Outcomes in Children With Idiopathic Pulmonary Arterial Hypertension

Delphine Yung, MD; Allison C. Widlitz, MS, PA; Erika Berman Rosenzweig, MD; Diane Kerstein, MD; Greg Maislin, MS, MA; Robyn J. Barst, MD

Background—Treatment for idiopathic pulmonary arterial hypertension in children includes calcium channel blockade (CCB) for acute responders with vasodilator testing and chronic epoprostenol for nonresponders. We sought to determine parameters associated with survival and treatment success.

Methods and Results—A previously identified cohort of 77 children diagnosed between 1982 and 1995 with idiopathic pulmonary arterial hypertension was followed up through 2002. For acute responders treated with CCB (n = 31), survival at 1, 5, and 10 years was 97%, 97%, and 81%, respectively; treatment success was 84%, 68%, and 47%, respectively. Survival for all children treated with epoprostenol (n = 35) at 1, 5, and 10 years was 94%, 81%, and 61%, respectively; treatment success was 83%, 57%, and 37%, respectively. Because of the inconsistent availability of epoprostenol before 1995, we defined a “recent medical era” subset by excluding children from the total 77 patient cohort for whom epoprostenol was recommended but was unavailable. Survival in the recent medical era (n = 44) at 1, 5, and 10 years was 97%, 97%, and 78%; treatment success was 93%, 86%, and 60%, respectively. Treatment success on CCB decreased significantly when acute responders became nonresponders. Age at diagnosis predicted treatment success in the recent medical era.

Conclusions—Survival for children with idiopathic pulmonary arterial hypertension has significantly improved with CCB and epoprostenol. Children who are acute responders are treated with CCB; they are treated with epoprostenol if they become nonresponders. The decrease in survival and in treatment success after 5 years in all children supports the role for transplant evaluation before treatment failure. (Circulation. 2004;110:660-665.)

Key Words: pediatrics ■ hypertension, pulmonary ■ prostaglandins ■ pulmonary heart disease

Untreated idiopathic pulmonary arterial hypertension (IPAH), previously known as primary pulmonary hypertension,1 has a poor prognosis in children. In the NIH Primary Pulmonary Hypertension Registry, although overall median survival for adults and children was 2.8 years, median survival in children was only 10 months.2 However, a single center in Mexico City subsequently reported a median survival of 4.1 years in children.3 In both studies, some patients were treated with chronic calcium channel blockade (CCB). CCB increases survival in children and adults who have an acute vasodilator response.4 In addition, chronic intravenous epoprostenol improves survival in children and adults with IPAH regardless of their acute vasodilator response.5-11

We previously reported outcomes in a cohort of IPAH children (n = 77) that spanned the era from when CCB was the only available vasodilator therapy through the era when epoprostenol was commercially available. However, in that report, the follow-up time on epoprostenol was only 26±14 months (range, 10 to 56 months), and because there was only 1 death during that period, the study did not have sufficient power to investigate outcome predictors.8 We have extended the follow-up by 7 years to further define long-term outcomes for treatment with CCB and epoprostenol and to determine overall survival for patients in the recent era.

Survival parameters in adult patients on epoprostenol include baseline functional class, hemodynamics,11 and age at disease onset.12 Recently, Sitbon et al13 defined stringent criteria for acute vasoreactivity that predict long-term success on CCB alone. We analyzed whether reported predictors of survival and treatment success in adults are applicable to children.

Methods
The Columbia University Institutional Review Board approved this study. Informed consent was obtained for each child. The studies were conducted in accordance with the amended Helsinki Declaration.
Subjects
We previously reported a cohort of 77 patients <16 years of age who were diagnosed with IPAH between 1982 and 1995 at the Columbia Presbyterian Medical Center, New York, NY, with follow-up through 1995.13 We have now extended the follow-up by 7 years, through 2002. Patients were classified as acute responders (ARs) or nonresponders (NRs) to acute vasodilator testing during cardiac catheterization at diagnosis. Responders to acute 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.2 There were 31 ARs, 43 NRs, and 3 children too sick to be tested.

