

A COMPARISON OF CONTINUOUS INTRAVENOUS EPOPROSTENOL (PROSTACYCLIN) WITH CONVENTIONAL THERAPY FOR PRIMARY PULMONARY HYPERTENSION

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Abstract Background. Primary pulmonary hypertension is a progressive disease for which no treatment has been shown in a prospective, randomized trial to improve survival.

Methods. We conducted a 12-week prospective, randomized, multicenter open trial comparing the effects of the continuous intravenous infusion of epoprostenol (formerly called prostacyclin) plus conventional therapy with those of conventional therapy alone in 81 patients with severe primary pulmonary hypertension (New York Heart Association functional class III or IV).

Results. Exercise capacity was improved in the 41 patients treated with epoprostenol (median distance walked in six minutes, 362 m at 12 weeks vs. 315 m at base line), but it decreased in the 40 patients treated with conventional therapy alone (204 m at 12 weeks vs. 270 m at base line; $P < 0.002$ for the comparison of the treatment groups). Indexes of the quality of life were improved only in the epoprostenol group ($P < 0.01$).

Hemodynamics improved at 12 weeks in the epoprostenol-

treated patients. The changes in mean pulmonary-artery pressure for the epoprostenol and control groups were -8 percent and $+3$ percent, respectively (difference in mean change, -6.7 mm Hg; 95 percent confidence interval, -10.7 to -2.6 mm Hg; $P < 0.002$), and the mean changes in pulmonary vascular resistance for the epoprostenol and control groups were -21 percent and $+9$ percent, respectively (difference in mean change, -4.9 mm Hg per liter per minute; 95 percent confidence interval, -7.6 to -2.3 mm Hg per liter per minute; $P < 0.001$). Eight patients died during the study, all of whom had been randomly assigned to conventional therapy ($P = 0.003$). Serious complications included four episodes of catheter-related sepsis and one thrombotic event.

Conclusions. As compared with conventional therapy, the continuous intravenous infusion of epoprostenol produced symptomatic and hemodynamic improvement, as well as improved survival in patients with severe primary pulmonary hypertension. (N Engl J Med 1996;334:296-301.)

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PRI-MARY pulmonary hypertension is a disease characterized by the progressive elevation of pulmonary-artery pressure and vascular resistance, ultimately producing right ventricular failure and death.¹⁻³ A variety of treatments have been used, including vasodilators,⁴⁻⁷ anticoagulant agents,^{6,8} and lung or heart-lung transplantation,⁹⁻¹³ but none have resulted in improved survival in a prospective, randomized trial.

Epoprostenol (formerly called prostacyclin or pros-

taglandin I₂) is a potent, short-acting vasodilator and inhibitor of platelet aggregation that is produced by vascular endothelium. Short-term infusions of epoprostenol decrease pulmonary vascular resistance in a dose-dependent manner in patients with primary pulmonary hypertension, and this response has been used to determine whether long-term oral vasodilator therapy is warranted.¹⁴

In an eight-week prospective, randomized trial, the continuous intravenous infusion of epoprostenol produced hemodynamic and symptomatic improvement.¹⁵ Patients treated with epoprostenol for up to three years appeared to live longer than historical controls from the Registry on Primary Pulmonary Hypertension of the National Institutes of Health (NIH) who received standard therapy.¹⁶ The objective of this study was to evaluate the effects of the continuous infusion of epoprostenol on exercise capacity, quality of life, hemodynamics, and survival in a 12-week open-label, prospective, randomized, multicenter study of patients with severe primary pulmonary hypertension who continued to be in New York Heart Association (NYHA) functional class III or IV despite conventional therapy.

METHODS

After giving their informed consent, 81 patients with primary pulmonary hypertension entered the study. We established a diagnosis in all patients before they entered, using the criteria of the Registry on Primary Pulmonary Hypertension of the NIH.¹ Patients were in NYHA functional class III or IV despite optimal medical therapy,

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which consisted of the administration of anticoagulants, oral vasodilators, diuretic agents, cardiac glycosides, and supplemental oxygen. The primary objective was to evaluate the effects of the continuous infusion of epoprostenol on exercise capacity. Other major, prospectively defined objects of study were the effects of epoprostenol on survival and its effects on the quality of life. We also evaluated the effects of epoprostenol on hemodynamics.

