Primary Pulmonary Hypertension

A National Prospective Study

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A national registry was begun in 1981 to collect data from 32 centers on patients diagnosed by uniform criteria as having primary pulmonary hypertension. Entered into the registry were 187 patients with a mean age ($\pm$ SD) of 36 ± 15 years (range, 1 to 81), and a female-to-male ratio of 1.7:1 overall. The mean interval from onset of symptoms to diagnosis was 2 years. The most frequent presenting symptoms included dyspnea (60%), fatigue (19%), and syncope (or near syncope) (13%). Raynaud phenomenon was present in 10% (95% of whom were female) and a positive antinuclear antibody test, in 29% (69% female). Pulmonary function studies showed mild restriction (forced vital capacity [FVC], 82% of predicted) with a reduced diffusing capacity for carbon monoxide ($D_{L_{CO}}$), and hypoxemia with hypocapnia. The mean ($\pm$ SD) right atrial pressure was 9.7 ± 6 mm Hg; mean pulmonary artery pressure, 60 ± 18 mm Hg; cardiac index, 2.3 ± 0.9 L/min·m²; and pulmonary vascular resistance index, 26 ± 14 mm Hg/L/min·m² for the group. Although no deaths or sustained morbid events occurred during the diagnostic evaluation of the patients, the typically long interval from initial symptoms to diagnosis emphasizes the need to develop strategies to make the diagnosis earlier.

[MeSH terms: alkalosis, respiratory; anoxemia; antinuclear factors; carbon monoxide; dyspnea; fatigue; hemodynamics; hypertension, pulmonary; Raynaud's disease; sex factors; syncope; vascular resistance; vital capacity. Other indexing terms: cardiac index; diffusing capacity; hypocapnia; pulmonary artery pressure; right atrial pressure]

THE RECOGNITION OF pulmonary vascular disease as a primary cause of pulmonary hypertension was first attributed to Romberg (1) in 1891 in a case report of a patient with unexplained pulmonary hypertension. In 1951, Dresdale and associates (2) collected data on 39 patients with unexplained pulmonary hypertension and coined the term *primary pulmonary hypertension* to describe the condition, a term that is still used today. Wood (3) described the clinical features of this disease in a series of 17 patients in 1959, and by 1971 more than 600 cases had been reported. Although the basic clinical presentation has been well documented, many questions remain as to the epidemiology, pathogenesis, natural history, and treatment of primary pulmonary hypertension. Until re-

cently, no single institution has been able to accumulate data on a sufficient number of patients to address many of these issues.

In 1973 the World Health Organization met to review the current state of knowledge regarding the epidemiologic, clinical, and pathologic features of primary pulmonary hypertension and proposed that consideration be given to establishing a multicenter collaborative study involving these patients (4). In 1981 the Division of Lung Disease of the National Heart, Lung, and Blood Institute, National Institutes of Health, initiated the Patient Registry for the Characterization of Primary Pulmonary Hypertension. The goals of the registry were to obtain and evaluate data on the natural history, cause pathogenesis, and treatment of primary pulmonary hypertension, with the hope that new strategies might evolve to allow early detection of the disease and the development of a rational therapeutic approach. We review baseline data from 187 patients with primary pulmonary hypertension who have been entered in the registry.

Methods

Thirty-two medical centers (*see* Appendix) were to report data on standardized reporting forms from patients with primary pulmonary hypertension who were seen between 1 July 1981 and 30 September 1985. Pulmonary hypertension was defined as the presence of a mean pulmonary arterial pressure of greater than 25 mm Hg at rest or 30 mm Hg with exercise at catheterization.

Because no clinical feature or laboratory variable is recognized as pathognomonic for primary pulmonary hypertension, the diagnosis was accepted only after the following secondary causes for pulmonary hypertension were excluded: pulmonary hypertension within the first year of life, and congenital abnormalities of the lungs, thorax, and diaphragm; congenital or acquired valvular or myocardial disease; pulmonary thromboembolic disease as evidenced either by lung perfusion scan (other than normal or low probability) or positive pulmonary angiogram, a diagnosis of sickle cell anemia, or a history of intravenous drug abuse; obstructive lung disease as manifested by hypoxemia and reduced flow rates (forced expiratory volume in 1 second/forced vital capacity > 2 SD from predicted norm); interstitial lung disease as evidenced by a reduction in total lung capacity of more than 2 SD from the predicted norm associated with pulmonary infiltrates on chest roentgenogram; arterial hypoxemia associated with hypercapnia; collagen vascular disease as classically defined (5); parasitic disease affecting the lungs; pulmonary artery or valve stenosis as documented by pulmonary artery pressure gradients during right heart catheriza-

tion; and pulmonary venous hypertension with pulmonary capillary wedge pressures in excess of 12 mm Hg. Cases in which doubt existed as to the primary nature of the pulmonary hypertension were reviewed by the steering committee and ruled by consensus as either meeting or not meeting criteria.

