Vasodilator Therapy for Primary Pulmonary Hypertension in Children

Robyn J. Barst, MD; Greg Maislin, MS, MA; Alfred P. Fishman, MD

Background—This report presents 13 years of experience with vasodilator therapy for primary pulmonary hypertension (PPH) in children. Two eras were involved: between 1982 and 1987, oral calcium channel blockers were the only agents available for long-term therapy; after 1987, prostacyclin (PGI_2) has been available for long-term intravenous use.

Methods and Results—Seventy-four children underwent short-term vasodilator testing with intravenous PGI_2. Those who manifested pulmonary vasodilation ("acute responders") were treated with oral calcium channel blockers. Until 1987, "acute nonresponders" were treated in the same way as long as they had no serious side effects. When PGI_2 became available for long-term administration, all nonresponders, as well as those who failed to improve clinically and hemodynamically on calcium channel blockers, were treated with long-term PGI_2. In the 31 responders, calcium channel blockers improved survival compared with the 43 nonresponders ($P=0.0002$). Survival was also better in 24 PGI_2-treated nonresponders compared with 22 nonresponders for whom PGI_2 was unavailable ($P=0.0005$) as well as in all children who failed conventional therapy (n=31; $P=0.002$).

Conclusions—Long-term vasodilator therapy improves survival in children with PPH. In acute responders, oral calcium channel blockers generally suffice. In both nonresponders to short-term testing and responders who fail to improve on calcium channel blockers, continuous intravenous infusion of PGI_2 improves survival. **(*Circulation*. 1999;99:1197-1208.)**

Key Words: hypertension, pulmonary ■ prostacyclin ■ epoprostenol ■ calcium channels

During the past 15 years, pulmonary vasodilator therapy has greatly improved the prognosis for adults with primary pulmonary hypertension (PPH).[1–4] However, extrapolations from adults to children is not straightforward, for 3 reasons: (1) the anticipated life span of children is longer; (2) children may have a more reactive pulmonary circulation, raising the prospect of greater vasodilator responsiveness and better therapeutic outcomes[5]; and (3) despite clinical and pathological studies suggesting increased vasoreactivity in children, before the advent of long-term vasodilator therapy, the mean survival time was ≤1 year in children, whereas it averaged 2 to 3 years in adults.[6,7]

This report reviews our 13-year experience with vasodilator therapy in children with PPH in whom the diagnosis was made between 1982 and 1995. The experience falls into 2 time periods: (1) in 1982, oral calcium channel blockers were the only agents available for long-term therapy; and (2) in 1987, when prostacyclin (PGI_2) became available for long-term administration, therapy was directed in accord with the results of short-term PGI_2 testing for responsiveness: those who manifested short-term pulmonary vasodilation ("acute responders") were managed as long as possible on calcium channel blockers taken orally; those who did not ("acute nonresponders") were treated with long-term PGI_2 administered intravenously. Two aspects of this experimental design warrant special mention: (1) once calcium channel blockers were started, they were continued, even after PGI_2 was begun, unless side effects precluded their use; and (2) in some children who were originally responders but subsequently deteriorated clinically and hemodynamically on long-term calcium channel blockers, long-term PGI_2 was added.

Methods

Subjects

Between 1982 and 1995, PPH was diagnosed in 77 children <16 years old at Columbia-Presbyterian Medical Center according to the criteria of the PPH NIH Registry.[8] Baseline characteristics are shown in Table 1. Patients ranged in age from 7 months to 13 years (7±4 years). Nine children were <1 year old at the time of diagnosis. Children with congenital heart disease other than a patent foramen ovale were excluded. Twelve children were reported previously: 6 in

Received July 13, 1998; revision received November 3, 1998; accepted November 23, 1998.

From the Department of Pediatrics, Columbia University, College of Physicians and Surgeons, New York, NY (R.J.B.), and the Department of Medicine, University of Pennsylvania, Philadelphia (G.M., A.P.F.).

Presented at the 68th Scientific Sessions of the American Heart Association, Anaheim, Calif, November 13, 1995, and published in abstract form (*Circulation*. 1995;92[suppl I]:I-126).

Reprint requests to Dr Robyn J. Barst, Division of Pediatric Cardiology, Department of Pediatrics, BH 262 N, Columbia University College of Physicians and Surgeons, 3959 Broadway, New York, NY 10032.

***Circulation* is available at http://www.circulationaha.org**

TABLE 1. Baseline Demographic and Hemodynamic Variables

No. of patients	77
Age, y	7±4
Sex, n (%)	
Male	27 (35)
Female	50 (65)
PAPm, mm Hg	65±22
RAPm, mm Hg	5±3
CI, L · min^{-1} · m^{-2}	3.1±1.1
PVR, U · m^2	22±13
M · Vo_2 Sat, %	64±10
Race, n (%)	
White	62 (81)
Black	5 (6)
Other	10 (13)
Short-term vasodilator testing, n (%)*	
Acute responder	31 (42)
Male	7 (27)
Female	24 (50)
Nonresponder	43 (58)
Male	19 (73)
Female	24 (50)
Warfarin, n (%)	
Yes	58 (75)
No	19 (25)

PAPm indicates mean pulmonary artery pressure; RAPm, mean right atrial pressure; CI, cardiac index; PVR, pulmonary vascular resistance index; and M · Vo_2 Sat, mixed venous oxygen saturation. Values are mean±SD.

*Three children (1 boy and 2 girls) did not undergo acute testing.

reports of clinical trials evaluating long-term PGI_2[3,4] and 6 in a report to assess the value of short-term vasodilator testing.[9] Informed consent was obtained for each child. Both studies, ie, short-term PGI2 testing and long-term PGI_2 therapy, were approved by the Institutional Review Board.

Short-Term Vasodilator Testing

After premedication with meperidine HCl (Demerol), promethazine HCl (Phenergan), and chlorpromazine HCl (Thorazine), right-heart catheterization was performed on room air under local anesthesia in all patients by standard techniques. PGI_2 was used for short-term testing in 74 patients; 3 children were too sick to be tested. On the basis of the response to short-term testing, responders and nonresponders were identified. Responders to short-term testing satisfied all 3 of the following criteria: (1) ≥20% decrease in mean pulmonary artery pressure, (2) no change or an increase in cardiac index, and (3) no change or a decrease in the ratio of pulmonary vascular resistance to systemic vascular resistance.[9] Arterial blood gas parameters were measured at baseline and during short-term testing. The arterial pH and $Paco_2$ were within normal range (7.41±0.5; range, 7.32 to 7.48; and 34±6 mm Hg; range, 23 to 48 mm Hg) throughout the studies.

