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Continuous Intravenous Epoprostenol for Pulmonary Hypertension Due to the Scleroderma Spectrum of Disease

A Randomized, Controlled Trial

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Background: Pulmonary hypertension is a progressive and often fatal complication of the scleroderma spectrum of disease for which no treatment has been proven effective in a randomized trial.

Objective: To determine the effect of epoprostenol on pulmonary hypertension secondary to the scleroderma spectrum of disease.

Design: Randomized, open-label, controlled trial.

Setting: 17 pulmonary hypertension referral centers.

Patients: 111 patients with moderate to severe pulmonary hypertension.

Intervention: Epoprostenol plus conventional therapy or conventional therapy alone.

Measurements: The primary outcome measure was exercise capacity. Other measures were cardiopulmonary hemodynamics, signs and symptoms of pulmonary hypertension and scleroderma, and survival.

Results: Exercise capacity improved with epoprostenol (median distance walked in 6 minutes, 316 m at 12 weeks compared with 270 m at baseline) but decreased with conventional therapy (192 m at 12 weeks compared with 240 m at baseline). The difference between treatment groups in the median distance walked at week 12 was 108 m (95% CI, 55.2 m to 180.0 m) ($P < 0.001$). Hemodynamics improved at 12 weeks with epoprostenol. The changes in mean pulmonary artery pressure for the epoprostenol and conventional therapy groups were -5.0 and 0.9 mm Hg, respectively (difference, -6.0 mm Hg [CI, -9.0 to -3.0 mm Hg]), and the mean changes in pulmonary vascular resistance were -4.6 and 0.9 mm Hg/L per minute, respectively (difference, -5.5 mm Hg/L per minute [CI, -7.3 to -3.7 mm Hg/L per minute]). Twenty-one patients treated with epoprostenol and no patients

receiving conventional therapy showed improved New York Heart Association functional class. Borg Dyspnea Scores and Dyspnea-Fatigue Ratings improved in the epoprostenol group. Trends toward greater improvement in severity of the Raynaud phenomenon and fewer new digital ulcers were seen in the epoprostenol group. Four patients in the epoprostenol group and five in the conventional therapy group died (P value not significant). Side effects of epoprostenol therapy included jaw pain, nausea, and anorexia. Adverse events related to the epoprostenol delivery system included sepsis, cellulitis, hemorrhage, and pneumothorax (4% incidence for each condition).

Conclusions: Continuous epoprostenol therapy improves exercise capacity and cardiopulmonary hemodynamics in patients with pulmonary hypertension due to the scleroderma spectrum of disease.

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Pulmonary hypertension is characterized by progressive elevation of pulmonary artery pressure and vascular resistance, often leading to right ventricular failure and death (1–3). Continuous intravenous infusion of epoprostenol improves prognosis and symptoms in patients with primary (idiopathic) pulmonary hypertension (4–8). Randomized, con-

See related article on pp 435-443 and editorial comment on pp 500-502.

Table 1. Key Inclusion and Exclusion Criteria

Inclusion criteria	
Diagnosis of the scleroderma spectrum of disease	
Age ≥ 16 y	
Able to walk at least 50 m in 6 minutes at baseline	
Moderate to severe pulmonary hypertension with the following conditions:	
Mean pulmonary arterial pressure ≥ 35 mm Hg	
Pulmonary vascular resistance ≥ 3 mm Hg/L per minute	
Right atrial pressure ≤ 20 mm Hg	
Absence of congenital heart disease	
Pulmonary capillary wedge pressure or left ventricular end-diastolic pressure ≤ 15 mm Hg. If it was not possible to measure the pulmonary capillary wedge pressure or left ventricular end-diastolic pressure, echocardiographic criteria to exclude left heart disease were applied.	
Ventilation-perfusion lung scan or pulmonary angiography not indicative of thromboembolic disease	
Pulmonary function tests or high-resolution computed tomography scanning showing no more than mild interstitial lung disease	
Exclusion criteria	
Any new long-term therapy for pulmonary hypertension or the scleroderma spectrum of disease added within the past month	
Any medication used to treat pulmonary hypertension or the scleroderma spectrum of disease discontinued within the last week, except anticoagulant agents	
Any type of current prostaglandin therapy	

trolled clinical trials of epoprostenol for secondary pulmonary hypertension have not been conducted.

