

Primary Pulmonary Hypertension: Improved Long-Term Effects and Survival With Continuous Intravenous Epoprostenol Infusion

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Objectives. This study sought to determine the long-term effects of continuous infusion of epoprostenol (epo) therapy on survival and pulmonary artery pressure in patients with primary pulmonary hypertension (PPH).

Background. PPH is a progressive disease for which there are few effective therapies.

Methods. Patients with PPH and New York Heart Association functional class III or IV symptoms of congestive heart failure underwent right heart catheterization and Doppler-echocardiography to measure the maximal systolic pressure gradient between the right ventricle and right atrium (ΔP) and cardiac output (CO). Doppler-echocardiography and catheterization data were compared. Patients were followed up long term with Doppler-echocardiography.

Results. Of 69 patients who went on to receive epo, 18 were followed up for >330 days (range 330 to 700). During long-term

follow-up, there was a significant reduction in ΔP , which decreased from 84.1 ± 24.1 to 62.7 ± 18.2 (mean \pm SD, $p < 0.01$). A Kaplan-Meier plot of survival of our study patients demonstrated improved survival compared with that of historical control subjects. The 1-, 2- and 3-year survival rates for our patients were 80% (n = 36), 76% (n = 22) and 49% (n = 6) compared with 10- (88%, n = 31), 20- (56%, n = 27) and 30-month (47%, n = 17) survival rates in historical control subjects.

Conclusions. Patients receiving continuous infusion of epo for treatment of PPH experience a decrease in pulmonary artery pressure. Long-term follow-up of this single-center patient group demonstrated improved long-term survival during epo therapy compared with that in historical control subjects and confirms predicted improved outcomes based on shorter follow-up periods.

(J Am Coll Cardiol 1997;30:343-9)

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Patients with primary pulmonary hypertension (PPH) pose a difficult management problem. There are few effective therapies. The disease is progressive, with increasing pulmonary vascular resistance (PVR) and pressures, resulting in right heart failure, dyspnea and decreasing functional status. Untreated, the mortality rate is substantial, and life expectancy after the development of congestive heart failure (CHF) can be measured in months. In a group of 90 patients with PPH referred for heart-lung transplantation, the mean survival from diagnosis was 42.9 ± 42.6 months, with a symptom duration of 65.9 ± 47.4 months (1). In a national registry of 194 patients

from 32 centers with PPH, the median survival was 2.8 years (2). In patients with a cardiac index < 2 liters/min per m^2 , the median survival was 17 months, and if the right atrial pressure (RAP) was > 20 mm Hg, it was 1 month without therapy. Using this hemodynamic data (RAP, mean pulmonary artery pressure and cardiac index), equations were derived to predict mortality (2). Over the past 30 years, a variety of agents have been studied as potential therapies for PPH. Hydralazine, nitroprusside and diazoxide have all been ineffective because of their profound effects on systemic vascular resistance and blood pressure, limiting their use (3). Work by Rich and Brundage (4), using calcium channel blocking agents, demonstrated sustained beneficial effects, including a long-term reduction in PVR. However, only ~25% of patients given either diltiazem or nifedipine responded. These agents could not be safely used in patients who had already developed significant CHF.

Epoprostenol (epo), a prostacyclin analogue, has been studied as an agent to lower pulmonary artery pressures in patients with PPH. In an 8-week randomized study, Rubin et al. (5) demonstrated short-term benefits, resulting in a lowering of pulmonary resistance and an improvement in cardiac output (CO). A prospective, nonrandomized, long-term study

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Manuscript received October 10, 1996; revised manuscript received April 7, 1997, accepted April 24, 1997.

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Abbreviations and Acronyms

CHF	= congestive heart failure
CO	= cardiac output
epo	= epoprostenol
HUMC	= Harbor-UCLA Medical Center
NIH	= National Institutes of Health
PPH	= primary pulmonary hypertension
PVR	= pulmonary vascular resistance
RAP	= right atrial pressure
ΔP	= right ventricular pressure gradient (difference between right ventricular and right atrial pressures)

of patients who participated in the short-term randomized study demonstrated sustained benefit after 1 year (6). Improvement in hemodynamic variables, quality of life and survival at 12 weeks was confirmed by a larger prospective, multicenter randomized study (7) in 81 patients comparing epo with conventional therapy. Exercise tolerance improved and correlated with changes in pulmonary pressures (7). There was a highly significant improvement in survival, even over 12 weeks. Thus, epo appears to prolong life in patients with PPH and to improve their functional status. The drug is continuously administered by infusion pump through a permanent indwelling central venous catheter to patients on an outpatient basis. Little is known about the effect on pulmonary artery pressure and CO over time in patients treated with epo. Barst et al. (6) followed up 18 patients with repeat right heart catheterization at 1 year. However, repeated invasive testing with right heart catheterization is expensive, uncomfortable and potentially risky because of the high pulmonary pressures.

