

# Prognosis of Pulmonary Arterial Hypertension\*

## ACCP Evidence-Based Clinical Practice Guidelines

Vallerie V. McLaughlin, MD, FCCP; Kenneth W. Presberg, MD, FCCP;

Ramona L. Doyle, MD, FCCP; Steven H. Abman, MD;

Douglas C. McCrory, MD, MHSc; Terry Fortin, MD; and Gregory Ahearn, MD

**Although idiopathic pulmonary arterial hypertension is perceived as a progressive disease with a uniformly poor outcome, the natural history of disease is heterogeneous, with some patients dying within months of diagnosis and others living for decades. The course of the disease has also been altered by advances in medical therapies. The outcome of patients with other types of pulmonary arterial hypertension (PAH) has been less well characterized. Assessment of prognosis of such patients is important, as it influences both medical therapy and referral for transplantation. This chapter will provide evidence based recommendations to assess the prognosis of patients with PAH.** (CHEST 2004; 126:78S-92S)

**Key words:** cardiopulmonary exercise testing; echocardiography; epoprostenol; functional class; hemodynamics; prognosis; pulmonary hypertension; 6 min walk test; survival; vasoreactivity

**Abbreviations:** ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; CHD = congenital heart disease; CI = cardiac index; CO = cardiac output; CPET = cardiopulmonary exercise test; DBP = diastolic BP; DLCO = diffusing capacity of the lung for carbon monoxide; HR = hazard ratio; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; MVO<sub>2</sub> = mixed venous oxygen saturation; NIH = National Institutes of Health; NYHA-FC = New York Heart Association functional class; O<sub>2</sub>Sat = oxygen saturation; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RA = right atrial; RCT = randomized controlled trial; RV = right ventricular; RVEDP = right ventricular end-diastolic pressure; SBP = systolic BP; TPR = total pulmonary resistance; TPRI = total pulmonary resistance index; TR = tricuspid regurgitation; UA = uric acid; VO<sub>2</sub>max = maximum oxygen consumption; vWF:Ag = Von Willebrand factor antigen; 6MWT = 6 min walk test

Although idiopathic pulmonary arterial hypertension (IPAH) is perceived as a progressive disease, usually with a poor outcome, the natural history of the disease is heterogeneous, with some patients dying within months of diagnosis and others living for decades. The outcome of patients with other types of pulmonary arterial hypertension (PAH) has been less well described. Over the past decade, advances in medical therapies have changed the course of the disease and have made decisions

regarding transplantation more complicated. The objective of this chapter is to answer two questions: what is the expected survival of patients with PAH, and what are the clinical factors associated with survival in patients with PAH?

### MATERIALS AND METHODS

We conducted a computerized search of the MEDLINE bibliographic database from 1992 to October 2002. We searched using the term *hypertension, pulmonary*. The search was limited to articles concerning human subjects that were published in the English language and accompanied by an abstract. In addition, we searched the reference lists of included studies, practice guidelines, systematic reviews, and meta-analysis, and consulted with clinical experts to identify relevant studies missed by the search strategy or published before 1992.

We selected studies that described survival over time and considered studies among patients with known or suspected IPAH or PAH associated with connective tissue diseases, chronic liver disease with portal hypertension, congenital heart disease (CHD) and Eisenmenger syndrome, HIV infection, and chronic thromboembolic disease. We excluded studies of pulmonary hypertension associated with COPD, other parenchymal lung disease, high altitude, or cardiac disease (eg, left-heart failure or

From the University of Michigan (Dr. McLaughlin), Ann Arbor, MI; Medical College of Wisconsin (Dr. Presberg), Milwaukee, WI; Stanford University (Dr. Doyle), Stanford, CA; University of Colorado Health Sciences Center (Dr. Abman), The Children's Hospital, Denver, CO; and Duke University Medical Center (Drs. McCrory, Fortin, and Ahearn), Durham, CA. For financial disclosure information see page 1S.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).

Correspondence to: Vallerie V. McLaughlin, MD, FCCP, University of Michigan, 1500 East Medical Center Dr, Women's Hospital-Room L3119, Ann Arbor, MI 48109-0273; e-mail: vmclaugh@umich.edu

valvular heart disease) except CHD. We also excluded studies of neonates and case series with < 10 subjects.

Two physicians (one with methodologic expertise and one with content area expertise) reviewed the abstracts of candidate articles and selected a subset to review in full text. Full-text articles were again reviewed by two physicians to determine whether they were study reports or review articles, and were pertinent to the key questions. The studies were further reviewed and classified according to primary diagnosis (IPAH vs PAH associated with another disease), treatment strategy, survival rates, risk factors, and type of analysis done. As the vast majority of studies included patients with IPAH, the bulk of this chapter will focus on IPAH. Comments regarding PAH associated with other diagnosis and pediatric considerations are also discussed.

## EXPECTED SURVIVAL IN PAH

The natural history of IPAH has been well described. The National Institutes of Health (NIH) Registry followed up 194 patients with IPAH enrolled at 32 clinical centers from 1981 to 1985.<sup>1</sup> The estimated median survival was 2.8 years, with 1-year, 3-year, and 5-year survival rates of 68%, 48%, and 34%, respectively. Other series have studied the natural history of IPAH with similar results. Among a cohort of 61 IPAH patients followed up in Mexico, the mean survival was  $25.9 \pm 20.7$  months ( $\pm$  SD).<sup>2</sup> The median survival was 33 months among a cohort of 223 patients followed up in Japan.<sup>3</sup> In a single-center, uncontrolled case series<sup>4</sup> from India, the median survival was 22 months, with 2-year, 5-year, and 10-year survival rates of 48%, 32%, and 12%, respectively. Table 1 summarizes survival for the entire data set, including all etiologies of PAH and all therapies.

### *Survival in PAH Associated With Underlying Etiologies*

Although survival curves have been most well described for IPAH, it is clear that the underlying diagnosis associated with PAH influences outcome. Early series have suggested that the prognosis in patients with PAH associated with the scleroderma spectrum of diseases may even be worse than those with IPAH. In a retrospective, single-center, uncontrolled series, Stupi et al<sup>5</sup> identified 673 patients with

systemic sclerosis between 1963 and 1983. Of these, 59 patients (9%) had PAH, 30 of whom had isolated PAH, and 20 of whom underwent cardiac catheterization. Among the patients with isolated PAH, the 2-year survival rate was 40%. It has also been suggested that even with epoprostenol therapy, patients with PAH related to the scleroderma spectrum of diseases have a less favorable outcome. In a series<sup>6</sup> of 91 patients with PAH treated with epoprostenol therapy, those with a diagnosis of scleroderma spectrum of disease had a worse outcome (hazard ratio [HR] for death, 2.32; 95% confidence interval, 1.08 to 4.99). Similarly, Kawut et al<sup>7</sup> compared the survival of 33 patients with IPAH and 22 patients with PAH related to the scleroderma spectrum of diseases at a single center. Patients underwent initial cardiac catheterization between January 1997 and June 2001, and were treated with usual medical therapies including digoxin, warfarin, and continuous IV epoprostenol. The risk of death was higher in the patients with the scleroderma spectrum of diseases than in IPAH (unadjusted HR, 2.9; confidence interval, 1.1 to 7.8;  $p = 0.03$ ). This increased risk persisted after adjustment for a variety of demographic, hemodynamic, and treatment variables.

Survival in patients with HIV-associated PAH appears similar to the IPAH population. Opravil et al<sup>8</sup> performed a prospective, case-controlled, single-center study in 19 patients with PAH associated with HIV. The probability of surviving was significantly decreased in patients with PAH compared with the control subjects (median survival, 1.3 years vs 2.6 years;  $p < 0.005$ ). In a retrospective, uncontrolled, single-center study, Petitpretz and coworkers<sup>9</sup> identified 20 patients with HIV-associated PAH and compared their outcome to that of 93 patients with IPAH identified between 1987 and 1992. Overall survival was poor and not significantly different between HIV-associated PAH and IPAH, with 46% and 53% survival rates, respectively, at 2 years. Notably, most of the deaths in the HIV group were related to PAH.

Although no studies have directly compared patients with PAH related to CHD with other types of

**Table 1—Survival in PAH\***

| Diagnosis                      | Year 1    | Year 2    | Year 3    | Year 4   | Year 5    |
|--------------------------------|-----------|-----------|-----------|----------|-----------|
| CHD                            | 0.92 (2)  | 0.885 (2) | 0.77 (1)  |          | 0.77 (1)  |
| Collagen vascular disease      | 0.67 (3)  | 0.405 (2) | 0.37 (2)  |          |           |
| HIV                            | 0.58 (1)  | 0.39 (2)  | 0.21 (1)  |          |           |
| Primary pulmonary hypertension | 0.79 (21) | 0.66 (12) | 0.59 (14) | 0.28 (3) | 0.48 (14) |
| Portopulmonary hypertension    |           |           | 0.64 (1)  |          |           |

\*Data are presented as unweighted and unadjusted averages of entire data set.

