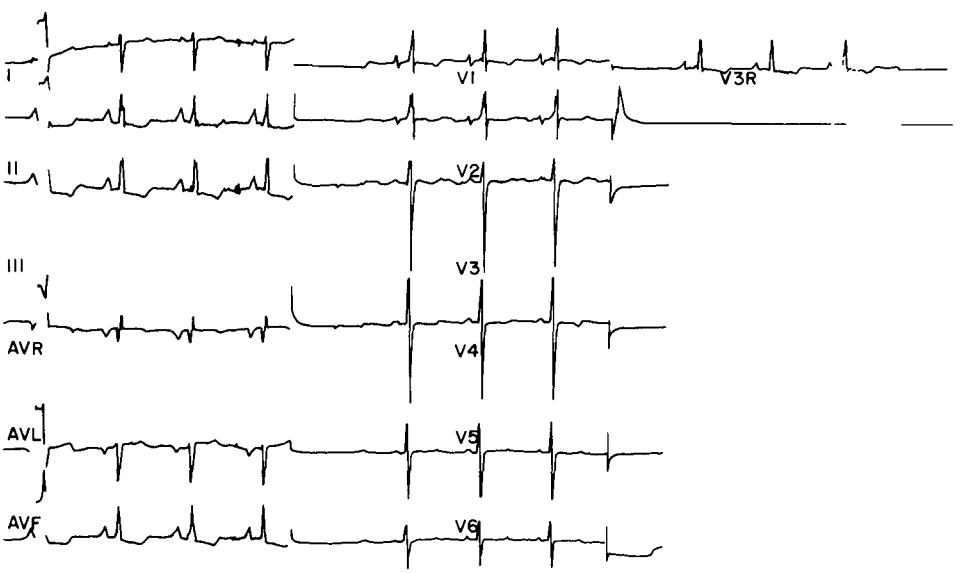

Fig. 2. Electrocardiogram in primary pulmonary hypertension showing normal sinus rhythm, right axis deviation, right atrial enlargement, and right ventricular hypertrophy.

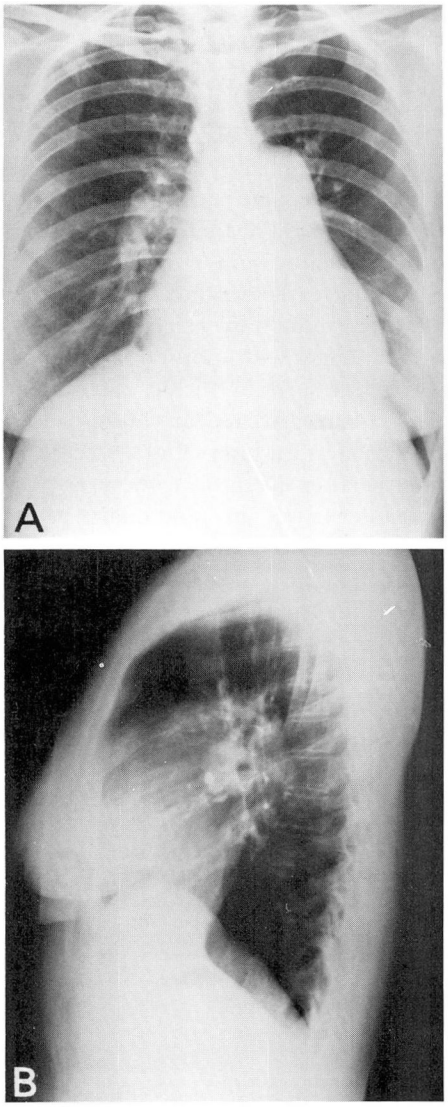

Fig. 3A and B. Posteroanterior and lateral chest roentgenograms revealing right ventricular hypertrophy, prominent pulmonary trunk, and peripheral pulmonary artery attenuation.