Medical Therapy
Patients were treated with conventional therapy, including digitalis, diuretics, and oxygen as needed. In 1990, oral anticoagulation was added for all patients (unless there was a contraindication).3,4 Before the availability of epoprostenol, all patients were started on CCB. If there was no clinical and hemodynamic improvement, epoprostenol was started when available, as previously reported.5 For patients without a patent foramen ovale, atrial septostomy was considered if symptoms of recurrent syncope and/or right-side heart failure persisted despite medical therapy. Serial cardiac catheterizations were performed; patients who were ARs at diagnosis underwent repeated acute vasodilator testing during follow-up catheterizations.

Statistical Methods
Survival was calculated starting at the time of diagnosis for ARs on CCB (group 1) and for patients in the recent medical era (group 3). Survival for all patients who received epoprostenol (group 2) was determined starting at the time epoprostenol was initiated. For all survival analyses, patients were censored at the time of transplantation, in addition, for ARs on CCB (group 1), initiation of epoprostenol was a second censoring event. Baseline demographic and hemodynamic variables, including acute response status (Table 1), were used in unadjusted and adjusted analyses to predict survival. Effects of interval variables on survival were expressed in terms of the hazard ratio for each 1-SD increase in value, along with 95% CIs. This permits meaningful comparisons among variables in terms of clinical effect sizes that do not depend on the unit of measurement for each variable.

Treatment success for ARs on CCB (group 1) was defined as freedom from death, transplantation, atrial septostomy, or initiation of epoprostenol. For patients on epoprostenol (group 2) and for patients in the recent medical era (group 3), treatment success was defined as freedom from death, transplantation, or atrial septostomy. Baseline demographics and hemodynamic variables, including acute response status (Table 1), were assessed as predictors for treatment success unadjusted and adjusted.

For patients on CCB, the statistical significance of the mean change from baseline to last follow-up study for each hemodynamic parameter was assessed with a paired $t$ test. For all patients on epoprostenol, hemodynamic changes from initiation of epoprostenol to last follow-up study were also assessed with paired $t$ tests. In descriptive analyses for AR, mean values of baseline hemodynamic parameters were compared by use of 2-sample $t$ tests for children who became NRs compared with children who remained ARs. A prognostic model using multiple logistic regression analyzed baseline demographic and hemodynamic variables as predictors for a change from AR to NR. A change from AR to NR status was analyzed as a predictor for survival and treatment success on CCB. Data are reported as mean±SE unless otherwise specified. Values of $P<0.05$ were considered statistically significant.

Results

Acute Responders
Of the initial 31 ARs, 11 died, 5 of whom had been started on epoprostenol. Two additional children underwent transplantation, both of whom had also been started on epoprostenol. Five other children were started on epoprostenol. Of the remaining 13 patients, 10 continued on CCB alone, and 3 were treated with an additional oral agent, ie, bosentan, during the last 9 months of the follow-up period. Atrial septostomy was performed in 2 patients.

Nonresponders
Of the 43 initial NRs, 22 died, 4 of whom had been started on epoprostenol; ie, 18 children died before epoprostenol availability. Nine additional children underwent transplantation, 5 of whom had been started on epoprostenol. The remaining 12 children are all on epoprostenol, and of these, 4 had bosentan added to their medical regimen during the last year of the follow-up period. Atrial septostomy was performed in 7 patients.

Survival and Treatment Success

ARs on CCB (n=31)
Kaplan-Meier curves are shown in Figure 1 for survival and treatment success, with time starting at diagnosis. For survival, transplantation and initiation of epoprostenol were censoring events. Survival rates at 1, 5, and 10 years were 97%, 97%, and 81%, respectively. The mean±SE survival
time was 122±6 months. For treatment success, death, transplantation, initiation of epoprostenol, and atrial septostomy were events, i.e., “treatment failures,” on CCB. Treatment success rates at 1, 3, 5, and 10 years were 84%, 71%, 68%, and 47%, respectively.

