Survival in Patients with Primary Pulmonary Hypertension

Results from a National Prospective Registry

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■ *Objective:* To characterize mortality in persons diagnosed with primary pulmonary hypertension and to investigate factors associated with survival.

■ *Design:* Registry with prospective follow-up.

■ *Setting:* Thirty-two clinical centers in the United States participating in the Patient Registry for the Characterization of Primary Pulmonary Hypertension supported by the National Heart, Lung, and Blood Institute.

■ *Patients:* Patients (194) diagnosed at clinical centers between 1 July 1981 and 31 December 1985 and followed through 8 August 1988.

■ *Measurements:* At diagnosis, measurements of hemodynamic variables, pulmonary function, and gas exchange variables were taken in addition to information on demographic variables, medical history, and life-style. Patients were followed for survival at 6-month intervals.

■ *Main Results:* The estimated median survival of these patients was 2.8 years (95% CI, 1.9 to 3.7 years). Estimated single-year survival rates were as follows: at 1 year, 68% (CI, 61% to 75%); at 3 years, 48% (CI, 41% to 55%); and at 5 years, 34% (CI, 24% to 44%). Variables associated with poor survival included a New York Heart Association (NYHA) functional class of III or IV, presence of Raynaud phenomenon, elevated mean right atrial pressure, elevated mean pulmonary artery pressure, decreased cardiac index, and decreased diffusing capacity for carbon monoxide (DL_{CO}). Drug therapy at entry or discharge was not associated with survival duration.

■ *Conclusions:* Mortality was most closely associated with right ventricular hemodynamic function and can be characterized by means of an equation using three variables: mean pulmonary artery pressure, mean right atrial pressure, and cardiac index. Such an equation, once validated prospectively, could be used as an adjunct in planning treatment strategies and allocating medical resources.

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Participating clinical centers are listed in the Appendix. For current author addresses, see end of text.

Primary pulmonary hypertension has been considered a progressive, intractable, and often fatal disease (1-4). Further, treatments used late in its course, such as continuous prostacyclin infusion or heart-lung transplant, are expensive and of limited availability. These factors necessitate some form of priority assignment for patients. Prioritization is based primarily on prognosis and severity of disease, among other factors.

Although estimates of survival in primary pulmonary hypertension are often pessimistic (1-4), considerable variation in these estimates does occur (5-8), as does spontaneous patient improvement or disease regression (9-11). Factors found in previous studies to be associated with increased mortality include hemodynamic variables (5, 12), use of oral contraceptives (13, 14), family history of primary pulmonary hypertension (9), and pregnancy (15, 16).

Some of these studies lacked rigorous criteria for the diagnosis of primary pulmonary hypertension. Others calculated survival from time of symptom onset, a subjective factor that relies on patient self-reports. The sample sizes used in other studies were too small to provide stable and reliable estimates of survival.

To overcome some of these problems, the Patient Registry for the Characterization of Primary Pulmonary Hypertension was established by the National Heart, Lung, and Blood Institute of the National Institutes of Health. Features of the Registry include prospective collection of data according to a standardized protocol; entry into the Registry of only those patients who satisfy diagnostic criteria established by a steering committee of cardiologists, pulmonologists, statisticians, epidemiologists, and other relevant professionals; use of the initial diagnostic catheterization as an index for determining survival; and recruitment and follow-up of 194 patients with primary pulmonary hypertension from 32 medical centers in the United States.

Using these criteria, we have obtained from the Registry what we believe to be stable estimates of survival patterns and have used the objective data obtained at the diagnostic cardiac catheterization to formulate an equation that estimates the probability of survival over a 3-year period. We believe such an estimate can be of considerable value in the planning of treatment strategies and in the allocation of scarce medical resources.

Patients and Methods

Thirty-two medical centers (*see* Appendix for list of participating centers) enrolled 194 patients with primary pulmonary hypertension in the Registry between 1 July 1981 and 30 September 1985. Follow-up for survival continued at 6-month intervals until 8 August 1988. A complete description of the criteria for patient entry into the Registry has been described previously (17).

