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## REDUCTION IN PULMONARY VASCULAR RESISTANCE WITH LONG-TERM EPOPROSTENOL (PROSTACYCLIN) THERAPY IN PRIMARY PULMONARY HYPERTENSION

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### ABSTRACT

**Background** Primary (idiopathic) pulmonary hypertension is a progressive, fatal disease. Conventional therapy with anticoagulant and vasodilator drugs may improve symptoms and survival among selected patients, but there is no evidence that the disease can be reversed.

**Methods** We evaluated the effects of long-term therapy (i.e., for more than one year) with intravenous epoprostenol (prostacyclin) in patients with advanced primary pulmonary hypertension. The base-line evaluation included an assessment of pulmonary vascular dilation in response to intravenous adenosine. The epoprostenol dose was increased monthly to the maximum tolerated. Long-term therapy was evaluated by measuring improvement in symptoms, exercise capacity, and hemodynamic variables.

**Results** We evaluated 27 patients with primary pulmonary hypertension over a mean ( $\pm$ SD) period of  $16.7 \pm 5.2$  months. Intravenous adenosine had a variable effect on pulmonary vascular resistance (mean reduction, 27 percent; range, 0 to 56;  $P < 0.001$ ). Epoprostenol therapy was initiated and the rate of infusion was increased by an average of 2.4 ng per kilogram of body weight per minute each month. Twenty-six of the 27 patients had improvement in symptoms and hemodynamic measures, and overall, pulmonary vascular resistance declined by 53 percent to  $7.9 \pm 3.8$  resistance units ( $P < 0.001$ ) at the time of re-study. The long-term effects of epoprostenol exceeded the short-term pulmonary vasodilator response to adenosine in all but one patient. Seven of the eight patients who had minimal pulmonary vasodilation in response to adenosine (mean reduction in resistance units,  $< 20$  percent) still had a significant reduction in pulmonary vascular resistance when treated with epoprostenol (mean,  $39 \pm 14$  percent;  $P = 0.002$ ).

**Conclusions** In primary pulmonary hypertension, long-term therapy with epoprostenol lowers pulmonary vascular resistance beyond the level achieved in the short term with intravenous adenosine. Epoprostenol appears to have sustained efficacy in this disorder. (N Engl J Med 1998;338:273-7.)

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THE treatment of primary (idiopathic) pulmonary hypertension is problematic. Long-term anticoagulation with warfarin has been associated with improved survival without affecting symptoms, suggesting that it slows the progression of the disease.<sup>1,2</sup> Calcium-channel blockers may produce immediate vasodilation that, when the drugs are given in relatively high doses, can be sustained and may be associated with improved symptoms and survival in a selected minority of patients.<sup>2</sup>

Recently, intravenous epoprostenol (Flolan, Glaxo Wellcome, Research Triangle Park, N.C.), also known as prostacyclin, was introduced as a treatment for advanced primary pulmonary hypertension.<sup>3</sup> It has antithrombotic properties related to its effects on platelets and is a potent vasodilator of both systemic and pulmonary arteries.<sup>4</sup> Previous studies of intravenous epoprostenol in primary pulmonary hypertension have shown that, when given over the short term, it can produce vasodilation more consistently than calcium-channel blockers.<sup>5-7</sup> For these reasons, it has become the preferred long-term treatment for patients with primary pulmonary hypertension who continue to have symptoms in spite of conventional therapy. Tolerance of the medication, which always occurs, has made dosing uncertain. We undertook this study to investigate the effectiveness and potential mechanisms of action of epoprostenol given according to an aggressive dosing strategy for longer than one year in patients with primary pulmonary hypertension.

### METHODS

The study included consecutive patients referred to our center for evaluation of pulmonary hypertension who began to receive epoprostenol between January 1, 1994, and October 31, 1995,

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and were followed for 12 to 24 months. The diagnosis of primary pulmonary hypertension was established according to the criteria of the National Institutes of Health Registry on Primary Pulmonary Hypertension.<sup>8</sup> Patients were in New York Heart Association (NYHA) functional class III or IV despite optimal medical therapy. The base-line evaluation included a history and physical examination, treadmill exercise testing, and cardiac catheterization.