Pulmonary hypertension frequently complicates the scleroderma spectrum of disease, which includes diffuse scleroderma, limited scleroderma (the CREST syndrome [calcinosis cutis, the Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia]), and the overlap syndrome. These multi-system diseases are characterized by connective tissue and vascular abnormalities; vascular lesions are prominent in all affected tissues (9). Pulmonary hypertension occurs in up to 33% of patients with diffuse scleroderma and 10% to 50% of those with the CREST syndrome (10, 11), in which it is one of the leading causes of death (12, 13). Pulmonary hypertension in the scleroderma spectrum of disease may be associated with interstitial pulmonary fibrosis or may consist of a direct involvement of small and medium-sized pulmonary arteries and arterioles with smooth-muscle hyperplasia, medial hypertrophy, and intimal proliferation (10, 13, 14). Principal involvement of the pulmonary vasculature is more common in the CREST syndrome, whereas patients with pulmonary hypertension and diffuse scleroderma more often have interstitial lung disease (13).

No therapies have been proven effective for pulmonary hypertension secondary to the scleroderma spectrum of disease. Small numbers of patients have responded to captopril (15), nifedipine (16–20), and prazosin. In a short-term study of intravenous epoprostenol in seven patients with scleroderma (two with diffuse scleroderma and five with limited scleroderma), six had a decrease in mean pulmonary artery pressure and pulmonary vascular resistance (21). In a small study of pulmonary hyperten-

sion secondary to connective tissue disease, long-term infusion therapy with a prostacyclin analogue, iloprost, resulted in improvement in New York Heart Association (NYHA) functional class and quality of life but a variable hemodynamic response (22). Results from a single-center, uncontrolled study suggest that long-term, continuously infused epoprostenol therapy can produce hemodynamic and symptomatic responses in patients with connective tissue disease who have severe pulmonary hypertension that is refractory to conventional medical therapy (23).

The rationale for using continuous epoprostenol infusion to treat pulmonary hypertension secondary to the scleroderma spectrum of disease was based on the efficacy of this therapy for primary pulmonary hypertension (4–8) and recognition that scleroderma is a disease characterized by vasospasm and structural changes in the walls of blood vessels. Prostacyclin is a naturally occurring substance produced by vascular endothelium that has vasodilating, antiplatelet aggregation, and cytoprotective effects (24–33). Endogenous production of prostacyclin is decreased in an animal model of neonatal pulmonary hypertension (34) and in adult humans with pulmonary hypertension (35). Continuous infusion of prostacyclin normalizes plasma markers of endothelial cell injury and platelet aggregation in patients with primary pulmonary hypertension (36). Endothelial dysfunction also plays an important role in the vascular manifestations of the scleroderma spectrum of disease (37, 38), including the Raynaud phenomenon and digital ischemia, which cause considerable morbidity. Calcium-channel blockers (39–45), enalapril (46), and intermittent intravenous infusions of prostacyclin (47–49) and iloprost (50–54) improve the Raynaud phenomenon in some patients. Mixed results have been obtained with oral prostacyclin analogues (55, 56), and a recent multicenter trial of oral iloprost showed no benefit (57). The effect of long-term, continuously infused epoprostenol on the severity of the Raynaud phenomenon and on digital ulcer counts has not been previously evaluated.

Our 12-week multicenter, open-label, randomized study was designed to determine whether the beneficial effect of epoprostenol seen in patients with primary pulmonary hypertension could be extended to patients with pulmonary hypertension secondary to the scleroderma spectrum of disease. Our objective was to evaluate the effects of continuous infusion of epoprostenol on exercise capacity in patients with pulmonary hypertension secondary to the scleroderma spectrum of disease. A secondary objective was assessment of the effects of long-term continuous epoprostenol infusion on cardiopulmonary hemodynamics, Borg Dyspnea Score, Dyspnea

Fatigue Rating, NYHA functional class, survival, and safety. Vasospastic manifestations, such as the Raynaud phenomenon and digital ulcerations, were also followed.