Patients judged to have satisfied the above criteria were also required to have the following data supporting the diagnosis of primary pulmonary hypertension for their cases to be classified as primary pulmonary hypertension: demographic data including age, sex, race, height, and weight; a chest radiograph; pulmonary function tests with arterial blood gas pressures measured during the breathing of room air; a lung perfusion scan or a pulmonary angiogram; evaluation of an intracardiac left-to-right shunt, either by angiogram, hydrogen curve, indicator dilution test, or oximetry; and baseline hemodynamic variables including right atrial pressure, pulmonary systolic, diastolic, and mean pressures, pulmonary capillary wedge pressure, systemic systolic and diastolic pressures, and cardiac output. Data on history, physical examination, and other laboratory findings were also collected.

STATISTICAL ANALYSIS

Statistical methods used to characterize the variables were descriptive (means, standard deviations, product moment correlation coefficients). Methods used to evaluate differences among groups included t-tests, chi-square tests, and, where appropriate, the Mantel-Haenszel test. The Cochran-Armitage test was used to test for trend when comparing several proportions. Values obtained for pulmonary function tests and arterial blood gases were standardized to previously published norms (6-9) and converted to the percent predicted value for that test. The p values reported are two-sided and nominal (not adjusted for multiple comparisons).

Results

DEMOGRAPHIC CHARACTERISTICS

The age and sex distribution of 187 patients with primary pulmonary hypertension entered into the registry are shown in Figure 1A. The mean age of patients enrolled was 36.4 years and was similar for male and female patients. Although the age distribution of patients with this disease showed the highest frequency in the third decade for female patients, and the fourth decade for male patients, 9% of the patients were more than 60 years of age. The female-to-male ratio was 1.7:1 and was relatively constant for each decade. Female patients tended to have more severe symptoms at presentation, with 75% in functional class III or IV (according to New York Heart Association criteria) compared with 64% for male patients ($p = 0.08$). The distribution of patients by race was similar to that of the general population, with 12.3% black and 2.3% Hispanic. Interestingly, there was a greater female-to-male preponderance in the black population (4.3:1), with a similar age distribution as the white population.

SYMPTOMS

Dyspnea was by far the commonest initial symptom, occurring in 60% of all patients. Ninety-eight percent, however, had dyspnea by the time they were enrolled at the clinical centers. Fatigue (19%), chest pain (7%), near syncope (5%), syncope (8%), leg edema (3%), and palpitations (5%) were less common initial symptoms. However, fatigue was present in 73% of the patients, chest pain in 47%, near syncope in 41%, syncope in 36%, edema in 37%, and palpitations in 33%, of the
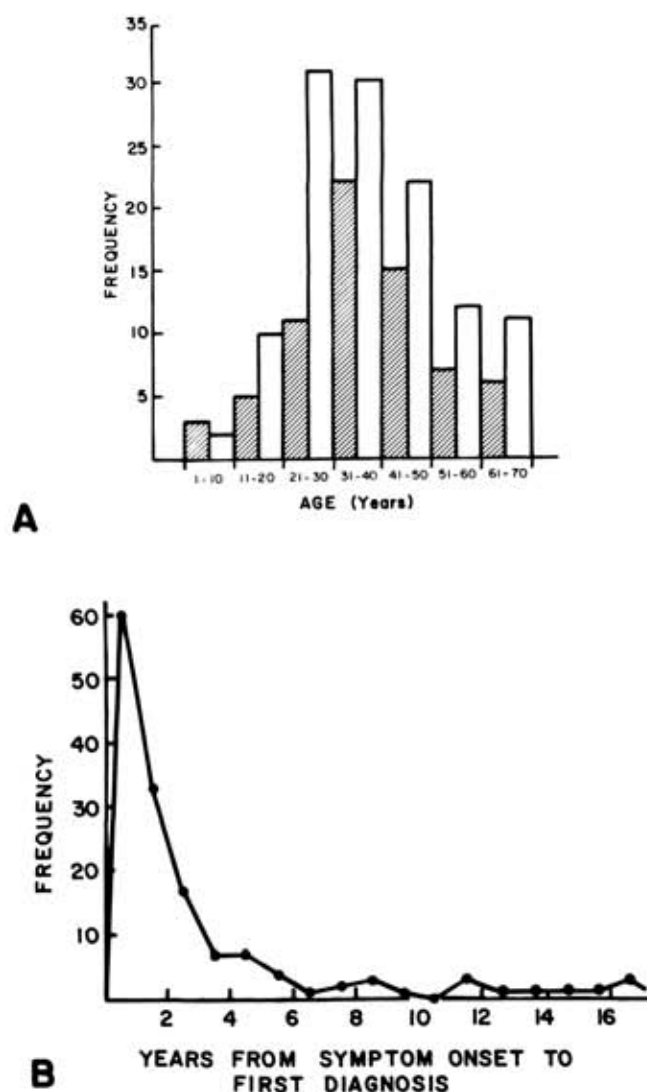
A