Long-Term Vasodilator Therapy

Conventional Therapy

Conventional therapy included digitalis, diuretics, and supplemental oxygen as needed. In 1990, warfarin was added in all patients after studies in adults showed improved survival.[1,10] Before PGI_2 became available for long-term use, all patients, ie, acute responders and nonresponders, received conventional therapy, including calcium channel blockers unless adverse effects precluded their use. The daily maintenance dose was based on the hemodynamic response to sublingual nifedipine testing after PGI_2 testing.[9] Untoward effects that precluded the use of calcium channel blockers included right heart failure during short-term testing or intolerable symptoms, such as nausea, vomiting, dizziness, or headaches, during long-term administration.

TABLE 2. Baseline Demographic and Hemodynamic Variables Comparing Acute Responders With Nonresponders

	Acute Responders (n=31)		Nonresponders (n=43)	
	Baseline	Acute PGI_2 Response	Baseline	Acute PGI_2 Response
Age, y*	5±4	...	8±4	...
PAPm, mm Hg*§	57±22	38±17†	72±20	73±20
RAPm, mm Hg	4±3	3±3	5±4	5±4
CI, L · min^{-1} · m^{-2}¶	3.4±1.4	4.6±1.5†	3.0±1.0	3.8±1.8‡
PVR, U · m^2*¶	17±11	8±6†	26±14	22±15‡
M · Vo_2 Sat, %¶	63±10	73±7†	65±10	70±9‡

Abbreviations as in Table 1.

*$P<0.005$ baseline hemodynamics: acute responders vs nonresponders.

†$P<0.0001$ vs baseline.

‡$P<0.0005$ vs baseline.

§$P<0.0001$ vs baseline (changes between acute responders and nonresponders during short-term PGI_2 testing).

¶$P<0.08$ vs baseline (changes between acute responders and nonresponders during short-term PGI_2 testing; ie, changes not as pronounced with nonresponders as with responders).

Long-Term PGI_2 Plus Conventional Therapy

PGI_2 was administered intravenously in children who failed to improve clinically and hemodynamically on conventional therapy. Calcium channel blockers were included as long as there were no adverse effects. For the infusion of PGI_2, a catheter was introduced into a jugular or subclavian vein as described previously[3,4]; PGI_2 was delivered continuously via a portable pump. The initial dose ranged from 2 to 10 ng · kg^{-1} · min^{-1} (4±2 ng · kg^{-1} · min^{-1}) and was increased to maintain an optimal therapeutic dose: at 1 year, the dose averaged 78±38 ng · kg^{-1} · min^{-1} (n=28); at 2 years, 116±48 ng · kg^{-1} · min^{-1} (n=17); and at 3 years, 122±36 ng · kg^{-1} · min^{-1} (n=8).

Cardiac catheterizations were performed yearly, and more frequently if the clinical state deteriorated. PGI_2 infusion was continued until either transplantation or death.

Patient Groups

In Table 2, the 77 children are categorized into acute responders and nonresponders. In Table 3, the 77 children are divided into 3 groups according to therapeutic interventions and physician recommendations.

Group 1: Long-Term PGI_2 Plus Conventional Therapy After Failure of Conventional Therapy

Thirty-one children were started on long-term PGI_2 after failing to manifest clinical and hemodynamic improvement on conventional therapy. In addition to lack of hemodynamic improvement on conventional therapy, hemodynamic deterioration occurred, ie, from diagnosis and start of conventional therapy to starting PGI_2: mean pulmonary artery pressure increased (69±24 to 76±24 mm Hg; n=31; $P<0.02$) and pulmonary vascular resistance increased (22±13 to 27±14 U · m^2; n=31; $P<0.002$). Twenty-four were acute nonresponders, 6 were acute responders who remained in NYHA functional class III/IV despite conventional therapy (including calcium channel blockers), and 1 who was in NYHA functional class IV was started on long-term PGI_2 without short-term testing because she was too sick for testing.

Calcium channel blockers were not used consistently. The indications and contraindications for long-term calcium channel blockers

TABLE 3. Demographic and Hemodynamic Variables at Baseline According to Treatment Group (N=77)

	Group 1 (n=31) PGI_2 Plus CT After Failure on CT	Group 2 (n=28) PGI_2 Indicated but Not Received: CT	Group 3 (n=18) PGI_2 Not Indicated: CT
Age, y*	8±4	8±5	4±4
Sex, n (%)			
Male	9 (29)	13 (46)	5 (28)
Female	22 (71)	15 (54)	13 (72)
PAPm, mm Hg†	74±24	69±18	53±19
RAPm, mm Hg‡	5±4	6±4	3±2
CI, $L \cdot min^{-1} \cdot m^{-2}$§	3.8±1.7	2.8±1.0	4.2±2.5
PVR, $U \cdot m^2$‖	23±14	26±15	13±6
MVO_2 Sat, %	65±8	62±11	64±7
Race, n (%)			
White	26 (83)	21 (75)	15 (83)
Black	2 (7)	2 (7)	1 (6)
Other	3 (10)	5 (18)	2 (11)
Short-term vasodilator testing, n (%)¶			
Responders	6 (20)	5 (19)	16 (89)
Nonresponders	24 (80)	22 (81)	2 (11)
Oral vasodilators, n (%)	10 (32)	8 (29)	18 (100)
Warfarin#	30 (97)	11 (39)	17 (94)

CT indicates conventional therapy. Other abbreviations as in Table 1.

Short-term vasodilator testing: For group 1, 6 acute responders failed to improve clinically and hemodynamically on CT including calcium channel blockers, and 1 patient was too sick to undergo short-term vasodilator testing at the start of long-term PGI_2 administration; for group 2, 1 child was started on calcium channel blockers before diagnostic catheterization and short-term testing; for group 3, although 2 children were nonresponders according to the criteria (see Methods and Reference 9), PAPm decreased 10% and 14%, respectively, in these 2 patients during short-term testing (with the other criteria fulfilled).

Oral vasodilators: For group 1, n (%) of patients on oral vasodilators, eg, calcium channel blockers, at the start of long-term PGI_2 administration; for groups 2 and 3, n (%) of patients who were treated with oral vasodilators, eg, calcium channel blockers, with initiation of CT after diagnosis.

Baseline parameters before start of long-term PGI_2 plus CT (group 1) or CT (groups 2 and 3).

*$P<0.002$ group 1 vs group 3; $P<0.002$ group 2 vs group 3.

†$P<0.001$ group 1 vs group 3; $P<0.01$ group 2 vs group 3.

‡$P<0.05$ group 1 vs group 3; $P<0.02$ group 2 vs group 3.

§$P<0.05$ group 1 vs group 2; $P<0.01$ group 2 vs group 3.

‖$P<0.02$ group 1 vs group 3; $P<0.001$ group 2 vs group 3.