Methods

Patient Selection

Eligible patients had pulmonary hypertension secondary to the scleroderma spectrum of disease in accordance with the inclusion and exclusion criteria summarized in **Table 1**. For the purposes of this study, the scleroderma spectrum of disease was defined as systemic sclerosis with diffuse or limited scleroderma (58); systemic sclerosis that overlapped with another connective tissue disease; or the presence of definite features of systemic sclerosis, including the Raynaud phenomenon and positive test result for antinuclear antibody, plus positive test results for anticentromere antibody, anti-Scl 70 antibody, or nailfold capillary abnormalities. Systemic sclerosis with limited cutaneous involvement (the CREST syndrome) was defined as the presence of any three of the following conditions: subcutaneous calcinosis, the Raynaud phenomenon, esophageal dysfunction (defined clinically), sclerodactyly, or telangiectasia. Patients with interstitial lung disease of a more than mild degree were not included in the study because such patients were thought to be less likely to show benefit.

On the basis of a previous 12-week study of the effects of epoprostenol infusion in patients with severe primary pulmonary hypertension (6) and using the 6-minute walk test as the primary outcome measure, we calculated that 50 patients per treatment group would provide 80% power to detect a difference of 50 meters in the average change from baseline, at an α level of 0.05 (two-tailed *t*-test).

Randomization and Treatment

The protocol was approved by the institutional review boards of the 17 participating centers. After giving informed consent, 111 eligible patients were randomly assigned (1:1) to receive continuous epoprostenol infusion (Flolan, Glaxo Wellcome, Inc., Research Triangle Park, North Carolina) plus conventional therapy or to receive conventional therapy alone. Investigators contacted a central randomization center to obtain treatment assignment, which was based on a stratified randomized block design. Assignments were stratified on the basis of vasodilator use at baseline (yes or no) and exercise capacity at baseline (50 to <200 m or \geq 200 m) and were randomized within blocks. Fifty-six patients were assigned to receive epoprostenol plus conventional therapy, and 55 patients were assigned to receive

conventional therapy alone. Investigators were not blinded to treatment group assignment; however, independent blinded observers assessed the primary efficacy measure, exercise capacity. Patients taking calcium-channel blockers at study entry continued to take them during the study period. Adjustments in concomitant medications were allowed during the study on the basis of clinical judgment. Patients in both groups were to receive oral anticoagulants during the study; 94 of the 111 enrolled patients took warfarin.

Venous access for epoprostenol infusion (in the epoprostenol group only) was obtained by insertion of a permanent indwelling central venous catheter. Epoprostenol was infused continuously by a portable infusion pump (CADD-1 Model 5100 HF, SIMS Deltec, St. Paul, Minnesota). Patients were instructed in sterile technique, catheter care, and drug preparation and administration. Epoprostenol therapy was initiated at a low dose (usually \leq 2 ng/kg of body weight per minute). During the 12-week study, doses were adjusted on the basis of signs or symptoms consistent with persistent pulmonary hypertension in the absence of intolerable adverse effects (**Figure 1**).

Outcome Measures

The primary measure of efficacy was exercise capacity, as defined by the distance a patient could walk in 6 minutes. Trained observers at each site who were not otherwise involved in patient care administered the 6-minute walk test. All patients wore an ambulatory infusion pump and a hospital gown over their clothes to mask the presence or absence of a long-term indwelling catheter, thereby blinding testers to the patients' treatment groups. Each patient performed one practice walk test. A standardized, unencouraged 6-minute walk test was performed as described elsewhere (59) at baseline and at 1, 6, and 12 weeks. The 6-minute walk test

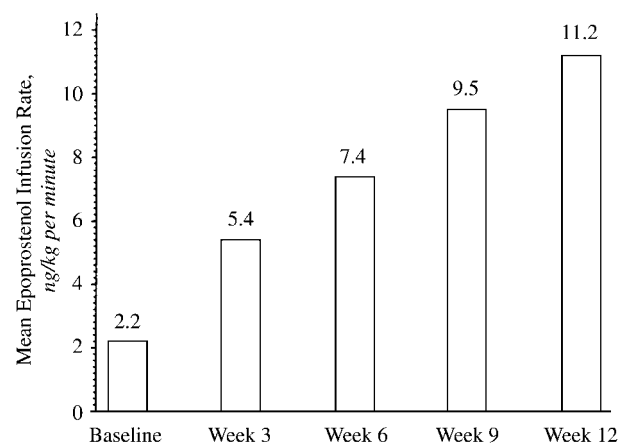


Figure 1. Epoprostenol dosing. Numbers at the tops of the bars represent exact mean rates.