Pulmonary blood flow and resistances were not measured. Systolic pulmonary artery pressures were equal to or exceeded systemic pressures in seven patients. Right-sided angiocardiograms were done in 25 patients. Selective right and left pulmonary artery injections were performed in 17 patients with right ventriculograms in four patients and main pulmonary artery injections in four patients. A dilated main pulmonary artery trunk was seen in 19 patients (*Fig. 5A*). Peripheral pulmonary artery attenuation and delayed clearance of contrast material were seen in 22 patients (*Fig. 5B and C*). Eight of 25 patients had angiographic evidence of mitral valve prolapse (without mitral insufficiency) on left ventriculography (*Fig. 5D*). Bulging of two or more scallops of the mitral leaflets into the left atrium during systole was considered angiographic evidence for prolapse.[8,9] Atrioventricular block, hypotension, and cyanosis developed in one of the four patients in whom an injection of contrast material was made into the main pulmonary artery, but the patient recovered. Coronary angiograms were done in 25 patients. Coronary artery circulation was normal in 20 patients, and in the others mild coronary atherosclerosis was observed with less than 50% reduction in luminal diameter. None of the coronary arteriograms demonstrated significant atherosclerosis.

Table 4 shows the cardiac catheterization-related complications in 12 patients. Cyanosis was the most common complication. One patient died 3 minutes after an aortogram, preceded by hypotension, cyanosis, atrioventricular block, and finally asystole.

Of the 38 patients, 28 died. There are nine survivors and one was lost to follow-up. The mean age at death was 44 years (range, 18 to 75 years). There was no correlation between longevity and the patient's sex, duration or severity of pulmonary hypertension, electrocardiographic or roentgenographic findings, echocardiographic evidence of pulmo-