All Patients Who Received Epoprostenol (n=35)
Kaplan-Meier curves are shown in Figure 2 for survival and treatment success, with time starting with the initiation of epoprostenol. For survival, transplantation was a censoring event. Survival rates at 1, 3, 5, and 10 years were 94%, 88%, 81%, and 61%, respectively. The mean±SE survival time was 84±6 months. Treatment success rates, for which death, transplantation, and atrial septostomy were events, i.e., treatment failures, at 1, 3, 5, and 10 years were 83%, 66%, 57%, and 37%, respectively.

Patients in the Recent Medical Era (n=44)
Kaplan-Meier curves are shown in Figure 3 for survival and treatment success, with time starting at diagnosis. For survival, transplantation was a censoring event. Survival rates at 1, 5, and 10 years were 97%, 97%, and 78%, respectively. The mean±SE survival time was 120±4 months. Treatment success rates, for which death, transplantation and atrial septostomy were events, i.e., treatment failures, at 1, 3, 5, and 10 years were 93%, 86%, 86%, and 60%, respectively.

Survival and Treatment Success Parameters

ARS on CCB (n=31)
There were no significant predictors of survival. Lower baseline pulmonary artery pressure was the only statistically significant (P=0.022) predictor of treatment success in unadjusted analyses (Table 2). For each 1-SD increase in pulmonary artery pressure (SD, 21.77 mm Hg), the risk of treatment failure increased by 1.65-fold (95% CI, 1.08 to 2.53).

All Patients Who Received Epoprostenol (n=35)
There were no significant predictors of survival or treatment success (Table 3).

Patients in the Recent Medical Era (n=44)
There were no significant predictors of survival. In adjusted analyses, the only significant predictor of treatment success was younger age at diagnosis (P=0.040). Adjusted analyses did not identify any additional significant predictors after we controlled for age (Table 4).

Hemodynamic Effects
The hemodynamic effects of chronic CCB for 12 of the 13 patients who remained ARs on CCB without starting epoprostenol are shown in Table 5. One patient remained clinically improved but declined follow-up catheterization. The mean±SD follow-up time to the last catheterization was 106±58 months (range, 12 to 201 months). In these 12 children, there were significant improvements in pulmonary artery pressure, pulmonary vascular resistance, and mixed venous saturation. Right atrial pressure and cardiac index remained normal and did not significantly change with CCB.
The hemodynamic effects of chronic epoprostenol for 31 of the 35 patients treated with epoprostenol are shown in Table 6. Of the 4 patients who were not restudied, 2 had undergone transplantation and 2 died; all 4 events occurred between 9 and 11 months after epoprostenol was started. The mean ± SD follow-up time to last catheterization was 53 ± 28 months (range, 9 to 102 months). In these 31 children, there were significant improvements in pulmonary artery pressure, cardiac index, pulmonary vascular resistance, and mixed venous saturation.

**Change From Acute Responder to Nonresponder**

Of the 31 patients who demonstrated acute responsiveness with vasodilator testing at initial catheterization, 14 (45%) became unresponsive to acute vasodilator testing during the follow-up period. Descriptive $t$ tests showed that there were no differences in age, gender, or hemodynamic variables at baseline between the group that remained ARs and the group that became NRs. The hemodynamic variables examined were resting pulmonary artery pressure, pulmonary artery pressure with acute vasodilator testing, absolute change in pulmonary artery pressure with acute vasodilator testing, and percent change in pulmonary artery pressure with acute vasodilator testing. These variables, in addition to the more recently accepted definition for an acute response,13 ie, decrease in mean pulmonary artery pressure of $\geq 10$ mm Hg with mean pulmonary artery pressure decreasing to $\leq 35$ mm Hg and a normal or high cardiac index, used as dichotomous variables, were not prognostic of a change from AR to NR status.10 However, when response status was used as a time-varying covariate for predicting treatment success on CCB, a change from AR to NR increased the risk of treatment failure on CCB. Moreover, when response status changed from an AR to an NR, the risk of treatment failure on CCB increased by a factor of 8.97 (95% CI, 2.54