¶$P<0.001$ group 1 vs group 3 and group 2 vs group 3.

#$P<0.001$ group 1 vs group 2 and group 2 vs group 3.

are described under Methods. Ten children continued on calcium channel blockers because the agent seemed to be well tolerated: 6 responders and 4 responders who had subsequently lost responsiveness to short-term PGI_2 testing; 2 of these 4 subsequently stopped calcium channel blockers because of side effects.

Group 2: Conventional Therapy (PGI_2 Indicated but Either Unavailable or Declined)

Twenty-eight patients who satisfied the criteria (as in group 1) for long-term PGI_2 were treated with conventional therapy alone for 1 of 2 reasons: (1) PGI_2 unavailable for long-term therapy (21 patients) and (2) parental refusal (7 patients). Twenty-two patients were acute nonresponders; 5 were responders who remained in NYHA functional class III/IV despite conventional therapy, including calcium channel blockers; and 1 who was empirically started on calcium channel blockers before short-term testing remained in NYHA III despite conventional therapy. Only 8 of the 28 children (group 2) could be treated with calcium channel blockers because of side effects in the others (as described under Methods): 5 were acute responders and 3 nonresponders. One nonresponder subsequently discontinued calcium channel blockade because of side effects.

Group 3: Conventional Therapy: PGI_2 Not Indicated

The remaining 18 children were treated with conventional therapy alone that included calcium channel blockers. Sixteen were acute responders and 2 were nonresponders. All improved clinically and hemodynamically, including the 2 nonresponders, thereby obviating the need for long-term PGI_2. Although the 2 nonresponders failed to satisfy the composite criteria for acute responsiveness, they did manifest decreases in mean pulmonary artery pressure of 10% and 14%, respectively, during short-term PGI_2 testing.[9]

Statistical Methods

Data are presented as mean±SD. The following comparisons were made: (1) survival of acute responders (n=31) versus nonresponders (n=43) on conventional therapy; (2) survival of all patients treated with long-term PGI_2 (group 1; Table 3; n=31) versus those treated with conventional therapy for whom PGI_2 was indicated but unavailable (group 2; Table 3; n=28); and (3) survival of only the nonresponders treated with PGI_2 (nonresponders, group 1; Table 3; n=24) versus the nonresponders treated with conventional therapy for whom PGI_2 was indicated but unavailable (nonresponders, group 2; Table 3; n=22). Kaplan-Meier curves, based on log-rank statistics, were used to compare

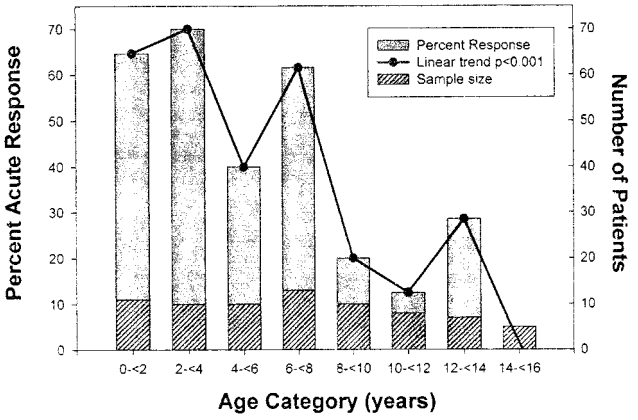

Figure 1. Response to short-term testing by age. The younger the child at the time of testing, the greater the likelihood of eliciting short-term pulmonary vasodilation ($P<0.005$).

survival patterns. Multivariable analyses used proportional hazards regression. In analysis of survival, 2 censoring events were used: (1) transplantation, ie, patients were included in survival data until the time of transplantation; thereafter, patients who received transplants were omitted from survival analyses as though they were lost to follow-up; and (2) the start of PGI_2 for patients treated with long-term PGI_2. Hemodynamic comparisons were based on ANOVA and *t* tests; a value of $P<0.05$ was considered statistically significant.

Results

Short-Term Vasodilator Testing

Among the baseline characteristics (Table 1), age, pulmonary artery pressure, and pulmonary vascular resistance were associated with an acute response. The younger the child at the time of testing, the greater the likelihood of an acute response (Figure 1); a linear trend was significant ($P<0.005$). Pulmonary artery pressure and pulmonary vascular resistance were also lower in the responders (Table 2; $P<0.005$), suggesting the possibility of a predictive model for acute responsiveness based on multiple logistic regression. When the variables were considered simultaneously and account was taken of the potential for nonlinear associations, the model was found to have significant predictive value (concordance index value of 0.885). The quadratic functions of age, pulmonary artery pressure, and right atrial pressure were the major predictors of acute vasoreactivity (Appendix 1).

Conventional Therapy Alone (No PGI_2)

All 31 acute responders improved clinically on calcium channel blockers. Sixteen continued to improve clinically during long-term follow-up on conventional therapy (15 to 144 months; 63±43 months; median, 47 months). Hemodynamic studies were repeated in 14 of these 16 responders (group 3, Table 3; Table 4). At the time of last follow-up catheterization (24 to 166 months after start of long-term calcium channel blockers; median, 47 months), mean pulmonary artery pressure had decreased 44% (52 to 31 mm Hg; $P<0.01$), and pulmonary vascular resistance had decreased 50% (13 to 6 U·m^2; $P<0.0001$; Table 4). Repeat short-term PGI_2 testing (while the patients continued on calcium channel blockers) demonstrated that all 14 remained acute responders during testing. Although the acute responsiveness suggested that long-term PGI_2 plus conventional therapy including calcium channel blockers might offer additional hemodynamic advantage to these children, risk-benefit considerations (including complications from the PGI_2 delivery system) prompted us to continue conventional therapy alone in acute responders who improved clinically to NYHA class I to II as well as improving hemodynamically.

Fifteen of the 31 acute responders deteriorated clinically and hemodynamically on calcium channel blockers after 2 to 126 months (47±44 months; median, 33 months). Ten were subsequently started on long-term PGI_2; the other 5 were not started on long-term PGI_2 either because PGI_2 was unavailable (3 patients) or because of parental refusal (2 children).

In contrast to the 31 responders, only 2 of the 43 nonresponders (Table 2) improved on conventional therapy including calcium channel blockers. Although these 2 children (in group 3, Table 3) had manifested modest responsiveness during short-term testing, both had failed to satisfy the full criteria.[9] Because of untoward effects during short-term testing, only 7 of the other nonresponders (groups 1 and 2, Table 3) were started on long-term calcium channel blockers, and 3 subsequently stopped the calcium channel blockers because of intolerable side effects.