Doppler-echocardiography has been used by investigators to estimate right heart pressures using the modified Bernoulli equation (8,9). Hatley and Angelsen (10) used the continuity equation to measure CO in a variety of clinical settings. We therefore sought to determine whether noninvasive studies using Doppler-echocardiography could provide adequate hemodynamic measurements in patients with PPH and then to evaluate changes in pulmonary artery pressures and cardiac function over time in patients treated with continuous infusion of epo. We first compared our noninvasive methods of estimating right-sided pressures with catheterization data and then followed up patients noninvasively with repeated measures of right-sided pressures and CO.

Methods

Patients. Patients with New York Heart Association functional class III or IV symptoms of CHF were referred because of a probable diagnosis of PPH. Before referral, patients underwent screening by their referring physicians to exclude other potential causes of pulmonary hypertension. These screening studies included chest radiograph, pulmonary func-

tion tests, ventilation perfusion scans and echocardiograms. Exclusion criteria included evidence of emboli on ventilation perfusion scans, airway disease on pulmonary function tests, although mild reduction of the pulmonary diffusion capacity or gas transfer factor for carbon monoxide and lung volumes were permitted; valvular heart disease (mitral); congenital heart disease; or left ventricular dysfunction on Doppler-echocardiography. Although the presence of mildly elevated antinuclear antibodies was permitted, patients with specific autoimmune diseases were excluded. Right heart catheterization was performed to measure pulmonary artery pressure, PVR and CO and to confirm the diagnosis. A mean pulmonary artery pressure >25 mm Hg was required at catheterization. Patients with other known causes of secondary pulmonary hypertension were excluded. Patients who were of child-bearing potential who were using an acceptable form of contraception were included in the study. Enrollment criteria and dosage adjustment protocol remained unchanged throughout the study.

Patients who were subsequently enrolled in the infusion protocol and were followed up locally at Harbor-UCLA Medical Center (HUMC) underwent repeat echocardiography on an outpatient basis at clinical follow-up. Patients who were followed up by their referring source had repeat studies performed when they returned to HUMC for follow-up. Their initial hemodynamic and echocardiographic data were used for baseline comparisons. Follow-up noninvasive measurements made at HUMC were used for long-term comparisons. The initiation of routine Doppler-echocardiographic measurements at the start of therapy began in 1993 after the enrollment of 13 patients who were only studied invasively at the time of enrollment. Patients enrolled before the use of Doppler-echocardiography as a routine part of the protocol underwent outpatient noninvasive studies after they were added to the protocol and are therefore included in the long-term follow-up data but not in comparisons of short-term or baseline data.

Right heart catheterization. Right heart catheterization was performed using a balloon flow-directed catheter placed in the pulmonary artery under fluoroscopy. Hemodynamic measurements of right atrial, right ventricular and pulmonary artery pressures were performed and recorded using a physiologic recorder. Thermodilution CO was measured in triplicate and averaged.

Total PVR. Total PVR was estimated using the following formula: Total PVR = (Mean pulmonary artery pressure)/CO. In many of the patients, pulmonary capillary wedge pressures could not be adequately obtained, and total PVR was therefore used.

Transthoracic echocardiograms (Doppler-echocardiography). Transthoracic echocardiograms were obtained within 15 min of invasive measurements to measure tricuspid regurgitant velocities using continuous wave Doppler. Color flow Doppler imaging was used to guide alignment of the continuous wave Doppler cursor with the regurgitant jet. The technician manipulated the probe to maximize the velocity obtained by finding the largest jet and visually aligning the continuous wave with

the color flow signal. No angle correction was used. The Doppler measurements were made from the right ventricular inflow, parasternal short-axis and apical four-chamber views. The highest velocity was reported. The right ventricular pressure gradient was calculated using the modified Bernoulli equation (9,10): $\Delta P = 4V^2$, where V = tricuspid regurgitant velocity; and ΔP = pressure gradient between the right ventricle and right atrium.