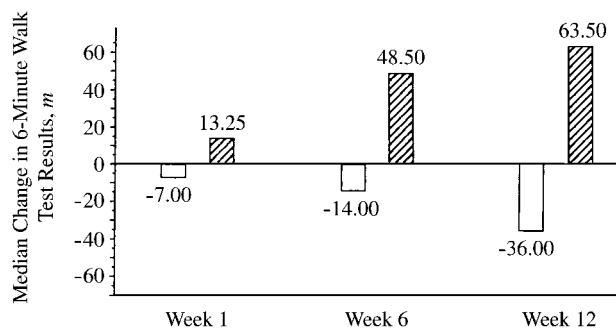


Figure 2. Median change from baseline in results of the 6-minute walk test at weeks 1, 6, and 12. Nonparametric analysis of covariance with adjustment for 6-minute walk values and use of vasodilators at baseline showed that the median distance walked in 6 minutes increased in patients who received epoprostenol (striped bars) compared with patients who received conventional therapy (white bars) at weeks 6 ($P = 0.003$) and 12 ($P < 0.001$).

has been shown to provide meaningful outcome data in assessing potential therapy for patients with pulmonary hypertension (6).

Secondary measures of efficacy were cardiopulmonary hemodynamics measured by performing right-heart catheterization using standard techniques at baseline and week 12; the Borg Dyspnea Score (60), obtained immediately after completion of the 6-minute walk test at baseline and 1, 6, and 12 weeks (6, 59); the Dyspnea-Fatigue Rating, obtained before the 6-minute walk test at baseline and weeks 1, 6, and 12 (61); NYHA functional class (62), measured at baseline and weeks 1, 6, and 12; digital ulcer counts, done at baseline and weeks 6 and 12; and the severity of the Raynaud phenomenon, assessed weekly. For determination of the Raynaud phenomenon severity score, patients were asked to score the severity of their Raynaud disease, taking into account the number of attacks per day, the duration of attacks, symptoms (such as numbness, burning, pain, and tingling), hand disability caused by the attack (but not by pain, ulcers, arthritis, or scleroderma skin), and influence of cold and stress exposure on daily activity and sense of well-being. Patients were asked to circle the number from 1 (no problems) to 10 (severe problems) that best described the severity of their Raynaud phenomenon over the past week. Only new digital ulcers were counted. Survival was also determined.

Safety was assessed by comparison of adverse experiences in the two treatment groups and by laboratory assessments (including hemoglobin level; platelet count; leukocyte count; serum creatinine concentration; and levels of blood urea nitrogen, alkaline phosphatase, and alanine aminotransferase) at baseline and week 12. An independent Data Safety and Monitoring Board reviewed safety data (including adverse effects and fatal events) after 15, 35, and 70 patients had completed the study.

Statistical Analysis

Categorical data are presented as frequencies and percentages by treatment group. Continuous data are presented as the mean \pm SE or the median. Six-minute walk data were analyzed in two intention-to-treat analyses: a nonparametric analysis of covariance (63), which was the primary analysis, and a parametric analysis of variance. In the nonparametric analysis of covariance, patients who had died or were unable to walk because of illness were assigned a value of 0 meters. An ordinary least-squares regression of the ranks of the distance walked at baseline compared with week 12 was performed, adjusting for baseline walk category (<200 m or ≥ 200 m) and vasodilator use (yes or no). The resulting residuals from the regression were analyzed by using the Cochran–Mantel–Haenszel test statistic, controlling for baseline walk category and vasodilator use. The parametric analysis of variance evaluated the change from baseline to week 12 in the distance walked. Patients at week 12 who had died or were too ill to walk had their last observations carried forward and used as their value at week 12.