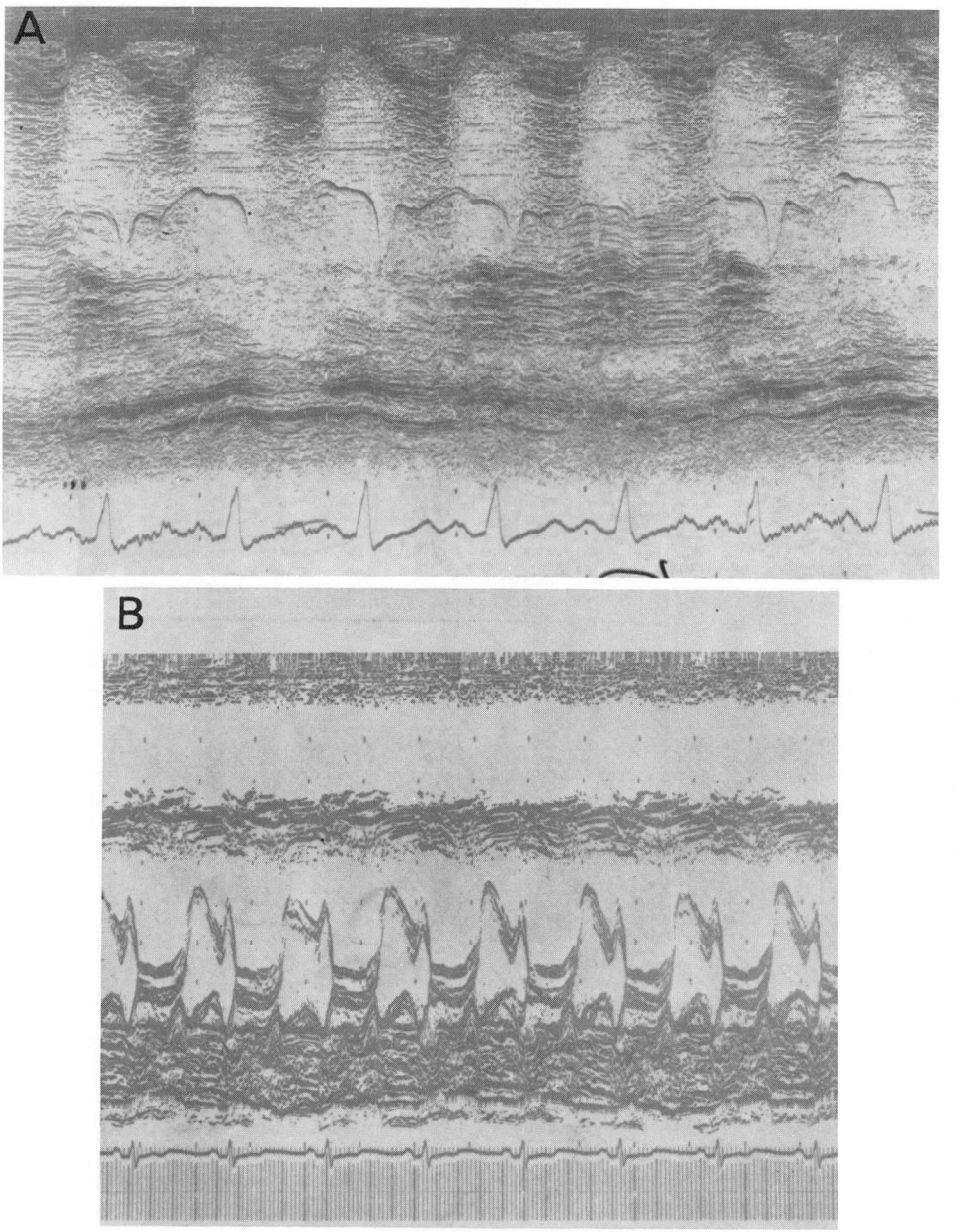

Fig. 4A. Echocardiogram showing motion of the posterior pulmonic leaflet. Tracing demonstrates the absence of *a* wave and mid-systolic notching of the pulmonary valve leaflet, and RVPEP/RVET equal to 0.78 (normal, <0.3). RVPEP = right ventricular pre-ejection period, RVET = right ventricular ejection time. **4B.** Echocardiogram illustrating pansystolic prolapse of the posterior mitral leaflet. Note increased right ventricular internal diameter.

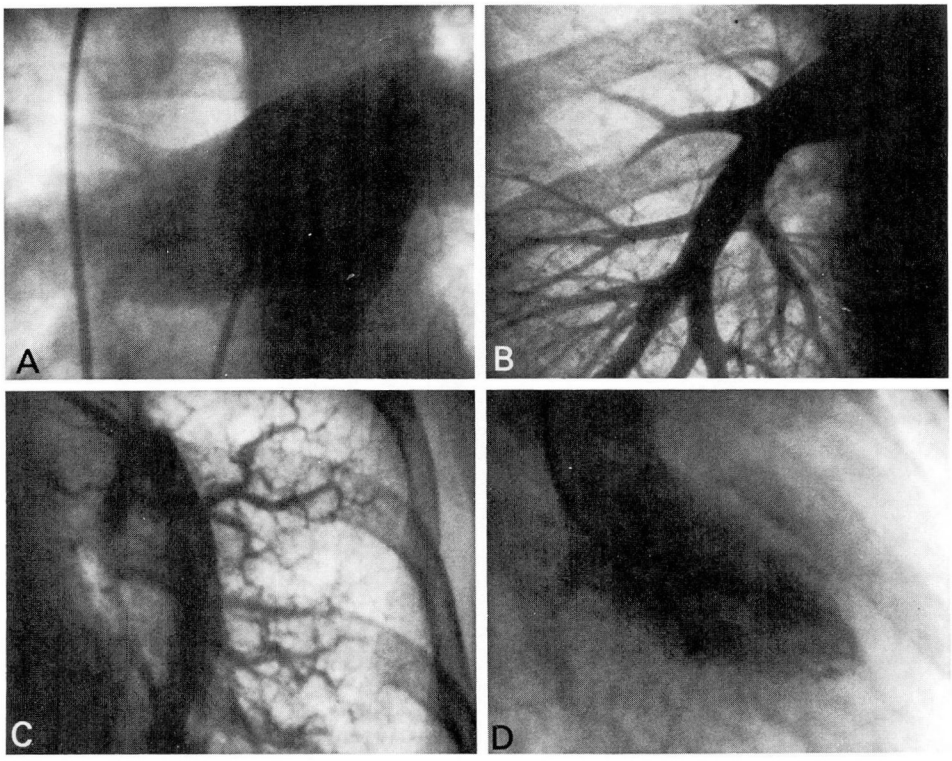

Fig. 5A. Pulmonary angiogram demonstrating marked dilatation of main pulmonary trunk. **5B.** Selective right lower pulmonary angiogram showing pruning of peripheral pulmonary arteries. **5C.** Later phase of selective left pulmonary arteriogram demonstrating delayed clearance of contrast material. **5D.** Systolic frame of left ventriculogram in the right anterior oblique projection showing prolapse of the posterior leaflet of the mitral valve.