CO. CO was obtained by measuring flow across the left ventricular outflow tract during systole. Flow was measured at the level of the aortic valve from the apical five-chamber view. The velocity time integral (VTI), the summation of flow during the time period, was obtained by integrating the pulsed wave systolic flow signal over the duration of systolic flow: $A = \pi(D/2)^2$ where A = aortic outflow tract area; D = diameter of left ventricular outflow tract, and $VTI \times A \times \text{Heart rate} = \text{CO}$ (8). Measurements were performed in triplicate and averaged.

Noninvasive follow-up. Patients underwent Doppler-echocardiography with color flow and continuous wave Doppler at follow-up clinic visits according to the frequency of clinic follow-up. They generally averaged three Doppler-echocardiography evaluations/year. CO, ΔP and RAP were measured in supine subjects at rest by the same methods as those used after catheterization.

Drug administration and titration. The patients received epo as a continuous intravenous infusion. The initial maximal dose was determined by titrating to symptoms over 24 to 48 h: nausea, headache and jaw pain or to a drop in systemic blood pressure >10 mm Hg. Pulmonary artery pressures obtained by cardiac catheterization or estimated by Doppler-echocardiography were not used for dosing. After the initial infusion, a Hickman or Broviac catheter was placed in a central vein, and the patient and family were trained in the use of a portable battery-operated infusion pump for outpatient continuous infusion of the drug. During long-term follow-up, the dose of epo was adjusted according to symptoms (dyspnea, declining exercise tolerance and or side effects) after consultation with the center nurse and physician. Side effects included lower extremity nonpruritic rashes, jaw pain, headache, diarrhea, foot pain and lower extremity pain, which were not indications for drug termination. Worsening exercise tolerance and subjective shortness of breath were also used to increase the dosage in patients who were without side effects. In general, the dosage was increased to 1 to 2 ng/kg body weight per min every 2 months in most patients. The same method for dosage adjustment was used throughout the study. The dosage changes (long term) were not based on the results of the noninvasive Doppler-echocardiographic measurements of ΔP or CO. Dosages at follow-up ranged from 2 to 62 ng/kg per min.

The study protocol was approved by the institutional review board of HUMC, and all patients provided written informed consent.

Statistical methods. Data were stored in a PC-based data spreadsheet. Analysis was performed using Sigma Stat (Jandel Corp.), a PC-based statistical package. Paired Student *t* tests

and signed rank tests were performed. Results are presented as mean value \pm SD; $p \leq 0.05$ was considered statistically significant.

A Kaplan-Meier observed survival probability curve for the study patients was constructed for comparison with survival data from historical control subjects from the National Institutes of Health (NIH) registry (2) ($n = 31$) and with data from Barst et al. (6). (Note that the data of Barst et al. were generated using a proportional hazards regression model based on hemodynamic variables and an equation developed from the NIH registry.)

Results

Demographics and baseline hemodynamic variables.

Seventy-three patients were initially evaluated (11 to 65 years old; 54 women). Four patients who underwent initial right heart catheterization did not go on to receive continuous outpatient infusion. One was excluded because of refusal to undergo long-term medical therapy and one because his pulmonary arterial pressure at catheterization was near normal. Of the remaining patients, a total of 69 went on to receive epo infusions and formed our outpatient study cohort. Forty-nine patients underwent right heart catheterization, with concomitant Doppler-echocardiographic studies at the initiation of therapy. Eighteen patients were followed up >330 days during epo infusion (range 330 to 480). There were no significant differences in baseline clinical variables (age, gender, functional class, catheterization data) between the returning patients followed up with repeat Doppler-echocardiographic evaluations and those followed up locally by their referring physicians and only returned annually for follow-up.

At the time of initial evaluation, all patients were in functional class III or IV. The average RAP was 14 mm Hg, with an average CO of 3.6 liters/min. Mean pulmonary artery systolic pressure was 99.8 ± 25.6 mm Hg. Thirty-seven patients had right heart failure with an RAP >10 mm Hg. At the time of evaluation, mean RAP for these patients was 17.4 ± 3.9 mm Hg, and mean CO was 3.3 ± 1 liters/min. For the 21 patients without right heart failure, mean RAP was 7.1 ± 2.4 mm Hg, with a mean CO of 4.1 ± 1.3 .