Hemodynamic variables were analyzed by calculating the change from baseline to week 12 for each patient. The difference in mean change between treatment groups was calculated, and a 95% parametric CI was derived by using a Student t -distribution. The Dyspnea-Fatigue Rating and the Borg Dyspnea Score were analyzed by calculating the change from baseline to week 12 for each patient. The difference in median change (Hodges–Lehmann estimate) between treatment groups was calculated and a two-sided 95% CI was derived by using a nonparametric Wilcoxon rank-sum statistic (64). New York Heart Association functional class was analyzed by categorizing a shift from baseline to week 12 (for example, class IV at baseline to class II at week 12).

The Raynaud phenomenon was analyzed by first ranking the severity scores across all patients without regard to treatment at each time point. Each patient's average rank across time points was then calculated. The average ranks were compared by using a Cochran–Mantel–Haenszel test statistic. This method was an area under the curve analysis on a rank scale. Only patients who had at least one attack of Raynaud disease during the study were included. Patients who did not have an attack during a specific time period were assigned a value of 0. Digital ulcers were summarized by the number of patients with one or more new ulcers over the 12-week period and by the total number of new ulcers over the 12-week period.

Survival analyses were based on the Kaplan–

Table 2. Demographic and Hemodynamic Characteristics at Baseline*

Characteristic	Epoprostenol Group	Conventional Therapy Group
Age, y	53.0 ± 13.1	57.3 ± 10.3
Sex, n (%)		
Male	5 (9)	10 (18)
Female	51 (91)	45 (82)
NYHA functional class, n (%)		
II	1 (2)	4 (7)
III	42 (75)	45 (82)
IV	13 (23)	6 (11)
Time since pulmonary hypertension diagnosis, mo	14.5 ± 17.9	15.2 ± 20.1
Classification of scleroderma spectrum of disease, n (%)		
Diffuse scleroderma	7 (13)	7 (13)
Limited scleroderma	38 (68)	39 (71)
Overlap syndrome	8 (14)	6 (11)
Features of scleroderma	3 (5)	3 (5)
Time since diagnosis of scleroderma spectrum of disease, mo	85.9 ± 93.0	94.8 ± 102.8
Oral vasodilator therapy, n (%)	38 (68)	38 (69)
Current use of anorexigens, n (%)	0 (0)	0 (0)
Past exposure to anorexigens, n (%)	8 (14)	6 (11)
Mean pulmonary arterial pressure, mm Hg	50.9 ± 10.6	49.1 ± 10.2
Mean right atrial pressure, mm Hg	13.1 ± 5.0	11.1 ± 5.5
Mean systemic arterial pressure, mm Hg	92.8 ± 12.4	89.1 ± 10.8
Cardiac index, L/min per m ²	1.9 ± 0.6	2.2 ± 0.7
Heart rate, beats/min	83.7 ± 10.9	84.5 ± 13.5
Systemic arterial oxygen saturation, %	92.7 ± 6.8	92.5 ± 6.6
Mixed venous oxygen saturation, %	57.4 ± 10.8	58.8 ± 9.9
Pulmonary vascular resistance, mm Hg/L per minute	14.2 ± 7.1	11.2 ± 5.3
Median distance walked in 6 minutes, m	271.5	240.0

* Values with a plus/minus symbol are the mean ± SD. NYHA = New York Heart Association.

Meier method (65) and were performed both with patient data censored at time of withdrawal (death or discontinuation) and with the same data not censored. The log-rank test was used to assess treatment differences.

Role of the Funding Source

The funding source for the study, Glaxo Wellcome, Inc., assisted in the collection, gathering, and analysis of data and was aware of the decision to submit the paper for publication.

Table 3. Changes from Baseline in Cardiopulmonary Hemodynamic Measurements

Variable	Change from Baseline*		Difference between Groups (95% CI)†
	Epoprostenol Group	Conventional Therapy Group	
Pulmonary artery pressure, mm Hg	-5.03 ± 1.09	0.94 ± 1.10	-5.97 (-8.98 to -2.96)
Pulmonary vascular resistance, mm Hg/L per minute	-4.58 ± 0.76	0.92 ± 0.56	-5.50 (-7.33 to -3.67)
Right atrial pressure, mm Hg	-1.26 ± 0.82	1.20 ± 0.69	-2.46 (-4.54 to -0.39)
Cardiac index, L/min per m ²	0.50 ± 0.08	-0.10 ± 0.08	0.60 (0.39 to 0.81)
Systemic arterial oxygen saturation, %	-0.33 ± 1.09	-0.31 ± 0.61	-0.02 (-2.45 to 2.42)
Mixed venous oxygen saturation, %	3.55 ± 1.42	-1.07 ± 1.24	4.62 (0.94 to 8.30)
Systemic arterial pressure, mm Hg	-8.26 ± 1.69	-0.63 ± 1.52	-7.63 (-12.07 to -3.20)
Heart rate, beats/min	3.74 ± 1.47	-0.90 ± 1.93	4.64 (-0.06 to 9.33)

* Data are expressed as the mean ± SE.