B YEARS FROM SYMPTOM ONSET TO FIRST DIAGNOSIS

Figure 1. Distribution of patients with pulmonary embolism plotted according to age based on sex (*A*) and according to onset of symptoms for both sexes (*B*). The disease was most prevalent in age groups in the third and fourth decades, but the female-to-male ratio of 1:7 to 1 was not significantly different among decades. The mean time to onset of initial symptoms, 2.03 years (median, 1.27), was similar for both male (*shaded bars*) and female (*open bars*) patients.

patients by the time they were enrolled. Twenty-nine percent of the patients had mild symptoms (functional class II) at the time of entry into the registry. When compared with the more symptomatic patients (functional class III and IV), these patients were less likely to have fatigue (58% compared with 79%; $p = 0.01$) or peripheral edema (23% compared with 41%; $p = 0.06$).

The time from onset of the first symptom until the diagnosis of primary pulmonary hypertension was made is shown in Figure 1B. The mean time from onset to diagnosis was 2.03 ± 4.9 years (median, 1.27) and was similar for male and female patients. Although more than 90% of the patients had their illness diagnosed within 3 years of presenting symptom onset, on occasion patients stated that their symptoms had been present for up to 20

years before the diagnosis was made. Only 10% of the patients reported symptoms of Raynaud phenomena, which occurred almost entirely (95%) in the female patients.

MEDICAL AND FAMILY HISTORY

Forty-five percent of the patients were previous or current cigarette smokers, and only 5% had histories of appetite suppressant drug use. Fifty-four percent of the female patients had taken oral contraceptives at some time. There were 2.3 live births per female patient in the registry. None of these frequencies appear to differ dramatically from those found in the general population. There were 12 cases (6%) of familial pulmonary hypertension (disease affecting a first-order blood relative), 7 in men and 5 in women. Patients who had positive family histories were usually diagnosed sooner after the onset of symptoms than were the other registry patients (0.68 compared with 2.56 years; $p = 0.0002$). There were no differences, however, in their ages or hemodynamic findings.

PHYSICAL FINDINGS

The physical findings of patients with primary pulmonary hypertension were typical of any patient with pulmonary hypertension. An increase in the pulmonic component of the second heart sound (P_2) was reported in 93%, a right-sided third heart sound (S_3), in 23%; and a right-sided fourth heart sound (S_4), in 38%. The presence of an S_3 was associated with elevated right atrial pressure (13 compared with 9 mm Hg; $p < 0.001$) and a reduced cardiac index (1.8 compared with 2.4 L/min·m²; $p < 0.0001$). Tricuspid regurgitation was noted in 40% and pulmonic insufficiency, in 13%. The presence of tricuspid regurgitation was also associated with increased right atrial pressure (12 compared with 8 mm Hg; $p < 0.0001$) and a reduced cardiac index (1.77 compared with 2.56 L/min·m²; $p < 0.001$), whereas the presence of pulmonic insufficiency was associated with a higher mean pulmonary artery pressure (70 compared with 59 mm Hg; $p < 0.03$). Cyanosis was reported in 20%, and peripheral edema, in 32%.

LABORATORY FINDINGS

The chest radiographs, which were subjectively graded at each center, showed the typical constellation of changes associated with pulmonary hypertension—namely, prominence of the main pulmonary artery (90%), enlarged hilar vessels (80%), and decreased peripheral vessels (51%). The presence of all three abnormalities (42%) was associated with a higher mean pulmonary artery pressure (66 compared with 53 mm Hg; $p < 0.001$) and lower cardiac index (2.0 compared with 2.4 L/min·m²; $p < 0.004$). Interestingly, the chest radiograph was reported to be normal in 6% of the patients.

The electrocardiogram showed right axis deviation in 79%, right ventricular hypertrophy in 87%, and right ventricular strain in 74%. All patients had an underlying sinus rhythm. The echocardiogram (M-mode) showed a normal to small left ventricular end-diastolic internal dimension in all patients and right ventricular enlargement in 75%. The calculated pulmonary vascular resistance index correlated inversely with left ventricular end-diastolic dimension ($r = 0.47$; $p < 0.001$) but not with right ventricular end-diastolic dimension. Paradoxic septal motion was described in 59% of the patients and partial systolic closure of the pulmonary valve, in 60%.