Variables

The date of diagnostic catheterization was established as the baseline from which survival was measured. Data on date of symptom onset and previous diagnosis of primary pulmonary hypertension were collected and were considered in our analyses.

We examined the relation of variables measured at diagnostic catheterization to subsequent mortality. The methods used to measure these variables have been described previously (17).

For each death that occurred among Registry patients, a cause-of-death form was completed by the investigator at the participating center. The reporting form requested date of death, cause of death (immediate or secondary), autopsy performed (yes or no), and a description of details. Based on a review of this form, the cause of death was categorized as "sudden death," "right ventricular failure," or "other." On review of the baseline examination and subsequent forms, it was determined whether each patient was receiving long-term drug therapy at the time of study entry and whether this therapy was continued after the patient was discharged.

Statistical Analysis

We analyzed the distribution of the data on survival time from diagnostic catheterization among Registry patients and determined the variables associated with survival.

Standard life-table analysis and the Kaplan-Meier statistic were used to estimate overall survival distribution (18). Univariate analysis based on the proportional hazards model (18) was used to examine relations between survival and selected demographic, medical-history, pulmonary-function, laboratory, and hemodynamic variables measured at baseline. Results are expressed as odds ratios with 95% confidence intervals (CIs). For continuous variables, the odds ratios are expressed per unit of measurement.

Multivariate analysis based on the proportional hazards model was used to examine the independent effect on survival of each variable, controlling for possible confounders. The number of covariates that could be entered simultaneously was limited by the high degree of colinearity among variables in the same category (for example, hemodynamic), the small number of patients, and the length of the follow-up period.

In the proportional hazards model, a patient's chance for survival is expressed as a product of two functions—one involving only time, the other involving levels of the particular set of risk factors specified in the model. Using the discrete-hazard model of Kalbfleisch and Prentice (19), we developed formulas that estimated a patient's chances for survival at 1, 2, and 3 years from baseline, given the values of the patient's three hemodynamic variables: mean pulmonary artery pressure, mean right atrial pressure, and cardiac index. These three variables were chosen because of their relation to survival found in this and other studies.

Differences between mean values (measured at baseline examination) for patients classified as "sudden death" and those classified as dying of right ventricular failure were evaluated using the Student *t*-test; differences between rates were evaluated by chi-square analysis.

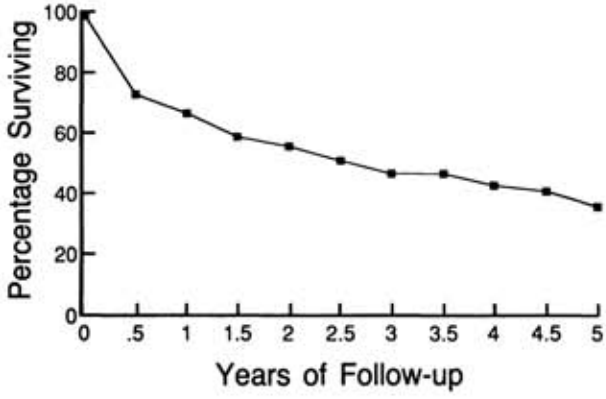

Figure 1. Estimated percentage of patients surviving over time from the baseline catheterization. Number of patients at risk are shown for 0 through 5 years. Median survival is estimated at 2.8 years. Estimated percentages of patients surviving at 1, 3, and 5 years are 68%, 48%, and 34%, respectively.

Results

As of 8 August 1988, 106 of the 194 patients had died, and 60 remained in follow-up. Thirteen patients who had heart-lung transplantation were followed only to the time of transplant. Fifteen patients who were lost to follow-up were considered for purposes of the analysis to be survivors. Of the 106 who died, 28 (26%) had an unexpected or sudden (witnessed or unwitnessed) death, and 50 (47%) died of right ventricular failure.