We compared baseline data for patients who died ($n = 14$) or who underwent transplantation ($n = 10$) with that for the total cohort. On average, patients who underwent transplantation had slightly higher pulmonary artery systolic pressures (107.3 ± 18 vs. 99.8 mm Hg). The mean systolic blood pressure of 113.6 ± 12 and CO (determined by thermodilution) of 3.5 were slightly lower than the values obtained for the total cohort and the subgroup who died, but these differences were not statistically significant.

Comparison between right heart catheterization and Doppler-echocardiographic measurements. Pressure gradients (ΔP) and COs correlated well with Swan-Ganz catheter data in patients who were studied both invasively and noninvasively at the initiation of therapy. Figure 1 (left) demon-

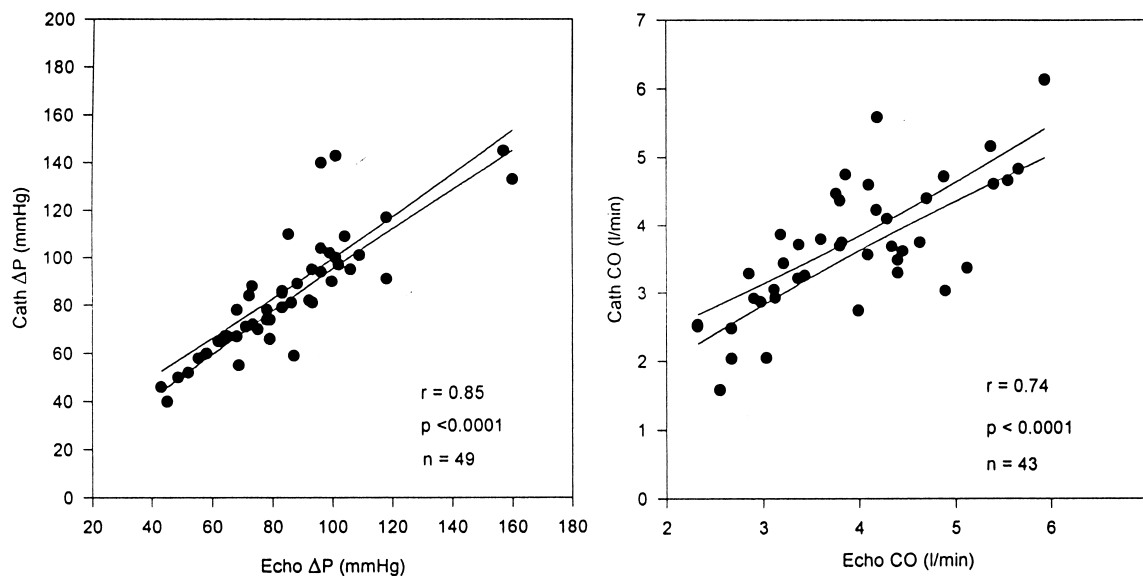


Figure 1. Left, Display of correlation between ΔP obtained echocardiographically (Echo ΔP) and ΔP obtained by measuring the right atrial and right ventricular pressures at catheterization (Cath ΔP) and computing the difference. Right, Correlation of CO measured using thermodilution at catheterization (Cath CO) and calculated CO (Echo CO) generated using the aortic outflow diameter and aortic flow. Circles = individual patients; Solid lines = 95% confidence intervals.

strates the correlation between measurements of ΔP measured by right heart catheterization and Doppler-echocardiography using the tricuspid regurgitant velocity and the Bernoulli equation in 49 patients ($r = 0.85$, $p < 0.0001$). Figure 1 (right) demonstrates the correlation between Doppler-echocardiography and right heart catheterization CO measurements in 43 patients ($r = 0.74$, $p < 0.0001$).

