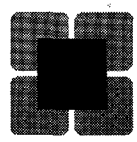

Primary pulmonary hypertension, then and now: 28 years of experience

BENJAMIN D. ROBALINO, MD AND DOUGLAS S. MOODIE, MD, MS

■ To determine whether a better understanding of primary pulmonary hypertension has affected its clinical presentation, natural history, and prognosis, we retrospectively compared patients with primary pulmonary hypertension presenting to our institution during two different periods: 1962 to 1978 (group 1, n=38) and 1979 to 1989 (group 2, n=33). Demographic characteristics were similar in both groups. Dyspnea on exertion was the most frequent presenting symptom in both groups. Fatigue, cough, dizziness, right heart failure, and cyanosis were more frequent in group 1. The electrocardiographic, radiographic, and echocardiographic findings did not differ between groups. Hemodynamic measurements revealed severe pulmonary hypertension and a normal pulmonary capillary wedge pressure and cardiac index; these measurements were similar in both groups. Complications related to cardiac catheterization were more frequent in group 1 (32%) than in group 2 (3%). Causes of death were comparable in both groups, the most frequent being progressive right heart failure, sudden death, and death of unknown cause. Patients from both groups received standard treatment with digitalis, diuretics, and vasodilators; however, group 2 had a higher probability of survival than group 1. We conclude that patients with pulmonary hypertension seen in more recent years tend to present at earlier stages of disease, have fewer complications during cardiac catheterization, and probably survive longer than those seen several decades ago. A clear cause for the longer survival could not be identified, although it may be partly related to earlier presentation in the course of disease.

□ INDEX TERMS: HYPERTENSION, PULMONARY □ CLEVE CLIN J MED 1992; 59:411–417

PRIMARY PULMONARY hypertension (PPH), the sustained elevation of pulmonary arterial pressure without an apparent cause, is better understood today than 30 years ago.[1] But has our improved knowledge of the etiology, pathophysiology, diagnosis, and management of PPH in any way changed the clinical presentation, natural history, and prognosis of the disease in these patients?

To determine this, we retrospectively reviewed the Cleveland Clinic Hospital medical records of the last 28 years and divided the patients with PPH into two groups according to the time of initial presentation: those seen between 1962 and 1978 (series previously reported[2]), and those who presented between 1979 and 1989. The two groups were then compared according to clinical, laboratory, and hemodynamic features, as

From the Department of Cardiology, The Cleveland Clinic Foundation.

Address reprint requests to D.S.M., Department of Cardiology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

TABLE 1
CLINICAL FEATURES OF TWO GROUPS OF PATIENTS WITH PRIMARY PULMONARY HYPERTENSION (GROUP 1, 1962 TO 1978; GROUP 2, 1979 TO 1989)

	Group 1 (n=38)		Group 2 (n=33)	
	Number	Percent	Number	Percent
Symptoms and signs				
Dyspnea on exertion	37	97	32	97
Fatigue	30	78	13	39*
Chest pain	15	39	13	39
Cough	15	39	2	6*
Dizziness	14	34	4	12†
History of murmur	13	34	7	21
Syncope	11	28	5	15
Orthopnea	11	28	5	15
Hemoptysis	3	8	0	0
Raynaud's phenomenon	3	8	0	0
Arthritis	3	8	0	0
Pyschological symptoms	2	5	5	15
Physical findings				
Loud P-2	31	81	31	94
Systolic murmur	20	52	29	88*
Edema	20	52	16	48
Right heart failure	19	50	6	18*
Cyanosis	16	42	4	12‡
Diastolic murmur	8	21	5	15

P-2, pulmonary component of second heart sound
*P <.01 compared with group 1
†P=.03 compared with group 1
‡P=.01 compared with group 1

well as survival. We present the results of this retrospective comparison.

METHODS

Study groups

In our study, PPH was defined as an elevation in mean pulmonary arterial pressure greater than 30 mm Hg in the absence of known secondary causes of pulmonary hypertension. As mentioned above, 38 cases of PPH were seen from 1962 to 1978 (group 1) and 33 cases between 1979 and 1989 (group 2). The diagnosis was established by cardiac catheterization in all patients except for one patient from group 1, in whom it was confirmed at autopsy. Electrocardiograms were available in all patients. Echocardiography was performed on 13 patients (34%) from group 1 and in 29 patients (88%) from group 2. Part of the information regarding chest radiographs and hemodynamic data was obtained from summarized data previously reported,[2] since all the original reports could not be obtained. Information on clinical course was available in all patients from group 1 and in 31 (94%) from group 2. This information was obtained through written or telephone communication with referring physicians, patients, or their relatives.