Sterile, lyophilized epoprostenol sodium powder, synthesized by Upjohn (Kalamazoo, Mich.), was formulated by Wellcome Research Laboratories (Beckenham, Kent, United Kingdom) as flolan. Immediately before administration, epoprostenol was reconstituted with sterile glycine buffer (pH 10.5) and filtered.

Right-heart catheterization was performed in all patients with the use of standard techniques. After base-line hemodynamic variables were measured, epoprostenol was infused at an initial rate of 2 ng per kilogram of body weight per minute, with increments of 2 ng per kilogram per minute every 15 minutes. The infusion was discontinued at the dose that produced one or more of the following effects: a decrease of more than 40 percent in systemic arterial pressure, an increase of more than 40 percent in heart rate, or signs or symptoms deemed sufficient to warrant discontinuation of the infusion — that is, nausea, vomiting, severe headache, lightheadedness, or severe restlessness and anxiety. The infusion was subsequently reduced by 2 ng per kilogram per minute, and hemodynamic measurements were recorded at this maximal tolerated dose.

Randomization and Treatment

Eighty-one patients completed the short-term dose-ranging phase of the study and entered the 12-week study. One additional patient, in whom a pneumothorax developed during the base-line cardiac catheterization, was not enrolled in the study. A computer-generated, adaptive randomization was performed, with stratification according to the functional class, study center, and base-line vasodilator use.¹⁷ Forty-one patients were randomly assigned to receive epoprostenol plus conventional therapy, and 40 patients were randomly assigned to receive conventional therapy alone. All the patients received oral anticoagulant agents during the study, with the exception of one patient in each treatment group. Adjustments in concomitant medications were allowed during the study on the basis of clinical judgment.

Venous access for the infusion of epoprostenol in the epoprostenol group was obtained by the insertion of a permanent catheter into a subclavian or jugular vein. Epoprostenol was infused continuously with the use of a portable infusion pump (CADD-1 Model 5100 HF, Pharmacia Deltec, St. Paul, Minn.). Before being discharged from the hospital, patients were trained in sterile technique, catheter care, and drug preparation and administration. Epoprostenol therapy was initiated at a dose of 4 ng per kilogram per minute below the maximal tolerated dose determined during dose ranging. Dose adjustments during the 12-week study were made on the basis of signs or symptoms consistent with clinical deterioration or the occurrence of adverse events. Hemodynamic measurements were repeated at the end of the study.

Exercise capacity was assessed at base line and at 1, 6, and 12 weeks with the use of the unencouraged six-minute-walk test.¹⁸ The patients' quality of life was evaluated at base line and at 6 and 12 weeks with the Chronic Heart Failure Questionnaire, the Nottingham Health Profile, and the Dyspnea-Fatigue Rating.¹⁹⁻²¹ Both the walk test and the quality-of-life instruments were administered by personnel not directly involved in patient care who were unaware of the treatment groups to which patients had been assigned. At the completion of the study, all patients were given the option of entering an open-label study of continuous epoprostenol therapy.

Statistical Analysis

Data are presented as means \pm SE, medians, and 95 percent confidence intervals. Six-minute-walk data were analyzed in two intention-to-treat analyses: a nonparametric analysis of covariance and a parametric analysis of variance.²² In the nonparametric analysis of covariance, patients who were unable to walk at base line were assigned a value of 0 m. Patients who had died or were unable to walk because of illness at week 12 were also assigned a value of 0 m. Patients who underwent transplantation during the study completed the

exercise test at week 12, and the data on this test were included in the nonparametric analysis of covariance. An ordinary least-squares regression of the ranks of walking distance at week 12 was performed, with adjustment for covariates. The resulting residuals were analyzed with the use of the Cochran-Mantel-Haenszel procedure.