### TABLE 2. Baseline Factors Related to Survival and Treatment Success for ARs on CCB

<table>
<thead>
<tr>
<th>Variable</th>
<th>SD</th>
<th>Survival,* Unadjusted Relative Hazard (95% CI)</th>
<th>$P$</th>
<th>Treatment Success,† Unadjusted Relative Hazard (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>3.50</td>
<td>1.45 (0.72–2.90)</td>
<td>0.296</td>
<td>1.27 (0.79–2.05)</td>
<td>0.329</td>
</tr>
<tr>
<td>Male</td>
<td>0.43</td>
<td>3.11 (0.62–15.5)</td>
<td>0.167</td>
<td>2.03 (0.68–6.08)</td>
<td>0.208</td>
</tr>
<tr>
<td>Class III/IV</td>
<td>0.25</td>
<td>1.52 (0.26–8.78)</td>
<td>0.638</td>
<td>1.30 (0.17–10.2)</td>
<td>0.804</td>
</tr>
<tr>
<td>PAPm</td>
<td>21.77</td>
<td>1.11 (0.48–2.57)</td>
<td>0.816</td>
<td>1.65 (1.08–2.53)</td>
<td>0.022</td>
</tr>
<tr>
<td>RAPm</td>
<td>2.58</td>
<td>0.93 (0.33–2.67)</td>
<td>0.898</td>
<td>1.70 (0.97–2.98)</td>
<td>0.065</td>
</tr>
<tr>
<td>CI</td>
<td>1.35</td>
<td>0.79 (0.35–1.81)</td>
<td>0.580</td>
<td>0.80 (0.45–1.42)</td>
<td>0.442</td>
</tr>
<tr>
<td>PVR</td>
<td>11.00</td>
<td>1.16 (0.53–2.54)</td>
<td>0.704</td>
<td>1.44 (0.97–2.14)</td>
<td>0.069</td>
</tr>
<tr>
<td>$\text{SvO}_2$</td>
<td>9.71</td>
<td>1.19 (0.43–3.31)</td>
<td>0.744</td>
<td>1.12 (0.61–2.08)</td>
<td>0.708</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.66</td>
<td>0.10–4.48)</td>
<td>0.669</td>
<td>0.43 (0.13–1.43)</td>
<td>0.171</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. n=31.

*Patients were censored at transplantation and initiation of epoprostenol.
†Events include death, transplantation, initiation of epoprostenol, and atrial septostomy.

### TABLE 3. Factors at Start of Epoprostenol Related to Survival and Treatment Success on Epoprostenol

<table>
<thead>
<tr>
<th>Variable</th>
<th>SD</th>
<th>Survival,* Unadjusted Relative Hazard (95% CI)</th>
<th>$P$</th>
<th>Treatment Success,† Unadjusted Relative Hazard (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>3.56</td>
<td>2.55 (0.93–7.02)</td>
<td>0.070</td>
<td>1.39 (0.84–2.30)</td>
<td>0.200</td>
</tr>
<tr>
<td>Male</td>
<td>0.47</td>
<td>1.53 (0.41–5.71)</td>
<td>0.529</td>
<td>0.71 (0.25–1.99)</td>
<td>0.515</td>
</tr>
<tr>
<td>AR</td>
<td>0.49</td>
<td>0.56 (0.12–2.13)</td>
<td>0.398</td>
<td>0.77 (0.30–2.02)</td>
<td>0.598</td>
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<tr>
<td>Class IV</td>
<td>0.46</td>
<td>0.23 (0.03–1.88)</td>
<td>0.171</td>
<td>1.11 (0.39–3.14)</td>
<td>0.844</td>
</tr>
<tr>
<td>PAPm</td>
<td>23.62</td>
<td>1.67 (0.84–3.32)</td>
<td>0.147</td>
<td>1.11 (0.70–1.75)</td>
<td>0.663</td>
</tr>
<tr>
<td>RAPm</td>
<td>3.28</td>
<td>0.94 (0.48–1.85)</td>
<td>0.865</td>
<td>1.01 (0.65–1.57)</td>
<td>0.959</td>
</tr>
<tr>
<td>CI</td>
<td>1.04</td>
<td>1.50 (0.82–2.73)</td>
<td>0.184</td>
<td>0.86 (0.55–1.37)</td>
<td>0.534</td>
</tr>
<tr>
<td>PVR</td>
<td>12.90</td>
<td>1.01 (0.50–2.05)</td>
<td>0.978</td>
<td>1.15 (0.73–1.80)</td>
<td>0.558</td>
</tr>
<tr>
<td>$\text{SvO}_2$</td>
<td>8.23</td>
<td>1.32 (0.64–2.74)</td>
<td>0.452</td>
<td>1.12 (0.64–1.97)</td>
<td>0.690</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.89</td>
<td>0.10–7.84)</td>
<td>0.916</td>
<td>0.45 (0.14–1.40)</td>
<td>0.169</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. n=35.