Results of an antinuclear antibody test were positive in 29% of the patients, with titers ranging from 1:10 to 1:10 000 (geometric mean, 1:103), although the antigen substrates used were not uniform among centers. There was a female-to-male ratio of 1.4:1 among those reported with a positive result. The lung perfusion scan was normal in 42% and characterized as abnormal in 58% (Table 1). Of the patients who had abnormal scintigrams, only one was reported as having a high probability of pulmonary embolism, and that patient had a normal pulmonary angiogram. Seventy-seven percent of the abnormalities were described as a diffuse patchy pattern; 7%, as single defects; and 12%, as multiple discrete defects. There was no relationship between the hemodynamic findings and the pattern of perfusion as shown by lung scan.

PULMONARY FUNCTION

Selected variables of pulmonary function are presented in Table 2 and Figure 2. Airways obstruction could not be shown, but there was a mild, albeit significant, reduction in total lung capacity in the female patients (mean, 89% of predicted; $p < 0.05$) and in forced vital capacity (FVC) for both male and female patients (mean, 82% of predicted; $p < 0.01$). Although there was wide scatter, the diffusing capacity for carbon monoxide (DL_{CO}) measured significantly less than that predicted (mean, 69% of predicted; $p < 0.001$). Hypoxemia and hypocapnia were almost an invariable finding. The arterial oxygen content correlated significantly with mixed venous oxygen content ($r = 0.48$; $p < 0.001$).

HEMODYNAMIC FINDINGS

Hemodynamic variables in patients at the time of catheterization at the clinical centers are summarized in Table 2 and shown in Figure 3. The patients had severe pulmonary hypertension with a threefold increase in mean pulmonary artery pressure (60 ± 18 mm Hg; range, 28 to 127), mild-to-moderate elevation in right atrial pressures (9 ± 6 mm Hg; range, 0 to 29) with normal pulmonary capillary wedge pressures, and mildly reduced cardiac indexes (2.27 ± 0.9 L/min·m²; range, 0.8 to 7.9). Female patients differed significantly from male patients only with respect to resting heart rates, with the female patients having a faster rate by an average of 7 beats/min ($p = 0.009$).

Correlations between hemodynamic findings and severity of symptoms were also investigated. Patients with more severe symptoms (functional class III and IV) had higher mean pulmonary artery pressures (62 compared with 56 mm Hg; $p = 0.06$), higher right atrial pressures (11 compared with 7 mm Hg; $p = 0.0001$), and lower

cardiac indexes (2.06 compared with 2.73 L/min·m²; $p = 0.0003$) than did their less symptomatic counterparts (functional class II). In contrast, we were unable to find differences in hemodynamic values among patients when they were analyzed according to duration of symptoms. Because young women have often been described as the group most severely afflicted by primary pulmonary hypertension, we compared values in female patients from the ages of 15 to 34 years with those in the men and the women aged 35 or more. No significant differences were found between these groups based on functional class or hemodynamic values.

ADVERSE CONSEQUENCES

None of the 163 patients who had lung perfusion scans reported any adverse complication. Only one adverse reaction (transient hypotension) occurred among the 50 patients reported to have had pulmonary angiography. Of the 187 patients who had cardiac catheterization, 10 reported adverse reactions from the catheterization (not including drug testing). Four had adverse effects that appeared unrelated to the presence of pulmonary hypertension—namely, inadvertent arterial puncture, oversedation, and pneumothorax (in 1 patient). Six patients had adverse effects that were probably related to the underlying pulmonary hypertension, with five episodes of transient hypotension and one of hemoptysis after an angiogram. Fortunately, there were no deaths or sustained morbidity associated with any of these procedures.

Discussion

A major distinction between this study of primary pulmonary hypertension and others, with the exception of the large number of patients enrolled, is its prospective nature compared with previous retrospective studies. The large collection of data from patients with primary pulmonary hypertension who have been enrolled in this registry has allowed better characterization of the disease than ever before. The data have shown that a long symptomatic period has preceded the diagnosis, which likely accounts for the advanced manifestations of pulmonary hypertension at the time of diagnosis. The data have also shown that untoward events from the work-up, including catheterization, were uncommon at the participating centers.

The criteria for patient enrollment into the registry

Table 1. Correlation Between Patterns of Abnormalities as Detected by Lung Perfusion Scans and Estimated Probability of Pulmonary Embolism*

Patterns	Estimated Probability			
	High	Low	Indeterminate	Total
	←———————— *n* ————————→			
Patchy	0	71	1	72
Single defect	0	7	0	7
Multiple discrete defects	1	8	2	11
Not specified	0	3	1	4

* Based on a total of 94 abnormal scintigrams; total number of normal scintigrams = 69.

