Effects of Long-term Infusion of Prostacyclin on Exercise Performance in Patients With Primary Pulmonary Hypertension*

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Study objectives: To determine whether long-term IV prostacyclin (PGI₂) use improves exercise capacity in patients with primary pulmonary hypertension (PPH).

Design: Cycle ergometry and the 6-min walk was used to evaluate the exercise performance of patients with PPH. The patients underwent serial exercise testing after starting continuous IV PGI₂ and were followed up for 19.5 ± 7.5 months. Peak work, peak oxygen consumption (Vo₂), peak O₂ pulse, and distance walked in 6 min were used to evaluate performance.

Background: PPH is characterized by medial hypertrophy and intimal proliferation of the pulmonary arterioles, leading to elevation of pulmonary artery pressure, right ventricular failure, and death. Palliative treatment consists of vasodilators, anticoagulants, cardiac glycosides, diuretics, and transplantation. PGI₂, a potent vasodilator and inhibitor of platelet aggregation, has been used for long-term treatment when conventional therapy has been unsuccessful.

Patients: Sixteen patients with PPH (10 women, 6 men; mean age, 24 years).

Results: At the initiation of PGI₂, peak work (± SD) was 35.5 ± 11% of predicted; peak Vo₂, 39 ± 10.4%; peak O₂ pulse, 5.0 ± 1.7 mL/min; and distance walked on the 6-min walk, 428 ± 78 feet. At 18 to 27 months, peak work increased to 58.8 ± 23% of predicted (p = 0.001), peak Vo₂ increased to 52 ± 15% of predicted (p = 0.02), peak O₂ pulse increased to 7.1 ± 3.0 mL/beat (p = 0.004), and performance on the 6-min walk increased to 526 ± 62 feet (p = 0.001). There was a positive correlation between peak Vo₂ and peak 6-min walk of 0.6 (p < 0.005) and between peak work and peak 6-min walk of 0.6 (p < 0.005).

Conclusions: Exercise capacity improved in our patients at up to 27 months of follow-up. Exercise testing is helpful in assessing the functional capacity of patients with PPH and may be useful in guiding therapy. Patients who deteriorate while receiving optimal conventional therapy should be considered for IV PGI₂ therapy.

Key words: exercise testing; primary pulmonary hypertension; prostacyclin

Abbreviations: PGI₂ = prostacyclin; PPH = primary pulmonary hypertension; PVR = pulmonary vascular resistance; Vo₂ = oxygen consumption

Primary pulmonary hypertension (PPH) is a rare disease of unknown origin that is characterized by medial hypertrophy and intimal proliferation of the pulmonary arterioles, leading to progressive elevation of pulmonary artery pressure and vascular resistance, right ventricular failure, and death. Treatment is palliative, consisting of vasodilators, anticoagulants, cardiac glycosides, diuretics, O₂, and transplantation (lung or heart-lung).¹⁻⁵ Prostacyclin (PGI₂), a potent vasodilator and inhibitor of platelet aggregation, has been used for acute testing to assess pulmonary vasoreactivity as well as for long-term treatment when conventional oral medical therapy has been unsuccessful.⁶⁻¹⁰

Exercise testing has been used as a measure of functional capacity in patients with PPH, and previous studies have shown that performance on exercise tests has prognostic significance and may be used to evaluate treatment efficacy.¹¹⁻¹⁴ Barst and colleagues⁴,⁶ reported that exercise capacity, measured...
by the 6-min walk test, correlates with hemodynamics obtained at cardiac catheterization and that treatment with continuous IV PGI₂ improves performance on this test.

Bicycle ergometry with continuous measurement of oxygen consumption (VO₂) is a sensitive measure of exercise tolerance, and normal values exist for a range of age groups, allowing for comparison of relative performance among patients of different ages. The objective of this study was to determine whether long-term IV PGI₂ therapy improves exercise capacity (measured by bicycle ergometry) in patients with PPH.

**Materials and Methods**

**Study Patients**

The study group consisted of 16 patients (10 women and 6 men) with a mean age of 24 years (range, 7 to 56 years). The group was drawn from all patients with PPH who began treatment with PGI₂ at Columbia Presbyterian Medical Center from February 1990 to March 1994. Patients were included in the study if they had PPH diagnosed by cardiac catheterization, were old enough to understand and follow instructions regarding exercise testing at the start of their enrollment, and were available for serial evaluation at our institution. Patients were excluded from the study if they had pulmonary hypertension associated with significant structural heart defects, laboratory findings consistent with autoimmune disease, evidence of chronic thromboembolic disease (by ventilation/perfusion scan and/or pulmonary angiography), or significant pulmonary parenchymal disease (by chest radiograph, chest CT, and pulmonary function testing).