Statistical analysis

The demographic data, clinical laboratory data, and causes of death were recorded in both groups and were expressed as percentages. Comparison was made between the two groups using exact chi-square tests. These comparisons between groups were not performed when information was incomplete, insufficient, or not available in either group. A Mantel-Haenszel test was used to compare the survival distributions of the two groups.

RESULTS

Tables 1 to *4* summarize and compare the demographic, clinical, and laboratory data from the two groups. *Figure 1* depicts the age distribution of the two groups, and *Figure 2* compares their survival curves.

Demographic characteristics

In group 1, 9 of the patients (24%) were male and 29 were female (76%). In group 2, 13 were male (39%) and 20 were female (61%). No significant differences were found in gender distribution. The age distribution was also similar between the two groups. The mean age at diagnosis was 42 in both groups.

Clinical findings

Dyspnea on exertion was the most frequent symptom in both groups (97% of the patients in each group), followed by fatigue, chest pain, and cough. Other symptoms such as dizziness, syncope, and orthopnea were present in one third or fewer of the patients in both groups. Fatigue (P<.01), cough (P<.01), and dizziness (P=.03) were seen more frequently in group 1. A loud pulmonary component of the second heart sound was the most prevalent physical finding in both groups (81% in group 1, and 94% in group 2). A systolic murmur was significantly more frequent in group 2 (88% vs 52%, P<.01), while right heart failure (50% in group 1 vs 18% in group 2,

$P<.01$) and cyanosis (42% in group 1 vs 12% in group 2, $P<.01$) were more frequently seen in group 1.

Noninvasive tests

Electrocardiographic findings were typical of those seen in PPH: namely, sinus rhythm with evidence of right ventricular hypertrophy and right axis deviation. These findings were comparable between the two groups. One patient in group 1 had a permanent pacemaker implanted because of complete heart block.

The majority of patients in group 1 had roentgenographic evidence of cardiomegaly, prominent main pulmonary arteries, and decreased peripheral pulmonary vascular markings (exact percentages were not available). In group 2, 88% of the patients showed cardiomegaly and 85% had prominent main pulmonary arteries on chest roentgenography by subjective assessment.

Only 13 patients (35%) in group 1 had M-mode echocardiograms, whereas 29 patients (88%) in group 2 had either M-mode only (7 patients) or M-mode and two-dimensional Doppler echocardiograms. Right ventricular enlargement or right atrial enlargement or both were observed in the great majority of patients. Indirect evidence of pulmonary hypertension, such as abnormal wall motion of the pulmonic valve or interventricular septum and right ventricular hypertrophy, were frequently seen. Tricuspid regurgitation was observed in all patients who underwent two-dimensional Doppler echocardiographic evaluation. The statistical comparisons between the two groups was not done because of the different echocardiographic modalities employed.