Table 4. Complications with cardiac catheterization; 12 patients

Number of patients	Complication	Subsequent course
4	Cyanosis	After pulmonary angiography
3	Cyanosis with hypotension	Two patients recovered; one patient died 3 minutes after aortogram
1	Ventricular fibrillation	During pulmonary angiogram; survived
1	Syncopal episode, seizure	Developed after right ventricular injection, hypotension; survived
1	A-V block	Developed A-V block with hypotension during hand injection into right pulmonary artery; survived
1	Progressive dyspnea	Died 2 days after catheterization
1	Progressive dyspnea	Died 3 weeks after catheterization

nary hypertension, angiographic evidence of dilatation of the main pulmonary trunk or attenuation of the peripheral pulmonary arteries or oxygen saturation in the systemic or pulmonary circulations. Survival was shortened in patients with presenting symptoms before age 40. Most of the patients lived less than one year after right heart failure developed.

Figure 6 demonstrates the 3-year survival rate of patients using actuarial life tables.[9] Approximately 90% of the patients died in less than 3 years after diagnosis. Only two survived more than 5 years.

Table 5 summarizes the causes of death in the 28 patients. Six patients died suddenly without warning, one while hurrying to dress, and another patient, while dancing.

Nine patients, three men and six women, survived. Age, sex, age at onset of symptoms, severity of pulmonary hypertension, and hemodynamic catheterization findings were not statistically different from those of the patients who died. The patients have survived for a mean of 6.5 years after onset of symptoms, with a range of 7 months to 15.5 years. Three of these patients were considered to have right heart failure and have been living for a mean of 11 months following its development.

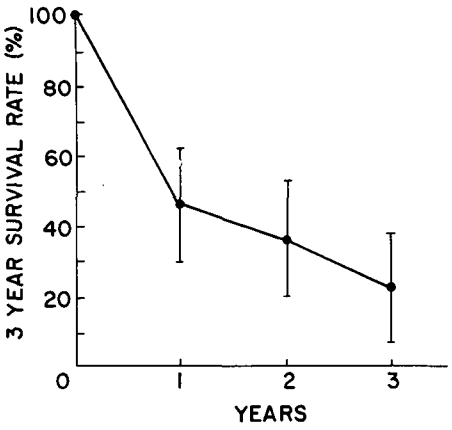

Fig. 6. Actuarial life table analysis shows 3-year survival rate from diagnosis. Note decrease in the 95% confidence interval for each year.[9]

Table 5. Causes of death; 28 patients

Unknown	14
Right heart failure	6
Sudden death	6
Died during catheterization	1
Died after minor surgery	1

Discussion

The most common symptoms in our patients with primary pulmonary hypertension were dyspnea on exertion, weakness, and fatigability. James[10] has suggested that sinoatrial and atrioventricular nodal disease in patients with primary pulmonary hypertension in addition to cerebral hypoxia, reflex vagotonia, and a fixed lowered cardiac output may predispose them to exercise intolerance and syncope.[11] Syncope occurred in 11 (28%) of our patients. The cyanosis, frequently seen in patients with primary pulmonary hypertension and in our patients as well, could be attributed to many factors: peripheral circulatory stasis secondary to decreased cardiac output, a stretched foramen ovale with right-to-left shunt at the atrial level (we found this to be unusual), or bronchopulmonary anastomosis and ventilation perfusion abnormalities similar to that which occurs in patients with pulmonary embolism.[12]

Raynaud's phenomenon has been reported frequently in patients with primary pulmonary hypertension.[13-16] However, in our series only three patients had Raynaud's phenomenon, which may precede the onset of primary pulmonary hypertension by several

years. Thus, based on our large series of patients, the postulate that patients with primary pulmonary hypertension may have a vasospastic process similar to that seen in the digital arteries of patients with Raynaud's could not be confirmed.

Several reports have been published concerning mortality and morbidity associated with cardiac catheterization in patients with primary pulmonary hypertension.[17–19] An increase in pulmonary artery pressure following injection of contrast material has been reported.[20,21] There is no question that these patients are at increased risk during cardiac catheterization (*Table 4*). However, the results of our study indicate that selective right and left pulmonary arteriography can be done with relative safety in these patients, particularly when other causes of pulmonary hypertension are ruled out. Sasahara[12] has suggested that only selective right and left pulmonary angiograms be done if the mean pulmonary artery pressure is greater than 40 mm Hg. Thus, if catheterization is necessary in these patients, it need not be deferred provided caution is observed with awareness of anticipated complications.