The parametric analysis of variance evaluated the changes from base line to week 12 in the distances walked. In this analysis, patients who died or received transplants before week 12 had their last observations (or six-minute-walk values before transplantation) carried forward and used as their values at week 12.

Survival was analyzed with the use of a log-rank test and included all the randomized patients. Survival analyses, adjusted for covariates, were based on the Cox regression model²³ and were performed both with data on some patients censored at transplantation and with such data not censored. For hemodynamic and quality-of-life measures, we determined the change from base line and constructed two-sided 95 percent confidence intervals^{24,25} for the differences between treatment groups. In the Spearman analyses of the correlation between the changes from base-line six-minute-walk values and long-term hemodynamic effects, the last observation carried forward was used for patients who died or received transplants. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

The base-line demographic and hemodynamic characteristics of the two groups are shown in Table 1. There were no significant differences between the groups in the severity of pulmonary hypertension, duration of illness, use of concomitant medication, or NYHA functional class. The base-line distance in the six-minute walk was greater, though not significantly greater, in the epoprostenol group.

Effects of the Short-Term Infusion

The maximal short-term hemodynamic responses to infused epoprostenol are shown in Table 2. Only chang-

Table 1. Demographic and Hemodynamic Characteristics at Base Line, According to Treatment Group.*

CHARACTERISTIC	EPOPSTENOL (N = 41)	CONVENTIONAL THERAPY (N = 40)
Age — yr	40 \pm 3	40 \pm 2
Sex — no. (%)		
Male	10 (24)	12 (30)
Female	31 (76)	28 (70)
NYHA functional class — no. (%) [†]		
III	31 (76)	29 (73)
IV	10 (24)	11 (28)
Months since diagnosis	32 \pm 8	25 \pm 6
Oral vasodilator therapy — no. (%)	27 (66)	24 (60)
Mean pulmonary-artery pressure — mm Hg	61 \pm 2	59 \pm 2
Mean right atrial pressure — mm Hg	13 \pm 1	12 \pm 1
Mean systemic-artery pressure — mm Hg	90 \pm 2	89 \pm 2
Mean pulmonary-capillary wedge pressure — mm Hg	10 \pm 1	10 \pm 1
Cardiac index — liter/min/m ²	2.0 \pm 0.1	2.1 \pm 0.2
Heart rate — beats/min	79 \pm 2	86 \pm 2
Systemic arterial oxygen saturation — %	91 \pm 2	92 \pm 1
Mixed venous oxygen saturation — %	62 \pm 2	59 \pm 2
Stroke volume — ml/beat	46 \pm 3	45 \pm 4
Pulmonary vascular resistance — mm Hg/liter/min	16 \pm 1	16 \pm 1
Systemic vascular resistance — mm Hg/liter/min	25 \pm 1	24 \pm 1
6-min walk — m [‡]	316 \pm 18	272 \pm 23

*Plus-minus values are means \pm SE. Percentages do not always sum to 100 because of rounding.

[†]NYHA denotes New York Heart Association.

[‡]The distance walked in meters in six minutes.

es in stroke volume and systemic vascular resistance were significantly different in the two treatment groups. The mean maximal tolerated dose of epoprostenol was 9.2 ± 0.5 ng per kilogram per minute in the group subsequently assigned to receive epoprostenol and 7.6 ± 0.5 ng per kilogram per minute in the conventional-therapy group. The initial dose in the patients treated with a long-term infusion of epoprostenol was 5.3 ± 0.5 ng per kilogram per minute; the dose was increased to 9.2 ± 0.8 ng per kilogram per minute by the end of the study.