PAH, observations suggest that those with CHD have a better prognosis. Hopkins et al<sup>10</sup> evaluated 100 adults with severe PAH, 37 of whom had Eisenmenger syndrome and 6 of whom had previously repaired congenital heart defects, who were followed up in a transplantation or adult CHD clinic. Hopkins et al<sup>19</sup> described an actuarial survival of patients who did not receive transplantation of 97%, 89%, and 77% at 1 year, 2 years, and 3 years, respectively, for the patients with Eisenmenger syndrome compared with 77%, 69%, and 35% at 1 year, 2 years, and 3 years, for patients with IPAH. Similarly, in a cohort of patients with PAH treated with epoprostenol, survival was greater for those with CHD than for IPAH.<sup>6</sup> Figure 1 summarizes the mean survival of patients with PAH based on etiology.

### *Impact of Medical Therapy on Survival in PAH*

The rationale for, and effects of epoprostenol therapy in IPAH is extensively discussed by Badesch et al (see section on Medical Therapy for Pulmonary Arterial Hypertension in this Supplement). To date, six series have demonstrated the positive impact of epoprostenol on survival in IPAH. Patients who had previously participated in a randomized controlled trial (RCT) of epoprostenol were followed up over a period of 37 to 69 months.<sup>11</sup> The observed survival rates at 1 year, 2 years, 3 years, and 5 years were 87%, 72%, 63%, and 54%, respectively, while the survival rates of 31 historical control subjects from the NIH Registry<sup>1</sup> were 77%, 52%, 41%, and 27%; the survival with epoprostenol was greater than control (HR, 2.9; 95% confidence interval, 1.0 to 8.0;  $p = 0.045$ ).

In an open-label RCT<sup>12</sup> of 81 patients with IPAH, 8 of 40 patients randomized to conventional therapy

alone died over the 12-week study period, while none of the 41 patients randomized to epoprostenol plus conventional therapy died over the study period. While this difference was statistically significant ( $p = 0.003$ ), it is important to note that the conventional therapy group appeared more ill from the onset, with a mean baseline 6-min walk test (6MWT) distance of  $272 \pm 23$  m, while the epoprostenol group had a mean baseline 6MWT distance of  $316 \pm 18$  m ( $\pm$  SD)]. All of the patients who died in the conventional therapy group had a baseline 6MWT distance of  $< 150$  m. 6MWT distance at baseline was an independent predictor of survival ( $p < 0.05$ ). With the publication of this trial<sup>12</sup> demonstrating a mortality benefit in patients with IPAH treated with epoprostenol in 1996, subsequent series evaluating survival have used either historical controls or projections based on the NIH Registry equation rather than concurrent subjects receiving conventional therapy.

Shapiro et al<sup>13</sup> reported a series of 69 patients with IPAH treated with epoprostenol, of whom 18 patients were followed up for  $> 330$  days. The 1-year, 2-year, and 3-year survival rates for these epoprostenol-treated patients were 80%, 76%, and 49%, respectively, while the 10-month, 20-month, and 30-month survival rates of historical control patients from the NIH Registry were 88%, 56%, and 47%. Serial exercise and cardiac catheterization data were not reported. Although the mean duration of therapy is not reported in this article, the number of patients at risk declines substantially after 1 year, making conclusions about long-term survival benefit with epoprostenol suspect in this series.

More recently, three large series have demonstrated a survival benefit in IPAH patients treated

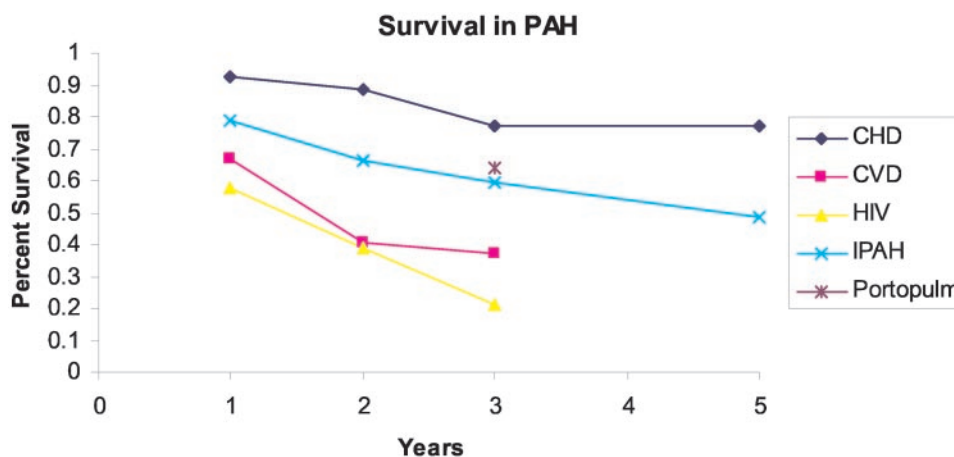


FIGURE 1. Mean survival of patients with PAH based on etiology. CHD = congenital heart disease; CVD = collagen vascular disease; HIV = human immunodeficiency virus related; IPAH = idiopathic pulmonary arterial hypertension; Portopulm = portopulmonary hypertension.

with epoprostenol therapy. Sitbon and colleagues<sup>14</sup> followed up 178 patients with IPAH over a mean of  $26 \pm 21$  months (range, 0.5 to 98 months) [ $\pm$  SD]. The survival rates at 1 year, 2 years, 3 years, and 5 years were 85%, 70%, 63%, and 55%. This survival curve compared favorably to the survival curve of historical control subjects at the same institution. There were also significant improvements in New York Heart Association functional class (NYHA-FC), exercise tolerance as measured by the 6MWT, and hemodynamics as measured at cardiac catheterization after 3 months of therapy. Baseline variables associated with a poor outcome on univariate analysis included the following: history of right-heart failure, NYHA-FC IV, 6MWT distance less than the median of 250 m, mean right arterial pressure (mRAP)  $\geq 12$  mm Hg, and mean pulmonary artery pressure (mPAP)  $< 65$  mm Hg. On multivariate analysis including both baseline variables and those measured after 3 months of epoprostenol treatment, a history of right-heart failure, persistence of NYHA-FC III or IV at 3 months, and absence of a fall in total pulmonary resistance (TPR) of  $> 30\%$  compared to baseline were associated with a poor survival.

Another large series<sup>15</sup> of 162 consecutive patients with IPAH treated with epoprostenol and followed up for a mean of  $36.3 \pm 27.1$  months (range, 1 to 122 months) [ $\pm$  SD] reported similar results. The observed survival rates at 1 year, 2 years, 3 years, 4 years, and 5 years were 88%, 76%, 63%, 56%, and 47%, respectively. The predicted survival rates based on the NIH Registry equation at 1 year, 2 years, and 3 years were 59%, 46%, and 35% ( $p < 0.001$  at all time points by  $\chi^2$  analysis). Significant improvements in NYHA-FC, exercise tolerance as assessed by low-level treadmill test, and hemodynamics as assessed by serial cardiac catheterization were also

reported. Baseline predictors of survival included NYHA-FC; exercise time, as assessed by low-level treadmill test; mRAP; and vasodilator response to adenosine. Predictors of survival after 1 year of therapy included NYHA-FC and change in exercise time, cardiac index (CI), and mPAP.

In a series<sup>6</sup> of 91 patients with PAH treated with epoprostenol and followed up for a mean of  $2.4 \pm 1.8$  years ( $\pm$  SD), 49 patients with IPAH had 1-year, 2-year, and 3-year survival rates of 85%, 76%, and 65%, respectively. The expected survival rates based on the NIH Registry equation were 62%, 49%, and 39%, at 1 year, 2 years, and 3 years, respectively. Also reported were significant improvements in exercise tolerance as measured by the 6MWT and hemodynamics measured at cardiac catheterization. They did not find any baseline or follow-up hemodynamic variables as predictors of survival. As noted previously, patients with PAH related to scleroderma had a worse survival than those with other forms of PAH. In a 12-week RCT<sup>16</sup> in PAH related to the scleroderma spectrum of diseases, epoprostenol did not affect survival. The impact that epoprostenol has made on survival in IPAH is displayed in Figure 2.