The exercise testing was performed according to a Naughton-Balke protocol with pulse oximetry at rest and during peak exercise. Hemodynamic variables were measured by means of right-sided heart catheterization by a thermodilution balloon-flotation catheter. Resting intracardiac pressure, systemic and pulmonary arterial oxygen saturation, and cardiac output were measured in all patients. After the base-line hemodynamic variables were recorded, the degree of pulmonary vasodilation in response to intravenous adenosine was measured.<sup>9</sup> The adenosine infusion was started at a dose of 50 to 100  $\mu\text{g}$  per kilogram of body weight per minute and increased by 50  $\mu\text{g}$  per kilogram per minute every two minutes until the patient had symptom-limiting side effects such as dyspnea or chest discomfort. If no side effects were experienced, the protocol was terminated at a peak dose of 350  $\mu\text{g}$  per kilogram per minute. All hemodynamic measurements were repeated at the peak dose of adenosine.

Epoprostenol therapy was initiated after the insertion of a Hickman catheter into a subclavian vein. Sterile, lyophilized epoprostenol sodium powder was used as long-term therapy and administered continuously with the use of a portable infusion pump (CADD 1, model 5100 HF, Pharmacia Deltec, St. Paul, Minn.). Patients were instructed in sterile techniques for mixing medication, catheter care, preparation of dressings, and drug administration by clinical nurse specialists. Epoprostenol therapy was begun at a dose of 2 ng per kilogram per minute and gradually increased to the maximal tolerated doses within seven days. Patients were then instructed to report to a nurse specialist every 30 days, or more often if they had symptoms of pulmonary hypertension (e.g., increased dyspnea) or if the side effects of the medication (e.g., jaw pain) disappeared. The dose of the medication was increased further if a reduction in side effects permitted or, in patients with minimal side effects, any time the patient had a return of symptoms that could be attributed to pulmonary hypertension. The goal was to have patients receive as high a dose of epoprostenol as possible.

At the time of the follow-up evaluation, another history was obtained and patients again underwent a physical examination, treadmill testing, and a hemodynamic assessment. In addition, a questionnaire was administered to identify any illness associated with treatment, with particular focus on pump malfunction and infections related to the Hickman catheter system.

### Statistical Analysis

Base-line demographic and hemodynamic variables were recorded and are presented as means  $\pm$ SD. Comparisons of variables measured at base line and during treatment in the same patients were made with use of Student's t-test for paired data. Comparisons between subgroups of patients were made with Student's t-test for unpaired data. The Pearson correlation coefficient was computed to test the association between base-line variables and measures of the drug's effectiveness. A chi-square analysis was used to determine the effect of treatment on the NYHA functional class. All tests were two-sided; P values below 0.05 were considered to indicate statistical significance.

## RESULTS

Of the 38 patients treated, 27 underwent a second evaluation at our institution during the study period. There were 19 women and 8 men, with a mean age of  $39.8 \pm 12.1$  years. The patients had severe symptoms; 63 percent were in NYHA functional class III, and 37 percent in NYHA functional class IV. Eleven of the original 38 patients were excluded,

for the following reasons: 5 had follow-up performed by a local doctor, 3 had follow-up catheterization performed more than 24 months after the initiation of epoprostenol therapy, and 3 declined to return for the second evaluation. Eight of these 11 patients underwent cardiac catheterization at various times after enrollment (3 to 36 months). In all eight, the pulmonary vascular resistance at base line ( $18.5 \pm 8.6$  resistance units) was lower on restudy ( $8.2 \pm 3.2$  resistance units,  $P=0.01$ ). None of the 11 patients died during the study period. One patient, who declined catheterization, died subsequently.

At base line, the mean duration of exercise was  $261 \pm 175$  seconds (range, 0 to 695). The mean pulmonary-artery pressure was  $67 \pm 10$  mm Hg, and the pulmonary vascular resistance was  $16.7 \pm 5.4$  units (Table 1). Adenosine caused a variable but significant decrease of  $27 \pm 18$  percent in pulmonary vascular resistance (range, 0 to 56 percent;  $P<0.001$ ) (Table 1). The mean dose of adenosine used was  $211 \pm 70$   $\mu\text{g}$  per kilogram per minute.