Exercise Capacity

Exercise capacity was evaluated by measuring the change in the distance the patient could walk in six minutes from base line to week 12. The nonparametric analysis of covariance, with adjustment for the six-minute-walk values and the use of vasodilators at base line, showed that the median change from base line was an increase of 31 m in the epoprostenol-treated patients (median distance walked, 362 m at week 12 as compared with 315 m at base line) and a decrease of 29 m in the patients receiving conventional therapy (204 m at week 12 as compared with 270 m at base line; $P < 0.002$ for the comparison of the treatment groups). Exercise capacity remained significantly improved ($P < 0.02$) in the epoprostenol-treated patients after adjustment for both (1) the hemodynamic changes in stroke volume and systemic vascular resistance that resulted from the short-term infusion of epoprostenol (the only significant differences between the treatment groups) and (2) six-minute-walk values and vasodilator use at base line.

The mean distance walked increased by 32 m in the epoprostenol group (mean distance walked, 348 ± 17 m

Table 2. Short-Term Hemodynamic Effects of Epoprostenol at the Maximal Tolerated Dose during Short-Term Dose Ranging.*

VARIABLE	CHANGE FROM BASE LINE		95% CONFIDENCE INTERVAL†
	EPOPROSTENOL (N = 41)	CONVENTIONAL THERAPY (N = 40)	
Mean pulmonary-artery pressure (mm Hg)	-2.4 ± 1.1	-1.4 ± 1.3	-4.4 to 2.4
Mean right atrial pressure (mm Hg)	-0.2 ± 0.4	-1.3 ± 0.6	-0.3 to 2.5
Mean systemic-artery pressure (mm Hg)	-13.6 ± 1.5	-11.9 ± 1.2	-5.5 to 2.2
Mean pulmonary-capillary wedge pressure (mm Hg)	1.5 ± 0.9	1.0 ± 0.8	-2.0 to 2.9
Cardiac index (liter/min/m ²)	0.9 ± 0.1	0.5 ± 0.2	0.0 to 0.8
Heart rate (beats/min)	6.8 ± 1.2	6.1 ± 1.9	-3.7 to 5.1
Systemic arterial oxygen saturation (%)	-0.6 ± 0.7	1.3 ± 1.0	-4.2 to 0.5
Mixed venous oxygen saturation (%)	5.8 ± 1.4	8.9 ± 1.3	-7.0 to 0.9
Stroke volume (ml/beat)	14.8 ± 2.7	5.8 ± 3.0	1.1 to 17.0
Pulmonary vascular resistance (mm Hg/liter/min)	-5.5 ± 0.8	-3.9 ± 0.8	-4.0 to 0.7
Systemic vascular resistance (mm Hg/liter/min)	-10.5 ± 0.9	-7.3 ± 0.9	-5.7 to -0.6

*Plus-minus values are mean (\pm SE) changes from base line. The maximal tolerated doses were 9.2 ± 0.5 ng per kilogram per minute in the epoprostenol group and 7.6 ± 0.5 ng per kilogram per minute in the conventional-therapy group.

†95 percent confidence intervals are for the differences in mean changes between treatment groups. A confidence interval that does not contain zero indicates statistical significance.

Table 3. Effects on the Quality of Life of Treatment with Epoprostenol as Compared with Conventional Therapy.*

TREATMENT EFFECT	CHANGE FROM BASE LINE					
	EPOPROSTENOL		CONVENTIONAL THERAPY		HODGES-LEHMANN ESTIMATE†	95% CONFIDENCE INTERVAL‡
	no. of patients	median change	no. of patients	median change		
Chronic Heart Failure Questionnaire§						
Dyspnea	35	8.0	26	0.0	7.0	4.0 to 10.0
Fatigue	39	5.0	31	0.0	5.0	3.0 to 7.0
Emotional function	38	6.0	30	-1.0	7.0	3.0 to 10.0
Mastery¶	39	3.0	30	-0.5	2.5	1.0 to 4.0
Nottingham Health Profile						
Emotional reaction	37	-10.0	31	0.0	-14.7	-24.5 to
Energy	39	-36.8	31	0.0	-36.8	-4.9
Pain	39	0.0	31	0.0	0.0	-60.8 to 0.0
Physical mobility	39	-11.2	30	-6.4	-9.2	-5.8 to 0.0
Sleep	41	-16.1	31	0.0	-21.7	-19.9 to 2.0
Social isolation	40	0.0	31	0.0	0.0	-34.3 to -9.1
Dyspnea-Fatigue Rating§	41	1.0	31	0.0	2.0	1.0 to 3.0

*Patients who died during the study were excluded from the quality-of-life analysis. For the three patients who underwent transplantation during the study, the 12-week quality-of-life assessment was performed after transplantation. For the two patients who discontinued the use of epoprostenol during the study, the 12-week quality-of-life assessment was performed at the end of the study.