*Patients were censored at transplantation.
†Events include death, transplantation, and atrial septostomy.
Significantly increased survival at 1 and 3 years (100% and 66%).

Limited data are available on long-term outcomes for IPAH children. Although we previously reported survival data for IPAH children, follow-up was limited for the epoprostenol-treated patients. On the basis of that report, our approach to the IPAH child was to stratify by response status to acute vasodilator testing and functional class. ARs in functional class II or III were considered for chronic oral CCB. In contrast, chronic intravenous epoprostenol was recommended for NRs, functional class IV patients, and patients who clinically and hemodynamically failed CCB.

At our center, epoprostenol has been available on an investigational or compassionate basis since 1987; epoprostenol was approved by the US Food and Drug Administration in 1995. Our previous study showed that patients who met the criteria for and were treated with epoprostenol had significantly increased survival at 1 and 3 years (100% and 94% versus 50% and 38%, respectively; \( P=0.0002 \)) compared with those not treated with epoprostenol because of a lack of availability or parental refusal. Therefore, the latter group of children was removed from the total cohort of 77 to create the recent medical era patients (n=44) in the current analyses. The recent medical era subset is composed of children started on epoprostenol at the time it was recommended and children for whom epoprostenol was not recommended. This allowed us to analyze the outcomes of patients in the recent era of epoprostenol availability.

In the survival analyses, transplantation was a censoring event. Because transplantation occurred in patients who were likely to die, censoring at transplantation may have biased the results. For the AR group, initiation of epoprostenol was also a censoring event in the survival analysis because it signaled a major change in therapy and likely signaled disease progression.

This report confirms the significantly improved long-term survival of IPAH children treated with CCB and/or epoprostenol compared with historical reports before the use of CCB and/or epoprostenol. At 10 years, survival was 81% for ARs on CCB and 61% for all patients treated with epoprostenol. These data strongly support the use of epoprostenol in children despite the invasive nature of its delivery system. The 10-year treatment success rates of 47% and 37% for CCB and 61% for all patients treated with epoprostenol were significantly different from historical reports before the use of CCB and/or epoprostenol.

**TABLE 5. Hemodynamic Effects of Long-Term Oral CCB in ARs**

<table>
<thead>
<tr>
<th>Variable</th>
<th>SD</th>
<th>Unadjusted Relative Hazard (95% CI)</th>
<th>( P )</th>
<th>Unadjusted Relative Hazard (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>3.75</td>
<td>1.57(0.79–3.11)</td>
<td>0.194</td>
<td>1.70(1.02–2.83)</td>
<td>0.040</td>
</tr>
<tr>
<td>Male</td>
<td>0.45</td>
<td>3.20(0.78–13.1)</td>
<td>0.107</td>
<td>1.53(0.52–4.52)</td>
<td>0.443</td>
</tr>
<tr>
<td>AR</td>
<td>0.50</td>
<td>1.76(0.40–7.78)</td>
<td>0.457</td>
<td>2.18(0.76–6.28)</td>
<td>0.150</td>
</tr>
<tr>
<td>Class III/IV</td>
<td>0.42</td>
<td>3.49(0.38–31.8)</td>
<td>0.268</td>
<td>6.16(0.80–47.3)</td>
<td>0.081</td>
</tr>
</tbody>
</table>