Summary statistics on survival and length of follow-up for the 194 evaluable patients are shown in Figure 1. Of the 194 patients, 124 (64%) were followed for at least 1 year; 101 (52%), for at least 2 years; 70 (36%), for at least 3 years; 41 (21%), for at least 4 years; and 19 (9%), for at least 5 years. The estimated median survival time was 2.8 years (CI, 1.9 to 3.69 years). Median survival times from baseline catheterization were 39 months for men and 32 months for women.

Previous Diagnosis

Of the 194 patients who were accepted into the Registry, 69 (36%) reported a previous diagnosis of primary pulmonary hypertension. The median time between first diagnosis and diagnosis at a Registry center was 1.6 years. There was no statistically significant difference in survival time between patients reporting a previous diagnosis of primary pulmonary hypertension and those for whom the diagnosis was made at a Registry center (median survival, 3.2 compared with 2.6 years).

Factors Associated with Survival Duration in Univariate Analysis

Results of the univariate analysis of the relation between survival and variables measured at entry into the Registry are shown in Table 1. Survival was not associated with patient gender, smoking history, the presence or absence of serum antinuclear antibody titer, a family history of primary pulmonary hypertension, a history of oral contraceptive use, or pregnancy. Of the 108 women entered in the study, 61 had used oral contraceptives, a frequency of use similar to that found among American women. Of the variables assessed, only the age at symptom onset for users of oral contraceptives compared with nonusers showed a difference

(30.9 ± 8.4 years compared with 39.9 ± 17.3 years) ($P < 0.002$).

The risk for death was higher among patients classified in New York Heart Association (NYHA) functional class III or IV than among those classified in functional class I or II (odds ratio, 1.93). Median survival time for patients who were in functional class I or II was 58.6 months compared with 31.5 months for patients who were in functional class III. Survival time decreased markedly to 6 months for patients in functional class IV. The presence of Raynaud phenomenon was associated with an increased risk for death (odds ratio, 2.11). Sixteen patients with Raynaud phenomenon, fifteen of whom were women, had a median survival of 11.8 months, compared with 43.9 months for those without the disorder ($P = 0.02$). When all other variables were examined, however, mean values in patients with and without Raynaud phenomenon were similar.

Three measured hemodynamic variables known to be associated with disease severity were also associated with an increased risk for death: increased mean right atrial pressure (odds ratio, 1.99), increased mean pulmonary arterial pressure (odds ratio, 1.16), and decreased cardiac index (odds ratio, 0.62). The effect of these hemodynamic variables on mortality is shown in Figure 2. An increase in mean pulmonary arterial pressure from less than 55 mm Hg to at least 85 mm Hg was associated with a decrease in median survival time from 48 months to 12 months. Similarly, an increase in right atrial pressure from normal or mildly elevated levels (< 10 mm Hg) to markedly elevated levels (≥ 20 mm Hg) was associated with a decrease in median survival time from 46 months to 1 month. Finally, an increase in cardiac index from less than 2.0 L/min per m^2 body surface area to at least 4.0 L/min per m^2 correlated with an increase in survival time from 17 months to 43 months. Variables derived from these hemodynamic measurements (higher pulmonary vascular resistance index, higher systemic vascular resistance index, and a lower stroke volume index) were also significantly related to mortality.

Of the pulmonary function tests, diffusing capacity for carbon monoxide (DL_{CO}) was weakly associated with mortality (odds ratio, 0.97), and none of the gas exchange variables was related to mortality.

Thirty-six persons (19%) were receiving some form of long-term drug therapy at the time of study entry. The drug therapy consisted of single or multiple vasodilators; vasodilators in combination with digitalis, diuretics, anticoagulants, or other drugs; or digitalis, diuretics, anticoagulants, oxygen, or other drugs alone or in combination. Patients receiving long-term drug therapy (median survival, 4.5 years; CI, 2.5 to 5.4 years) showed no significant difference in survival time compared with patients not receiving such therapy at study entry (median survival, 2.6 years; CI, 0.7 to 5.7 years).