All patients underwent a complete noninvasive and invasive evaluation. In the cardiac catheterization laboratory, patients underwent acute drug testing to determine the reactivity of their pulmonary vascular bed, first with IV PGI₂ and then with sublingual nifedipine if responsive to PGI₂ according to our previously published protocol.¹⁰

**Treatment Protocols**

Fifteen of the 16 patients were followed up at Columbia Presbyterian Medical Center before starting continuous PGI₂ and were treated with maximal conventional therapy, including cardiac glycosides, anticoagulants, diuretics, O₂, and, in 11 patients, oral calcium-channel blockers (long-acting nifedipine or diltiazem). PGI₂ was started when clinical and laboratory findings demonstrated that a patient was no longer improving or was deteriorating while receiving conventional therapy. One patient was started on PGI₂ immediately after her initial evaluation and was not treated with conventional therapy. Infusion was started at 2 to 4 ng/kg/min and was increased by 2-ng/kg/min increments as tolerated. Conventional therapy was continued after initiation of PGI₂ unless the patient had an adverse response to oral vasodilators, in which case they were discontinued.

**Exercise Testing**

Fifteen of the patients had exercise tests while receiving conventional therapy, again immediately before starting PGI₂, and then at regular intervals. The patient who was not treated with conventional therapy (patient 15) had her first exercise test just before starting PGI₂. Symptom-limited upright cycle ergometry was performed according to standard protocol.¹⁵ Patients were instructed to pedal at a rate of 60 revolutions/min using a metronome to keep cadence. After 3 min of warm-up pedaling against no resistance, workload was increased stepwise at 1-min intervals. The size of the increase, a multiple of 5 W, was estimated to allow each patient to reach their maximum workload in 10 min. The peak work performed was taken to be the load at which the patient could no longer maintain a steady pace or requested to stop the test. ECG (Quinton Status 1000 Recorder; Quinton; Bothell, WA) and O₂ saturation (Nellcor N200; Nellcor Puritan Bennett; Pleasanton, CA) were continuously monitored, and systemic BP was recorded at the end of each minute of exercise. Breath-by-breath VO₂, CO₂ production, and ventilation were also continuously monitored (Medtronic 2001). Peak work (watts), peak VO₂ (mL/min), peak heart rate (beats/min), and peak O₂ pulse (mL/beat) were used to evaluate exercise performance. Oxygen pulse was derived by dividing the VO₂ by the heart rate and is a noninvasive estimate of stroke volume.¹³ For analysis, the maximum work and peak VO₂ were evaluated as a percentage of predicted,¹⁵ which allowed for comparison of patients of different ages and for comparison of different performances of the same patient as they grew. Most patients also performed a 6-min walk test for each follow-up period, and this was compared with their performance on cycle ergometry.

**Hemodynamic Data**

Fifteen of the patients had cardiac catheterizations before starting PGI₂ (Table 1). Mean pulmonary artery pressure was 65.2 ± 12.9 mm Hg (range, 54 to 89 mm Hg); mean right atrial pressure was 5 ± 5.8 mm Hg (range, 1 to 23 mm Hg); cardiac index was 3.0 ± 1.4 L/min/m² (range, 1.2 to 5.0 L/min/m²); and pulmonary vascular resistance (PVR) was 26.5 ± 14.3 Wood units (range, 11.3 to 67.0 Wood units). Several of the patients had follow-up catheterizations during the course of the study, but not enough data were available to make meaningful comparisons between hemodynamic variables and exercise performance at follow-up.

**Statistical Analysis**

Data are presented as mean ± SD. Student’s paired t test was used to test for significance (p < 0.05).