**TABLE 6. Hemodynamic Effects of Long-Term Epoprostenol in Children Treated With Epoprostenol**

<table>
<thead>
<tr>
<th>Variable</th>
<th>At Start of Epoprostenol</th>
<th>Last Follow-Up*</th>
<th>Mean Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPm, mm Hg</td>
<td>76±22</td>
<td>57±26</td>
<td>-19 (-27 to -11)†</td>
</tr>
<tr>
<td>RAPm, mm Hg</td>
<td>5±3</td>
<td>6±4</td>
<td>-10 (-18 to 0)†</td>
</tr>
<tr>
<td>CI, L·min⁻¹·m⁻²</td>
<td>3.1±1.1</td>
<td>4.5±1.8</td>
<td>1.4 (0.8 to 2.1)†</td>
</tr>
<tr>
<td>PVR, U·m²</td>
<td>26±13</td>
<td>12±9</td>
<td>-14 (-19 to -9)†</td>
</tr>
<tr>
<td>( \text{SvO}_{2} ) %</td>
<td>64±8</td>
<td>72±7</td>
<td>8 (6 to 10)†</td>
</tr>
</tbody>
</table>

**Abbreviations as in Table 1.**

*Time from baseline to last cardiac catheterization was 106±58 months (range, 12 to 201 months).
†\( P<0.05 \).
the cohort of patients in the recent medical era, survival and treatment success rates also show significant improvement compared with historical control subjects, validating the current treatment paradigm for IPAH children; however, survival and treatment success curves show an ongoing decrease after 5 years. As has been reported in adults, age was the most significant factor for treatment success.

Our previous study showed a 5-year survival rate of 97% for ARs treated with CCB. However, at the extended 10-year follow-up, the survival rate was only 81%, and treatment success was only 47%. This finding is similar to the data recently reported by Sitbon et al13 that showed that only 52% of IPAH adults who were ARs at diagnosis had a sustained long-term benefit, ie, treatment success, with CCB at 6.5 ± 4.0 years. Sitbon et al also were able to retrospectively define more stringent criteria at baseline that identified the ARs who had the sustained long-term benefit. Although we showed that a change from AR to NR was a surrogate marker for treatment failure on CCB, we were unable to demonstrate that the stringent criteria of Sitbon et al at baseline predict the change from AR to NR status in children. However, in children, pulmonary artery pressure at diagnosis was a predictor of treatment success for ARs on CCB. Therefore, in contrast to our earlier findings, children who are ARs at diagnosis have a significant risk for treatment failure long term on CCB and need close follow-up, including serial acute vasodilator testing.

Until this point, epoprostenol was the only agent available for patients who failed CCB, and transplantation was the only consideration for patients who failed epoprostenol. We recommend epoprostenol not only to prolong survival but also to improve overall quality of life for patients on a daily basis. Although the currently recommended standard therapy demonstrates improvement in long-term survival, overall risk-benefit considerations should be assessed for all treatment options on an individual basis. Whether the efficacy of CCB and/or epoprostenol will increase with the addition of bosentan or other novel agents emerging in the therapeutic armamentarium for IPAH requires further investigation.

Study Limitations
This was an observational study with a cohort limited to a 13-year diagnostic period during which time epoprostenol became available for chronic therapy. In addition, because of the retrospective nature of the study, survival and treatment success predictors were limited to baseline demographic and hemodynamic variables because all patients did not have follow-up hemodynamic studies at the same time intervals.

Conclusions
Long-term survival of IPAH children has significantly improved with the advent of pulmonary vasodilator therapy. In the present era, the overall survival rate is 78% at 10 years. Children who are ARs are treated with CCB as first-line therapy with frequent follow-up, including serial acute vasodilator testing, to assess the persistence of an AR versus change to an NR. Patients who are NRs at diagnosis are considered for more aggressive therapy at the outset with agents such as epoprostenol. Epoprostenol should not be avoided because of the invasive nature of its delivery system because it remains a current standard for IPAH therapy. The decrease in survival and treatment success after 5 years in all IPAH children supports the role for transplant evaluation before treatment failure.

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References
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