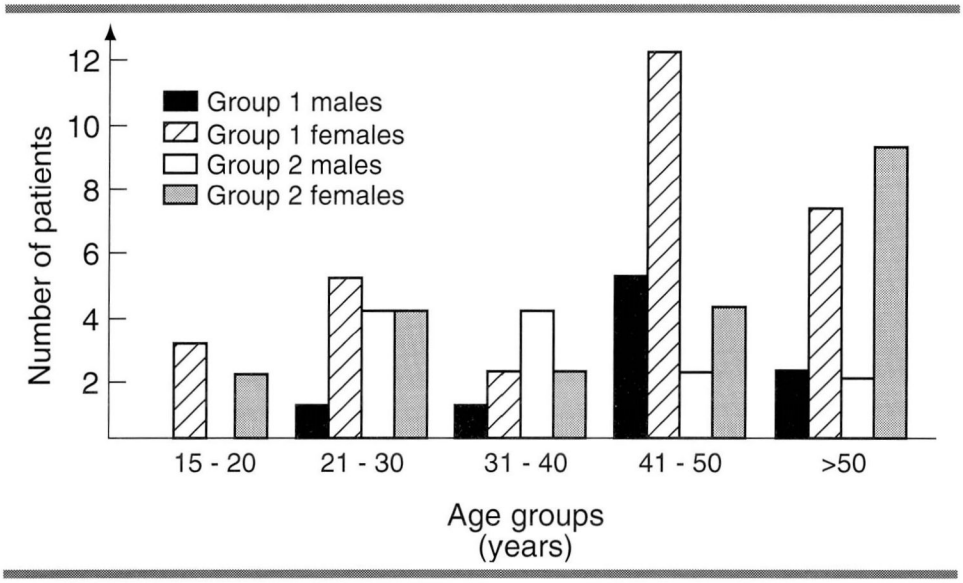

FIGURE 1. No differences in age and sex distribution were seen between the two groups of patients with primary pulmonary hypertension (group 1, 1962 to 1978; group 2, 1979 to 1989).

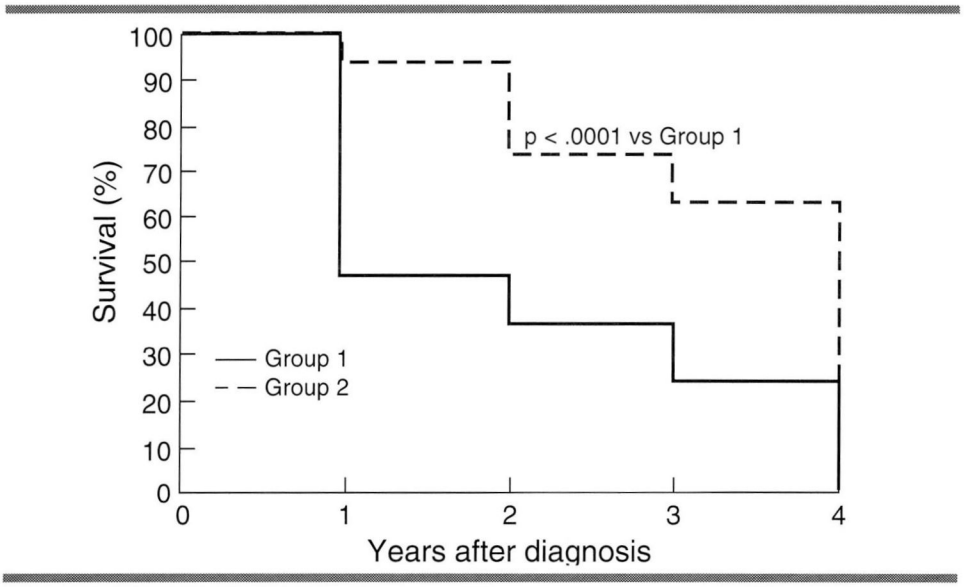

FIGURE 2. Survival curves of two cohorts of patients with primary pulmonary hypertension who presented during two different periods (group 1, 1962 to 1978; group 2, 1979 to 1989) show increased long-term survival in the more recent group. Note that 4-year survival is 3% in group 1 and 25% in group 2.

TABLE 2
RESULTS OF NONINVASIVE TESTS IN TWO GROUPS OF PATIENTS WITH PRIMARY PULMONARY HYPERTENSION (GROUP 1, 1962 TO 1978; GROUP 2, 1979 TO 1989)

	Group 1 (n=38)		Group 2 (n=33)	
	Number	Percent	Number	Percent
Electrocardiography*				
Sinus rhythm	37	97	33	100
Right ventricular hypertrophy	28	73	30	91
Right-axis deviation	27	71	28	85
Right atrial enlargement	18	47	18	55
Left atrial enlargement	4	10	1	3
Normal electrocardiogram	4	10	1	3
Complete right bundle branch block	3	8	3	9
Pacemaker rhythm	1	3	0	0
Chest roentgenography				
Cardiomegaly	N/A	N/A	29	88
Prominent main pulmonary arteries	N/A	N/A	28	85
Echocardiography†				
Right ventricular enlargement	13		28	97
Right atrial enlargement	N/A		19	86
Abnormal septal motion	N/A		15	52
Tricuspid regurgitation	N/A		12	100
Right ventricular systolic pressure (mean ± standard deviation)	N/A		79.1 ± 15.1	
Right ventricular hypertrophy	13		8	36
Pericardial effusion	N/A		6	21
Pulmonary hypertension signs (M-mode)	13		9	31
Mitral valve prolapse	4		1	3

N/A, not available
* The electrocardiographic signs did not differ significantly between the groups.
†Performed in 13 patients from group 1 (M-mode only) and in 29 patients from group 2 (M-mode only in 7, M-mode and two-dimensional in 22, Doppler in 12). Percentages are based on the number of patients on which each echocardiographic modality was done. A statistical comparison between the two groups was not made because of the different echocardiographic modalities used.