A similar proportion of both groups (patients receiving and those not receiving long-term drug therapy at study entry) received discharge drug therapy as well. These two groups were similar in all other baseline data investigated. Of the 194 Registry patients, 160 (83%) received some drug therapy on hospital discharge. Of these, 56 (35%) received single or multiple vasodilators; 73 (46%) received vasodilators in combination with digitalis, diuretics, anticoagulants, or other drugs; and 31 (19%) received digitalis, diuretics, anticoagulants, oxygen, or other drugs alone or in combination. A total of 21 (11%) Registry patients received no drug therapy on hospital discharge.

We compared survival times for patients receiving drug therapy at discharge with those of patients not receiving such therapy. All persons surviving fewer than 8 days after the baseline catheterization were excluded from the analysis because it was considered unlikely that these patients would have survived hospitalization. Among those surviving at least 8 days after the initial catheterization, the median survival time was 2.9 years (CI, 0.5 to 4.7 years) for those not given drugs at discharge and 3.8 years (CI, 2.2 to 4.9 years) for those receiving drug therapy $P > 0.2$.

Length of survival after diagnosis was not influenced by the altitude of the reporting centers. When patients studied at high altitude (greater than 4000 feet) were excluded and survival data for all demographic, medical-history, pulmonary function, and hemodynamic variables were compared, no differences were apparent.

Table 1. Univariate Analysis Relating Survival Time to Selected Baseline Variables*

Variable	Odds Ratio (95% CI)
Demographic and historical data	
Age	1.00 (0.99 to 1.01)
Age at symptom onset	1.00 (0.99 to 1.02)
Symptom duration	0.98 (0.66 to 1.47)
Sex (men:women)	1.07 (0.71 to 1.61)
NYHA functional class I, II compared with III, IV	1.93 (1.17 to 3.17)
NYHA functional class I, II, III compared with IV	2.38 (1.45 to 3.88)
Raynaud phenomenon (presence/absence)	2.11 (1.18 to 3.78)
Pulmonary function tests	
Total lung capacity	0.93 (0.80 to 1.08)
Forced vital capacity	0.89 (0.75 to 1.07)
Forced expiratory volume in one second	0.87 (0.69 to 1.10)
Diffusion capacity for carbon monoxide	0.97 (0.94 to 0.99)
Hemodynamic	
Heart rate	1.006 (0.997 to 1.015)
Mean vascular pressures	
Right atrial	1.99 (1.47 to 2.69)
Pulmonary arterial	1.16 (1.05 to 1.28)
Systemic arterial	0.94 (0.87 to 1.01)
Cardiac index	0.62 (0.46 to 0.82)
Indexed vascular resistance	
Pulmonary arterial	1.04 (1.01 to 1.04)
Systemic arterial	1.01 (1.00 to 1.03)
Gas exchange	
Arterial oxygen content	
Systemic arterial	1.02 (0.92 to 1.12)
Pulmonary arterial	0.91 (0.84 to 0.99)
Arterial P_{O_2}	0.98 (0.97 to 1.00)
Arterial P_{CO_2}	0.95 (0.90 to 1.00)
Oxygen consumption	1.00 (0.997 to 1.001)

* NYHA = New York Heart Association; P_{O_2} = partial pressure of oxygen in arterial blood; P_{CO_2} = partial pressure of carbon dioxide in arterial blood.