Less data evaluating the impact of medical therapies other than epoprostenol on survival in PAH are available. One small retrospective series<sup>17</sup> evaluated survival in 24 patients with IPAH treated with the oral prostacyclin analog beraprost compared to that of 34 patients treated with conventional therapy. Kaplan-Meier survival curves demonstrated that the 1-year, 2-year, and 3-year survival rates for the patients receiving beraprost were 96%, 86%, and 76%, respectively, while the survival rates were 77%, 47%, and 44% in the conventional therapy group (log-rank test,  $p < 0.05$ ). A serious concern in this study is the much shorter duration of observation in

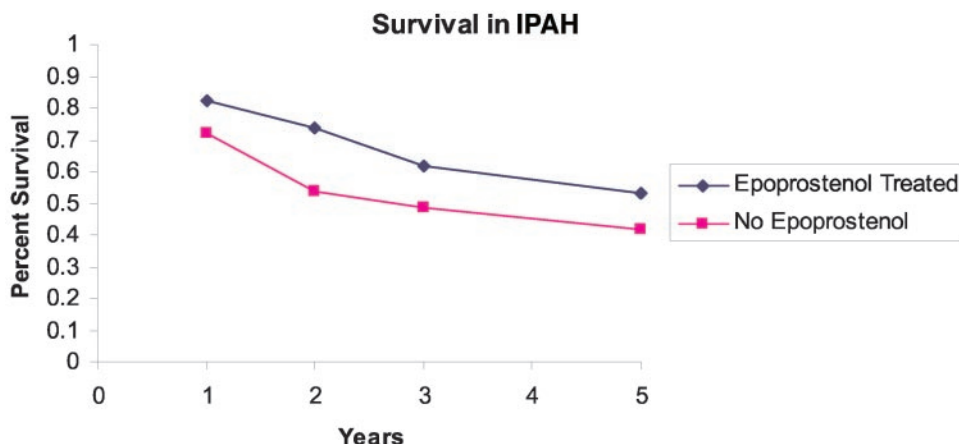


FIGURE 2. Impact made by epoprostenol on survival in patients with IPAH.

the beraprost group as opposed to the conventional therapy group, in addition to the relatively small sample size.

Three series have demonstrated that anticoagulation therapy has a favorable influence on survival, two series in IPAH and one series in anorectic drug-induced pulmonary hypertension. Fuster et al<sup>18</sup> evaluated 120 patients in a retrospective, uncontrolled, single-center study. This study, published in 1984, was performed before the widespread use of the ventilation-perfusion scanning in the setting of suspected IPAH, and 32 of 56 subjects in whom lung tissue was evaluated at autopsy had thromboembolic disease. The median time from diagnosis to death was 1.9 years; on multivariate analysis, treatment with anticoagulation was predictive of a better outcome. In a prospective, single-center study, Rich et al<sup>19</sup> described a better outcome among patients treated with warfarin who were not calcium-channel blocker responders. The 1-year, 3-year, and 5-year survival rates in those treated with warfarin were 91%, 62%, and 47%, respectively, compared to 52%, 31%, and 31% in those not treated with warfarin ( $p = 0.025$ ). In a retrospective study of 173 patients, 104 of whom received the anorexigen aminorex, Frank et al<sup>20</sup> also demonstrated a survival benefit in those receiving warfarin anticoagulation.

As discussed by Badesch et al (see page 000), in a select patient group, calcium-channel blocker therapy may favorably influence survival. Calcium-channel blockers may favorably influence survival in a small proportion of patients with IPAH who demonstrate a significant vasodilator response when tested with a short-acting agent. The definition of a positive vasodilator response, and the long-term outcome with calcium-channel blocker therapy in patients with IPAH has been extensively reviewed by Badesch et al. There are no data on which to make conclusions regarding the use of calcium-channel blockers in other forms of PAH.

### *Survival in Children with PAH*

As in adults, the prognosis in children with PAH is closely linked with its underlying etiology. The spectrum of diseases associated with PAH in children is broadly similar to adults, but there are several unique diseases and key features that distinguish pediatric PAH from adult PAH. Neonatal disorders such as persistent pulmonary hypertension of the newborn, bronchopulmonary dysplasia, congenital diaphragmatic hernia, primary lung hypoplasia, and alveolar capillary dysplasia are beyond the scope of this text. As observed in adults, pulmonary hypertension can accompany other childhood disorders, including obstructive sleep apnea, cystic fibrosis,

sickle-cell disease, liver disease, clotting disorders, connective tissue disease, and others. Data on the prognosis in these settings are extremely limited, and mostly consist of case reports or small patient series. Pulmonary vascular disease in children with interstitial lung disease is particularly associated with high mortality.<sup>21</sup>

PAH complicates the course of children with CHD, and represents the most important determinant of morbidity and mortality in these patients. An estimated 30% of patients with CHD acquire significant PAH without early surgical repair. The age at which lesions with left-to-right shunting causes significant pulmonary vascular disease is variable, but is rare after repair in the first 2 years of life. Long-term prostacyclin therapy improves prognosis and quality of life in patients with PAH associated with CHD,<sup>22</sup> but few studies have addressed long-term prognosis or the effects of pharmacologic therapy.

IPAH can present during early infancy, within the first months of life, or later in childhood. Although uniformly fatal in the recent past, children with IPAH are now treated with similar strategies as adults, and the outlook has improved with advances in medical therapies. Barst and colleagues<sup>23</sup> demonstrated that young children tend to demonstrate greater acute pulmonary vascular reactivity to vasodilators during cardiac catheterization (40% in children vs 20% in adults). In addition, treatment of children with either calcium-channel blockade (if reactive) or long-term prostacyclin infusion seemed to improve survival to a similar degree as reported in adults.<sup>23,24</sup>

## CLINICAL FACTORS ASSOCIATED WITH SURVIVAL

### *Demographics*

Data regarding the prognostic implications of demographic variables such as age, gender, and time of onset of symptoms to diagnosis are inconsistent. The NIH Registry was the first large-scale evaluation of prognostic factors in IPAH. Age, time from onset of symptoms to diagnosis, and gender were not predictive of survival.<sup>1</sup> In a retrospective, single center, uncontrolled case series<sup>4</sup> of 61 patients with IPAH from India, younger age was associated with a worse prognosis. It should be noted that this population was younger than that included in the NIH Registry (mean age,  $24.6 \pm 11.8$  years as compared to  $36 \pm 15$  years [ $\pm$  SD]). In a study<sup>6</sup> that included patients with many etiologies of PAH who were treated with epoprostenol, older age at diagnosis indicated a worse prognosis (HR, 3.20; 95% confidence interval, 1.32 to 7.76) for those above the median. This, however, may be confounded by the

inclusion of patients with the scleroderma spectrum of disease who tend to be older and also had a worse prognosis. A national survey of IPAH was conducted in Israel from 1988 to 1997 and identified 44 patients with a mean age of  $43 \pm 13$  years ( $\pm$  SD).<sup>25</sup> Although they did not find age to be a prognostic variable, longer time of onset from symptoms to diagnosis was associated with a worse prognosis.

### *Hemodynamics*

That hemodynamics are predictive of outcome in IPAH seems intuitive. The NIH Registry was the first large-scale evaluation of prognostic factors in IPAH.<sup>1</sup> In this registry, three measured hemodynamic variables were associated with an increased risk of death by univariate analysis: increased mPAP (odds ratio, 1.16; confidence interval [CI], 1.05 to 1.28), increased mRAP (odds ratio, 1.99; CI, 1.47 to 2.69), and decreased CI (odds ratio, 0.62; CI, 0.46 to 0.82). In a multivariate analysis, these three hemodynamic variables were also predictive. In fact, data from the NIH Registry was used to formulate a regression equation in which these three hemodynamic variables were used to estimate survival.

Sandoval et al<sup>2</sup> conducted a prospective dynamic cohort study of 61 patients with IPAH at a single center in Mexico referred between 1977 and 1991. The mean age was  $22.6 \pm 11$  years, and the mean survival was  $25.9 \pm 20.7$  months ( $\pm$  SD). In a univariate analysis, three measured hemodynamic variables were predictive of survival: increased mRAP (HR, 3.87 [1.59–9.44];  $p = 0.004$ ), decreased CI (HR, 4.2 [1.18–14.9];  $p = 0.027$ ), and decreased mixed venous oxygen saturation ( $MVO_2$ ) [HR, 4.28; CI, 1.57 to 11.6;  $p = 0.005$ ]. Interestingly, mPAP was not predictive of survival. In a multivariate analysis, both increased mRAP and decreased CI remained significant predictors of survival. One of the major objectives of this series was to analyze the usefulness of the NIH equation. Despite the highly variable clinical course of the disease, positive predictive values of the NIH equation in this patient population at 1 year, 2 years, and 3 years were 87%, 91%, and 89%, respectively.

In a retrospective nationwide survey<sup>3</sup> on IPAH conducted in Japan, 223 patients were identified in the period from 1980 to 1990. Although the length of observation was not defined, the median survival time was 33 months, and 139 of the 223 patients had died at the time of the survey in 1991. Demographic and cardiorespiratory variables at the time of the initial cardiac catheterization were compared between the survivors and the nonsurvivors. Survivors had a higher  $PaCO_2$ , lower heart rate, lower mRAP, lower mPAP, higher stroke volume index, and lower

pulmonary vascular resistance (PVR) than the nonsurvivors. Interestingly, there was no difference in CI between the groups.

A national survey of IPAH was conducted in Israel from 1988 to 1997, and identified 44 patients with a mean age of  $43 \pm 13$  years ( $\pm$  SD).<sup>25</sup> This retrospective cohort study found mPAP, mRAP, and CI to be predictive of survival. In fact, in a multivariate analysis of this population, the most positive predictive values were time until the diagnosis and mRAP.