On conventional therapy, survival was significantly better for acute responders than for nonresponders (Table 2; Figure 2; log-rank $P=0.0002$): the 1-, 3-, and 5-year survival rates for the 31 responders (all treated with calcium channel blockers) were 97%, 97%, and 97%, respectively, compared

TABLE 4. Hemodynamic Effects of Chronic Calcium Channel Blockers in Acute Responders*

Variable	At Start of Oral Vasodilator Therapy	Last Follow-Up Study	Mean Change (95% CI)†
PAPm, mm Hg	52±21	31±15	−21.6 (−35.6 to −7.5)‡
RAPm, mm Hg	4±2	3±3	−0.1 (−1.4 to 1.1)
CI, L·min^{-1}·m^{-2}	3.7±1.5	5.1±2.1	1.4 (0.5 to 2.3)‡
PVR, U·m^2	13±5	6±5	−7.3 (−10.2 to −4.6)‡
M·Vo_2 Sat, %	64±7	71±5	7.1 (1.9 to 12.3)§

Abbreviations as in Table 1.
*n=14 with follow-up study at median=47 mo (range, 24 to 166 mo).
†Mean change from baseline. A CI that does not contain zero indicates statistical significance.
‡Paired *t* test $P<0.005$.
§Paired *t* test $P=0.01$.

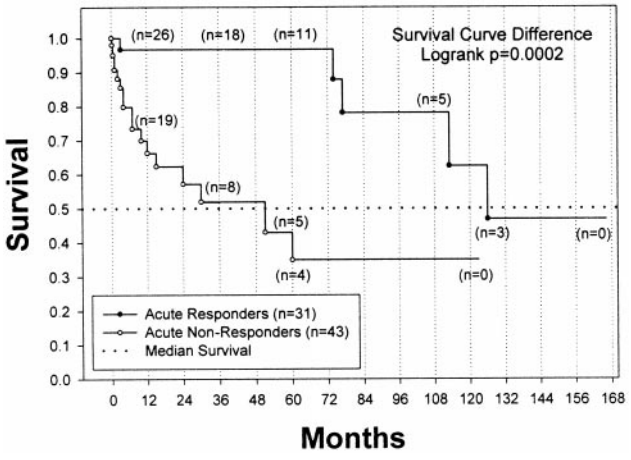

Figure 2. Kaplan-Meier survival curves comparing survival on conventional therapy in responders versus nonresponders: 1-, 3-, and 5-year survival probabilities for 31 responders were 97%, 97%, and 97%, respectively, compared with 66%, 52%, and 35%, respectively, for 43 nonresponders ($P=0.0002$).

with 66%, 52%, and 35%, respectively, for the 43 nonresponders (only 6 treated with calcium channel blockers).

Patients Treated With Long-Term PGI_2 Plus Conventional Therapy

All 31 children treated with long-term PGI_2 improved (group 1, Table 3). According to the NYHA functional criteria, functional capacity improved: 3.30±0.54 before PGI_2 to 1.96±0.71 at the time of last follow-up catheterization (3 to 46 months after PGI_2 was started; 21±11 months; n=27; $P<0.0001$). Twenty-seven of the 31 patients on long-term PGI_2 had ≥1 follow-up catheterization. Because of their considerable variability, the hemodynamic data obtained during the short-term and long-term administration of PGI_2 are shown for all patients in Appendix 2. As seen in Table 5, which summarizes these data, mean pulmonary artery pressure decreased 33% (76 to 51 mm Hg ($P<0.0001$), cardiac index increased 42% (3.1 to 4.4 L · min^{-1} · m^{-2}; $P<0.0001$), and pulmonary vascular resistance decreased 59% (27 to 11 U · m^2; $P<0.0001$). Table 5 also illustrates that lack of an acute response to PGI_2 did not preclude significant hemodynamic improvement on long-term PGI_2. This improvement of acute nonresponders on long-term PGI_2 contrasts with the failure of long-term calcium channel blockers to elicit hemodynamic improvement in acute nonresponders.[1] Moreover, calcium channel blockers in nonresponders can be hazardous or even fatal.

Twenty-four of the 31 children who were started on long-term PGI_2 continue to receive PGI_2 (follow-up, 10 to 56 months; 26±14 months). All 24 remain clinically improved: 22 underwent repeat catheterization, which demonstrated significant hemodynamic improvement in 21 and no change in 1 patient. The clinical and hemodynamic improvement in 11 of the 14 who had been listed for transplantation resulted in their being taken off the transplant list. Six patients (Appendix 2; patients 1, 4, 9, 10, 16, and 17) underwent transplantation after 10 to 43 months on PGI_2 (24±12 months). The decision to proceed to transplantation in these 6 children was based on persistence of symptoms, lack of hemodynamic improvement, and the preference of the patients and their families. All 6 patients are alive, 1 after undergoing repeat transplantation. One patient died (Appendix 2; patient 6).

The 31 children treated with long-term PGI_2 plus conventional therapy (group 1; Table 3) survived longer than the 28 children on conventional therapy (group 2; Table 3) for whom either long-term PGI_2 was unavailable (n=21) or whose parents refused (n=7). Thirty of the 31 patients in group 1 are alive after a mean follow-up of 26 months on long-term PGI_2 (range, 10 to 56 months). One death occurred after 22 months on PGI_2 as a result of severe hemorrhage during central venous line replacement. In contrast to the improved survival in group 1, only 5 of the 28 children in group 2 are alive after a mean follow-up of 44 months (range, 10 to 81 months). On average, death in this group occurred 27 months after entry into this study (range, 0.2 to 126 months): 14 children (61%) died of right heart failure and 9 (39%) died suddenly (complications of respiratory tract infections in 6, hemoptysis in 2, and during a platelet transfusion precipitating a presumed pulmonary hypertensive crisis in 1).

Survival rates on PGI_2 (n=31; group 1; Table 3) were 100% at 1 year and 94% at 2, 3, and 4 years compared with 50% at 1 year, 43% at 2 years, and 38% at 3 and 4 years for the children in group 2 (n=28; Table 3) treated with conventional therapy

TABLE 5. Hemodynamic Effects of Short-Term and Long-Term PGI_2 in 27 of the 31 Patients Treated With Long-Term PGI_2*

Variable	At Diagnosis	At Start of Prostacyclin		Last Follow-Up Study†	Mean Change Baseline to Last Follow-Up (95% CI)
		Baseline	Acute Response‡		
PAPm, mm Hg§	72±26	76±23	71±26	51±21	−25.3 (−33.3 to −17.3)‡
RAPm, mm Hg	5±3	5±3	5±3	5±3	0.20 (−1.2 to 1.6)
CI, L · min^{-1} · m^{-2}	3.5±1.5	3.1±1.1	3.9±1.3	4.4±1.7	1.4 (0.8 to 2.0)‡
PVR, U · m^2¶	24±16	27±13	20±12	11±8	−15.6 (−20.2 to −11.1)‡
M · Vo_2 Sat, %	65±10	63±9	70±8	72±7	8.5 (5.2 to 11.9)‡

Abbreviations as in Table 1. At diagnosis indicates before start of conventional therapy; baseline, before addition of long-term PGI_2 to conventional therapy.