†Hodges-Lehmann estimates²⁴ are estimates of the true median changes from base line.

‡95 percent confidence intervals are for comparisons between treatment groups. A confidence interval that does not contain zero indicates statistical significance.

§Positive values for changes indicate improvements over base-line values.

¶Mastery is defined as a patient's feeling of control over his or her disease.

||Negative values for changes indicate improvements over base-line values.

at week 12 as compared with 316 ± 18 m at base line) and decreased by 15 m in the conventional-therapy group (257 ± 24 m at week 12 as compared with 272 ± 23 m at base line; $P < 0.003$ for the comparison of the treatment groups, as determined with a parametric analysis of variance).

There were significant inverse correlations between the change in the distance the patient could walk in six minutes and the corresponding changes in mean pulmonary-artery pressure, right atrial pressure, mean systemic-artery pressure, pulmonary vascular resistance, and systemic vascular resistance from base line to week 12. There were also significant correlations between the change in the six-minute-walk value and the corresponding changes in cardiac index and stroke volume from base line to week 12.

Clinical and Hemodynamic Measures

The results of assessments of quality of life are shown in Table 3. Patients who received epoprostenol for 12 weeks had significant improvements in all four parts of the Chronic Heart Failure Questionnaire, in two of the six parts of the Nottingham Health Profile, and in the Dyspnea-Fatigue Rating ($P < 0.01$).

Functional class was assessed in all patients who were alive and had not received transplants by the end of the 12-week study period (40 in the epoprostenol group and 31 in the conventional-therapy group). In the epoprostenol group, the functional class improved

in 16 patients (40 percent), worsened in 5 (13 percent), and was unchanged in 19 (48 percent). In the conventional-therapy group, in contrast, the functional class improved in only 1 patient (3 percent), worsened in 3 (10 percent), and was unchanged in 27 (87 percent; $P<0.02$ for the comparison of the treatment groups).

The changes in the hemodynamic measures from base line to week 12 are shown in Table 4. Comparisons of the treatments showed that the epoprostenol-treated patients had significant improvement in mean pulmonary-artery pressure, cardiac index, and pulmonary vascular resistance. The changes in mean pulmonary-artery pressure for the epoprostenol and control groups were -8 percent and $+3$ percent, respectively ($P<0.002$), and the mean changes in pulmonary vascular resistance were -21 percent and $+9$ percent, respectively ($P<0.001$).

Transplantation and Survival

Three patients underwent lung transplantation during the 12-week study: one epoprostenol-treated patient at 11 days and two patients treated with conventional therapy at 63 and 68 days. All three were alive at the end of the study. Therapy for two patients randomly assigned to receive epoprostenol was discontinued before the end of the study: in one patient, because of adverse effects (jaw pain and diarrhea), and in the other, because the patient was unable to manage the drug-delivery system.

Eight patients died during the 12-week study; all were in the conventional-therapy group ($P=0.003$) (Fig. 1). Among those who died, there was an equal distribution of patients in NYHA functional classes III and IV. The six-minute-walk values at base line were significantly lower in these 8 patients than in the 73 survivors in both groups (195 ± 63 m vs. 305 ± 14 m, $P<0.03$). There were, however, no significant differences in base-line hemodynamic variables or short-term responses during dose ranging between the survivors in both treatment groups and the eight patients who died. Performance in the six-minute walk at base line was an independent predictor of survival ($P<0.05$); however, survival remained significantly improved in the epoprostenol group after adjustment for that variable ($P<0.002$). Survival also remained significantly improved in the epoprostenol group ($P<0.001$) after adjustment for the changes in stroke volume and in systemic vascular resistance in response to the short-term infusion of epoprostenol (the only significant differences between treatment groups).