A retrospective, single center, uncontrolled case series<sup>4</sup> from India identified 61 patients with IPAH from 1977 to 1991 (mean age,  $24.6 \pm 11.8$  years) [ $\pm$  SD]. Sixty-one percent of the patients received vasodilator therapy during the observation period. In this population, the median survival was 22 months, with 2-year, 5-year, and 10-year survival rates of 48%, 32%, and 12%, respectively. In a univariate analysis, the following hemodynamic variables were predictive of survival: pulmonary artery (PA) saturation ( $p = 0.002$ ), mRAP ( $p = 0.023$ ), right ventricular end-diastolic pressure (RVEDP) [ $p = 0.009$ ], mPAP ( $p = 0.028$ ), and CI ( $p = 0.038$ ). A multivariate analysis was not performed. In a series<sup>26</sup> of 13 patients with IPAH from Korea, CI was the only hemodynamic variable that was correlated with survival (HR, 4.10; 95% confidence interval, 1.20–17.1;  $p = 0.04$ ).

Glanville and coworkers<sup>27</sup> followed up a group of 90 patients with IPAH referred for heart-lung transplantation in the 1980s; the mean survival from the time of diagnosis was  $42.9 \pm 42.6$  months ( $\pm$  SD). The only hemodynamic variable that was predictive of a poor outcome was low cardiac output (CO). Similarly, among a group of 42 patients with IPAH treated with epoprostenol and evaluated for lung transplantation, the CO was lower among those who died while on the waiting list compared to those who survived to transplantation, remained active on the waiting list, and those who were taken off the waiting list.<sup>28</sup>

Baseline hemodynamic variables appear to have less prognostic value in patients with IPAH who that are treated with epoprostenol. In a series of 178 patients with IPAH treated with epoprostenol, Sitbon et al<sup>14</sup> found lower mPAP and higher mRAP to have negative prognostic implications by univariate analysis, while only mRAP was prognostic by multivariate analysis. In a univariate analysis of a series of 81 patients with IPAH treated with epoprostenol, Raymond et al<sup>29</sup> found mRAP,  $MVO_2$ , and heart rate to be significant predictors of survival. Only  $MVO_2$  was entered into the multivariate analysis, and it was significant. In a series of 162 patients with IPAH treated with epoprostenol, McLaughlin and col-

leagues<sup>15</sup> found that only mRAP was predictive of survival in a univariate analysis.

Evidence (Tables 2–4) summarize the prognostic value of hemodynamics in patients with IPAH, based on treatment received. As the patient populations and statistical methods varied in these studies, it is difficult to give absolute hemodynamic values that predict survival. In patients who received only conventional therapy, higher baseline mRAP was of significant prognostic value by univariate analysis in three of three studies and by multivariate analysis in three of four studies. Higher mPAP was of significant prognostic value by univariate analysis in three of five studies, and in the one study that evaluated it in multivariate analysis. Lower baseline CI was of prognostic significance in three of four studies by both univariate and multivariate analysis. In patients who have been treated with epoprostenol, baseline mRAP still appears to have significant prognostic value as demonstrated in all three studies that evaluated this parameter by univariate analysis and in the one study that evaluated it by multivariate analysis. Lower baseline mPAP was predicted a worse outcome by univariate analysis in one of the three studies, but was not predictive in the multivariate model. None of the three studies found CI to be predictive by univariate analysis. Overall, the most powerful hemodynamic predictor of survival is mRAP. Because of the heterogeneity of the patient populations, conclusions regarding the studies in Table 4 will not be summarized. There is a paucity of data on which to base recommendations regarding the prognostic value of hemodynamics in patients

with IPAH treated with agents other than epoprostenol and for patients with PAH with a diagnosis other than IPAH.

### Vasodilator Responsiveness

It is currently the standard of care to perform acute vasodilator testing with a short-acting agent (such as IV adenosine, IV epoprostenol, or inhaled nitric oxide) when evaluating a patient with IPAH. A consensus of the definition of a responder is delineated by Badesch et al (see page 000) in the Medical Therapies chapter of these guidelines. While it has been suggested that the incidence of “responders” is approximately 20%, more recent data suggests that the true incidence is much less than this. True responders do have an excellent prognosis, with one study<sup>19</sup> indicating 95% at 5 years. Although the main purpose of acute vasodilator testing is to identify that “privileged” group of patients that might respond to oral calcium-channel blockers, the results of vasodilator testing also have prognostic implications.

Raffy et al<sup>30</sup> evaluated the acute vasodilator response to IV epoprostenol in 91 consecutive patients with IPAH. They classified patients into three groups based on their acute response to epoprostenol: highly responsive with a reduction in TPR index (TPRI) of > 50%, moderately responsive with a fall in TPRI of between 20% and 50%, and nonresponsive with a fall in TPRI of < 20%. Patients who were either highly or moderately responsive were treated with prolonged oral vasodilator therapy, while all patients received anticoagulation. The survival rate

**Table 2—Hemodynamic Predictors, IPAH Conventional Therapy\***

| Study                         | n   | PVR | mPAP | mRAP | CO/CI | O <sub>2</sub> Sat | MVO <sub>2</sub> | SBP | Heart Rate | RVEDP |
|-------------------------------|-----|-----|------|------|-------|--------------------|------------------|-----|------------|-------|
| Sandoval et al <sup>2</sup>   |     |     |      |      |       |                    |                  |     |            |       |
| Multivariate analysis         | 61  |     |      |      | Y     | Y                  |                  | Y   |            |       |
| Univariate analysis           | 61  | Y   | N    | Y    | Y     | N                  | Y                | N   | N          | N     |
| D'Alonzo et al <sup>1</sup>   |     |     |      |      |       |                    |                  |     |            |       |
| Multivariate analysis         | 194 |     | Y    | Y    | Y     |                    |                  |     |            |       |
| Univariate analysis           | 194 | Y   | Y    | Y    | Y     | N                  | Y                | N   | N          |       |
| Eysmann et al <sup>32</sup>   |     |     |      |      |       |                    |                  |     |            |       |
| Multivariate analysis         | 26  |     |      |      | Y     |                    |                  |     |            |       |
| Univariate analysis           | 26  | N   | Y    | N    | Y     |                    |                  |     | Y          |       |
| Fuster et al <sup>18†</sup>   |     |     |      |      |       |                    |                  |     |            |       |
| Multivariate analysis         | 120 |     |      |      |       | Y                  |                  |     |            |       |
| Univariate analysis           | 120 | Y   | Y    |      |       | Y                  | Y                |     |            | Y     |
| Frank et al <sup>20</sup>     |     |     |      |      |       |                    |                  |     |            |       |
| Multivariate analysis         | 69  |     | Y†   |      |       |                    |                  |     |            |       |
| Sandoval et al <sup>24§</sup> |     |     |      |      |       |                    |                  |     |            |       |
| Multivariate analysis         | 18  |     |      | Y    | N     |                    | N                |     |            | N     |
| Univariate analysis           | 18  | N   | N    | Y    | N     | N                  | N                | N   | N          | N     |

\*Y = yes; N = no.

†PPH and thromboembolic.

‡Systolic PA pressure.

§Children.

**Table 3—Hemodynamic Predictors, IPAH Epoprostenol Therapy\***

| Study                               | n    | PVR | mPAP | mRAP | CO/CI | O <sub>2</sub> Sat | MVO <sub>2</sub> | SBP | Heart Rate | RVEDP |
|-------------------------------------|------|-----|------|------|-------|--------------------|------------------|-----|------------|-------|
| Raymond et al <sup>29</sup> (710)   |      |     |      |      |       |                    |                  |     |            |       |
| Multivariate analysis               | 81   |     |      |      |       |                    | Y                |     |            |       |
| Univariate analysis                 | 81   | N   | N    | Y    | N     |                    | Y                |     | Y          |       |
| Sitbon et al <sup>14</sup> (110)    |      |     |      |      |       |                    |                  |     |            |       |
| Multivariate analysis               | 178  |     | N    | Y    |       |                    |                  |     |            |       |
| Univariate analysis                 | 178  | N†  | Y§   | Y    | N     |                    |                  |     |            |       |
| McLaughlin et al <sup>15</sup> (10) |      |     |      |      |       |                    |                  |     |            |       |
| Multivariate analysis               | 162† | N   | N    | Y    | N     |                    |                  |     |            |       |

\*See Table 2 for expansion of abbreviations.

†Multivariate analysis.

‡TPR.

§Inverse correlation.

was significantly higher among the highly responsive patients compared to the nonresponsive and moderately responsive patients (62% vs 38% and 47%, respectively). Interestingly, the survival was not significantly greater among the moderate responders compared to the nonresponders in this series.

Sandoval et al<sup>2</sup> followed up a group of 60 patients with IPAH longitudinally after most had undergone acute vasodilator testing. They defined a “complete response” as a > 20% reduction in both mPAP and PVR index, and a “partial response” as a > 20% reduction in only PVR index. Both complete and partial responders were treated with oral vasodilators, while nonresponders and those who did not undergo vasodilator testing were not. The median survival for those not given vasodilator treatment was 2.12 years (95% confidence interval, 1.0 to 3.2), while the mean survival for those receiving vasodilator treatment was 5.04 years (95% confidence interval, 4.16 to 5.92), a statistically significant difference ( $p = 0.03$  by log-rank test).