Familial primary pulmonary hypertension has been reported previously.[22–24] In our series, in only four patients was there a suggestion of familial primary pulmonary hypertension and the mode of inheritance appeared to be that of an autosomal dominant. One asymptomatic patient of interest underwent cardiac catheterization for evaluation of a heart murmur because her sister had died of right heart failure. Cardiac catheterization revealed severe pulmonary hypertension. She is alive 2.5 years after catheterization, but is presently in the New York Heart Association Functional Classification, Class III. Thus, our large clinical series would suggest the familial incidence of pulmonary hypertension may not be as frequent as other authors have described.

The demonstration of mitral valve prolapse in 12 (30%) patients was surprising in that the classic auscultatory findings were not present. Goodman et al[25] found that four of nine patients (44%) with primary pulmonary hypertension had mitral valve prolapse with no clinical evidence of prolapse. In none of their cases, nor in any of our cases, was there echocardiographic evidence of tricuspid valve prolapse. The cause of mitral valve prolapse in patients with primary pulmonary hypertension is unknown.

The clinical course in our adult patients with primary pulmonary hypertension seems to be more malignant than that of many other cardiac defects. The clinical course following onset of symptoms is usually progressive leading to death within 2 to 10 years after initial symptoms. There have been rare reports of survival as long as 20 years.

The results of treatment of primary pulmonary hypertension are disappointing. The disease is usually well advanced at the time of diagnosis and its course remains unaltered by treatment. The most difficult problem has been to differentiate primary pulmonary hypertension from pulmonary embolism. Since patients with primary pulmonary hypertension often have thrombi, cause or effect is still debated. This has led to treatment with anticoagulants, but they have had no definite value. Reactive and nonreactive types of primary pulmonary hypertension have been described on the basis of response to agents such as oxygen inhalation, isoproterenol (Isuprel),[26–30] tolazoline, nitroprusside, and nitroglycerin. Long-term oxygen therapy has been successful in occasional patients.[31] The response to sym-

pathectomy and creation of a shunt at the atrial level has been poor.[32] There does appear to be a role for digoxin and diuretics in those patients with primary pulmonary hypertension who have right heart failure. One recent report[33] has described the response in a 19-year-old patient with primary pulmonary hypertension to intravenous and oral diazoxide. Further evaluation of the use of diazoxide in primary pulmonary hypertension is warranted.

Primary pulmonary hypertension may mimic many other congenital and acquired cardiac diseases. The clinical features, unfortunately, are not specific and may lead to the diagnosis of other defects. Based on our large clinical study, the possibility of primary pulmonary hypertension should be considered when the following clinical features are present:

1. History of dyspnea on exertion with generalized weakness and fatigability, and syncopal episodes on exertion.
2. Family history of pulmonary hypertension and death at a young age.
3. Physical findings suggestive of right ventricular hypertrophy with a loud palpable pulmonary component of the second heart sound.
4. Electrocardiographic changes of right axis deviation, right atrial enlargement, and right ventricular hypertrophy.
5. Chest roentgenogram with evidence of right ventricular enlargement, prominent pulmonary artery trunk, and normal-sized left atrium with decreased peripheral pulmonary artery markings.
6. Echocardiographic evidence of normal-sized left atrium with normal appearing left-sided structures and evidence of increased right ventricular thickness and dilatation, prolapse of the mitral valve and pulmonary valve motion, and indices suggestive of pulmonary hypertension.

Cardiac catheterization findings include the following:

1. Elevated pulmonary artery pressure.
2. Normal pulmonary capillary wedge pressure.
3. Absence of left-sided obstruction or significant mitral regurgitation.
4. Absence of primary myocardial disease or significant coronary arteriosclerotic disease.
5. A dilated main pulmonary artery trunk with peripheral pruning of the pulmonary arteries and delayed clearance of contrast material.
6. The absence of significant intracardiac or extracardiac shunts.

We conclude that despite the difficulties in diagnosis and no satisfactory treatment regimen, the search for a treatable lesion in patients with elevated pulmonary artery pressures should not be abandoned. The echocardiogram has been helpful in our most recent patients in diagnosing and suggesting primary pulmonary hypertension. Still, if the diagnosis is not conclusive, cardiac catheterization can be done relatively safely in these patients. Catheterization may be indicated in all patients to define the response to pharmacologic agents as a possible means of defining an appropriate therapeutic regimen for these patients.

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