*Four patients did not have follow-up cardiac catheterization, and 2 did not have short-term testing.

†Last follow-up: range, 3 to 46 mo; 21±11 mo.

‡$P<0.0001$.

§$P<0.02$ baseline vs at diagnosis.

¶$P<0.002$ baseline vs at diagnosis.

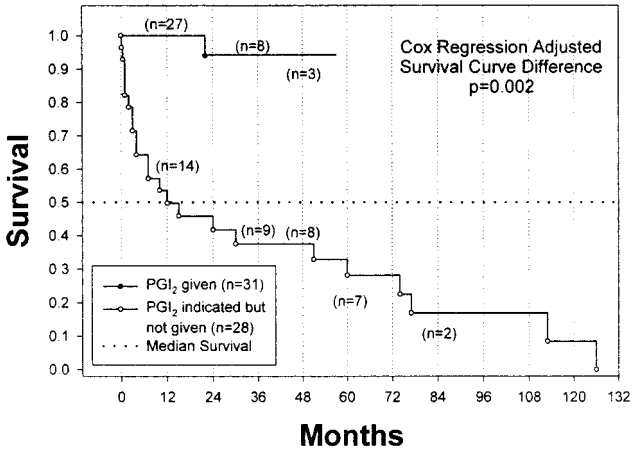

Figure 3. Kaplan-Meier survival curves comparing survival on long-term PGI_2 with survival of patients for whom PGI_2 was indicated but unavailable: 1,- 2-, 3-, and 4-year survival probabilities for PGI_2 group (group 1; Table 3; n=31) were 100%, 94%, 94%, and 94%, respectively, compared with 50%, 43%, 38%, and 38%, respectively, for patients not treated with PGI_2 (group 2; Table 3; n=28; P=0.002).

alone (Figure 3; P=0.002). The only significant difference between the 2 groups (groups 1 and 2; Table 3) was a lower cardiac index in group 2 (P=0.01). In Figure 4, survival for all nonresponders to short-term testing is shown. Survival was significantly better for the 24 nonresponders treated with long-term PGI_2 (group 1, Table 3) than for the 22 nonresponders for whom long-term PGI_2 was unavailable (group 2; Table 3): survival rates for the PGI_2 group at 1, 2, 3, and 4 years were 100%, 100%, 92%, and 92%, respectively, versus 45%, 34%, 29%, and 29%, respectively, for the conventional therapy alone group (P=0.0005). In contrast to the comparison above, in which the cardiac index was higher in group 1 than in group 2 (Table 3), there were no significant differences between these 2 groups of nonresponders.

Because our 13-year experience spanned 2 treatment eras, we added to our model (as a covariate) the year patients entered the study. Time was not associated with survival (P=0.69). In addition, because more children in the PGI_2 group (group 1) were treated with warfarin sodium than in the conventional therapy group (group 2), the comparison was repeated adjusting for warfarin sodium. After warfarin sodium was controlled for as a time-dependent covariate (along with hemodynamic variables, age, sex, and response to short-term testing), survival on PGI_2 (group 1; Table 3) remained significantly better than on conventional therapy (group 2; Table 3; P=0.002).

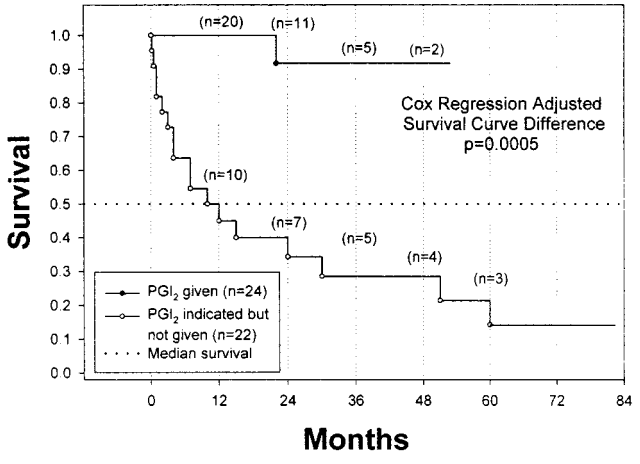

Figure 4. Kaplan-Meier survival curves comparing survival of nonresponders (n=24) treated with long-term PGI_2 with survival of nonresponders (n=22) for whom PGI_2 was indicated but unavailable: 1-, 2-, 3-, and 4-year survival probabilities for PGI_2 group were 100%, 100%, 92%, and 92%, respectively, compared with 45%, 34%, 29%, and 29%, respectively, for patients not treated with PGI_2 (P=0.0005).

Complications of Long-Term PGI_2 Therapy

The 1 death on PGI_2 has been noted above. Complications attributable to the use of PGI_2 were frequent and, as previously reported, included jaw pain, diarrhea, flushing, headache, nausea and vomiting, foot and leg pain, and tolerance.[2–4] Local irritations or infections at the catheter site were common. More serious complications due to the delivery system included 7 episodes of nonfatal, catheter-related sepsis. Episodes of malfunction of the drug delivery system resulting in temporary interruptions were not uncommon: these included occlusions, perforations, and dislodgments of the catheter and pump malfunction. During temporary interruption of PGI_2 infusion, symptoms such as dyspnea, pallor, fatigue, abdominal pain, and dizziness occurred.

Comparisons With Published Studies in Children and Adults

Studies in adults have related survival to hemodynamic parameters, the use of warfarin, and demographic factors.[1,6,7,10–12] However, because only 1 child died while on PGI_2, our study lacked sufficient power to investigate treatment by prognostic variable interactions. Therefore, our primary analysis examined these associations on conventional therapy, ie, by censoring patient data when PGI_2 was started. Table 6 shows the associations between age, sex, response to short-term testing, baseline hemodynamics, use of warfarin (as a time-dependent covariate), and survival while on conventional therapy (patients censored at initiation of PGI_2 and at transplantation).

As previous studies have shown,[6,7,12] right atrial pressure, pulmonary artery pressure, and pulmonary vascular resistance were significant parameters of survival. In addition, in the present study, cardiac index, mixed venous saturation, response to short-term vasodilator testing, age, and sex were also individually related to survival. In a multivariable model that included all factors, only age, male sex, acute response, and mixed venous saturation remained significant. Moreover, although long-term anticoagulation has been reported to improve survival in adults,[1,10] the present study was not designed to evaluate the effect of anticoagulation as an independent survival parameter.