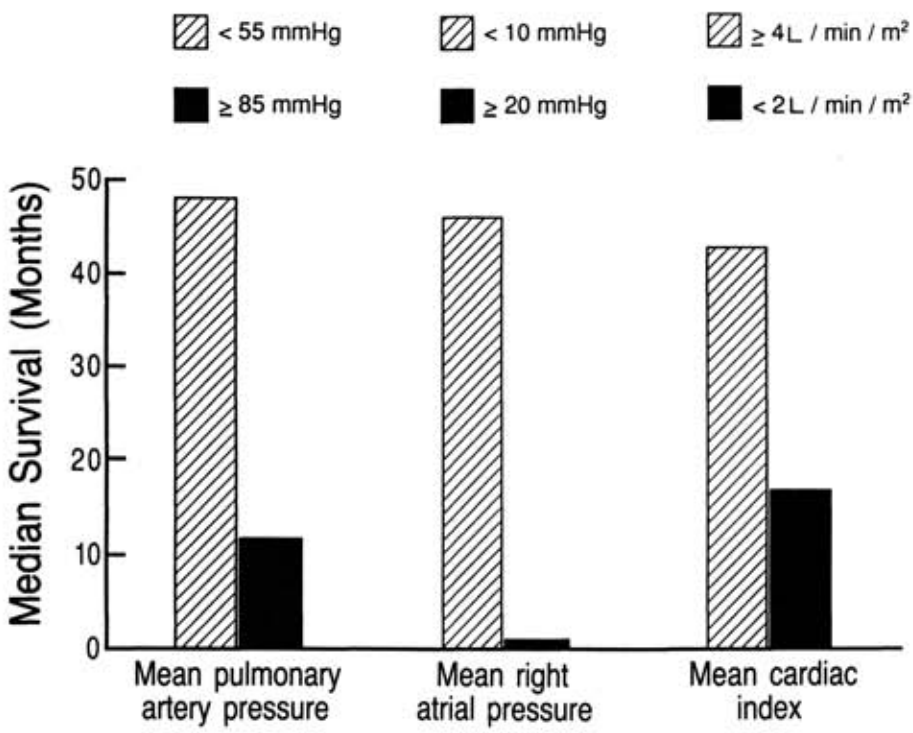

Figure 2. Median survival in months for patients with primary pulmonary hypertension compared with three hemodynamic variables.

Multivariate Analysis

In the univariate analysis described previously, three hemodynamic variables (mean right atrial pressure, mean pulmonary artery pressure, and cardiac index) and one pulmonary function variable (DL_{CO}) were significantly related to mortality.

In addition, NYHA functional class and presence of Raynaud phenomenon were significantly related to mortality. In the multivariate analysis, we examined the independent effect on mortality of each independent variable in the presence of others. The high degree of intercorrelation among many of these variables (especially the hemodynamic variables), however, made it impossible to examine all of them simultaneously. Therefore, we did three separate regressions, each including four variables: presence of Raynaud phenomenon, NYHA functional class (IV compared with I, II, and III combined), and DL_{CO}, along with one of the hemodynamic variables. The results of this analysis are summarized in Table 2. In each of these regressions, odds ratios for the hemodynamic variables showed little or no change from values shown in the univariate analysis, whereas odds ratios for functional class and Raynaud phenomenon were substantially reduced to levels that are not statistically significant. The odds ratios for DL_{CO} did not change substantially from those obtained in the univariate analysis, but in two of the regressions, the 95% CIs overlap unity.

Analysis of survival data considered the 13 patients receiving heart-lung transplantation. For purposes of statistical analysis, we placed these patients in the group that died and later in the "withdrawn alive" group. Patient placement did not affect significantly the data on group mortality or survival time.

Based on estimates obtained from the proportional hazards model, we obtained the following equation to predict a patient's chances of survival (where P (t) indicates the patient's chances of survival and t = 1, 2, or 3 years) after diagnosis:

$$P(t) = [H(t)]^{A(x,y,z)}$$
$$H(t) = [0.88 - 0.14t + 0.01t^2]$$
$$A(x,y,z) = e^{(0.007325x + 0.0526y - 0.3275z)}$$

where x = mean pulmonary artery pressure
y = mean right atrial pressure
z = cardiac index

