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 (PGI₂) has been available for long-term intravenous use.

Methods and Results—Seventy-four children underwent short-term vasodilator testing with intravenous PGI₂. 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 PGI₂ 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 PGI₂. In the 31 responders, calcium channel blockers improved survival compared with the 43 nonresponders (P=0.0002). Survival was also better in 24 PGI₂-treated nonresponders compared with 22 nonresponders for whom PGI₂ 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 PGI₂ 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 outcomes5; 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 (PGI₂) became available for long-term administration, therapy was directed in accord with the results of short-term PGI₂ 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 PGI₂ administered intravenously. Two aspects of this experimental design warrant special mention: (1) once calcium channel blockers were started, they were continued, even after PGI₂ 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 PGI₂ 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...
TABLE 1. Baseline Demographic and Hemodynamic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute Responders (n=31)</th>
<th>Nonresponders (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>5 ± 4</td>
<td>8 ± 4</td>
</tr>
<tr>
<td>PAPm, mm Hg</td>
<td>57 ± 22</td>
<td>38 ± 17†</td>
</tr>
<tr>
<td>RAPm, mm Hg</td>
<td>4 ± 3</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>CI, L · min⁻¹ · m⁻²</td>
<td>3.4 ± 1.4</td>
<td>4.6 ± 1.5†</td>
</tr>
<tr>
<td>PVR, U · m⁻²</td>
<td>17 ± 11</td>
<td>8 ± 6‡</td>
</tr>
<tr>
<td>M · VO₂ Sat, %</td>
<td>63 ± 10</td>
<td>73 ± 7†</td>
</tr>
<tr>
<td>Warfarin, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58 (75)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>19 (25)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. *P<0.0005 baseline hemodynamics: acute responders vs nonresponders. †P<0.0001 vs baseline. ‡P<0.0001 vs baseline. §P<0.0001 vs baseline. ¶P<0.08 vs baseline (changes between acute responders and nonresponders during short-term PGI2 testing). ¶¶P<0.02 vs baseline (changes between acute responders and nonresponders during short-term PGI2 testing; ie, changes not as pronounced with nonresponders as with responders).

PAPm indicates mean pulmonary artery pressure; RAPm, mean right atrial pressure; CI, cardiac index; PVR, pulmonary vascular resistance index; and M · VO₂ Sat, mixed venous oxygen saturation. Values are mean±SD.

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

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. PGI2 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.6 Arterial blood gas parameters were measured at baseline and during short-term testing. The arterial pH and PaCO₂ 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 PGI2 became available for long-term use, all patients, ie, acute responders and nonresponders, received conventional therapy, including calcium chan-
TABLE 3. Demographic and Hemodynamic Variables at Baseline According to Treatment
Group (N=77)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=31) PGI2 Plus CT After Failure on CT</th>
<th>Group 2 (n=28) PGI2 Indicated but Not Received: CT</th>
<th>Group 3 (n=18) PGI2 Not Indicated: CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>8±4</td>
<td>8±5</td>
<td>4±4</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (29)</td>
<td>13 (46)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Female</td>
<td>22 (71)</td>
<td>15 (54)</td>
<td>13 (72)</td>
</tr>
<tr>
<td>PAPm, mm Hg†</td>
<td>74±24</td>
<td>69±18</td>
<td>53±19</td>
</tr>
<tr>
<td>RAPm, mm Hg‡</td>
<td>5±4</td>
<td>6±4</td>
<td>3±2</td>
</tr>
<tr>
<td>CI, L·min⁻¹·m⁻²§</td>
<td>3.8±1.7</td>
<td>2.8±1.0</td>
<td>4.2±2.5</td>
</tr>
<tr>
<td>PVR, U·m⁻²</td>
<td></td>
<td></td>
<td>23±14</td>
</tr>
<tr>
<td>MVO2, Sat, %</td>
<td>65±8</td>
<td>62±11</td>
<td>64±7</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>26 (83)</td>
<td>21 (75)</td>
<td>15 (83)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (7)</td>
<td>2 (7)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (10)</td>
<td>5 (18)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Short-term vasodilator testing, n (%)¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders</td>
<td>6 (20)</td>
<td>5 (19)</td>
<td>16 (89)</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>24 (80)</td>
<td>22 (81)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Oral vasodilators, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin#</td>
<td>30 (97)</td>
<td>11 (39)</td>
<td>17 (94)</td>
</tr>
</tbody>
</table>

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 PGI2 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).

Group 1: Conventional Therapy: PGI2 Indicated and Available

The remaining 23 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 PGI2. 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 PGI2 testing.