Discussion

Until a few years ago, the diagnosis of PPH was almost tantamount to a death sentence. This was particularly true for children.[7,11,12] Before the present era of vasodilator therapy, the mean survival for children was ≤1 year. The grimmer outlook for children than for adults was underscored by data in the PPH NIH Registry.[6] In this registry, the median

TABLE 6. Baseline Factors Related to Survival on Conventional Therapy

	Unadjusted Relative Hazard (95% CI)	*P*	Adjusted Relative Hazard (95% CI)	*P*
Age, y	1.139 (1.031–1.259)	0.011	1.185 (1.024–1.372)	0.023
Male sex	2.685 (1.176–6.130)	0.019	4.511 (1.365–14.91)	0.014
Acute nonresponse	6.683 (2.154–29.74)	0.001	7.882 (1.668–37.25)	0.009
PAPm, mm Hg	1.018 (1.000–1.037)	0.047	1.021 (0.970–1.075)	0.430
RAPm, mm Hg	1.214 (1.070–1.377)	0.003	1.044 (0.869–1.254)	0.647
CI, $L \cdot min^{-1} \cdot m^{-2}$	0.586 (0.387–0.909)	0.017	0.624 (0.202–1.929)	0.412
PVR, $U \cdot m^2$	1.039 (1.013–1.066)	0.004	0.960 (0.866–1.064)	0.438
$M \cdot V_{O_2}$ Sat, %	0.956 (0.914–0.999)	0.046	0.928 (0.864–0.996)	0.040
Warfarin	1.136 (0.461–2.803)	0.781	1.194 (0.354–4.021)	0.775

Abbreviations as in Table 1.
Patients were censored at initiation of PGI_2 and at transplantation.

survival for all of the 194 patients was 2.8 years, whereas it was only 10 months for children <16 years old.

The present study demonstrates that long-term vasodilator therapy using calcium channel blockers in acute responders to vasodilator testing and continuous intravenous infusion of PGI_2 in nonresponders (as well as in responders who fail to improve on calcium channel blockers) is at least as effective in children as in adults with respect to increasing survival, improving hemodynamics, and relieving symptoms.[1–4,7,11,12] In children[9] as well as in adults,[1] the choice of vasodilator for long-term therapy is determined by short-term testing: those who manifest pulmonary vasodilatation in response to short-term testing can be treated with calcium channel blockers[1,9] and nonresponders with long-term PGI_2. However, in contrast to the published experience in adults, ≤25% of whom are responders,[1] >40% of children are responders. Accordingly, more children than adults can be successfully treated with calcium channel blockers. Indeed, the acute response in children is age-dependent (Figure 1 and Table 2).

The predictive model (Appendix 1) is not intended to serve as a substitute for short-term testing. However, it may be useful before short-term testing to anticipate the likelihood of an acute response versus nonresponse and therefore the likelihood of the need to start long-term PGI_2.

In children who fail to improve on conventional therapy, long-term PGI_2 seems to prolong survival more than previously reported in adults.[3,13] Unfortunately, the present study sheds no light on the mechanisms responsible for the hemodynamic improvement on long-term PGI_2 in patients who fail to respond to short-term PGI_2 testing (Table 5).[14]

Limitations of our study include the facts that (1) this was an observational study that spanned a 13-year period; during this time, a change occurred in the availability of vasodilators that could be used for long-term treatment from calcium channel blockers as the sole practical vasodilators for long-term use to the availability of PGI_2 for long-term administration; (2) ethical reasons precluded a clinical trial based on withholding vasodilator therapy in a dreaded disease for the sake of having a control group[1,3,4,9]; and (3) our recommendations for specific treatment regimens were not always acceptable to the families of our young patients.

In conclusion, this study demonstrates improved survival in children with PPH treated long-term with pulmonary vasodilators. In those who were shown by short-term PGI_2 testing to have a responsive pulmonary vascular bed, oral calcium channel blockers generally sufficed. In others, who did not demonstrate reactive vascular beds during short-term PGI_2 testing, long-term PGI_2 relieved symptoms, improved hemodynamics, and prolonged survival. Since the advent of PGI_2 for long-term therapy, we now reserve calcium channel blockers for children who manifest pulmonary vasodilation in response to short-term PGI_2 testing. Nonresponders are started on long-term PGI_2. In addition, PGI_2 infusion is added to conventional therapy in acute responders in whom hemodynamics fail to improve on long-term calcium channel blockers. In this study, nonresponders were treated with conventional therapy alone only before PGI_2 was available for long-term use (or if parents refused long-term PGI_2); furthermore, calcium channel blockers were used in these nonresponders as part of the conventional therapy only if there were no untoward effects with either short-term testing or long-term calcium channel blockers.

Appendix 1

Prediction Model of Response to Short-Term Vasodilator Testing

Multiple logistic regression analysis was used to develop a prediction equation for the likelihood of acute response based on age as well as hemodynamics at initial evaluation. Candidate hemodynamic variables included mean pulmonary artery pressure (PAPm), mean right atrial pressure (RAPm), cardiac index, and mixed venous oxygen saturation. Both linear and nonlinear relationships were considered. The best model included linear and quadratic functions of age, mean pulmonary artery pressure, and mean right atrial pressure. The probability of acute response is obtained using Equation 1 to compute a value for x and then using x in Equation 2 to compute the probability of acute response. For example, a 5-year-old patient with a PAPm of 57 mm Hg and a RAPm of 4 mm Hg has a predicted probability of 0.85 of a positive response to short-term vasodilator drug testing. In contrast, an 8-year-old patient with a PAPm of 72 mm Hg and a RAPm of 5 mm Hg has only an acute response predicted probability of 0.30.

(1) $$x = 9.3046 + 0.1566 \times \text{age} - 0.0326 \times \text{age}^2 - 0.2611 \times \text{PAPm} + 0.0014 \times \text{PAPm}^2 + 0.7919 \times \text{RAPm} - 0.0700 \times \text{RAPm}^2.$$

(2) $$\text{Probability of response} = e^x/(1+e^x).$$

Appendix 2

Appendix 2 is presented as Table 7.