Table 2. Pulmonary Function Variables and Hemodynamic Findings at Entry into Registry*

	Males	Females
Total lung capacity, % predicted†	95 ± 16	89 ± 17
FVC, % predicted‡	86 ± 19	79 ± 19
FEV₁, % predicted‡	86 ± 19	83 ± 17
FEV₁/FVC	78 ± 10	82 ± 9
D$_{\text{CO}}$, % predicted§	62 ± 25	73 ± 24
Arterial Po₂, mm Hg‖	70 ± 13	72 ± 16
Arterial Pco₂, mm Hg‖	30 ± 6	31 ± 5
Heart rate, beats/min	82.2 ± 14.7	89.1 ± 19.1
Right atrial pressure, mm Hg	10.4 ± 6.3	9.3 ± 6.2
Pulmonary artery pressure, mm Hg		
Systolic	90.4 ± 27.2	91.7 ± 23.0
Diastolic	45.2 ± 16.8	43.3 ± 14.1
Mean	60.7 ± 19.7	60.3 ± 16.5
Pulmonary capillary wedge pressure, mm Hg	8.69 ± 3.9	7.94 ± 3.7
Systemic arterial pressure, mm Hg		
Systolic	120.7 ± 19.4	121.5 ± 18.0
Diastolic	75.2 ± 12.1	73.3 ± 11.9
Mean	90.6 ± 15.3	91.9 ± 13.6
Cardiac index, L/min·m²	2.35 ± 1.0	2.21 ± 0.9
Pulmonary vascular resistance index, mm Hg/L/min·m²	23.87 ± 11.2	27.69 ± 15.9
Systemic vascular resistance index, mm Hg/L/min·m²	37.89 ± 12.4	43.45 ± 17.1
Stroke volume index, mL/beat·m²	28.92 ± 11.9	25.89 ± 11.1

* All values are expressed as mean ± SD. FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; D$_{\text{CO}}$ = diffusing capacity of the lungs for carbon monoxide.
† Calculated according to methods described by Goldman and Becklake (7).
‡ Calculated according to methods described by Morris and colleagues (6).
§ Calculated according to methods described by Bradley and colleagues (8).
‖ Pressures in patients seen in centers at high altitude (Denver, Colorado; and Salt Lake City, Utah) are not included in calculations of the mean.

were established in an attempt to obtain as uniform a group of patients as possible without excluding actual cases. Most exclusionary criteria were objectively determined and straightforward. The finding of a ventilation-perfusion lung scan showing normal or low probability for pulmonary emboli has correlated with normal pulmonary angiograms in patients with primary pulmonary hypertension (12, 13) and was thus deemed sufficient to rule out pulmonary embolic disease. Underlying lung disease presents a more difficult issue. Because hypoxemia is the predominant cause of pulmonary hypertension in obstructive lung disease (14), this condition was required to be present, in addition to decreased flow rates, before the pulmonary hypertension was attributed to the lung disease. Pulmonary hypertension caused by restrictive lung disease results primarily from the underlying infiltrative or destructive parenchymal process (14), and thus, diffuse abnormalities shown on the chest roentgenogram were required in addition to a decrease in lung volumes to form exclusion criteria for these patients. Coexistent collagen vascular disease was diagnosed if the patient met well-defined criteria, because the presence of isolated abnormal serologic studies was not deemed sufficient (5).

One common feature in patients with primary pulmonary hypertension is that by the time the diagnosis is made, the patients have clinical and hemodynamic
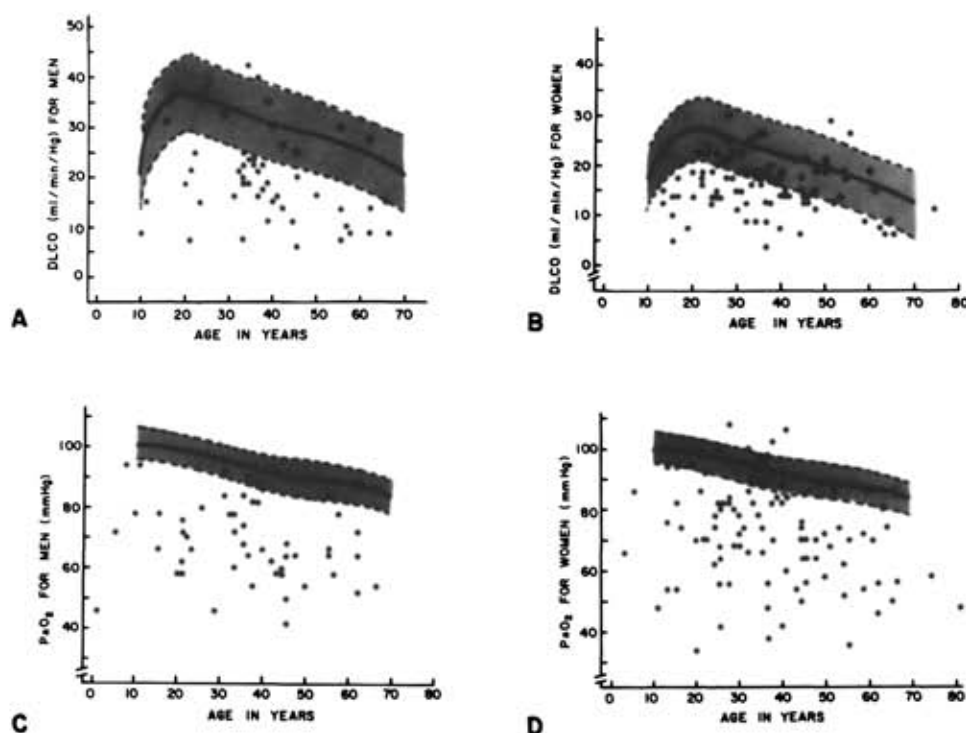
Figure 2. Distribution of findings for diffusing capacity of the lungs for carbon monoxide (*DLCO*) in men (*A*) and women (*B*) is shown, with respect to the predicted values (± SD) (*shaded area*) based on age and the average American height for that age (7). Distribution of findings of arterial Po₂ with room air for men (*C*) and women (*D*) is shown, along with predicted values based on age and sex (10). Diffusing capacity was generally less than predicted, and hypoxemia was almost an ubiquitous finding.