† A confidence interval that does not contain 0 implies statistical significance.

Results

Comparability of Study Groups at Baseline

Baseline demographic and hemodynamic characteristics of the two groups are shown in **Table 2**. The groups did not differ significantly in severity of pulmonary hypertension, duration of illness, or NYHA functional class. Six patients (11%) in the conventional therapy group and 8 (14%) in the epoprostenol group had been previously exposed to anorectic agents. Sixteen patients (29%) in the conventional therapy group and 10 (18%) in the epoprostenol group were taking prednisone at baseline. In the epoprostenol group, there was a non-significant trend toward a greater median distance walked at baseline, as well as a trend toward a higher mean pulmonary vascular resistance at baseline.

Exercise Capacity

The distance walked in 6 minutes improved at week 12 in the epoprostenol group from a median of 270 m to 316 m and decreased in the conventional therapy group from a median of 240 m to 192 m. The difference in median distance walked (epoprostenol group minus conventional therapy group) at week 12 was 108 m (95% CI, 55.2 m to 180.0 m, Hodges-Lehmann estimate of the median difference) ($P < 0.001$, nonparametric analysis of covariance). Furthermore, the median change in distance walked by the two groups consistently diverged over time during the study (**Figure 2**). These differences, as analyzed by using parametric methods, were similar ($P < 0.001$).

Cardiopulmonary Hemodynamics

The changes in hemodynamic measures from baseline to week 12 are shown in **Table 3**. The epoprostenol-treated patients had significant improvement in mean pulmonary artery pressure, pulmonary vascular resistance, right atrial pressure, cardiac index, and mixed venous oxygen saturation,