TABLE 7. Hemodynamic Effects of Short-Term* and Long-Term PGI_2 in 31 Children Treated With Long-Term PGI_2

Patient	Baseline	Acute Response	Months of Treatment					
			3	6	12	24	36	48
1								
Mean pulmonary artery pressure, mm Hg	72	76		77	90	78		
Mean right atrial pressure, mm Hg	9	9		5	16	3		
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	1.7	2.5		3.1	3.3	3.0		
Pulmonary vascular resistance index, $U \cdot m^2$	39	26		23	24	17		
Mixed venous oxygen saturation, %	59	72		73	77	80		
2								
Mean pulmonary artery pressure, mm Hg	63	38	76		15			14
Mean right atrial pressure, mm Hg	3	2	18		4			4
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.8	3.0	2.6		6.5			6.9
Pulmonary vascular resistance index, $U \cdot m^2$	21	12	25		1			1
Mixed venous oxygen saturation, %	52	63	49		79			70
3								
Mean pulmonary artery pressure, mm Hg	57	58				41		49
Mean right atrial pressure, mm Hg	1	2				1		5
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	4.0	4.7				6.6		4.7
Pulmonary vascular resistance index, $U \cdot m^2$	17	14				6		9
Mixed venous oxygen saturation, %	72	76				70		79
4								
Mean pulmonary artery pressure, mm Hg	42	44	61			45		
Mean right atrial pressure, mm Hg	0	1	6			5		
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.5	3.1	3.7			4.6		
Pulmonary vascular resistance index, $U \cdot m^2$	15	13	14			8		
Mixed venous oxygen saturation, %	71	75	78			73		
5								
Mean pulmonary artery pressure, mm Hg	67	73	57			62	60	
Mean right atrial pressure, mm Hg	6	6	5			4	4	
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.2	3.0	2.4			3.5	4.0	
Pulmonary vascular resistance index, $U \cdot m^2$	29	23	26			18	13	
Mixed venous oxygen saturation, %	72	78	76			76	83	
6								
Mean pulmonary artery pressure, mm Hg	79	79	80					
Mean right atrial pressure, mm Hg	3	3	3					
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	3.1	3.0	2.4					
Pulmonary vascular resistance index, $U \cdot m^2$	25	21	32					
Mixed venous oxygen saturation, %	70	74	71					
7†								
Mean pulmonary artery pressure, mm Hg	74			11	24	16	24	
Mean right atrial pressure, mm Hg	6			0	5	3	8	
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.5			7.2	5.3	4.3	6.2	
Pulmonary vascular resistance index, $U \cdot m^2$	27			2	4	2	2	
Mixed venous oxygen saturation, %	51			67	69	77	76	
8								
Mean pulmonary artery pressure, mm Hg	48	49		48		27		
Mean right atrial pressure, mm Hg	5	5		5		0		
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	3.3	3.6		3.3		4.1		
Pulmonary vascular resistance index, $U \cdot m^2$	10	10		10		4		
Mixed venous oxygen saturation, %	79	81		79		81		

TABLE 7. Continued

Patient	Baseline	Acute Response	Months of Treatment 3	6	12	24	36	48
9								
Mean pulmonary artery pressure, mm Hg	83	91			65			
Mean right atrial pressure, mm Hg	6	3			1			
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.1	2.7			3.2			
Pulmonary vascular resistance index, $U \cdot m^2$	61	54			20			
Mixed venous oxygen saturation, %	49	59			66			
10								
Mean pulmonary artery pressure, mm Hg	103	93				94		
Mean right atrial pressure, mm Hg	0	1				6		
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	4.3	7.6				4.9		
Pulmonary vascular resistance index $U \cdot m^2$	22	12				19		
Mixed venous oxygen saturation, %	64	66				62		
11								
Mean pulmonary artery pressure, mm Hg	75	84				45	50	
Mean right atrial pressure, mm Hg	10	9				3	7	
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.3	3.7				3.7	2.5	
Pulmonary vascular resistance index, $U \cdot m^2$	28	20				10	16	
Mixed venous oxygen saturation, %	65	71				79	68	
12								
Mean pulmonary artery pressure, mm Hg	116	106			72	55		
Mean right atrial pressure, mm Hg	9	7			10	11		
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	3.2	3.7			5.8	5.0		
Pulmonary vascular resistance index, $U \cdot m^2$	35	28			11	8		
Mixed venous oxygen saturation, %	66	74			76	76		
13								
Mean pulmonary artery pressure, mm Hg	76	64			64	67		
Mean right atrial pressure, mm Hg	8	6			6	10		
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.4	3.8			2.8	2.9		
Pulmonary vascular resistance index, $U \cdot m^2$	30	16			15	16		
Mixed venous oxygen saturation, %	66	73			66	60		
14								
Mean pulmonary artery pressure, mm Hg	105	118			80	58		
Mean right atrial pressure, mm Hg	2	8			9	5		
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	3.0	3.6			3.2	5.8		
Pulmonary vascular resistance index, $U \cdot m^2$	32	31			21	9		
Mixed venous oxygen saturation, %	57	62			65	73		
15								
Mean pulmonary artery pressure, mm Hg	84	64			27	30		
Mean right atrial pressure, mm Hg	9	6			3	6		
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.6	3.7			2.9	4.5		
Pulmonary vascular resistance index, $U \cdot m^2$	30	17			7	5		
Mixed venous oxygen saturation, %	55	65			67	64		
16‡								
Mean pulmonary artery pressure, mm Hg	43	44						
Mean right atrial pressure, mm Hg	9	8						
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.6	2.7						
Pulmonary vascular resistance index, $U \cdot m^2$	13	13						
Mixed venous oxygen saturation, %	65	60						

TABLE 7. Continued

Patient	Baseline	Acute Response	Months of Treatment 3	6	12	24	36	48
17§								
Mean pulmonary artery pressure, mm Hg	109	102						
Mean right atrial pressure, mm Hg	9	10						
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.5	2.7						
Pulmonary vascular resistance index, $U \cdot m^2$	33	32						
Mixed venous oxygen saturation, %	76	72						
18								
Mean pulmonary artery pressure, mm Hg	32	18			20			
Mean right atrial pressure, mm Hg	2	1			6			
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	4.8	5.6			7.8			
Pulmonary vascular resistance index, $U \cdot m^2$	6	3			1			
Mixed venous oxygen saturation, %	62	72			79			
19								
Mean pulmonary artery pressure, mm Hg	57	45			35			
Mean right atrial pressure, mm Hg	7	6			8			
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	5.6	5.5			5.6			
Pulmonary vascular resistance index, $U \cdot m^2$	8	6			5			
Mixed venous oxygen saturation, %	79	79			79			
20								
Mean pulmonary artery pressure, mm Hg	44	52			48			
Mean right atrial pressure, mm Hg	4	4			9			
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.4	5.9			2.7			
Pulmonary vascular resistance index, $U \cdot m^2$	15	7			14			
Mixed venous oxygen saturation, %	68	85			66			
21								
Mean pulmonary artery pressure, mm Hg	75	82			54			
Mean right atrial pressure, mm Hg	0	5			0			
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	4.0	4.7			4.4			
Pulmonary vascular resistance index, $U \cdot m^2$	24	18			14			
Mixed venous oxygen saturation, %	55	55			62			
22								
Mean pulmonary artery pressure, mm Hg	115	107			66			
Mean right atrial pressure, mm Hg	8	4			8			
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	1.9	2.2			2.5			
Pulmonary vascular resistance index, $U \cdot m^2$	52	45			21			
Mixed venous oxygen saturation, %	57	64			60			
23								
Mean pulmonary artery pressure, mm Hg	95	93			69			
Mean right atrial pressure, mm Hg	5	5			2			
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.8	3.3			2.8			
Pulmonary vascular resistance index, $U \cdot m^2$	31	26			22			
Mixed venous oxygen saturation, %	70	72			70			
24								
Mean pulmonary artery pressure, mm Hg	75	73			51			
Mean right atrial pressure, mm Hg	4	4			5			
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	3.2	3.2			3.5			
Pulmonary vascular resistance index, $U \cdot m^2$	21	21			8			
Mixed venous oxygen saturation, %	68	67			77			