Hemodynamic and angiographic findings

In group 1, systolic pulmonary arterial pressures ranged from 50 to 130 mm Hg, and diastolic pressures from 18 to 83 mm Hg. Mean pulmonary arterial pressures ranged from 30 to 100 mm Hg. Mean values for these pressures were not available. Only one patient had an abnormal pulmonary capillary wedge pressure. Pulmonary vascular resistance was not measured. The respective measurements for group 2 are shown in *Table 3*.

Six patients in group 1 had repeat cardiac catheterization at an interval of 2 weeks to 3 months after diagnosis without any significant change in pulmonary arterial pressures. In group 2, two patients underwent repeat catheterization. One of them had no significant change in mean pulmonary arterial pressure (65 to 70 mm Hg), but his mean right atrial pressure increased from 5 to 34 mm Hg 44 months after the initial catheterization. The second patient had increases in mean pulmonary arterial pressure (from 55 to 80 mm Hg) and in mean right atrial pressure (from 2 to 28 mm Hg) 50 months after the initial procedure.

Two patients in group 1 had a patent foramen ovale, and one patient in group 2 had a partial anomalous pulmonary venous return (persistent left superior vena cavae draining into the coronary sinus). None of these three patients had evidence of hemodynamically significant shunting by oximetry.

Pulmonary angiographic findings (*Table 4*) showed no differences in the frequency of selective or nonselective pulmonary angiograms performed, nor in the incidence of dilated main pulmonary arteries, pruning of peripheral pulmonary arteries, or delayed contrast clearance. Right atriography or right ventriculography or both were performed in four patients from group 1 and two from group 2 and showed dilated right heart chambers with reduced systolic function. An interesting finding was the angiographic evidence of mitral valve prolapse in 8 out of 25 patients from group 1 and in none from group 2 (*Table 4*).

In group 1, 25 patients underwent coronary arteriography; results were normal in 20, and 5 showed mild coronary atherosclerotic changes with luminal obstruction of less than 50%. In group 2, 21 patients underwent coronary arteriography, with normal results in all but 1 patient. This patient had severe single-vessel coronary artery disease with normal left ventricular function and left ventricular end-diastolic pressure. Left ventriculography was performed in 25 patients from group 1 and 23 from group 2; results were normal in all but 1 patient, who had mild left ventricular dysfunction.

Cardiac catheterization was associated with complications in 12 patients from group 1 (32%) and in one patient from group 2 (3%) ($P<.01$). The complica-

tions in group 1 were as follows: cyanosis in 4 patients; cyanosis with hypertension in 2; progressive dyspnea in 2; and ventricular fibrillation, syncope, atrioventricular block, and death in 1 patient each. In group 2, one patient had transient visual disturbances during the procedure.

TABLE 3
HEMODYNAMIC MEASUREMENTS IN PATIENTS WITH PRIMARY PULMONARY HYPERTENSION SEEN BETWEEN 1979 AND 1989 (GROUP 2)

	Mean ± standard deviation	Range
Pressures (mm Hg)		
Right atrium, mean (n=33)	10.2 ± 6.1	2-24
Right ventricle, systolic (n=32)	92.0 ± 23.6	55-150
Right ventricle, diastolic (n=32)	12.5 ± 6.7	2-30
Pulmonary artery, systolic (n=32)	92.3 ± 23.6	55-150
Pulmonary artery, diastolic (n=32)	38.9 ± 13.0	15-80
Pulmonary artery, mean (n=28)	60.0 ± 16.5	42-105
Pulmonary capillary wedge, mean (n=32)	9.1 ± 4.8	4-26
Cardiac output (L/min) (n=20)	4.1 ± 2.0	2.3-9.5
Cardiac index (L/min/m^2) (n=20)	2.3 ± 1.1	1.3-5.0
Pulmonary vascular resistance (dyne/second/cm^{-5}) (n=15)	1,293.7 ± 598.3	367-2,608
Total pulmonary resistance (dyne/second/cm^{-5}) (n=18)	1,435.6 ± 596.9	471-2,953
Systemic O_2 saturation, room air(%)(n=25)	92.3 ± 4.2	81-100
Systemic O_2 saturation, 100% oxygen(%)(n=11)	96.8 ± 4.1	88-100

Treatment regimens

Information on the specific treatment received by patients in group 1 was not available. In group 2, however, 12 patients received vasodilators; 7 patients received anticoagulants (warfarin in 5, aspirin in 2, dipyridamole in 1); 15 patients received digitalis; and 19 received diuretics. No drug treatment was used in 4 patients. Twenty patients in group 2 received more than one type of medication.