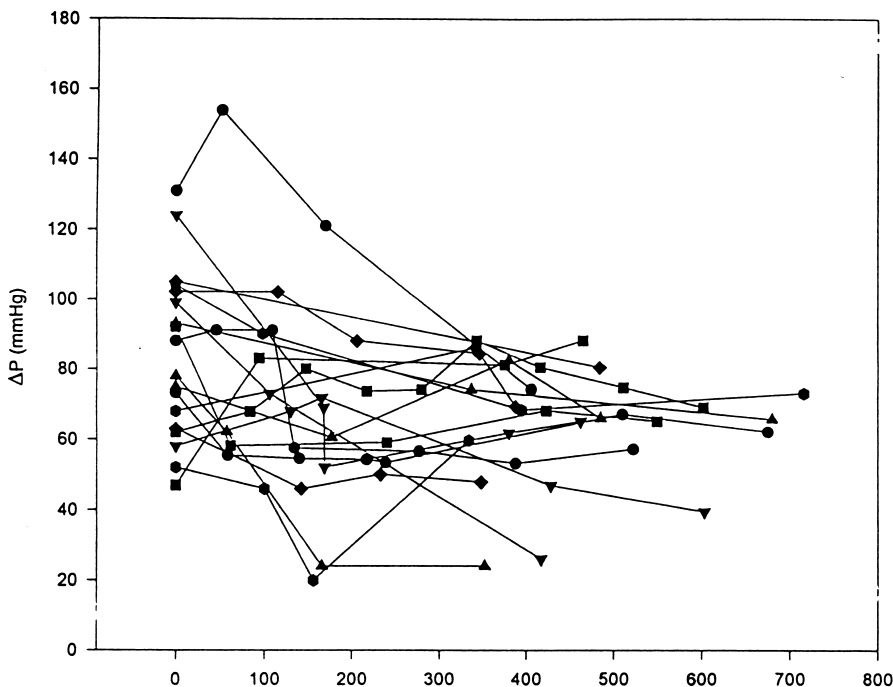
Short-term changes in hemodynamic variables resulting from epo infusion. The effects of epo on hemodynamic variables could be discerned within the first 24 to 48 h after stabilization with an acceptable dose. Systemic blood pressure dropped from a mean of 122 ± 18 to 117 ± 16 mm Hg ($p < 0.006$, $n = 49$). There was a similar but small drop in diastolic blood pressure from 76 ± 12 to 72 ± 11 mm Hg ($p = 0.006$). Mean heart rate increased from 85 ± 11 to 90 ± 13 beats/min ($p < 0.005$). The thermodilution CO increased from 3.6 ± 1.2 to 4.4 ± 1.4 liters/min ($p < 0.0001$). This change in CO could not be explained by the increase in heart rate only but reflected an increase in stroke volume, which increased from 41.5 to 47.1 ml in 43 of 49 patients ($p < 0.001$). CO data were not available in 6 of the 49 patients with short-term study data. In contrast, the changes in pulmonary artery systolic and diastolic pressures were not statistically significant (systolic: 102 ± 23 to 99 ± 23 mm Hg; diastolic: 44 ± 18 to 43 ± 16 mm Hg). There was a significant decrease in RAP measured by catheterization, from 14 ± 6 mm Hg before to 12 ± 6 mm Hg after epo ($p = 0.0063$). Total PVR before epo was 31.8 ± 12.5 and decreased significantly to 25.1 ± 9.0 after epo ($p < 0.001$, signed rank

test). The initial responses to epo were similar in the transplant recipients, the patients who died and the total group that received epo.

Thirteen of 18 patients with long-term follow-up (>270 days) also had Doppler-echocardiography performed at the initiation of therapy. A short-term decrease in $\Delta P \geq 10\%$ was seen in 6 of 13 patients, 5 of whom demonstrated a persistent long-term reduction in ΔP , and all 6 had a persistent decrease in the $\Delta P/CO$ ratio. However, five of seven patients without a short-term decrease in ΔP also demonstrated a persistent decline in ΔP , and six of seven had a reduction in the $\Delta P/CO$ ratio. Therefore, the absence of a short-term change in ΔP did not predict the long-term effects of epo in this group of patients. A short-term drop in the $\Delta P/CO$ ratio of 15% was also not predictive of a long-term response.