A patient having, for example, a mean pulmonary artery pressure of 40 mm Hg, a mean right atrial pressure of 3.5 mm Hg, and a cardiac index of 3.3 L/min per m^2 body surface area would have 1-, 2-, and 3-year survival estimates as follows:

$$A(x,y,z) = e^{[(0.007325)(40) + (0.0526)(3.5) - (0.3275)(3.3)]} = 0.5468$$
$$H(1) = [0.88 - (0.14)(1) + (0.01)(1^2)] = 0.75$$
$$H(2) = [0.88 - (0.14)(2) + (0.01)(2^2)] = 0.64$$
$$H(3) = [0.88 - (0.14)(3) + (0.01)(3^2)] = 0.55$$

and

$$P(1) = 0.75^{(0.5468)} = 0.85 \quad P(2) = 0.64^{(0.5468)} = 0.78$$
$$P(3) = 0.55^{(0.5468)} = 0.72$$

Of the 184 patients for whom the formula could be computed, 36 had 1-year survival estimates below 0.5, and 18 (50%) of these patients did not survive longer than 1 year after the entry catheterization. The remaining 148 patients had 1-year survival estimates above 0.5, and 106 (71.6%) of these survived longer than 1 year. Of 98 patients having 3-year survival estimates below 0.5, 73 (74.5%) did not survive longer than 3 years. Also, of 66 patients having 3-year survival estimates above 0.5, 45 (68.2%) survived for 3 years or more.

Discussion

Previous reports of data from this large prospective Registry have described the initial clinical characteristics of its patients (17); the abnormalities of the lung and heart from biopsy and autopsy material (23); and the effects of various forms of vasodilator therapy on primary pulmonary hypertension (24). This report describes survival and mortality in 194 patients with primary pulmonary hypertension that conformed to the Registry's definition.

The main conclusion of our study is that mortality in primary pulmonary hypertension appears to correlate best with indices of right ventricular hemodynamic function. Of the hemodynamic variables recorded at baseline cardiac catheterization, very high correlations with mortality were obtained for three independent variables: pulmonary arterial pressure, right atrial pressure, and cardiac index. A regression equation was then developed to describe the relation between these three hemodynamic variables and mortality.

This equation, although requiring additional validation on independent data, has use as a potential adjunct in planning treatment strategies and allocating scarce medical resources. For example, a patient presenting with a mean pulmonary artery pressure of 40 mm Hg, a mean right atrial pressure of 3.5 mm Hg, and a cardiac index of 3.3 L/min per m^2 would have an estimated 85% chance of surviving for at least 1 year from the time these data were collected and a 72% chance of surviving for at least 3 years. A patient presenting with mean pulmonary artery pressure of 80 mm Hg, a mean right atrial pressure of 16 mm Hg, and a cardiac index of 1.3 L/min per m^2, however, would have an estimated 46% chance of surviving 1 year and an estimated 20% chance of surviving 3 years. Thus, this form of prediction of survival probability has not only a numerical value in years but also a definitive baseline (the cardiac catheterization) from which survival is calculated.

Other investigators have used hemodynamic measurements to predict survival. In one study (12), patients with primary pulmonary hypertension who survived less than 6 months from the time of cardiac catheterization had significantly higher right atrial pressures, lower cardiac and stroke volume indices, and higher systemic and pulmonary vascular resistances than did the surviving group of patients. Regression analysis showed that stroke volume index and mean right atrial pressure were the best predictors of increased mortality (5, 9, 19, 20). In addition to the hemodynamic variables already discussed, an elevated pulmonary arterial pressure (19, 20) and low pulmonary systemic oxyhemoglobin saturations (19) have been reported to correlate with shortened survival among patients with primary pulmonary hypertension.

Survival from time of admission to the Registry was also related to the NYHA functional class. Patients in functional classes I and II (combined because of the paucity of class I patients) had a markedly better median survival rate than did patients in classes III and IV; class III patients had a better median survival rate than class IV patients. The median survival time among patients in functional classes I and II was nearly 6 years, compared with 2.5 years for patients in class III and 6 months for patients in class IV. Because a deterioration in functional class is often a consequence of deteriorating hemodynamic state, it is not surprising that NYHA functional class was not strongly associated with mortality in the presence of the hemodynamic variables.