Survival time and causes of death

Death from unknown etiology, progressive right heart failure, and sudden death were the most frequently reported causes of death in both groups (*Table 5*). There were no statistically significant differences in the cause of death between the two groups. However, patients in group 2 had a higher probability of survival ($P<.0001$).

DISCUSSION

Rather than describe the clinical, laboratory, and hemodynamic findings in our patients with PPH, which are similar to those reported in previous series,[3,4] this discussion will try to emphasize the possible difference found between two groups of patients seen at our institution during different periods of time over 28 years.

Age and sex distribution was the same for groups 1 and 2 (*Figure 1*). Dyspnea on exertion was the most frequent symptom, equally prevalent in both groups. Fatigue ($P<.01$), cough ($P<.01$), and dizziness ($P=.03$) were more frequent in group 1. Patients with more symptoms—ie, New York Heart Association Functional Class III-IV—were found to have a higher incidence of fatigue in the national prospective study of PPH.[4] In addition, group 1 patients had a higher frequency of right heart failure and cyanosis, suggesting that this group of patients presented at more advanced stages of disease. However, the age of presentation was similar in the two groups. A family history of PPH was found in four patients in group 1 and one in group 2. These patients, as found in the National Institutes of Health (NIH) registry of PPH,[4] are usually diagnosed sooner after the onset of symptoms. One of our patients with a family history of PPH was asymptomatic.

The electrocardiographic findings were typical of those reported in PPH and did not differ between groups. Similarly, the chest roentgenographic results showed changes associated with pulmonary hypertension, although a statistical comparison could not be made between the groups. Echocardiographic studies revealed enlarged right heart chambers and other indirect evidence of pulmonary hypertension in both groups. As expected, patients in group 1 had only M-mode readings, whereas most patients in group 2 had both M-mode and two-dimensional Doppler echocardiograms.

The range of right atrial, right ventricular (systolic and diastolic), and pulmonary arterial pressures (systolic, diastolic, and mean) were very similar between the groups and were consistent with series previously reported. Indeed, the mean ± standard deviation values for these parameters in group 2 were remarkably similar to those reported in the NIH registry of PPH, which were mean pulmonary arterial pressure of 60±18 mm

TABLE 4
ANGIOGRAPHIC FINDINGS IN TWO GROUPS OF PATIENTS WITH PRIMARY PULMONARY HYPERTENSION (GROUP 1, 1962 TO 1978; GROUP 2, 1979 TO 1989)

	Group I		Group II	
	Number	Percent	Number	Percent
Pulmonary angiography				
– Performed on	25	100	19	100
– Type				
– Selective	21	84	11	58
– Nonselective	4	16	8	42
– Findings				
– Dilated main pulmonary artery	19	76	18	95
– Pruning of primary and peripheral pulmonary artery and/or delayed contrast clearance	22	88	18	95
Right atriography or ventriculography				
– Performed on	4	100	2	100
– Findings				
– Dilated chamber	4	100	2	100
Coronary arteriography				
– Performed on	25	100	21	100
– Findings				
– Normal	20	80	20	95
– Abnormal	5*	20	1†	5
Left ventriculography				
– Performed on	25	100	23	100
– Findings				
– Normal	25	100	22	96
– Abnormal	0	0	1	4
– Mitral valve prolapse	8	32	0	0

* All with less than 50% obstruction in coronary arteries.
† Severe single-vessel coronary artery disease with normal left ventricular function and normal left ventricular end-diastolic pressure.

Twelve patients (32%) in group 1 and one patient (3%) in group 2 had complications related to cardiac catheterization or pulmonary arteriography or both. This difference could not be attributed to the use of selective injections of contrast in the pulmonary artery, since they were used with equal frequency in both groups; instead, it is probably related to the awareness of potential problems in patients with PPH, with early intervention when complications arise, as well as to the more frequent use of non-ionic contrast agents. We have learned to be extremely cautious when performing cardiac catheterizations in these patients, even when angiography is not performed, and this is probably reflected in the very low incidence of complications in the patients studied more recently.