Complications

Minor complications related to the use of epoprostenol were frequent and included jaw pain, diarrhea, flushing, headaches, nausea, and vomiting. Serious complications were most often due to the delivery system and included four episodes of nonfatal, catheter-related sepsis and one nonfatal thrombotic event (a paradoxical embolism). There were 26 episodes of malfunction of the drug-delivery system resulting in temporary in-

terruption of the infusion. These included occlusions, perforations, and dislodgements of the catheter and pump malfunction. While epoprostenol therapy was interrupted, patients experienced an increase in their symptoms. Additional problems related to the delivery system included irritation or infection at the catheter site in seven patients, bleeding at the catheter site in four, and catheter-site pain in four.

DISCUSSION

Since the description of the characteristic hemodynamic abnormalities over 40 years ago, primary pulmonary hypertension has been regarded as a progressive disease that is usually refractory to treatment.²⁶ In the present study, a randomized, controlled trial, we documented improvement in exercise capacity and survival in patients with severe primary pulmonary hypertension who were treated with epoprostenol in addition to conventional therapy, as compared with patients treated with conventional therapy alone. The eight patients who died had been randomly assigned to the conventional-therapy group, and all died as a result of their underlying pulmonary vascular disease. Even when these patients were excluded from the analyses of exercise-test results, exercise capacity remained significantly improved in the epoprostenol-treated patients as compared with the conventional-therapy group. In addition, hemodynamic function and exercise capacity tended to deteriorate or remain unchanged with conventional ther-

Table 4. Hemodynamic Effects of Epoprostenol or Conventional Therapy at 12 Weeks.*

VARIABLE	CHANGE FROM BASE LINE		DIFFERENCE BETWEEN TREATMENTS	95% CONFIDENCE INTERVAL†
	EPOPROSTENOL	CONVENTIONAL THERAPY		
Mean pulmonary-artery pressure (mm Hg)	-4.8 ± 1.3	1.9 ± 1.6	-6.7	-10.7 to -2.6
Mean right atrial pressure (mm Hg)	-2.2 ± 1.1	0.1 ± 0.9	-2.3	-5.2 to 0.7
Mean systemic-artery pressure (mm Hg)	-4.8 ± 2.1	-0.9 ± 1.7	-3.9	-9.6 to 1.7
Mean pulmonary-capillary wedge pressure (mm Hg)	0.4 ± 1.2	-1.0 ± 1.6	1.4	-2.5 to 5.3
Cardiac index (liter/min/m ²)	0.3 ± 0.1	-0.2 ± 0.2	0.5	0.2 to 0.9
Heart rate (beats/min)	-0.9 ± 2.5	-1.8 ± 1.5	0.9	-5.2 to 7.2
Systemic arterial oxygen saturation (%)	2.0 ± 1.6	-0.6 ± 1.4	2.6	-1.8 to 7.1
Mixed venous oxygen saturation (%)	1.2 ± 1.8	-2.6 ± 2.0	3.8	-1.6 to 9.2
Stroke volume (ml/beat)	6.6 ± 2.2	-3.5 ± 3.3	10.1	2.5 to 17.8
Pulmonary vascular resistance (mm Hg/liter/min)	-3.4 ± 0.7	1.5 ± 1.2	-4.9	-7.6 to -2.3
Systemic vascular resistance (mm Hg/liter/min)	-4.0 ± 1.0	2.1 ± 1.4	-6.1	-9.5 to -2.8

*Plus-minus values are the mean (\pm SE) changes from base line. Patients who died or underwent transplantation during the study, as well as the two patients who discontinued epoprostenol during the study, were excluded from the hemodynamic analysis.

†95 percent confidence intervals are for comparisons between treatment groups. A confidence interval that does not contain zero indicates statistical significance.