Long-term follow-up of patients. Of a total of 69 patients who went on to receive epo, 13 have died. One patient died during the initial 24-h infusion, and one discontinued therapy after several months because of depression. This patient subsequently died 4 months after stopping the infusion. Of nine patients who underwent single-lung transplantation, three died. Of the remaining patients taking epo, eight died of progressive right heart or renal failure. A total of 56 patients remain alive, many of whom are being followed up at our facility with repeated noninvasive evaluations of cardiac function and pulmonary pressure gradients. Of this group, 18 patients have undergone follow-up with Doppler-echocardiography during long-term epo infusion >330 days. We used ΔP for the follow-up echocardiographic hemodynamic measurements. Echocardiographically derived hemodynamic measurements made in patients between 330 and 480 days during therapy were compared with baseline measurements. There was a significant reduction in ΔP , which dropped from 84.1 ± 24.1 to 62.7 ± 18.2 mm Hg ($p < 0.01$). Figure 2 graphically displays the long-term changes in ΔP over several time points for all the patients with long-term follow-up >330

Figure 2. Change in ΔP measured echocardiographically over time (days) for the 18 patients for whom long-term data >330 days are available. Each point represents the measurement for an individual patient; solid lines connect measurements made in the same patient. Because of patient schedules, the measurements were not made at the same time interval or frequency in all patients. The trend is toward a gradual and sustained reduction in ΔP and therefore in pulmonary artery pressure.



days. The overall trend was a continued reduction in ΔP over time. Figure 3 demonstrates the changes in the ratio of ΔP to CO for 17 patients in whom CO could be adequately measured noninvasively. The ratio of ΔP to CO decreased significantly from 22.8 ± 9.4 to 14.9 ± 6.5 ($p < 0.01$), suggesting a reduction in PVR. These results suggest that over time, the initial improvements in hemodynamic variables are maintained or enhanced.

A larger group of patients ($n = 25$) have been followed up for 90 to 190 days (mean 141 ± 26). A comparison of their baseline ΔP to ΔP measured between 90 and 190 days demonstrated a drop in ΔP from 86.4 ± 25.7 to 68.6 ± 24 mm Hg ($p < 0.001$). Similarly, CO increased from 4.0 ± 1.22 to 4.7 ± 1.27 liters/min ($p < 0.02$).

Survival. A Kaplan-Meier plot of survival is shown in Figure 4. Patients who underwent transplantation were censored at the time of transplantation. This graph demonstrates the improved survival in this severely compromised patient group. The 1-, 2- and 3-year survival rates for our patients were 80% ($n = 36$), 76% ($n = 22$) and 49% ($n = 6$) compared with 10- (88%, $n = 31$), 20- (56%, $n = 27$) and 30-month (47%, $n = 17$) survival rates in historical control subjects (6), which confirms the predicted survival proposed by Barst et al. (6), also shown.

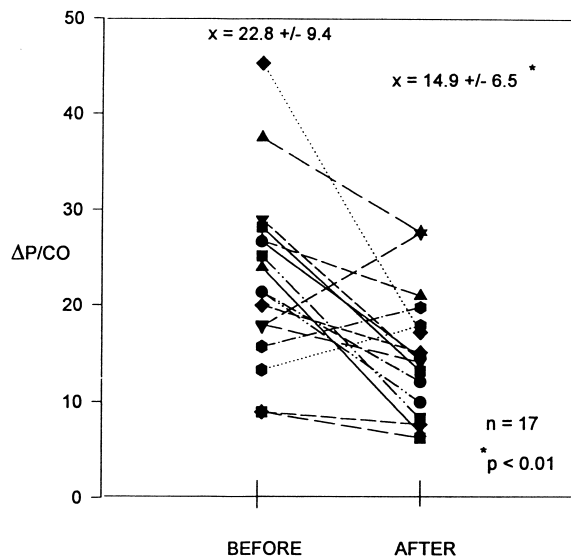
Relation between clinical features and response to epo. Pulmonary hypertension is a pleomorphic disease whose true etiology is unclear. Although the patients were all considered to have PPH as the etiology of their elevated pulmonary artery pressures and symptom complexes, they could be classified into several broad groups: antinuclear antibody positive ($n = 5$), mild underlying lung disease ($n = 1$), hepatic disease ($n = 7$), previous drug abuse ($n = 10$) and no associations ($n = 46$).

There was no difference among the groups in their response to epo, although the numbers are small.

Discussion

Survival. This study provides information on the long-term follow-up of patients who have been treated with one of the few effective agents for stabilizing PPH. The patients in our

Figure 3. Ratio of ΔP to CO (obtained echocardiographically) before initiation of epo infusion and after a time period of between 330 and 480 days, displayed for each individual patient ($n = 17$). Lines connect the preinfusion value with the value obtained between 330 and 480 days. Data shown are mean value ($x \pm SD$).