**Results**

Patients were followed up for an average of 19.5 ± 7.5 months (range, 3 to 27 months). Because not all patients could be restaged at exactly the same intervals, follow-up was grouped into periods of 2 to 8 months, 11 to 18 months, and 18 to 27 months. Eighteen months was used in two periods because it allowed for three periods of follow-up in all patients, i.e., a patient tested at 3, 12, and 18 months would have three periods of follow-up, as would a patient tested at 7, 18, and 26 months. All patients were restaged 2 to 8 months after starting PGI₂. Three patients were removed from the study after the first period of follow-up: patient 8, who had shown little
change in exercise capacity at 3 months, died of thrombocytopenia and hemorrhage after 9 months of PGI2 therapy; patient 1 had improved performance at 6.5 months and died after 13 months of therapy of chronic hepatic failure secondary to hepatitis C; and patient 14 underwent bilateral lung transplantation at 14 months after follow-up study at 8 months showed improvement.

Fifteen patients had been followed up by Columbia Presbyterian Medical Center before beginning PGI2 and had exercise tests while being treated with conventional therapy. Figure 1 shows the deterioration in exercise performance while on conventional therapy. The first column of each series represents the best performance of the patients within 1 year of starting PGI2 (6 ± 3.2 months; range, 1 to 11 months). The second column is the performance immediately before starting PGI2 and shows significant deterioration in peak VO2 (p < 0.01), peak work (p < 0.05), and peak O2 pulse (p < 0.01). Figures 2 through 6 show the exercise performance just before starting PGI2 and at serial follow-up studies. At the initiation of PGI2, peak work was 35.5 ± 11% of predicted; peak VO2, 39 ± 10.4% of predicted; and distance on the 6-min walk, 428 ± 78 feet. At the 2- to 8-month follow-up study, peak work increased 38%, to 44 ± 16% of predicted (p = 0.10); peak VO2 increased 32%, to 49 ± 16% of predicted (p = 0.02); and distance on the 6-min walk increased 9%, to 467 ± 111 feet (not significant). At the 18- to 27-

Table 1—Effects of Continuous IV PGI2 on Exercise Performance

<table>
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<tr>
<th>Patient</th>
<th>Age at Start of Continuous PGI2 yr</th>
<th>Acute Response to PGI2 at First Evaluation</th>
<th>Acute Response to PGI2 at Start of PGI2</th>
<th>NYHA Class at Start of PGI2</th>
<th>Listed for Transplant at Time of Last Follow-up</th>
<th>PAP, mm Hg</th>
<th>RAP, mm Hg</th>
<th>PVR, Woods Units</th>
<th>CI, L/min/m²</th>
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*NR = nonresponder; R = responder; PAP = mean pulmonary artery pressure; RAP = mean right atrial pressure; CI = cardiac index; NA = not available; Y = yes; N = no.

Figure 1. Deterioration in exercise performance while receiving conventional therapy (CT). The first column in each series is the performance while receiving conventional therapy 1 to 11 months before starting PGI2, and the second column is the performance just before starting PGI2. Values for peak VO2 and peak work are percent predicted. Values for peak O2 pulse are in milliliters per beat (*p < 0.05).
month follow-up study, the longest period of follow-up, peak work continued to improve to 58.8 ± 23% of predicted (p = 0.001 vs baseline), peak VO$_2$ remained significantly increased at 51 ± 15% of predicted (p = 0.02 vs baseline), and performance on the 6-min walk increased to 526 ± 62 feet (p = 0.001 vs baseline). The O$_2$ pulse was 5.0 ± 1.7 mL/beat at baseline and improved continuously through all periods of follow-up to 7.1 ± 3.0 mL/beat at the 18- to 27-month follow-up period (p = 0.004 vs baseline). Heart rate did not change significantly from baseline at any follow-up evaluation (71 ± 8.4% of predicted at baseline vs 75 ± 11% of predicted at 18 to 27 months).

**Six-Minute Walk vs Cycle Ergometry**

Using data from all test periods, there was a positive correlation between peak VO$_2$ and peak 6-min walk of 0.6 (p < 0.005) and between peak work and peak 6-min walk of 0.6 (p < 0.005). We did not have enough data to compare the changes in cycle ergometry and gas exchange over time to the changes in the 6-min walk.