TABLE 7. Continued

Patient	Baseline	Acute Response	Months of Treatment 3	6	12	24	36	48
25‖								
Mean pulmonary artery pressure, mm Hg	100	110			57			
Mean right atrial pressure, mm Hg	7	8			5			
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	1.9	2.0			4.1			
Pulmonary vascular resistance index, $U \cdot m^2$	47	51			12			
Mixed venous oxygen saturation, %	58	59			76			
26								
Mean pulmonary artery pressure, mm Hg	45	33			17			
Mean right atrial pressure, mm Hg	5	5			6			
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	5.1	4.9			6.6			
Pulmonary vascular resistance index, $U \cdot m^2$	8	6			1			
Mixed venous oxygen saturation, %	71	69			76			
27								
Mean pulmonary artery pressure, mm Hg	98	98			67			
Mean right atrial pressure, mm Hg	3	4			6			
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.9	2.9			3.4			
Pulmonary vascular resistance index, $U \cdot m^2$	30	30			18			
Mixed venous oxygen saturation, %	65	66			76			
28								
Mean pulmonary artery pressure, mm Hg	86	91			57			
Mean right atrial pressure, mm Hg	13	12			6			
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	1.7	3.1			3.9			
Pulmonary vascular resistance index, $U \cdot m^2$	43	27			12			
Mixed venous oxygen saturation, %	49	57			68			
29								
Mean pulmonary artery pressure, mm Hg	50	46						
Mean right atrial pressure, mm Hg	6	6						
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	3.3	4.0						
Pulmonary vascular resistance index, $U \cdot m^2$	14	10						
Mixed venous oxygen saturation, %	66	70						
30								
Mean pulmonary artery pressure, mm Hg	86	51		29	28			
Mean right atrial pressure, mm Hg	1	5		4	2			
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	5.0	4.0		6.6	3.5			
Pulmonary vascular resistance index, $U \cdot m^2$	17	11		3	5			
Mixed venous oxygen saturation, %	...	...		73	76			
31								
Mean pulmonary artery pressure, mm Hg	101	98						
Mean right atrial pressure, mm Hg	7	6						
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	1.9	2.2						
Pulmonary vascular resistance index, $U \cdot m^2$	47	40						
Mixed venous oxygen saturation, %	59	63						

*The values for short-term testing were obtained during short-term dose-ranging and represent the maximum tolerated dose.
†Data obtained 2 months before start of PGI_2; marked deterioration precluded repeat catheterization with short-term PGI_2 testing before start of PGI_2.
‡Data obtained 16 months before start of PGI_2; marked deterioration precluded repeat catherization before start of PGI_2.
§Data obtained 19 months before start of PGI_2; marked deterioration precluded repeat catheterization before start of PGI_2.
‖Data obtained 1 month before start of PGI_2; marked deterioration precluded repeat cathetherization before start of PGI_2.

Acknowledgments

This study was supported in part by Burroughs Wellcome Co, Research Triangle Park, NC, and grant RR-00645 from the National Institutes of Health, National Center for Research Resources.

References

1. Rich S, Kaufman 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.

2. Higenbottam TW, Wells F, Wheeldon D. Wallwork J. Treatment of primary pulmonary hypertension with continuous intravenous epoprostenol (prostacyclin). *Lancet*. 1984;1:1046–1047.
3. Barst RJ, Rubin LJ, McGoon MD, Caldwell EJ, Long WA, Levy PS. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. *Ann Intern Med*. 1994;121:409–415.
4. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, Koerner SK, Langleben D, Keller CA, Murali S, Uretsky BF, Clayton LM, Jobsis MM, Blackburn SD, Shortino D, Crow JW. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med*. 1996;334:296–301.
5. Yamaki S, Wagenvoort CA. Comparison of primary plexogenic arteriopathy in adults and children: a morphometric study in 40 patients. *Br Heart*. 1985;54:423–434.
6. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky E, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, Levy PS, Pietra GG, Reid LM, Reeves JT, Rich S, Vreim CE, Williams GW, Wu M. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. *Ann Intern Med*. 1991;115:343–349.
7. Sandoval J, Bauerie O, Gomez A, Palomar A, Martinez Guerra ML, Guruya ME. Primary pulmonary hypertension in children: clinical characterization and survival. *J Am Coll Cardiol*. 1995;25:466–474.
8. Rich S, Dantzker DR, Ayres SM, Bergofsky E, Brundage BH, Detre KM, Fishman AP, Goldring RA, Groves BM, Koerner SK, Levy PC, Reid LM, Vreim CE, Williams GW. Primary pulmonary hypertension: a national prospective study. *Ann Intern Med*. 1987;107:216–223.
9. Barst RJ. Pharmacologically induced pulmonary vasodilatation in children and young adults with primary pulmonary hypertension. *Chest*. 1986;89:497–503.
10. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation*. 1984;70:580–587.
11. Houde C, Bohn DJ, Freedom RM, Rabinovitch M. Profile of paediatric patients with pulmonary hypertension judged by responsiveness to vasodilator. *Br Heart J*. 1993;70:461–468.
12. Clabby ML, Canter CE, Moller JH, Bridges ND. Hemodynamic data and survival in children with pulmonary hypertension. *J Am Coll Cardiol*. 1997;30:554–560.
13. Shapiro SM, Oudiz RJ, Cao T, Romano A, Beckmann XJ, Georgiou D, Mandayam S, Ginzton LE, Brundage BH. Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. *J Am Coll Cardiol*. 1997;30:343–349.
14. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med*. 1998;338:273–277.

Vasodilator Therapy for Primary Pulmonary Hypertension in Children

Robyn J. Barst, Greg Maislin and Alfred P. Fishman

Circulation. 1999;99:1197-1208
doi: 10.1161/01.CIR.99.9.1197
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539