Hg, mean right atrial pressure of 9±6 mm Hg, and cardiac index of 2.27±0.9 L/min/m^2. Twelve patients from group 1 and none from group 2 had angiographic evidence of mitral valve prolapse. Echocardiographically, this defect was evident in four patients in group 1 and one in group 2. We do not have a clear explanation for the higher incidence of mitral valve prolapse in group 1. Mitral valve prolapse has been described in echocardiographic studies performed in patients with PPH.[5,6] Goodman et al[5] found M-mode echocardiographic evidence of mitral valve prolapse in four of nine patients. However, in three of them the left ventricular diastolic dimension was below normal. Goodman et al hypothesized that a connective tissue disorder involving the mitral valve leaflets could be responsible for the abnormality. Arditti et al[6] found abnormal septal motion with prolapse of the mitral and tricuspid valves in four of six patients and suggested that prolapse of these valves was secondary to hemodynamic changes in ventricular pressure gradients across the interventricular septum.

The causes of death were comparable in both groups. Progressive right failure and sudden death are recognized as the most frequent causes of death in PPH.[4] However, the higher prevalence of unknown etiology for death may reflect the retrospective nature of the study, as well as the fact that many patients die at home and do not undergo autopsy, and that relatives ignore the exact cause of death. Interestingly, the survival for group 2 patients was longer than for group 1 ($P<.0001$). The shorter survival in group 1 may be related, at least in part, to presentation at a later stage of disease, since they had a higher incidence of fatigue, cyanosis, and clinical right heart failure, all of which are manifestations observed usually in advanced phases of PPH.

Our study is limited by its retrospective nature and by the lack of part of the roentgenographic and hemodynamic data in the group seen in earlier years. Despite these limitations, however, this study shows that patients with PPH seen in more recent years tend

to present at earlier stages of disease, have fewer complications during cardiac catheterization, and probably survive longer after diagnosis than patients seen several decades ago. A clear reason for the longer survival could not be determined in this investigation, although it may be related to earlier presentation in the course of disease or to differences in treatment or both. Chronic vasodilator therapy was first used in patients with PPH in the mid-1970s; therefore, it is more likely that patients in group 2 received vasodilator therapy (as 36% of them actually did), which would have had favorable effects on their survival. Other authors[7] also have observed that patients with PPH in the 1980s appear to live longer than those whose diagnosis was made in the 1960s and 1970s. Both groups of patients received treatment with drugs such as digitalis and diuretics, and none of them received newer therapeutic modalities such as prostaglandin inhibitors or high-dose calcium antagonists.

TABLE 5
CAUSES OF DEATH IN TWO GROUPS OF PATIENTS WITH PRIMARY PULMONARY HYPERTENSION (GROUP 1, 1962 TO 1978; GROUP 2, 1979 TO 1989)

	Group1(n=28)	Group 2 (n=22)
Unknown	14	8
Right heart failure	6	7
Sudden death	6	4
Cardiac catheterization	1	0
Minor surgery	1	0
Infection	0	2
Cancer	0	1

ACKNOWLEDGMENT

We are grateful to Marlene Goormastic for her expert statistical advice.

REFERENCES

1. Rich S. Primary pulmonary hypertension. Prog Cardiovasc Dis 1988; **31**:205–238.
2. Gupta BD, Moodie DS, Hodgman JR. Primary pulmonary hypertension in adults. Cleve Clin Q 1980; **47**:275–284.
3. Hugh JD, Rubin LJ. Primary pulmonary hypertension: an analysis of 28 cases and a review of the literature. Medicine (Baltimore) 1986; **65**:56–72.
4. Rich S, Dantzker DR, Ayres SM et al. Primary pulmonary hypertension: a national prospective study. Ann Intern Med 1987; **107**:216–223.
5. Goodman, DJ, Harrison DC, Popp RL. Echocardiographic features of primary pulmonary hypertension. Am J Cardiol 1974; **33**:438–443.
6. Arditti A, Lewin RF, Dean Hi Aygen M, Agmon J. Echocardiographic findings of mitral and tricuspid valve prolapse in primary pulmonary hypertension. Isr J Med Sci 1985; **21**:504–510.
7. Glanville AR, Burke CM, Theodore J, Robin ED. Primary pulmonary hypertension. Length of survival in patients referred for heart-lung transplantation. Am J Cardiol 1987; **91**:675–681.