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 PGI2 (group 1; Table 3; n=31) versus those treated with conventional therapy for whom PGI2 was indicated but unavailable (group 2; Table 2; n=28); and (3) survival of only the nonresponders treated with PGI2 (nonresponders, group 1; Table 3; n=24) versus the nonresponders treated with conventional therapy for whom PGI2 was indicated but unavailable (nonresponders, group 2; Table 3; n=22). Kaplan-Meier curves, based on log-rank statistics, were used to compare
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 PGI2 for patients treated with long-term PGI2. 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 eliciting short-term pulmonary vasodilation (P<0.005).

Conventional Therapy Alone (No PGI2)

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·min⁻¹; P<0.0001; Table 4). Repeat short-term PGI2 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 PGI2 plus conventional therapy including calcium channel blockers might offer additional hemodynamic advantage to these children, risk-benefit considerations (including complications from the PGI2 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 PGI2; the other 5 were not started on long-term PGI2 either because PGI2 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. 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

![Figure 1](http://circ.ahajournals.org/)

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).

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>At Start of Oral Vasodilator Therapy</th>
<th>Last Follow-Up Study</th>
<th>Mean Change (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPm, mm Hg</td>
<td>52±21</td>
<td>31±15</td>
<td>−21.6 (−35.6 to −7.5)‡</td>
</tr>
<tr>
<td>RAPm, mm Hg</td>
<td>4±2</td>
<td>3±3</td>
<td>−0.1 (−1.4 to 1.1)</td>
</tr>
<tr>
<td>CI, L·min⁻¹·m⁻²</td>
<td>3.7±1.5</td>
<td>5.1±2.1</td>
<td>1.4 (0.5 to 2.3)‡</td>
</tr>
<tr>
<td>PVR, U·m⁻²</td>
<td>13±5</td>
<td>6±5</td>
<td>−7.3 (−10.2 to −4.6)‡</td>
</tr>
<tr>
<td>M·V̇O₂ Sat, %</td>
<td>64±7</td>
<td>71±5</td>
<td>7.1 (1.9 to 12.3)§</td>
</tr>
</tbody>
</table>

*Abbreviations as in Table 1.

†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.
Patients Treated With Long-Term PGI₂ Plus Conventional Therapy

All 31 children treated with long-term PGI₂ improved (group 1, Table 3). According to the NYHA functional criteria, functional capacity improved: 3.30±0.54 before PGI₂ to 1.96±0.71 at the time of last follow-up catheterization (3 to 46 months after PGI₂ was started; 21±11 months; n=27; P<0.0001). Twenty-seven of the 31 patients on long-term PGI₂ had ≥1 follow-up catheterization. Because of their considerable variability, the hemodynamic data obtained during the short-term and long-term administration of PGI₂ 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·m²; P<0.0001). Table 5 also illustrates that lack of an acute response to PGI₂ did not preclude significant hemodynamic improvement on long-term PGI₂. This improvement of acute nonresponders on long-term PGI₂ contrasts with the failure of long-term calcium channel blockers to elicit hemodynamic improvement in acute nonresponders.² Moreover, calcium channel blockers in nonresponders can be hazardous or even fatal.

Twenty-four of the 31 children who were started on long-term PGI₂ continue to receive PGI₂ (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 PGI₂ (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 PGI₂ 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 PGI₂ 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 PGI₂ (range, 10 to 56 months). One death occurred after 22 months on PGI₂ 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 PGI₂ (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 PGI₂ in 27 of the 31 Patients Treated With Long-Term PGI₂*

<table>
<thead>
<tr>
<th>Variable</th>
<th>At Start of Prostacyclin</th>
<th>Last Follow-Up Study†</th>
<th>Mean Change Baseline to Last Follow-Up (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At Diagnosis</td>
<td>Baseline</td>
<td>Acute Response‡</td>
</tr>
<tr>
<td>PA Pm, mm Hg§</td>
<td>72±26</td>
<td>76±23</td>
<td>71±26</td>
</tr>
<tr>
<td>RAPm, mm Hg</td>
<td>5±3</td>
<td>5±3</td>
<td>5±3</td>
</tr>
<tr>
<td>CI, L·min⁻¹·m⁻²</td>
<td>3.5±1.5</td>
<td>3.1±1.1</td>
<td>3.9±1.3</td>
</tr>
<tr>
<td>PVR, U·m⁻²¶</td>
<td>24±16</td>
<td>27±13</td>
<td>20±12</td>
</tr>
<tr>
<td>M·Vo₂ Sat, %</td>
<td>65±10</td>
<td>63±9</td>
<td>70±8</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. At diagnosis indicates before start of conventional therapy; baseline, before addition of long-term PGI₂ 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<0.0002 baseline vs at diagnosis.
Complications of Long-Term PGI2 Therapy