changes of severe pulmonary hypertension. The commonest presenting symptoms, dyspnea and fatigue, were usually present more than 2 years before the diagnosis was made. However, because the sensation of dyspnea and fatigue occur commonly in active people, it is understandable that patients failed to seek medical attention early, or that physicians may have delayed in pursuing the diagnosis. We confirm a female-to-male predomi-

nance, although it is not as high as that found previously (15, 16). For the black patients in our registry, however, the female-to-male predominance was more pronounced, at 4.3:1. The registry also confirms that primary pulmonary hypertension may occur relatively late in life, with 9% of the patients having the diagnosis made at 60 or later (17). The incidence of familial cases was 6.4%. There were no distinctive features about these cases, with
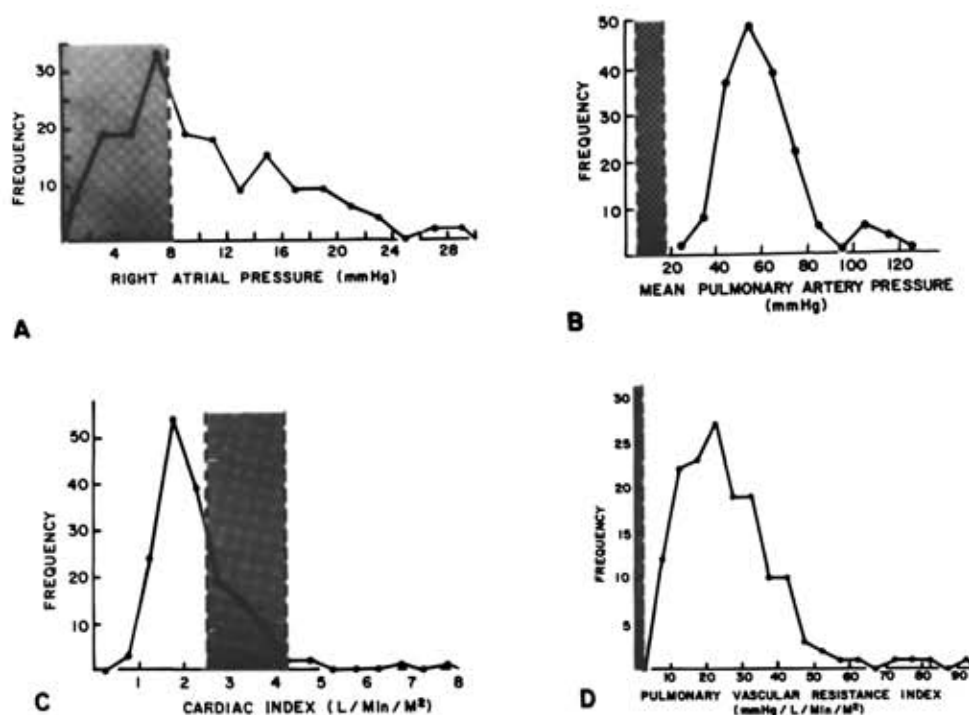

Figure 3. Distribution of hemodynamic findings is shown, in relation to published normal values (11). The right atrial pressure (*A*) was elevated in 72%. All patients, by definition, had an elevation in mean pulmonary artery pressure (*B*), with some having mean pulmonary artery pressures in excess of 100 mm Hg. The cardiac index (*C*) was reduced in 71% and reached a nadir value of 0.9 L/min· m². The pulmonary vascular resistance index (*D*) averaged 15 times greater than normal. Normal ranges are indicated by shaded regions.

the exception of shorter intervals from the onset of symptoms to diagnosis, which is probably a result of the patient's heightened awareness about the presenting symptoms of pulmonary hypertension.