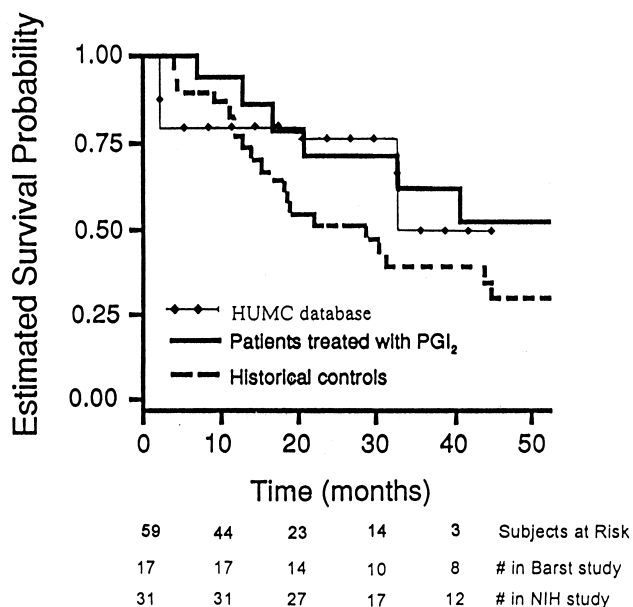


Figure 4. Kaplan-Meier survival plot for study patients (HUMC) displayed with the estimated survival probabilities from the NIH registry and from Barst et al. (6). **Numbers** below the graph are subjects at risk for each cohort. Patients who underwent transplantation were censored at the time of transplantation. PGI₂ = prostacyclin. Modified, with permission, from Barst et al. (6).

study lived longer and improved clinically, long enough for some to ask to be removed from the transplant list. Although this was not a blinded study, nor was there a control group (i.e., patients with PPH referred to us and followed up without prostacyclin therapy), there are historical data from the NIH registry and groups of patients treated with other agents (calcium channel blockers). Compared with historical control subjects, patients treated with prostacyclin appear to have a markedly improved outcome. Our data on long-term follow-up also support and match the model of survival proposed by Barst et al. (6), predicting improved long-term outcome in patients treated with continuous intravenous prostacyclin. The NIH data demonstrated a clear relation between hemodynamic variables and survival. Using the relation between hemodynamic variables and survival, Barst et al. (6) demonstrated short-term improvement in hemodynamic variables and survival and predicted longer term survival benefits. We saw a similar relation between hemodynamic variables and outcome.

Although improvement in survival has been demonstrated in patients responding to calcium channel blockers, the percent of adult responders is small. Many of the patients in the present study could not be treated with calcium channel blockers because of the inability to tolerate or respond hemodynamically to calcium channel blockers or because of the danger of using them in the setting of severe right heart failure.

Doppler-echocardiography. We described a method for noninvasive long-term follow-up of patients with PPH and demonstrated the relation between invasive and noninvasive measures as well the results of the long-term treatment. Most

of the published studies in patients with PPH have depended on invasive measurements to determine the response to therapy. This difficulty in monitoring precludes frequent hemodynamic assessment and therefore the use of hemodynamic measurements to direct further adjustments in the rate of infusion. In the present study, there was no perspective titration of dose to meet hemodynamic end points. We were able to show good correlation between invasive and noninvasive measurements of right-sided pressure gradients and CO. Thus, Doppler-echocardiography may enable the use of hemodynamic measures to adjust dosage more effectively, with firmer end points, although this will need to be tested prospectively.

Although right ventricular pressure can be determined using the Bernoulli equation, assuming an RAP of 10 mm Hg, this assumption was not valid for our patients. The wide range of RAP (3 to 29 mm Hg) at the time of catheterization, including a markedly elevated RAP in many patients, invalidates the use of an average or presumed RAP. Repeat measurement of jugular venous pressure would require physician intervention at the time of echocardiography. Although such intervention may be feasible in the clinical setting, it would have biased our Doppler-echocardiographic data. Estimation of RAP using caval size and response to respiration was not feasible in some patients. We therefore chose to compare ΔP determined echocardiographically and by catheterization and were able to demonstrate a decline in ΔP and an increase in CO with therapy. Our patients almost uniformly demonstrated a reduction in RAP as the pulmonary artery pressure declined over time. Thus, the drop in pulmonary artery pressure was probably greater than that indicated by the reduction in ΔP .