The 1 death on PGI2 has been noted above. Complications attributable to the use of PGI2 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 PGI2 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 PGI2, 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 PGI2 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 PGI2 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 survival in children was 12 months, and 30% of the children died within 2 months of diagnosis. The prognosis for survival on conventional therapy was particularly grim, with 2-year survival rates of 60% for older infants and 10% for children more than 1 year. In the present study, Kaplan-Meier survival curves comparing survival on long-term PGI2 with survival of patients for whom PGI2 was indicated but unavailable: 1-, 2-, 3-, and 4-year survival probabilities for PGI2 group (group 1; Table 3) remained significantly better than on conventional therapy (group 2; Table 3; P=0.002).

Figure 3. Kaplan-Meier survival curves comparing survival on long-term PGI2 with survival of patients for whom PGI2 was indicated but unavailable: 1-, 2-, 3-, and 4-year survival probabilities for PGI2 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 PGI2 (group 2; Table 3; n=28; P=0.002).

Figure 4. Kaplan-Meier survival curves comparing survival of nonresponders (n=24) treated with long-term PGI2 with survival of nonresponders (n=22) for whom PGI2 was indicated but unavailable: 1-, 2-, 3-, and 4-year survival probabilities for PGI2 group were 100%, 100%, 92%, and 92%, respectively, versus 45%, 34%, 29%, and 29%, respectively, for patients not treated with PGI2 (P=0.0005).
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 PGlu 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 as well as in adults,1 the choice of vasodilator for long-term therapy is determined by short-term testing: those who manifest pulmonary vasodilation in response to short-term PGlu are treated with calcium channel blockers,1,9 whereas patients who fail to improve on calcium channel blockers are started on long-term PGlu. In this study, nonresponders were treated with conventional therapy alone only before PGlu was available for long-term use (or if parents refused long-term PGlu); 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.

### TABLE 6. Baseline Factors Related to Survival on Conventional Therapy

<table>
<thead>
<tr>
<th>Unadjusted Relative Hazard (95% CI)</th>
<th>P</th>
<th>Adjusted Relative Hazard (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.139 (1.031–1.259)</td>
<td>0.011</td>
<td>1.185 (1.024–1.372)</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.685 (1.176–6.130)</td>
<td>0.019</td>
<td>4.511 (1.365–14.91)</td>
</tr>
<tr>
<td>Acute nonresponse</td>
<td>6.683 (2.154–29.74)</td>
<td>0.001</td>
<td>7.882 (1.668–37.25)</td>
</tr>
<tr>
<td>PAPm, mm Hg</td>
<td>1.018 (1.000–1.037)</td>
<td>0.047</td>
<td>1.021 (0.970–1.075)</td>
</tr>
<tr>
<td>RAPm, mm Hg</td>
<td>1.214 (1.070–1.377)</td>
<td>0.003</td>
<td>1.044 (0.869–1.254)</td>
</tr>
<tr>
<td>CI, L · min⁻¹ · m⁻²</td>
<td>0.586 (0.387–0.909)</td>
<td>0.017</td>
<td>0.624 (0.202–1.929)</td>
</tr>
<tr>
<td>PVR, U · m⁻²</td>
<td>1.039 (1.013–1.066)</td>
<td>0.004</td>
<td>0.960 (0.866–1.064)</td>
</tr>
<tr>
<td>M · Vo₂ Sat, %</td>
<td>0.956 (0.914–0.999)</td>
<td>0.046</td>
<td>0.928 (0.864–0.996)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.136 (0.461–2.803)</td>
<td>0.781</td>
<td>1.194 (0.544–4.021)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

Patients were censored at initiation of PGlu and at transplantation.

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In children 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 PGlu are treated with calcium channel blockers,1,9 whereas patients who fail to improve on calcium channel blockers are started on long-term PGlu. In this study, nonresponders were treated with conventional therapy alone only before PGlu was available for long-term use (or if parents refused long-term PGlu); 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. 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 PGI₂ in 31 Children Treated With Long-Term PGI₂

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*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 PGI₂; marked deterioration precluded repeat catheterization with short-term PGI₂ testing before start of PGI₂.
‡Data obtained 16 months before start of PGI₂; marked deterioration precluded repeat catheterization before start of PGI₂.
§Data obtained 19 months before start of PGI₂; marked deterioration precluded repeat catheterization before start of PGI₂.
||Data obtained 1 month before start of PGI₂; marked deterioration precluded repeat catheterization before start of PGI₂.

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**References**


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