The issue of whether degree of vasodilator responsiveness has prognostic implications in patients

who are treated with medical therapies other than calcium-channel blockers is controversial. In a large series<sup>15</sup> of patients with IPAH receiving long-term IV epoprostenol, the change in PVR acutely with adenosine was predictive of survival by a univariate analysis. Another study<sup>31</sup> in a diverse patient population including a large proportion of patients with chronic thromboembolic pulmonary hypertension determined that vasodilator responsiveness was not a prognostic factor. Vasodilator responsiveness has not been adequately assessed in patients with PAH with a diagnosis other than IPAH.

### Echocardiography

The echocardiogram is an integral part of the evaluation of a patient with PAH. Common echocardiographic findings in PAH include right atrial (RA) and right ventricular (RV) enlargement, reduced RV function, displacement of the intraventricular septum, and tricuspid regurgitation (TR). Several studies have correlated echocardiographic findings with outcome in pulmonary hypertension. In a series of

**Table 4—Hemodynamic Predictors, IPAH Mixed/Other/Not Specified Treatment\***

| Study                         | n    | PVR | mPAP | mRAP | CO/CI | O <sub>2</sub> Sat | MVO <sub>2</sub> | SBP | Heart Rate | RVEDP |
|-------------------------------|------|-----|------|------|-------|--------------------|------------------|-----|------------|-------|
| Bossone et al <sup>39</sup>   | 51†  | Y   | N    | Y    | Y     |                    |                  |     | N          |       |
| Applebaum et al <sup>25</sup> |      |     |      |      |       |                    |                  |     |            |       |
| Multivariate analysis         | 44   |     |      | Y    |       |                    |                  |     |            |       |
| Univariate analysis           | 44   | N   | Y    | Y    | Y     | N                  |                  |     |            |       |
| Chun et al <sup>26</sup>      | 13†  |     | N    | N    | Y     | N                  |                  | N   |            | N     |
| Nagaya et al <sup>40</sup>    | 58†  |     | N    | N    | Y     | N                  | N                |     |            |       |
| Paciocco et al <sup>38</sup>  | 34†  | Y   | N    | N    | N     | N                  |                  |     |            |       |
| Wensel et al <sup>37</sup>    | 86‡  | Y   |      | Y    | Y     | Y                  | Y                |     | Y          |       |
| Glanville et al <sup>27</sup> | 90‡  | N   | Y    | Y    | Y     |                    |                  |     |            |       |
| Okada et al <sup>3</sup>      | 223‡ | Y   | Y    | Y    | N     | N                  |                  |     | Y          |       |
| Rajasekhar et al <sup>4</sup> | 61‡  | Y   | Y    | Y    | Y     | Y                  | Y                |     |            | Y     |

\*See Table 2 for expansion of abbreviations.

†Multivariate analysis.

‡Univariate analysis.

26 patients with IPAH receiving conventional therapy in the late 1980s, Eysmann and colleagues<sup>32</sup> studied 41 echocardiographic variables and 9 cardiac catheterization variables. Although several factors were prognostic on univariate analysis, multivariate life-table analysis of noninvasive variables revealed the severity of pericardial effusion to be independently significant ( $p = 0.006$ ). Echocardiographic factors that were predictive on univariate analysis included only the following: heart rate  $> 87$  beats/min, pulmonic flow acceleration time of  $< 62$  ms, tricuspid early flow deceleration  $\leq 300$  cm<sup>2</sup>/s, and mitral early flow/atrial flow ratio  $\leq 1.0$ .

In an analysis of 79 of 81 IPAH patients who participated in the randomized trial<sup>33</sup> of IV epoprostenol, pericardial effusion was noted in 43 patients (54%). Patients with larger effusions generally had more severely impaired exercise performance. Larger effusion size was also correlated with more RA dilatation, greater displacement of the intraventricular septum during diastole, and more TR than patients with no or trace effusion. Although there was not an association between pericardial effusion and mortality at the end of the 12-week study, effusion size was correlated with death ( $p = 0.02$ ) or a composite end point of death or lung transplantation ( $p = 0.05$ ) at 1 year.

A more detailed analysis<sup>29</sup> with longer follow-up of this same group of 81 patients with IPAH was published several years later. The mean duration of follow-up was  $36.9 \pm 15.4$  months ( $\pm$  SD). During the observation period, 20 patients died and 21 patients underwent lung transplantation. On univariate analysis, the echocardiographic indices that were predictive of survival were the presence of a pericardial effusion (HR, 3.89;  $p = 0.003$ ) and RA area index (HR, 1.54;  $p = 0.005$ ). In a multivariate analysis incorporating clinical, hemodynamic, and echo-

cardiographic variables, pericardial effusion (HR, 4.38;  $p = 0.011$ ) remained a significant predictor of death.

Two studies have evaluated Doppler echocardiographic-derived indices of RV function in patients with IPAH. The Doppler echocardiographic index, at times referred to as the Tei index, is calculated as follows: the sum of the RV isovolumetric contraction time and the isovolumetric relaxation time are obtained by subtracting RV ejection time from the interval between cessation and onset of the tricuspid velocities with pulsed-wave Doppler echocardiography. The index of combined RV systolic and diastolic function is obtained by dividing the sum of both isovolumetric intervals by ejection time. In a small study<sup>38</sup> of 26 consecutive patients with IPAH, all six patients who died during the follow-up period had a Doppler echocardiography RV index above the median. A larger series of 53 patients with IPAH followed up over a mean of 2.9 years from the same institution confirmed the predictive value of the Doppler echocardiography RV index.<sup>35</sup> On univariate analysis, an elevated Doppler echocardiography RV index ( $\chi^2$  20.7,  $p < 0.0001$ ) was the strongest predictor of an adverse outcome, which was defined as death or lung transplantation. Other echocardiographically derived univariate predictors included severity of TR ( $\chi^2 = 8.8$ ,  $p = 0.004$ ) and heart rate ( $\chi^2 = 5.06$ ,  $p = 0.02$ ). Multivariate regression analysis also identified the Doppler echocardiography RV index as prognostic of adverse outcome ( $\chi^2 = 8.33$ ,  $p = 0.004$ ).

The echocardiogram is an important tool both in terms of diagnosis and prognosis in IPAH. Table 5 summarizes the evidence regarding the prognostic value of the most commonly studied echocardiographic variables in IPAH. The presence of a pericardial effusion had negative prognostic implications

**Table 5—Echocardiographic Predictors, IPAH Treatment as Indicated\***

| Study                        | n   | Treatment    | Heart Rate | Doppler Echocardiography RV Index | TR Severity | PASP/Maximum TR Velocity | Pericardial Effusion | Indexed RA Area | Diastolic Eccentricity Index | Systolic Eccentricity Index |
|------------------------------|-----|--------------|------------|-----------------------------------|-------------|--------------------------|----------------------|-----------------|------------------------------|-----------------------------|
| Yeo et al <sup>35</sup>      |     |              |            |                                   |             |                          |                      |                 |                              |                             |
| Multivariate analysis        | 53  | NS           | N          | Y                                 | N           |                          |                      |                 |                              |                             |
| Univariate analysis          | 53  | NS           | Y          | Y                                 | Y           | N                        |                      |                 |                              |                             |
| Raymond et al <sup>29</sup>  |     |              |            |                                   |             |                          |                      |                 |                              |                             |
| Multivariate analysis        | 81  | Epoprostenol |            |                                   |             |                          | Y                    | Y               |                              |                             |
| Univariate analysis          | 81  | Epoprostenol |            |                                   | N           | N                        | Y                    | Y               | N                            | N                           |
| Eysmann et al <sup>32</sup>  |     |              |            |                                   |             |                          |                      |                 |                              |                             |
| Multivariate analysis        | 26  | Conventional |            |                                   |             |                          | Y                    |                 |                              |                             |
| Univariate analysis          | 26  | Conventional | Y          |                                   |             | N                        | Y                    |                 |                              | N                           |
| Tei et al <sup>34</sup>      | 26† | NS           |            | Y                                 |             |                          |                      |                 |                              |                             |
| Miyamoto et al <sup>36</sup> | 43† | Mixed        | N          |                                   |             |                          | N                    |                 |                              |                             |

\*See Table 2 for expansion of abbreviations. NS = not specified; PASP = pulmonary artery systolic pressure.

†Multivariate analysis.

in the two-univariate analysis and two of the three multivariate analysis.<sup>29,32,36</sup> The indexed RA area had negative prognostic implications by both univariate and multivariate analysis in the one study that considered it.<sup>29</sup> The Doppler echocardiography RV index was prognostic in both studies that evaluated it in a multivariate analysis.<sup>34,35</sup> Notably, the estimated PA systolic pressure was not predictive in any of the three studies that evaluated it by univariate analysis.