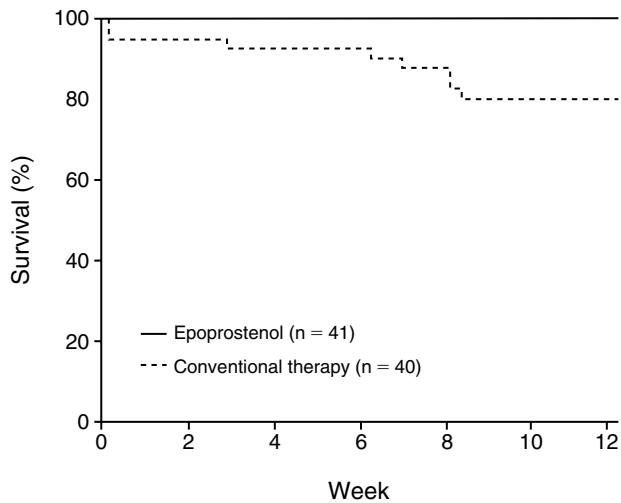


Figure 1. Survival among the 41 Patients Treated with Epoprostenol and the 40 Patients Receiving Conventional Therapy. Data on patients who underwent transplantation during the 12-week study were censored at the time of transplantation. Estimates were made by the Kaplan–Meier product-limit method. The two-sided P value from the log-rank test was 0.003. Survival analysis with data on patients receiving transplants not censored at transplantation resulted in the same level of significance (two-sided P = 0.003 by the log-rank test).

apy, whereas it was consistently improved with the use of epoprostenol.

The rationale for using continuous epoprostenol infusion to treat primary pulmonary hypertension was based initially on the demonstration that epoprostenol is a potent pulmonary vasodilator when administered to laboratory animals with acute pulmonary vasoconstriction induced by constrictor stimuli.^{27,28} Our results, consistent with these findings, indicate that the short-term infusion of epoprostenol reduces pulmonary-artery pressure and pulmonary vascular resistance in patients with primary pulmonary hypertension. However, randomization in this and in our previous study¹⁵ was performed independently of the short-term responses to epoprostenol during dose ranging, and we have previously observed that long-term effects are frequently seen even in the patients in whom no short-term changes were manifested.^{15,16} Thus, the long-term effects of epoprostenol in primary pulmonary hypertension may be only partially related to its vasodilator properties and may be due, at least in part, to poorly defined effects on vascular growth, remodeling, or platelet function.²⁹⁻³² Unlike the use of other vasodilators to treat pulmonary hypertension (which should be reserved for patients who have short-term pulmonary vasoreactivity),^{4,6,7} the use of continuous intravenous epoprostenol may be worth investigating in patients who continue to have severe symptoms despite conventional therapy, even if they have no short-term response to epoprostenol or if their condition has deteriorated with conventional therapy.

Several factors have been shown to determine survival in patients with primary pulmonary hypertension, in-

cluding hemodynamic variables and functional class.^{2,8} Determining the status of these factors may be helpful when one is selecting and timing a more aggressive approach to treatment, such as transplantation. In this study, we found that performance in the six-minute walk at base line was also an independent predictor of survival. Thus, assessing exercise capacity in this inexpensive and noninvasive way may be useful in determining whether alternative treatment options should be considered in individual patients.

Since epoprostenol is unstable at pH values below 10.5, it cannot be given orally, and continuous intravenous infusion is necessary because of its short half-life in the circulation.³³ Although the delivery system for continuous infusion is complex, most patients were capable of learning how to prepare and infuse the drug. Only one patient was withdrawn from this study because of the inability to master drug delivery. Despite the cumbersome nature of treatment with epoprostenol, the patients' quality of life was significantly improved. Thus, the complexity of the treatment may be offset by the overall improvement in well-being in most patients.

Continuous intravenous epoprostenol therapy is not, however, devoid of potentially serious complications (most of which are attributable to the delivery system), including catheter-related infections, thrombosis, and temporary interruption of the infusion due to malfunction of the pump. Although these adverse events were not associated with death in this study, they are potentially life-threatening and underscore the need for an alternative mode of drug delivery.