After the base-line evaluation, epoprostenol therapy was initiated, and the dose was increased to the maximal tolerated dose over a period of seven days. Doses were subsequently increased by 2 ng per kilogram per minute every month if side effects permitted, or whenever the patient reported an increase in dyspnea or fatigue that was attributed to primary pulmonary hypertension. The mean duration of treatment at follow-up was  $16.7 \pm 5.2$  months (range, 12 to 24). The mean dose of epoprostenol at the time of the follow-up study was  $40 \pm 15$  ng per kilogram per minute, which corresponds to a mean increase of 2.4 ng per kilogram per minute each month. Concurrent medications also included digoxin (used by 93 percent of patients), diuretics (85 percent), warfarin (100 percent), and calcium-channel blockers (41 percent). Patients whose condition had deteriorated while they were receiving calcium-channel blockers had this medication withdrawn before the initiation of epoprostenol therapy. Patients whose condition was stable but who had symptoms while receiving calcium-channel blockers continued to receive these drugs throughout the study period. In no instance were calcium-channel blockers added to the patient's treatment regimen while he or she was receiving epoprostenol.

At the time of the follow-up evaluation, all patients had improvement in their symptoms; 22 percent were in NYHA functional class I, 74 percent in class II, and 4 percent in class III ( $P<0.001$ ). The duration of exercise on the treadmill increased by 142 percent to  $631 \pm 283$  seconds ( $P<0.001$ ). The improvement in treadmill time did not correlate with the decrease in pulmonary vascular resistance ( $r=0.33$ ,  $P=0.16$ ). Systemic arterial oxygen saturation during exercise at base line ( $93 \pm 6$  percent) was not significantly changed at follow-up ( $91 \pm 4$  percent,  $P=0.11$ ).

At the time of repeated cardiac catheterization, the mean pulmonary arterial pressure was 22 percent lower than at base line (range, 0 to 51 percent lower;  $P < 0.001$ ), and the cardiac output had increased by 67 percent (range, -15 to 155 percent;  $P < 0.001$ ) (Table 1). Pulmonary vascular resistance fell to  $7.9 \pm 3.8$  units ( $P < 0.001$ ), a mean reduction of 53 percent (range, 3 to 78 percent). Twenty-six of the 27 patients had a long-term reduction of at least 20 percent in pulmonary vascular resistance.

We compared the short-term vasodilator response to adenosine with the long-term effects of epoprostenol. In all but one instance, the decrease in pulmonary vascular resistance with long-term epoprostenol therapy exceeded the short-term decrease in resistance in response to adenosine challenge at base line (Fig. 1). In addition, the greater the short-term decrease in pulmonary vascular resistance with adenosine, the lower the pulmonary vascular resistance became with long-term epoprostenol therapy ( $r = 0.65$ ,  $P = 0.01$ ). However, seven of eight patients with a minimal response to adenosine (decrease in resistance,  $< 20$  percent; mean,  $6 \pm 13$ ) still had a significant long-term reduction in pulmonary vascular resistance with epoprostenol (mean,  $39 \pm 14$  percent; range, 20 to 66;  $P = 0.002$ ) (Fig. 2). One patient who had a minimal decrease in pulmonary vascular resistance in response to adenosine had little further reduction after 15 months of epoprostenol.

The change in pulmonary vascular resistance after long-term epoprostenol therapy was not related to pulmonary vascular resistance at base line ( $r = 0.117$ ,  $P = 0.56$ ). Thus, even patients with extremely advanced disease and markedly elevated pulmonary vascular resistance had a significant improvement with epoprostenol.

Eleven patients received epoprostenol and calcium-channel blockers concurrently. To test whether the combination treatment influenced the long-term response to epoprostenol, we compared these 11 patients with the 16 who received epoprostenol but not calcium-channel blockers. The patients who received both epoprostenol and calcium-channel blockers were similar to those who received epoprostenol but not calcium-channel blockers with respect to the severity of their pulmonary hypertension (pulmonary vascular resistance, 14.3 vs. 18.2 units;  $P = 0.07$ ), the short-term vasodilator response to adenosine (decrease in pulmonary vascular resistance, 29 percent vs. 26 percent;  $P = 0.67$ ), and the long-term reduction in pulmonary vascular resistance achieved (56 percent vs. 50 percent,  $P = 0.40$ ).