Except possibly for DL_{CO}, pulmonary function assessment and most historical and demographic variables were not strong predictors of survival. A study by Rich and colleagues (17) suggests that DL_{CO} is a poor indicator of the severity of primary pulmonary hypertension, primarily due to the wide distribution of measurements in DL_{CO} and the common finding of normal values among the Registry patients.

In our study, 16 patients (8.2%), 15 of whom were women, reported symptoms of Raynaud phenomenon. This prevalence rate is similar to the 6% reported in subjects without primary pulmonary hypertension (21). Nonetheless, the presence of Raynaud phenomenon in our patients was associated with reduced survival.

The Registry did not attempt to control the use of pharmacologic, surgical, or other therapies. The choice of management options was controlled entirely by the clinical centers and the patients' physicians. Although certain therapeutic interventions may have influenced survival and mortality, the design of the Registry did

Table 2. Multivariate Analysis Relating Survival Time to Selected Variables

Variable	Odds ratio (95% CI)		
	Regression 1†	Regression 2‡	Regression 3§
Raynaud phenomenon (presence or absence)	1.56 (0.81 to 3.03)	1.76 (0.91 to 3.39)	1.37 (0.66 to 2.83)
NYHA functional class (IV compared with I, II, III)*	1.69 (0.91 to 3.13)	1.67 (0.91 to 3.05)	1.50 (0.79 to 2.83)
Mean right atrial pressure	1.07 (1.03 to 1.10)		
Mean pulmonary arterial pressure		1.02 (1.01 to 1.03)	
Cardiac output (indexed)			0.59 (0.42 to 0.84)
Diffusion capacity for carbon monoxide	0.99 (0.96 to 1.02)	0.96 (0.93 to 1.00)	0.97 (0.94 to 1.00)

* NYHA = New York Heart Association.

† Independent variables in regression 1 include Raynaud phenomenon, NYHA functional class, mean right atrial pressure, and diffusion capacity for carbon monoxide.

‡ Independent variables in regression 2 include Raynaud phenomenon, NYHA functional class, mean pulmonary artery pressure, and diffusion capacity for carbon monoxide.

§ Independent variables in regression 3 include Raynaud phenomenon, NYHA functional class, cardiac output (indexed), and diffusion capacity for carbon monoxide.

not permit valid assessment of the effects of these interventions.

No deaths or sustained morbidity resulted from the diagnostic procedures done during baseline assessment (17). However, 28 of the 106 patients who died were considered to have died of causes other than sudden death or right ventricular failure. These included medications, surgery other than cardiac catheterization, pneumonia, and cerebrovascular accidents.

The two commonest causes of death recorded by the Registry were progressive right ventricular failure and the sudden death syndrome, the former being the more prevalent. No differences in clinical presentation or baseline hemodynamic data were apparent between these two groups.

In summary, the prognoses of patients with primary pulmonary hypertension are largely determined by the integrity of right ventricular function, which can be evaluated using easily evaluable measures of right ventricular function. Our experience with the 194 patients in the primary pulmonary hypertension Registry permitted these hemodynamic variables to be correlated with survival. The equation developed from the proportional hazards model describes the role played by three of these variables in characterizing mortality and, if validated by future studies, has potential use in planning patient management strategies. We emphasize, however, that precise and reliable application to individual patients must be complemented by more complete clinical assessment.

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, New York (Fredrick Feit); State University of New York, Stony Brook, New York (Afam 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 Sunderland); 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).