### *Exercise Tolerance*

Exercise capacity in patients with PAH has been commonly measured by the 6MWT due to its ease of administration and reproducibility. Other measures of exercise capacity have included standard cycle ergometry cardiopulmonary exercise testing (CPET), shuttle walk test, and treadmill walk time. However, patients with advanced PAH and RV dysfunction may not be able to complete these other forms of exercise; however, all but the most debilitated patient can walk and complete the 6MWT. In one study<sup>36</sup> in patients with IPAH, 37% of patients were not able to complete CPET but all patients could perform the 6MWT. Thirty-eight of these 44 patients were NYHA-FC III or IV. In another study<sup>37</sup> with less severely ill patients with PAH (20 patients in NYHA-FC II, 56 patients in NYHA-FC III, and 10 patients in NYHA-FC IV), 19% of patients were still not able to perform cycle ergometry. Miyamoto and colleagues<sup>36</sup> compared these two measures in a cohort of 27 patients with IPAH who were able to complete both forms of exercise testing. They found a good correlation between maximum oxygen consumption ( $\dot{V}O_2\text{max}$ ) and 6MWT distance in this cohort ( $r = 0.70$ ). Therefore, even though the 6MWT is a submaximal exercise test, it is well tolerated by the vast majority of patients with PAH and it may have a good correlation to maximal exercise testing in patients with PAH.

Three studies<sup>12,29,36</sup> have shown 6MWT distance to be an independent predictor of survival for patients with IPAH. However, the treatment varied between survivors and nonsurvivors in these studies, thereby limiting interpretation of these findings. Barst and colleagues<sup>12</sup> studied 81 patients with IPAH over a 12-week period; 41 patients received epoprostenol therapy and 40 patients received conventional therapy. Eight patients died and all were in the conventional therapy group. The “unencouraged” 6MWT distance was less in the nonsurvivors vs the survivors from both groups ( $195 \pm 63$  m vs  $305 \pm 14$  m,  $p < 0.03$ ) [ $\pm$  SD]. Performance in the unencouraged 6MWT was found to be an independent predictor of survival ( $p < 0.05$ ), and the authors<sup>12</sup> suggested that distance walked in the 6MWT should be considered for future randomization of

patients with IPAH in clinical trials. Raymond and colleagues<sup>29</sup> studied this same cohort of patients through the period, including the 12-week randomization period and subsequent treatment period, when all but a few of the surviving patients were treated with IV epoprostenol. The mean follow-up period was for  $36.9 \pm 15.9$  months ( $\pm$  SD), and 73 of the 81 patients were available for follow-up at 1 year. These investigators focused on echocardiographic measurements but also included hemodynamic parameters and the unencouraged 6MWT distance at baseline in the survival analyses. 6MWT distance  $< 500$  feet (153 m) at baseline was associated with worse survival by univariate analysis, but did not reach statistical significance as an independent predictor of survival by multivariate analysis.

Miyamoto et al<sup>36</sup> also studied a population of 43 patients with IPAH who were referred between 1994 and 1999. All patients underwent right-heart catheterization, encouraged 6MWT, blood sampling for catecholamines, and echocardiographic assessment. They had a 100% follow-up rate over a mean follow-up period of  $21 \pm 16$  months ( $\pm$  SD). Thirteen patients were treated with IV epoprostenol, 25 patients were treated with the oral prostacyclin analog beraprost, and 5 patients were intolerant to prostacyclin therapy; no patients received lung or heart-lung transplantation during the study. Among the noninvasive variables that were studied (6MWT distance, age, sex, plasma norepinephrine, heart rate, arterial oxygen saturation [ $O_2\text{Sat}$ ], and echocardiographic parameters [presence of pericardial effusion or left ventricular deformity index]), only 6MWT distance was independently associated with survival. The authors divided the group according to the median 6MWT distance (332 m), and performed Kaplan-Meier survival curves for the two groups. The short-distance group ( $< 332$  m) had a significantly lower survival rate than the long-distance group ( $\geq 332$  m).

$\dot{V}O_2\text{max}$  determined by progressive, exercise testing with cycle ergometry was found to be an independent predictor of survival in one study<sup>37</sup> in patients with IPAH. Wensel and colleagues<sup>37</sup> studied 86 consecutive patients with IPAH, and 70 of the patients were able to undergo exercise testing. Curiously, no 6MWT was reported in these patients. Baseline treatments included calcium-channel blockers, oral anticoagulants, nasal oxygen supplementation, and inhaled iloprost (two patients). Subsequent treatment included IV iloprost in 13 patients; inhaled iloprost in 55 patients, followed by IV iloprost in 25 of these patients; and oral beraprost in 5 patients. After multivariate analysis,  $\dot{V}O_2\text{max}$ , peak systolic BP (SBP) during exercise, and peak diastolic BP (DBP) emerged as independent predictors of survival. Twelve-month receiver operating

characteristic curves were plotted, and optimal cutoff values were determined. Subsequent Kaplan-Meier survival analysis showed that patients with a  $\dot{V}O_2\text{max}$   $> 10.4$  mL/kg/min had a significantly better 1-year survival rate than patients with lower  $\dot{V}O_2\text{max}$  values (91% [95% confidence interval, 82 to 97%], vs 50% [95% confidence interval, 40 to 67%];  $p < 0.0001$ ). Additionally, patients with a peak SBP  $> 120$  mm Hg were also shown to have a better 1-year survival than those patients who did not achieve this pressure.

Paciocco and colleagues<sup>38</sup> did not find the pretreatment 6MWT distance to be independently correlated with survival time in their cohort of 34 patients with IPAH who were treated in a standardized fashion with oral calcium-channel blockers or IV epoprostenol. Nevertheless, they did note that pulse oximetry  $O_2\text{Sat}$  at peak 6MWT distance and change in  $O_2\text{Sat}$  were independently related to survival time. However, their 6MWT protocol called for the test to be terminated if  $O_2\text{Sat}$  by pulse oximetry decreased to  $< 86\%$ ; this could have limited the distances traversed by patients and thereby limited the utility of the 6MWT in this study.

Sitbon and colleagues<sup>14</sup> also studied factors associated with long-term survival in patients with IPAH who were treated with IV epoprostenol. “Nonencouraged” 6MWT distance at baseline and after 3 months of therapy was associated with survival by univariate analysis. However, it should be noted that change in 6MWT distance at 3 months was not associated with survival even by univariate analysis in this study. After multivariable analysis, 6MWT was not independently associated with survival, even though 6MWT distance improved in 90% of patients. The greatest increase in 6MWT distance was seen in the patients with NYHA-FC IV, but their total distance walked remained less than that in patients with lower NYHA-FC

symptoms. Others have also found that baseline exercise tolerance and an increase in exercise capacity is associated with increased survival time by univariate analysis in patients with IPAH treated with epoprostenol therapy.<sup>15</sup>

Table 6 summarizes the evidence regarding the prognostic value of the 6MWT and CPET variables in IPAH. Both studies<sup>14,29</sup> that evaluate 6MWT in a univariate fashion found it to be predictive of survival, while two of four studies<sup>12,14,29,36</sup> found it to be predictive in a multivariate fashion. Only one study has evaluated the prognostic implications of CPET.<sup>37</sup> It found  $\dot{V}O_2\text{max}$ , peak exercise SBP, and peak exercise DBP to be predictive of survival in a multivariate analysis, while the minute ventilation/ $\dot{V}CO_2$  slope and peak heart rate were also predictive when studied in a univariate analysis.

## ECG

The ECG is a simple, safe, and relatively inexpensive test in the evaluation of patients with PAH, although the sensitivity for findings such as RA enlargement and RV hypertrophy are limited. In a study of 51 patients with untreated IPAH, several ECG variables, including increased P-wave amplitude in lead II, qR pattern in lead  $V_1$ , and World Health Organization criteria for RV hypertrophy were associated with an increased risk of death.<sup>39</sup> The prognostic value of these factors remained even after controlling for PVR.

## NYHA-FC

NYHA-FC has been included in several studies of patients with PAH, and has been used in two ways in these reports: as a variable that might be predictive of survival in patients with PAH, and as an outcome

**Table 6—Exercise Predictors, IPAH Treatment as Indicated\***

| Study                        | n   | Treatment                          | 6MWT | $\dot{V}O_2\text{max}$ | Peak Exercise SBP | Peak Exercise DBP | Minute Ventilation/ $\dot{V}CO_2$ Slope | Peak Heart Rate |
|------------------------------|-----|------------------------------------|------|------------------------|-------------------|-------------------|-----------------------------------------|-----------------|
| Raymond et al <sup>29</sup>  |     |                                    |      |                        |                   |                   |                                         |                 |
| Multivariate analysis        | 81  | Epoprostenol                       | N    |                        |                   |                   |                                         |                 |
| Univariate analysis          | 81  | Epoprostenol                       | Y    |                        |                   |                   |                                         |                 |
| Barst et al <sup>12</sup>    | 81  | RCT (epoprostenol vs conventional) | Y    |                        |                   |                   |                                         |                 |
| Sitbon et al <sup>14</sup>   |     |                                    |      |                        |                   |                   |                                         |                 |
| Multivariate analysis        | 178 | Epoprostenol                       | N    |                        |                   |                   |                                         |                 |
| Univariate analysis          | 178 | Epoprostenol                       | Y    |                        |                   |                   |                                         |                 |
| Miyamoto et al <sup>36</sup> | 43† | Mixed                              | Y    |                        |                   |                   |                                         |                 |
| Wensel et al <sup>37</sup>   |     |                                    |      |                        |                   |                   |                                         |                 |
| Multivariate analysis        | 70  | Iloprost/beraprost                 |      | Y                      | Y                 | Y                 |                                         | N               |
| Univariate analysis          | 70  | Iloprost/beraprost                 |      | Y                      | Y                 | Y                 | Y                                       | Y               |

\*Studies by Raymond et al<sup>29</sup> and Barst et al<sup>12</sup> are the same patient population. See Table 2 for expansion of abbreviations.