Physical and noninvasive test findings correlated with the level of pulmonary hypertension in most patients. The presence of a right ventricular third sound was associated with a higher right atrial pressure and reduced cardiac output, and the presence of pulmonic insufficiency was associated with increased pulmonary artery pressures. The changes in the pulmonary vasculature noted in a chest radiograph correlated with all of these findings. Curiously, in approximately 6% of patients, the chest radiograph, echocardiogram, and electrocardiogram were relatively normal despite significant pulmonary hypertension, which underlines the lack of sensitivity of these tests in some patients.

Measurements of lung function showed that as a group, patients with primary pulmonary hypertension have a mild restrictive defect without obstruction, a reduced DL_{CO}, and hypoxemia with chronic respiratory alkalosis. Previous studies have described greater reductions in lung volume than in this series (17), but those patients would have been excluded before entry into the registry. The reduced DL_{CO} has been a common finding in these patients (18-20). Although obliteration of the small pulmonary arteries is one explanation for this reduction (21), no significant correlation was found in our patients between the DL_{CO} and any index of the severity of pulmonary hypertension. However, because of the wide distribution of measurements, with normal lung volumes and diffusing capacities a common finding, these tests are insensitive markers of the disease.

The almost universal finding of mild-to-moderate hypoxemia has been attributed to the effect of a low mixed venous PO_2 (resulting from the inadequate cardiac output), which amplified a mild degree of ventilation perfusion inequality (16). Severer degrees of hypoxemia have been attributed to right-to-left shunting through a patent foramen ovale. The chronic respiratory alkalosis we found has also been well described (18), and is usually attributed to increased afferent activity from intrapulmonary stretch receptors or intravascular baroreceptors (22, 23).

The data did not show a common cause for primary pulmonary hypertension. Neither pregnancy (24, 25) nor oral contraceptive use (26) appeared to be etiologic factors because their frequencies were similar to those of the general population. In addition, there were no apparent drug-related cases such as those that had occurred in Europe after the introduction of aminorex (11). There was a 29% incidence of a positive antinuclear antibody, but the frequency of Raynaud phenomenon, almost exclusively seen in the female patients, was only 11%, or slightly higher than the 6% reported in normal subjects (27). This incidence could, however, still be consistent with a type of primary pulmonary hypertension that presents as a collagen vascular disease affecting the lung (28). The female-to-male predominance of positive antinuclear antibodies is also consistent with findings from

previous studies (28, 29).

There were two predominant patterns detected in perfusion lung scans in these patients. Although clinical-pathologic correlations have not yet been completed in the registry, previous studies that have described these patterns of perfusion lung scans in patients with unexplained pulmonary hypertension have suggested that the normal pattern represents plexiform lesions and that the patchy distribution indicates microthrombi or venoocclusive disease (11, 30).

Analysis of the anatomic changes in the heart by M-mode echocardiography showed, as has been previously described, an increase in right ventricular size with characteristic changes in ventricular septal motion (31). Although it would be expected that the left ventricle would be uninvolved in primary pulmonary hypertension, the findings of the inverse relationship between left ventricular end-diastolic dimension and pulmonary vascular resistance index is interesting. Because the filling pressure of the left ventricle is, by definition, normal in primary pulmonary hypertension, this probably reflects the decreased volume loading of the left heart as determined by the severity of pulmonary vascular disease (32). Admittedly, the measurement of left ventricular size by M-mode echocardiography was not a highly sensitive measurement of pulmonary vascular resistance, although two-dimensional echocardiography may prove to be more accurate. If left ventricular size does reflect pulmonary vascular resistance, it may be useful to investigate the way in which this measurement might relate to the pathologic changes in the vascular bed or to patient survival.

The hemodynamic features of the patients entered showed severe elevations in pulmonary artery pressure and pulmonary vascular resistance. Right atrial pressure and cardiac index were abnormal in 72% and 71% of the patients, respectively, and were associated with clinical symptoms by New York Heart Association functional class. These same hemodynamic variables have been shown to reflect patient survival in primary pulmonary hypertension as well (33). The only difference between male and female patients was in resting heart rate, with the female patients averaging 7 beats/min faster than the male patients. However, previous studies done with normal populations have shown that female subjects normally have faster resting heart rates; thus, this factor cannot necessarily be attributed to the underlying disease (34).

The hemodynamic findings suggest that the severity of symptoms can be related to rising right atrial pressure and falling cardiac index, both of which are reflections of right ventricular function. The fact that the mean pulmonary artery pressure is of similar level in patients whose duration of symptoms is less than 1 year compared with those who were symptomatic for more than 3 years suggests that the pulmonary artery pressure rises to high levels during the course of disease. Patients whose only symptoms were dyspnea during exertion already had severe pulmonary hypertension with normal cardiac indexes. The onset of fatigue and edema, symptoms that reflect right ventricular failure, were more likely to appear later

in the clinical course. Although physicians tend to relate the severity of the disease with its duration of symptoms, this association was not evident when hemodynamic comparisons were made. Therefore, the severity of the disease process, as evidenced by histologic changes in the pulmonary vasculature, may not parallel the duration of symptoms of the disease, and the disease progression may differ considerably among patients.