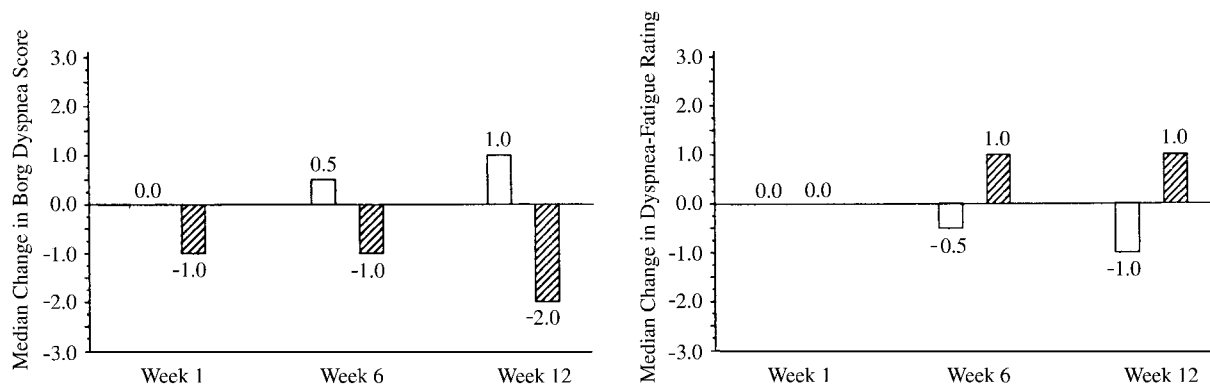


Figure 3. Median changes from baseline in Borg Dyspnea Score (left) and Dyspnea-Fatigue Rating (right) for the conventional therapy group (white bars) and the epoprostenol group (striped bars). A negative change from baseline (to a lower score) reflects an improvement in symptoms. Borg Dyspnea Scores improved (decreased) in the epoprostenol group and worsened (increased) in the conventional therapy group over 12 weeks. The Hodges–Lehmann estimate for the true treatment effect of epoprostenol compared with conventional therapy, based on the difference in change from baseline in the median Borg Dyspnea Score, was 1.0 (95% CI, 0.5 to 2.0) at week 1, 1.5 (CI, 1.0 to 2.5) at week 6, and 2.5 (CI, 1.5 to 3.5) at week 12. Dyspnea-Fatigue Ratings improved (increased) in the epoprostenol group and worsened (decreased) in the conventional therapy group over 12 weeks. The Hodges–Lehmann estimate for the true treatment effect of epoprostenol compared with conventional therapy, based on the difference in change from baseline in the median Dyspnea-Fatigue Rating, was 0.0 (CI, –1.0 to 0.0) at week 1, –2.0 (CI, –2.0 to –1.0) at week 6, and –2.0 (CI, –3.0 to –2.0) at week 12. Confidence intervals that do not contain 0 indicate statistical significance.

whereas these variables generally worsened in patients receiving conventional therapy. Systemic arterial pressure decreased in epoprostenol-treated patients.

Signs and Symptoms

At the end of 12 weeks, 21 patients (38%) treated with epoprostenol and no patients receiving conventional therapy showed improved NYHA functional class. Borg Dyspnea Scores and Dyspnea-Fatigue Ratings improved in the epoprostenol group and worsened in the control group (Figure 3).

A trend toward greater improvement in the Raynaud phenomenon severity score (a negative change) was seen in the epoprostenol group (mean change [\pm SE] from baseline at week 12, 1.69 ± 0.42 compared with -0.50 ± 0.54 in the conventional therapy group). When area under the curve analysis was done for severity of the Raynaud phenomenon

over time based on a rank scale, values obtained were 43.1 ± 2.9 for the epoprostenol group and 52.3 ± 3.2 for the conventional therapy group ($P = 0.038$). Over the course of the study, a similar number of patients in each group had at least one new digital ulcer or ischemic demarcation event (10 of 52 patients [19%] in the epoprostenol group and 11 of 52 patients [20%] in the conventional therapy group). A total of 36 new digital ulcers occurred in the epoprostenol group and 72 occurred in the conventional therapy group.

Safety and Survival

During the 12-week study period, 5 patients in the conventional therapy group and 4 in the epoprostenol group died (P value not significant). Causes of death in the conventional therapy group were respiratory failure (2 patients), progressive right-heart failure (1 patient), acute pulmonary edema (1 patient), and arrhythmia (1 patient). Causes of death in the epoprostenol group were progressive right-heart failure (1 patient), myocardial infarction (1 patient), septic shock (1 patient), and sudden death (1 patient). Patients who died tended to have a longer median duration of the scleroderma spectrum of disease than survivors in both the epoprostenol (90 and 60 months) and conventional therapy (168 and 40 months) groups. In contrast, patients who died and those who survived had the same duration of pulmonary hypertension (7 and 8 months).

Selected adverse events attributed to the underlying disease, epoprostenol, or the drug delivery system are shown in Table 4. Disease-related or cardiovascular events, including syncope and pallor, occurred less commonly in patients receiving

Table 4. Incidence of Selected Adverse Events

Adverse Event	Epoprostenol Group	Conventional Therapy Group
	n (%)	
Disease-related		
Syncope	4 (7)	11 (20)
Pallor	18 (32)	29 (53)
Ascites	13 (23)	18 (33)
Epoprostenol-related		
Anorexia	37 (66)	26 (47)
Nausea	23 (41)	9 (16)
Diarrhea	28 (50)	3 (5)
Jaw pain	42 (75)	0 (0)
Depression	7 (13)	2 (4)
Drug delivery system-related		
Sepsis	2 (4)	–
Cellulitis	2 (4)	–
Hemorrhage	2 (4)	–
Pneumothorax	2 (4)	–

epoprostenol. Although events involving the digestive system were common in both treatment groups, anorexia, nausea, and diarrhea were more common in epoprostenol-treated patients. Jaw pain occurred commonly in the epoprostenol group. The drug delivery system, including the central venous catheter and the infusion pump, was associated with eight catheter-related adverse events, including sepsis, cellulitis, hemorrhage, and pneumothorax (Table 4). No clinically significant changes in hematologic or biochemical variables were seen.