The determination of ΔP required meticulous echocardiographic and Doppler imaging. Alignment of the tricuspid regurgitant jet with the Doppler beam was critical to avoid underestimation of the gradient, creating a false impression that the patients were responding to therapy. Many of the patients had an enlarged right atrium and eccentric jets, which necessitated off-angle views and careful tracking of the color flow Doppler jet to align the continuous wave beam.

Dosage adjustment. We showed that the use of epo resulted in beneficial hemodynamic results over time that were achieved by almost monthly titration of the dosages. The adjustments in dosage were made in conjunction with a nurse according to protocol-defined symptoms. Patients appeared to develop a "tolerance" to the drug, with a decrease in side effects and an increase in symptoms of pulmonary hypertension (i.e., shortness of breath and reduction in exercise tolerance). This drug tolerance may explain the increases in ΔP seen in some patients. Because echocardiographic measures were not used to adjust the dosage of epo we do not know whether we could have reversed the pressure increase by adjusting the dose upward. We also do not know whether the increasing pulmonary artery pressures were due to drug tolerance or to progression of the disease.

Patients who tolerated the initial infusion received long-term therapy regardless of the initial hemodynamic response,

in contrast to studies that have limited drug therapy to responders (11,12). Our data on a subset of patients who were evaluated noninvasively at the initiation of therapy and then followed up with Doppler-echocardiography fail to demonstrate a relation between initial hemodynamic response and long-term reduction in ΔP . In fact, almost all the patients ultimately responded with a reduction in right-sided pressures. In the study by Raffy et al. (11), response to epo was used to predict response to calcium channel blockers. Because our patients were too sick to receive a trial of these agents, we are unable to confirm the predictive value of an initial epo infusion for a response to calcium channel blockers.

Other limitations. PPH is a rare disease. Patients who were very ill (functional class III or IV) came from great distances to start epo therapy and received their day to day care locally. Thus, hemodynamic follow-up was variable and for some patients, very limited. Although by phone and clinical follow-up, patients appeared to do better, formal exercise testing and quantitative quality of life measurements were not performed. The patients were clinically assessed, but the study was not designed to measure changes in functional class or clinical symptoms as end points; these end points will be explored in other studies. Despite these limitations, we believe that our data support the premise that epo improves quality of life in patients with PPH and reduces pulmonary artery pressures.

Future goals. Our study provides the basis for additional approaches to current management strategies for patients receiving epo. We plan to incorporate Doppler-echocardiographic criteria in the clinical algorithm that we use to adjust the dose of epo to maximize the improvement in CO and reduction in pulmonary artery pressures. This approach might allow more aggressive reduction in pulmonary pressures. The development of a strategy that uses hemodynamic measurements is particularly important because although we demonstrated reduction in ΔP over time, not all patients responded equally. It is unclear whether the patients without a reduction in ΔP might have benefited clinically if the doses were adjusted to achieve an adequate reduction or whether there are beneficial effects of epo beyond those measured by changes in pressure.

It could be argued that measuring pulmonary resistance would be better than ΔP to assess the drug effect; however, even with right heart catheterization, measurement of wedge pressure is often unreliable. Thus, the use of ΔP remains a measure of pulmonary pressure and, indirectly, resistance.

Conclusions. Transthoracic echocardiography using Doppler can be used to follow up patients undergoing treatment for PPH. The estimates of right ventricular pressure gradients

correlate well with invasive measurements. Therapy with epo appears to cause a gradual reduction in right ventricular pressures and an increase in CO over time. These changes are accompanied by a reduction in clinical symptoms of right heart failure. Treatment with epo prolongs life in patients with PPH and can be safely used in patients with right heart failure who cannot tolerate calcium channel blockers or in whom calcium channel blocker therapy has failed. Longer follow-up of patients receiving epo will be needed to determine whether hemodynamic benefits persist and whether these changes are associated with maintenance of clinical improvement. Finally, we propose that studies be designed to use Doppler-echocardiography as a tool not just to monitor pulmonary pressures in patients with PPH, but to adjust the dosage of prostacyclin toward a desired hemodynamic effect.

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