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References

1. **Walcott G, Burchell HB, Brown AL.** Primary pulmonary hypertension. Am J Med. 1970;49:70-9.
2. **Voelkel N, Reeves JT.** Primary pulmonary hypertension. In: Moser KM; ed. Pulmonary Vascular Diseases. v. 14. New York: Marcel Dekker; 1979:573-629.
3. **Fuster V, Giuliani ER, Brandenburg RO, Weidman WH, Edwards WD.** The natural history of idiopathic pulmonary hypertension. Am J Cardiol. 1981;47:422.
4. **Abraham MT, Chernian G.** Primary pulmonary hypertension in India. Indian Heart J. 1981;33:5-7.
5. **Glanville AR, Burke CM, Theodore J, Robin ED.** Primary pulmonary hypertension: length of survival in patients referred for heart-lung transplantation. Chest. 1987;91:675-81.
6. **Charters AD, Baker W de C.** Primary pulmonary hypertension of unusually long duration. Br Heart J. 1970;32:130-3.
7. **Trell E.** Benign, idiopathic pulmonary hypertension? Two further cases of unusually long duration. Acta Med Scand. 1973;193:137-43.

8. **Suarez LD, Sciandro EE, Llera JJ, Perosio AM.** Long-term follow-up in primary pulmonary hypertension. Br Heart J. 1979;41: 702-8.
9. **Rozkovec A, Montanes P, Oakley CM.** Factors that influence the outcome of primary pulmonary hypertension. Br Heart J. 1986;55: 449-58.
10. **Bourdillon PD, Oakley CM.** Regression of primary pulmonary hypertension. Br Heart J. 1976;38:264-70.
11. **Fujii A, Rabinovitch M, Matthews EC.** A case of spontaneous resolution of idiopathic pulmonary hypertension. Br Heart J. 1981;46: 574-7.
12. **Rich S, Levy PS.** Characteristics of surviving and nonsurviving patients with primary pulmonary hypertension. Am J Med. 1984;76: 573-8.
13. **Oakely C, Somerville J.** Oral contraceptives and progressive pulmonary vascular disease. Lancet. 1968;1:890-3.
14. **Kleiger RE, Boxer M, Ingham RE, Harrison DC.** Pulmonary hypertension in patients using oral contraceptives. A report of six cases. Chest. 1976;69:143-7.
15. **McCaffrey RM, Dunn LJ.** Primary pulmonary hypertension in pregnancy. Obstet Gynecol Surv. 1964;19:567-91.
16. **Nelson DM, Main E, Crafford W, Ahumada GG.** Peripartum heart failure due to primary pulmonary hypertension. Obstet Gynecol. 1983;62:58S-63S.
17. **Rich S, Dantzker DR, Ayres SM, et al.** Primary pulmonary hypertension: A national prospective study. Ann Intern Med. 1987;107: 216-23.
18. **Lee E.** Statistical Methods for Survival Analysis. California: Lifetime Learning Publication; 1980.
19. **Kalbfleisch JD, Prentice RL.** The Statistical Analysis of Failure Time Data. New York: John Wiley and Sons; 1980.
20. **Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL.** Primary pulmonary hypertension: natural history and the importance of thrombosis. Circulation. 1984;70:580-7.
21. **Kanemoto N, Sasamoto H.** Pulmonary hemodynamics in primary pulmonary hypertension. Jpn Heart J. 1979;20:395-405.
22. **Zahavi I, Chagnac A, Hering R, Davidovich S, Kuritzky A.** Prevalence of Raynaud's phenomenon in patients with migraine. Arch Intern Med. 1984;144:742-4.
23. **Pietra GG, Edwards WD, Kay MJ, et al.** Histopathology of primary pulmonary hypertension. A qualitative and quantitative study of pulmonary blood vessels from 58 persons in the National Heart, Lung, and Blood Institute, Primary Pulmonary Hypertension Registry. Circulation. 1989;80:1198-206.
24. **Weir EK, Rubin LJ, Ayres SM, et al.** The acute administration of vasodilators in primary pulmonary hypertension. Experience from the NIH Registry on PPH. Am Rev Respir Dis. 1989;140:1623-30.