An important function of the registry was to monitor the frequency of adverse consequences that might occur in the patients during their evaluation. No adverse consequences of lung perfusion scans were reported, and only one mild adverse consequence occurred in the 50 patients reported to have had pulmonary angiography. The fact that patients can have chronic proximal pulmonary thromboemboli mimicking primary pulmonary hypertension (35) underscores both the safety and necessity of ruling out chronic pulmonary thromboemboli in any patient who presents with unexplained pulmonary hypertension. Ten adverse consequences were reported to have been caused by catheterization used in diagnosis (excluding all drug evaluations), and six of the ten were probably related to the pulmonary hypertension itself. No deaths or sustained morbidity were associated with any of these procedures.

This registry has provided the characterization of the demographic and clinical features of a large number of patients with primary pulmonary hypertension. These data show that the disease is not usually diagnosed until advanced abnormalities are detected by physical examination, laboratory tests, or hemodynamic assessments of the pulmonary circulation. Although no curative therapy exists for primary pulmonary hypertension, we emphasize the need to focus on strategies of making an early diagnosis before these advanced abnormalities occur.

Appendix: Participating Clinical Centers

University of California, Cedars-Sinai Medical Center, Los Angeles, California (Spencer K. Koerner); University of California, San Diego, California (Kenneth M. Moser); University of California, San Francisco, California (Bruce H. Brundage, Thomas A. Ports); University of Colorado, Denver, Colorado (Bertron M. Groves); Mount Sinai Medical Center, Miami Beach, Florida (Tahir Ahmed); University of Illinois, Chicago, Illinois (Stuart Rich); Johns Hopkins University, Baltimore, Maryland (Warren R. Summer); Harvard University, Children's Hospital, Boston, Massachusetts (Donald C. Fyler); Boston University, Boston, Massachusetts (Sharon Rounds); University of Michigan, Ann Arbor, Michigan (David R. Dantzker, John G. Weg); Henry Ford Hospital, Detroit, Michigan (Fareed Khaja); University of Minnesota, Minneapolis, Minnesota (Jay N. Cohn); St. Louis University, St. Louis, Missouri (Susan Marshall); Mayo Clinic, Rochester, Minnesota (Guy S. Reeder); University of Missouri, Kansas City, Missouri (Ute Rosa); Creighton University, Omaha, Nebraska (Syed M. Mohiuddin); New York University Bellevue Medical Center, New York (Fredrick Feit); State University of New York, Stony Brook, New York (Adam Hurewitz); Columbia University, New York, New York (Robert B. Mellins, Robyn J. Barst); Cornell University Medical Center, New York, New York (Jeffrey Fisher); Mount Sinai Medical Center, New York, New York (Andreas Niarchos, Valentin Fuster); Duke University, Durham, North Carolina (Robert H. Peter); University of Cincinnati, Cincinnati, Ohio (Noble O. Fowler); Oregon Health Sciences University, Portland, Oregon (Cecille Sunder-

land); Temple University, Philadelphia, Pennsylvania (Stanley B. Fiel); Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania (Alfred P. Fishman); Vanderbilt University, Nashville, Tennessee (John H. Newman); University of Texas, Houston, Texas (Gilbert D'Alonzo); Veterans Administration Hospital, Dallas, Texas (Lewis J. Rubin); LDS Hospital, Salt Lake City, Utah (C. Gregory Elliott); University of Washington, Seattle, Washington (David O. Ralph); Marshfield Clinic, Marshfield, Wisconsin (Michael J. Kryda).

Data and Coordinating Center: University of Illinois, Chicago, Illinois (Paul S. Levy, Sc.D.; Stuart Rich, M.D.; Christopher Barker, Ph.D.; Geoffrey Page; Janet Kernis).

Pathology Center: University of Pennsylvania, Philadelphia, Pennsylvania (Guiseppe G. Pietra, M.D.).

National Heart, Lung, and Blood Institute: Carol E. Vreim, Ph.D.; Margaret Wu, Ph.D.

Steering Committee: Edward H. Bergofsky, M.D., Chairman; Stephen M. Ayres, M.D.; Bruce H. Brundage, M.D.; Katherine M. Detre, M.D., Dr.P.H.; Alfred P. Fishman, M.D.; Roberta M. Goldring, M.D.; Bertron M. Groves, M.D.; Paul S. Levy, Sc.D.; Giuseppe G. Pietra, M.D.; Lynne M. Reid, M.D.; Stuart Rich, M.D.; Carol E. Vreim, Ph.D.; George W. Williams, Ph.D.

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