Discussion

Pulmonary hypertension in patients with the scleroderma spectrum of disease is associated with a poor prognosis, and no therapy has been proven effective. Moreover, many patients with scleroderma are not candidates for lung transplantation because of the systemic nature of the disease. We documented improvement in exercise capacity, cardiopulmonary hemodynamics, and indices of dyspnea in patients with pulmonary hypertension secondary to the scleroderma spectrum of disease who received epoprostenol plus conventional therapy rather than conventional therapy alone. As expected, exercise capacity and hemodynamic function tended to deteriorate or remained unchanged with conventional therapy. Trends toward greater improvement in the severity of the Raynaud phenomenon and fewer new digital ulcers were observed in the epoprostenol group.

Continuous infusion of epoprostenol is associated with dose-related side effects, including jaw pain, headache, nausea, anorexia, and diarrhea, and with complications related to the drug delivery system, such as cellulitis, sepsis, hemorrhage, and pneumothorax (6). Patients can tolerate many of the side effects well, and intolerable side effects often respond to a slight reduction in dose. Serious or life-threatening drug-related complications are rare. Patients with suspected pulmonary veno-occlusive disease should be approached cautiously because epoprostenol may precipitate acute and potentially fatal pulmonary edema (4, 66).

Our study differs from a previous study of continuously infused epoprostenol in patients with primary pulmonary hypertension (6) in several ways. In our study, the severity of pulmonary hypertension at baseline was defined hemodynamically as opposed to by NYHA class. In contrast to the previous study (6), our patients did not undergo hemodynamically monitored short-term dose-ranging of epoprostenol, nor were they required to have had unsuccessful previous conventional vasodilator therapy. Hemodynamically monitored short-term dose ranging was performed in the previous study because approxi-

mately 25% of patients with primary pulmonary hypertension will respond to an acute vasodilator challenge, and these patients may be treated effectively with conventional vasodilators (67–74). Furthermore, short-term dose-ranging of epoprostenol with hemodynamic monitoring is not required for the safe institution of long-term epoprostenol therapy. Despite these differences in patient population and study design, the physiologic results of our study were similar to those of the previous study (6). In both studies, exercise capacity, cardiopulmonary hemodynamics, and NYHA functional class significantly improved with epoprostenol therapy.

Unlike the earlier study of epoprostenol in primary pulmonary hypertension (6), we did not find a survival benefit. In designing our study, a power analysis indicated that enrollment of least 235 patients would be needed to give an 80% likelihood of detecting a survival benefit. A study of such size was not feasible. Additional possible reasons for the lack of a survival difference between treatment groups in the current study include the greater complexity of illness and multiorgan involvement in scleroderma and perhaps differences in the structural component of pulmonary vascular involvement (75–77). The finding that a greater duration of scleroderma was associated with poorer survival in both the epoprostenol and control groups supports the former possibility.

As in the earlier study of continuous intravenous epoprostenol therapy in primary pulmonary hypertension (6), a limitation of our study was that it was not a double-blind, placebo-controlled trial. Because of the known incidence of sepsis caused by indwelling central venous catheters (6, 78, 79), a placebo-controlled study was considered unethical. Furthermore, unique and predictable symptoms known to occur during long-term epoprostenol treatment (such as flushing, jaw pain, and diarrhea) prevented blinding of physicians and patients. Another limitation of our study is the lack of formal quality-of-life instruments and cost data, although the assessment of exercise capacity, Borg Dyspnea Score, Dyspnea-Fatigue Rating, NYHA functional class, and indices of the severity of the Raynaud phenomenon provides some information on quality of life.

We conclude that continuous intravenous infusion of epoprostenol plus conventional therapy in patients with pulmonary hypertension secondary to the scleroderma spectrum of disease improved exercise capacity, cardiopulmonary hemodynamics, NYHA functional class, and indices of dyspnea compared with conventional therapy alone. This is the first randomized trial of therapy for secondary pulmonary hypertension. Although the results of this study apply specifically to pulmonary hypertension in the scleroderma spectrum of disease, the potential ther-

apeutic implications for a broader group of patients warrant further consideration.

Appendix

Members of the Data Safety Monitoring Board

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