†Multivariate analysis.

to assess the impact of therapies for PAH. Because NYHA-FC relies on patient reporting of symptoms as an outcome, it may hold special importance for patients themselves, but it is also useful for clinicians trying to assess prognosis and response to therapy in patients with PAH.

NYHA-FC has been associated with improved survival in several studies, but was found to be a significant predictor of mortality in only four studies.<sup>1,6,25,31</sup> The NIH cohort study<sup>1</sup> showed that among 194 patients who received a diagnosis of IPAH between 1981 and 1985, the risk of death was higher among patients in NYHA-FC III or IV than among those in NYHA-FC I or II. The median survival time among NYHA-FC I or II patients was nearly 6 years, compared with 2.5 years for patients in NYHA-FC III and 6 months for patients in NYHA-FC IV. There was no assessment of drug therapy in the NIH Registry. In a subsequent cohort study<sup>25</sup> of 44 patients with IPAH, a few of whom received epoprostenol therapy ( $n = 6$ ), patients who were in NYHA-FC IV at the time of diagnosis had a significantly higher risk of death than patients in NYHA-FC I, II, or III. In another retrospective study<sup>39</sup> of 51 patients with IPAH (37 of whom received epoprostenol), patients in NYHA-FC III or IV had a shorter survival time than patients in NYHA-FC II ( $HR = 2.04$ ). A third study<sup>6</sup> of 91 patients with PAH, all of whom were treated with epoprostenol, demonstrated that patients who were in NYHA-FC IV (compared with NYHA-FC I, II, and III patients combined) had a significantly decreased survival ( $HR = 3.07$ ). In a retrospective study of 162 patients with IPAH receiving epoprostenol those who were in NYHA-FC III at baseline had a 3-year and 5-year survival rates of 81% and 79%, respectively, while those who were in NYHA-FC IV had a 3-year and 5-year survival rates of 47% and 27% ( $p = 0.0001$ ).<sup>15</sup> After a mean of 17 months of therapy, those in NYHA-FC I or II had subsequent 3-year and 5-year survival rates of 89% and 73%, vs 62% and 35% for patients in NYHA-FC III, while NYHA-FC IV patients had a 2-year survival of 42%. In a retrospective study<sup>14</sup> of 178 patients with IPAH treated with epoprostenol, all of whom were in NYHA-FC III or IV at the start of therapy, the authors similarly showed that the survival was lower for those in NYHA-FC IV than in NYHA-FC III. Additionally, they demonstrated that the persistence of NYHA-FC III or IV after 3 months of therapy was associated with poor survival. In summary, higher NYHA-FC (III or IV) is associated with increased mortality both in treated and untreated patients with IPAH; in those receiving

therapy, failure to improve NYHA-FC or deterioration in NYHA-FC, in and of itself, may be predictive of poor survival.

### Biomarkers

Candidate serum biomarkers that have been studied to assess prognosis in IPAH include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), catecholamines, and uric acid (UA).<sup>39–42</sup> Nagaya and colleagues<sup>41</sup> studied 63 consecutive patients with IPAH who were referred between 1994 and 1999; 3 patients were excluded from study due to kidney dysfunction (creatinine  $> 1.5$  mg/dL). They also studied 15 age-matched, healthy control subjects. Patients with IPAH underwent blood sampling at the time of baseline catheterization. Subsequent treatment included vasodilator treatment in 55 patients (IV epoprostenol,  $n = 14$ ; oral beraprost,  $n = 41$ ); 3 patients could not tolerate prostacyclin therapy, and 5 patients did not receive prostacyclin therapy. Patients were followed up for a mean follow-up period of 24 months. Plasma ANP and BNP levels were low in control subjects, and both were increased and correlated with functional class in patients with IPAH. ANP and BNP levels were also correlated with mRAP, mPAP, CO, and TPR. Among the noninvasive parameters studied (NYHA-FC, echocardiographic parameters, and plasma levels of ANP, BNP, and catecholamines), only BNP was found to be an independent predictor of survival. Additionally, follow-up measurements were performed at 3 months after receiving prostacyclin therapy in 53 patients. Changes in plasma BNP levels correlated closely with changes in RVEDP and TPR. Again, BNP level at 3 months was found to be an independent predictor of mortality. Furthermore, Kaplan-Meier survival curves demonstrated a marked increase in survival in those patients with a follow-up BNP level below the median value of 180 pg/mL. Two studies<sup>37,42</sup> assessed the relationship between plasma norepinephrine and mortality in patients with IPAH, and it was not found to be an independent predictor of mortality in either.

Increased UA levels are believed to reflect impaired oxidative metabolism, since tissue hypoxia depletes adenosine triphosphate with degradation of adenosine nucleotides to compounds including UA.<sup>43,44</sup> Since UA levels were shown to be associated with a poor prognosis in other disorders, investigators studied the association between serum UA levels and prognosis in patients with IPAH. Nagaya et al<sup>40</sup> studied 102 consecutive patients over a long period of time (September 1980 to April 1998). Follow-up was concluded in June 1998, for a mean duration of follow-up of  $31 \pm 37$  months. Twelve patients were

excluded due to absent UA levels or elevated creatinine ( $> 1.5$ ). Ninety-four percent of these patients were in NYHA-FC III or IV. Treatments were not specified for a majority of patients. Thirty age-matched, healthy volunteers served as control subjects. UA levels were significantly elevated in patients with IPAH as compared to control subjects for each gender group and the group as a whole. Serum UA levels increased in proportion to the severity of the functional class and correlated with CO, TPR, and  $MVO_2$ . Among the noninvasive variables that were studied, serum UA levels were independently related to mortality. Wensel and colleagues<sup>37</sup> also studied serum UA levels in 86 consecutive patients with IPAH (58 female and 28 male) between 1996 and 2001. Baseline treatments included calcium-channel blockers, oral anticoagulants, nasal oxygen supplementation, and inhaled iloprost (2 patients). Subsequent treatment included IV iloprost in 13 patients; inhaled iloprost in 55 patients, followed by IV iloprost in 25 of these patients; and oral beraprost in 5 patients. Follow-up was for a mean of  $567 \pm 48$  days, and UA levels for the group were  $7.6 \pm 0.4$  mg/dL ( $\pm$  SEM). Values were not separated by gender groups in this study. These investigators also showed that UA levels were independently related to survival in patients with IPAH. However, subsequent receiver operating characteristic curve analysis did not demonstrate substantial predictive power for this variable.

Lopes and colleagues<sup>45</sup> reported that plasma von Willebrand factor antigen (vWF:Ag) is elevated in patients with IPAH, PAH associated with CHD, and other assorted disorders. von Willebrand factor is a large multimeric glycoprotein that is synthesized and stored in endothelial cells. Therefore, it was hypothesized that levels of von Willebrand factor could be elevated in patients with PAH due to the associated abnormalities in endothelial cell function. Lopes and colleagues<sup>45</sup> studied 11 patients with IPAH and 24 patients with PAH associated with CHD over a 1-year period. Twenty healthy volunteers served as the control group. Treatment included anticoagulation, antiplatelet agents, and “anticongestive” measures. vWF:Ag was elevated in patients with PAH as compared to control subjects, and more so in patients with IPAH than with CHD. Multivariate analysis showed that cause of PH and vWF:Ag levels were independently associated with survival.

### *Pulmonary Function Tests*

Data regarding the prognostic implications of pulmonary function tests in PAH are scant and conflicting. In the NIH Registry, which included 194 patients with IPAH patients, diffusing capacity of the

lung for carbon monoxide (DLCO) was weakly correlated with mortality (odds ratio, 0.97).<sup>1</sup> In a more recent study<sup>6</sup> of 91 patients with PAH patients treated with epoprostenol, DLCO was weakly correlated with outcome, but was not statistically significant. One study of 20 patients with PAH related to the scleroderma spectrum of diseases demonstrated that a  $DLCO < 45\%$  of predicted in the absence of interstitial fibrosis portends a poor prognosis.<sup>5</sup> One study<sup>2</sup> of 61 patients with IPAH found reduced FVC to be predictive of a poor outcome by multivariate analysis ( $p = 0.02$ ).