The principal limitation of this study was that it was not a double-blind, placebo-controlled trial. Therefore, we cannot completely exclude the possibility of investigator or patient bias, particularly with regard to exercise capacity. We felt we could not design this study as a double-blind, placebo-controlled trial because of ethical considerations based on the known incidence of sepsis caused by central venous catheters in control patients^{34,35} and because unique or highly predictable symptoms during long-term epoprostenol treatment — that is, jaw pain and diarrhea — prevented the blinding of physicians and patients.

The changes in stroke volume and systemic vascular resistance during the short-term infusion of epoprostenol were greater in the group subsequently assigned to receive the drug, raising the possibility that these patients had greater vasoreactivity at base line. However, none of the hemodynamic variables that are predictors of survival (pulmonary-artery pressure, right atrial pressure, cardiac index, and mixed venous oxygen saturation)^{2,8} and none of the markers of pulmonary vasoreactivity with short-term vasodilator testing (short-term changes in pulmonary-artery pressure, cardiac index, and pulmonary vascular resistance)^{4,6,7} were different in the two groups.

An additional limitation of this study is the suggestion that the base-line exercise capacity of the patients randomly assigned to receive conventional therapy was slightly worse than that of the patients assigned to re-

ceive epoprostenol. Although these differences were not statistically significant, it is possible that the epoprostenol-treated patients may have been less impaired at base line. On the basis of our observation that exercise capacity is an independent predictor of survival in patients with primary pulmonary hypertension, future trials should include randomization based on performance in the six-minute walk at base line in addition to other known predictors of survival.

In conclusion, the continuous intravenous infusion of epoprostenol plus conventional therapy for primary pulmonary hypertension resulted in better hemodynamics, exercise endurance, quality of life, and survival than conventional therapy alone. Although we did not address the long-term effects of therapy, our previous study suggests that the beneficial effects of epoprostenol on hemodynamics and exercise capacity persist with long-term therapy.¹⁶ When epoprostenol is used as a bridge to transplantation, stabilizing the patient's hemodynamics could lower perioperative rates of morbidity and mortality. The continuous intravenous infusion of epoprostenol may be useful in the management of severe primary pulmonary hypertension when it is refractory to conventional medical therapy.

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APPENDIX

Other participants in the North American Primary Pulmonary Hypertension Study included E. Horn and J. Kirkpatrick, Columbia-Presbyterian Medical Center, New York; K. Wynne, University of Colorado Health Sciences Center, Denver; W. Knight, University of Alabama Medical Center, Birmingham; D. Georgiou and J. Beckman, Harbor-UCLA Medical Center, Torrance, Calif.; W.R. Clarke, D. Ralph, and P. Schrader, Children's Hospital and University Hospital, University of Washington, Seattle; E.J. Caldwell, W. Williams, and B. Vogel, Maine Medical Center, Portland; N.A. Ettinger and D. Canfield, Barnes Hospital, Washington University, St. Louis; N.S. Hill and C. Carlisle, Rhode Island Hospital, Providence; A. Hinderliter and P.W. Willis IV, University of North Carolina Hospitals, Chapel Hill; A.E. Frost and K. Chafizedah, Methodist Hospital, Baylor College of Medicine, Houston; D. Ross and D. Claire, Cedars-Sinai Medical Center, Los Angeles; E. Shalit, Sir Mortimer B. Davis Jewish General Hospital, McGill University, Montreal; B. Edwards, C. Severson, and K. Kosberg, Mayo Medical Center, Rochester, Minn.; T. Tokarczyk, Presbyterian-University Hospital, University of Pittsburgh, Pittsburgh; L. Kaufman, University of Illinois at Chicago; L. Hartle, University of Maryland School of Medicine, Baltimore; W.R. Sumner, B. deBoisblanc, and B. Everett, Charity Hospital, Louisiana State University Medical Center, New Orleans; and A. Krichman, Duke University Medical Center, Durham, N.C.

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