#### Morbidity

Side effects related to the use of epoprostenol were common and included diarrhea, jaw pain, headaches, and flushing in all patients. All the serious complications were related to the delivery system. No patient

**TABLE 1.** HEMODYNAMIC VARIABLES AT BASE LINE, IN RESPONSE TO THE ADMINISTRATION OF ADENOSINE, AND AFTER LONG-TERM EPOPROSTENOL THERAPY.\*

VARIABLE	AT BASE LINE	ADENOSINE	EPOPROSTENOL
Systemic mean arterial pressure (mm Hg)	102±18	99±16	87±10†
Right atrial mean pressure (mm Hg)	15±6	16±6	9±7†
Pulmonary-artery mean pressure (mm Hg)	67±10	65±13	52±12†
Cardiac output (liters/min)	3.76±1.19	5.09±1.68†	6.29±1.97†
Systemic arterial oxygen saturation (%)	91±5	94±4†	93±6‡
Pulmonary-artery oxygen saturation (%)	53±8	65±8†	64±10†
Pulmonary vascular resistance (units)	16.7±5.4	12.1±4.6†	7.9±3.8†
Systemic vascular resistance (units)	25.1±8.9	17.7±6.2†	13.5±4.9†

\*Values are means ±SD.

† $P < 0.001$  for the comparison with base line.

‡ $P < 0.05$  for the comparison with base line.

had failure of the ambulatory infusion pump or thrombosis of the Hickman catheter. Ten patients had a total of 17 local infections at the exit site of the Hickman catheter; these were successfully treated with oral antibiotic agents. Three of these 10 patients also had an episode of sepsis, documented by positive blood cultures, that required treatment with intravenous antibiotic agents. The rate of local infection was 0.49 per patient-year, and that of blood-borne infections was 0.09 per patient-year.

#### DISCUSSION

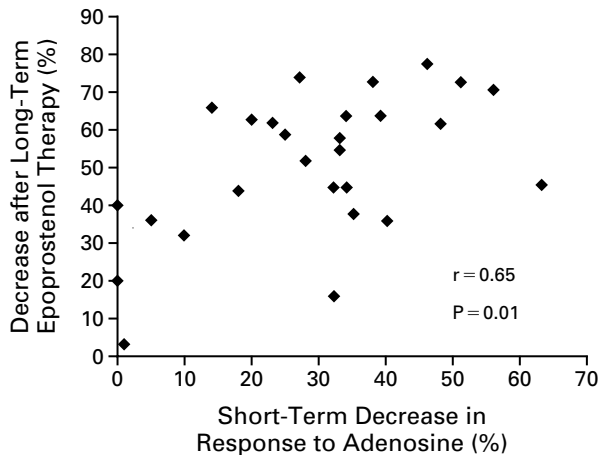
Primary pulmonary hypertension is caused by a pulmonary vascular arteriopathy that affects predominantly the arteriolar vessels, the mechanism of which is unclear. Pathological studies reveal medial hypertrophy, intimal proliferation and fibrosis, and thrombotic lesions, which are unevenly distributed throughout the pulmonary vasculature.<sup>10,11</sup> Although some of these lesions appear histologically very complex, it remains unknown which lesions reflect irreversible vascular changes.<sup>12</sup>

The established conventional therapy for this disease has been anticoagulant and vasodilator agents. Anticoagulant agents are believed to reduce or halt in situ thrombosis, thus slowing the progression of the disease. In this respect, one prospective and one retrospective study suggest that they are effective.<sup>1,2</sup> There are no data, however, demonstrating that warfarin directly influences the extent of medial hypertrophy, vasoconstriction, or intimal proliferation.

Calcium-channel blockers have been used to reduce the level of vasoconstriction, and they appear to be effective in selected patients.<sup>2,13</sup> They are not



**Figure 1.** Pulmonary Vascular Resistance at Base Line, after the Administration of Intravenous Adenosine to Test Pulmonary Vasoreactivity, and after Long-Term Epoprostenol Therapy. In all but one patient, the long-term effects of epoprostenol in lowering pulmonary vascular resistance exceeded the short-term pulmonary vasodilator response to adenosine.



**Figure 2.** Reduction in Pulmonary Vascular Resistance with Epoprostenol Therapy in Relation to the Short-Term Reduction after the Administration of Adenosine.