## RECOMMENDATIONS

As the majority of the evidence reviewed above is applicable to patients with IPAH, the following recommendations pertain to patients with IPAH. In most instances, data are insufficient to make recommendations for patients with PAH due to diagnosis other than IPAH. In patients with IPAH, the following parameters, as assessed at baseline, may be used to predict a worse prognosis:

1. **Advanced NYHA-FC.** Quality of evidence: good; net benefit: substantial; strength of recommendation: A.
2. **Low 6MWT distance.** Quality of evidence: good; net benefit: substantial; strength of recommendation: A.
3. **Presence of a pericardial effusion.** Quality of evidence: good; net benefit: substantial; strength of recommendation: A.
4. **Elevated mRAP.** Quality of evidence: fair; net benefit: substantial; strength of recommendation: A.
5. **Reduced CI.** Quality of evidence: fair; net benefit: substantial; strength of recommendation: A.
6. **Elevated mPAP.** Quality of evidence: fair; net benefit: intermediate; strength of recommendation: B.
7. **Elevated Doppler Echocardiography RV (Tei) index.** Quality of evidence: low; net benefit: intermediate; strength of recommendation: C.
8. **Low  $\dot{V}O_{2\max}$  and low peak exercise SBP and DBP as determined by CPET.** Quality of evidence: low; net benefit: intermediate; strength of recommendation: C.
9. **ECG findings of increased P-wave amplitude in lead II, qR pattern in lead  $V_1$ , and World Health Organization criteria for RV hypertrophy.** Quality of evidence: low; net benefit: intermediate; strength of recommendation: C.

10. **Elevated BNP (> 180 pg/mL).** Quality of evidence: low; net benefit: intermediate; strength of recommendation: C.
11. **In patients with IPAH treated with epoprostenol, persistence of NYHA-FC III or IV status after at least 3 months of therapy may be used to predict a worse prognosis.** Quality of evidence: fair; net benefit: substantial; strength of recommendation: A.
12. **In patients with scleroderma-associated PAH, reduced DLCO (< 45% of predicted) may be used to predict a worse prognosis.** Quality of evidence: low; net benefit: small/weak; strength of recommendation: C.
13. **In pediatric patients with IPAH, younger age at diagnosis may be used to predict a worse prognosis.** Quality of evidence: low; net benefit: small/weak; strength of recommendation: C.

## REFERENCES

- 1 D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. *Ann Intern Med* 1991; 115:343-349
- 2 Sandoval J, Bauerele O, Palomar A, et al. Survival in primary pulmonary hypertension: validation of a prognostic equation. *Circulation* 1994; 89:1733-1744
- 3 Okada O, Tanabe N, Yasuda J, et al. Prediction of life expectancy in patients with primary pulmonary hypertension: a retrospective nationwide survey from 1980-1990. *Intern Med* 1999; 38:12-16
- 4 Rajasekhar D, Balakrishnan KG, Venkitachalam CG, et al. Primary pulmonary hypertension: natural history and prognostic factors. *Indian Heart J* 1994; 46:165-170
- 5 Stupi AM, Steen VD, Owens GR, et al. Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. *Arthritis Rheum* 1986; 29:515-524
- 6 Kuhn KP, Byrne DW, Arbogast PG, et al. Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. *Am J Respir Crit Care Med* 2003; 167:580-586
- 7 Kawut SM, Taichman DB, Archer-Chicko CL, et al. Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. *Chest* 2003; 123: 344-350
- 8 Opravil M, Pechere M, Speich R, et al. HIV-associated primary pulmonary hypertension: a case control study; Swiss HIV Cohort Study. *Am J Respir Crit Care Med* 1997; 155:990-995
- 9 Petitpretz P, Brenot F, Azarian R, et al. Pulmonary hypertension in patients with human immunodeficiency virus infection: comparison with primary pulmonary hypertension. *Circulation* 1994; 89:2722-2727
- 10 Hopkins WE, Ochoa LL, Richardson GW, et al. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. *J Heart Lung Transplant* 1996; 15:100-105
- 11 Barst RJ, Rubin LJ, McGoon MD, et al. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. *Ann Intern Med* 1994; 121:409-415
- 12 Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996; 334:296-302
- 13 Shapiro SM, Oudiz RJ, Cao T, et al. Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. *Am Coll Cardiol* 1997; 30:343-349
- 14 Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *Am Coll Cardiol* 2002; 40:780-788
- 15 McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; 106:1477-1482
- 16 Badesch DB, Tapsen VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease: a randomized, controlled trial. *Ann Intern Med* 2000; 132:425-434
- 17 Nagaya N, Uematsu M, Okano Y, et al. Effect of orally active prostacyclin analogue on survival of outpatients with primary pulmonary hypertension. *J Am Coll Cardiol* 1999; 34:1188-1192
- 18 Fuster V, Steele PM, Edwards WD, et al. Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation* 1984; 70:580-587
- 19 Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; 327:76-81
- 20 Frank H, Mlczech J, Huber K, et al. The effect of anticoagulant therapy in primary and anorectic drug-induced pulmonary hypertension. *Chest* 1997; 112:714-721
- 21 Sondheimer HM, Lung MC, Brugman SM, et al. Pulmonary vascular disorders masquerading as interstitial lung disease. *Pediatr Pulmonol* 1995; 20:284-288
- 22 Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. *Circulation* 1999; 99:1858-1865
- 23 Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for PPH in children. *Circulation* 1999; 99:1197-1208
- 24 Sandoval J, Bauerle O, Gomez A, et al. Primary pulmonary hypertension in children: clinical characterization and survival. *J Am Coll Cardiol* 1995; 25:466-474
- 25 Appelbaum L, Yigla M, Bendayan D, et al. Primary pulmonary hypertension in Israel: a national survey. *Chest* 2001; 119:1801-1806
- 26 Chun KJ, Kim SH, An BJ, et al. Survival and prognostic factors in patients with primary pulmonary hypertension. *Korean J Intern Med* 2001; 16:75-79
- 27 Glanville AR, Burke CM, Theodore J, et al. Primary pulmonary hypertension: length of survival in patients referred for heart-lung transplantation. *Chest* 1987; 91:675-681
- 28 Conte JV, Gaine SP, Orens JB, et al. The influence of continuous intravenous prostacyclin therapy for primary pulmonary hypertension on the timing and outcome of transplantation. *J Heart Lung Transplant* 1998; 17:679-685
- 29 Raymond RJ, Hinderliter AL, Willis PW, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. *J Am Coll Cardiol* 2002; 39:1214-1219
- 30 Raffy O, Azarian R, Brenot F, et al. Clinical significance of the pulmonary vasodilator response during short-term infusion of prostacyclin in primary pulmonary hypertension. *Circulation* 1996; 93:484-488
- 31 Higebottam T, Butt AY, McMahon A, et al. Long-term intravenous prostaglandin (epoprostenol or iloprost) for treat-

- ment of severe pulmonary hypertension. *Heart* 1998; 80:151–155
- 32 Eysmann SB, Palevsky HI, Reichel N, et al. Two-dimensional and Doppler-echocardiographic and cardiac catheterization correlates of survival in primary pulmonary hypertension. *Circulation* 1989; 80:353–360
  - 33 Hinderliter AL, Willis PW 4th, Long W, et al. Frequency and prognostic significance of pericardial effusion in primary pulmonary hypertension. PPH Study Group. *Am J Cardiol* 1999; 84:481–484, A10
  - 34 Tei C, Dujardin KS, Hodge DO, et al. Doppler echocardiographic index for assessment of global right ventricular function. *J Am Soc Echocardiogr* 1996; 9:838–847
  - 35 Yeo TC, Dujardin KS, Tei C, et al. Value of a Doppler-derived index combining systolic and diastolic time intervals in predicting outcome in primary pulmonary hypertension. *Am J Cardiol* 1998; 81:1157–1161
  - 36 Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension: comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000; 161:487–492
  - 37 Wensel R, Opitz CF, Anker SD, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. *Circulation* 2002; 106: 319–324
  - 38 Paciocco G, Martinez FJ, Bossone E, et al. Oxygen desaturation on the six-minute walk test and mortality in untreated primary pulmonary hypertension. *Eur Respir J* 2001; 17:647–652
  - 39 Bossone E, Paciocco G, Iarussi D, et al. The prognostic role of the ECG in primary pulmonary hypertension. *Chest* 2002; 121:513–518
  - 40 Nagaya N, Uematsu M, Satoh T, et al. Serum uric acid levels correlate with the severity and the mortality of primary pulmonary hypertension. *Am J Respir Crit Care Med* 1999; 160:487–492
  - 41 Nagaya N, Nishikimi T, Uematsu M, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000; 102:865–870
  - 42 Nootens M, Kaufmann E, Rector T, et al. Neurohormonal activation in patients with right ventricular failure from pulmonary hypertension; relation to hemodynamic variables and endothelin levels. *J Am Coll Cardiol* 1995; 26:1581–1585
  - 43 Fox AC, Reed GE, Meilman H, et al. Release of nucleosides from canine and human hearts as an index of prior ischemia. *Am J Cardiol* 1979; 3:52–58
  - 44 Mentzer RM, Rubio R, Berne RM. Release of adenosine by hypoxic canine lung tissue and its possible role in pulmonary circulation. *Am J Physiol* 1975; 229:1625–1631
  - 45 Lopes AA, Maeda NY, Goncalves RC, et al. Endothelial cell dysfunction correlates differentially with survival in primary and secondary pulmonary hypertension. *Am Heart J* 2000; 139:618–623