Patients with the greatest short-term reduction in pulmonary vascular resistance had the greatest long-term reduction as well. However, the patients who had little or no reduction in pulmonary vascular resistance in response to adenosine challenge still had a significant reduction in pulmonary vascular resistance with long-term epoprostenol therapy.

expected to be effective in patients whose vascular changes are not related to vasoconstriction (such as those with changes caused by thrombotic lesions) and who are thus unresponsive to vasodilator challenge. Calcium-channel blockers are also unlikely to be effective in patients with vasoconstriction that is associated with extensive intimal proliferation and fibrosis that is too severe to be reversed. Studies

of the long-term effectiveness of calcium-channel blockers in patients who respond to these agents in the short term demonstrate that the level of vasodilation achieved in the short term remains relatively constant when therapy continues.<sup>2,13,14</sup>

Epoprostenol is an appealing therapy because of its antithrombotic and vasodilator properties.<sup>4</sup> The use of intravenous epoprostenol in this illness represents a novel treatment strategy. It is the first instance in which a substance produced by normal vascular endothelium has been used as a treatment for a vasculopathy. Clearly, some of the therapeutic properties of epoprostenol are not yet understood.

When epoprostenol was introduced as a treatment for primary pulmonary hypertension, it was characterized as a bridge to lung transplantation, and it was hoped that it could cause immediate vasodilation that might be sustained until the patient could receive a graft.<sup>15</sup> Subsequently, prospective studies have shown sustained clinical benefits of epoprostenol and improved long-term survival in patients who received this agent, as compared with historical controls.<sup>3,7,16</sup> Its mechanism of action has been attributed to long-term pulmonary vasodilation and possibly to its antiplatelet effects.

Our results, however, show that long-term treatment is associated not only with vasodilation, but also with significant reductions in pulmonary vascular resistance that go beyond immediate vasodilation. Although there was no control group in this study, spontaneous reductions in pulmonary vascular resistance would be unlikely to occur.<sup>8</sup> The fact that epoprostenol caused a long-term reduction in pulmonary vascular resistance that exceeded that which could be

achieved through vasodilator challenge is consistent with the drug's having a different effect on the pulmonary vasculature when given over the long term. The existence of such a different mechanism is supported by the fact that long-term epoprostenol therapy was effective in lowering pulmonary vascular resistance in patients who had no short-term response to adenosine at all. The process by which epoprostenol affects the pulmonary vasculature in such patients remains speculative, since only serial open-lung biopsies could reveal the precise nature of the vascular changes. However, experimental data from studies of epoprostenol in animals with vascular disease have demonstrated its potential to reverse vascular lesions.<sup>4,17</sup>

Tolerance of epoprostenol with long-term treatment, manifested by a return of symptoms, is poorly understood, but it can be overcome by continuing to increase the dosage over time. The optimal strategy is unclear. In previous studies, the dose was increased if the patient had worsening symptoms or if his or her condition was deteriorating.<sup>7,16</sup> Our strategy was more aggressive and was designed to maintain therapy at the highest dose tolerated. Patients often received a dose increase even if they had clinical improvement, if side effects permitted. Whether this aggressive strategy is essential to achieve this level of long-term reduction in pulmonary vascular resistance was not tested.

The fact that all but one of our patients had a significant improvement in hemodynamic variables with long-term epoprostenol treatment indicates the remarkable success rate of this therapy. Indeed, were it not for the complexity and expense of the delivery system, epoprostenol might be considered first-line therapy for all patients with primary pulmonary hypertension. The chief adverse effects of treatment were serious infections related to the delivery system. The incidence of sepsis, however, was lower than previously reported in a multicenter trial.<sup>3</sup> We attribute this lower rate to the careful measures taken to educate the patients and referring physicians about the use of a sterile technique in mixing the medications and the early detection of any serious infection.

In summary, in this study epoprostenol caused substantial long-term reductions in pulmonary vascular resistance in patients with severe primary pulmonary hypertension; these reductions exceeded the short-term reductions in pulmonary vascular resistance achieved with adenosine. Our results should encourage physicians to consider long-term epoprostenol treatment for patients with less advanced disease, with

the possibility of achieving even better results. As pulmonary vascular resistance returns toward normal with long-term use, patients waiting for lung grafts may no longer need transplantation. This study also raises the question of whether epoprostenol could eventually be withdrawn or substituted for calcium-channel blockers, other oral agents, or both. The answers to these questions may hold promise for the long-term treatment of this once fatal illness.

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