**Individual Patients**

Demographic information and hemodynamic findings at the patient’s catheterization before starting PGI$_2$ are shown in Table 1. The individual results for the 13 patients available for retesting at 18 to 24 months are summarized in Figure 7. Eight of 13 patients (61%) demonstrated improved overall performance compared with the start of PGI$_2$. Six of the eight patients had ≥10% increase in all of the variables measured (peak work, peak VO$_2$, O$_2$ pulse, and 6-min walk, and two of the eight patients improved on all except the 6-min walk, for which they were unchanged. One of 13 patients (8%) had deteriorated in overall performance compared with the start of PGI$_2$ with no change in peak work but
10% decrease in all other variables measured. The results for the remaining 4 of the 13 patients (31%) were more difficult to interpret because they had inconsistent results at 18 to 24 months of follow-up. Despite improving in one or more variables, all four of these patients were unchanged or had a lower peak VO₂ than at the start of PGI₂. We are uncertain why peak VO₂, a relatively sensitive indicator of work performed, did not correlate with other variables measured in these patients. It is possible that the patients who performed more work without increasing their peak VO₂ were performing more anaerobic work, although this was not directly measured in this study.

Transplantation

Twelve patients were listed for lung transplantation at the start of PGI₂ therapy. One patient (patients 14) underwent a transplantation operation after 14 months of treatment with PGI₂. She had improved her exercise capacity at the 2- to 8-month follow-up study but remained < 50% of predicted for peak work and peak VO₂. The two patients who died during the course of the study (patients 1, 8) were both awaiting transplantation at the time of their deaths, and their peak work was < 50% of predicted (47% and 41%) at their last follow-up evaluation (2- to 8-month period). At the time of last follow-up evaluation, 3 of 12 patients still on PGI₂ remain on the active transplantation list and 6 of 12 patients have been taken off the active transplantation list because of clinical and hemodynamic improvement. Although the exercise capacities of the three patients who remain on the transplantation list were at the lower end of the group, there was considerable overlap between their performance and those of the patients not listed. However, when evaluating change in performance over time, a difference was observed: the three patients who remain on the transplantation list all showed < 30% improvement in peak work (vs baseline) at the 18- to 27-month follow-up study. The 10 patients not listed for transplantation (6 patients taken off the list and 4 patients never listed) all had > 30% improvement in peak work (vs baseline) at the 18- to 27-month follow-up study (Fig 7).

Discussion

Exercise testing has been used to evaluate the functional capacity of patients with PPH and to assess the effectiveness of treatment.11–14 We have shown that at up to 27 months of follow-up, continuous infusion of PGI₂ has beneficial effects on the
exercise function of patients with PPH who have deteriorated while receiving conventional therapy. Janicki and colleagues\textsuperscript{14} used symptom-limited exercise to evaluate nine patients with PPH. They divided the patients into two groups: patients with moderately elevated PVR (4.5 to 12.5 Wood units) and patients with severely elevated PVR (>12.5 Wood units) and compared both groups with a control group of normal volunteers (PVR, 1 to 2 Wood units). The patients with elevated PVR had decreased exercise capacity and maximal \( \dot{V}_{O_2} \), and the patients in the group with the highest PVR had the greatest compromise and were unable to increase their stroke volume in response to exercise. Rhodes and colleagues\textsuperscript{11} demonstrated that, in 16 patients with PPH, exercise capacity averaged 40% of normal and was inversely correlated with right atrial pressure, pulmonary artery pressure, and PVR. They also reported that performance on exercise testing predicted response to acute vasodilator drug testing. Comparing hemodynamics obtained at cardiac catheterization with exercise performance in 10 patients with pulmonary hypertension, D’Alonzo et al\textsuperscript{12} demonstrated that after 8 weeks of oral calcium-channel blockade therapy, exercise capacity was improved in the patients who had improved hemodynamics.

In the present study, 16 patients with PPH treated with chronic IV \( \text{PGI}_2 \) were evaluated by serial exercise testing. After significantly deteriorating before starting \( \text{PGI}_2 \) therapy, at the first follow-up study (2 to 8 months of treatment), there was a significant increase in mean peak \( \dot{V}_{O_2} \) and mean peak \( O_2 \) pulse, and a trend toward improvement in mean peak work \((p = 0.10)\). Two patients died and one underwent transplantation after their first follow-up test. The performance of the two patients who died after their first follow-up evaluation was not significantly different from that of the surviving patients. The 13 remaining patients were reevaluated at 18 to 27 months and, as a group, continued to have significantly improved peak \( \dot{V}_{O_2} \) and peak \( O_2 \) pulse as well as showing a significant improvement in peak work.

Five of 13 patients had unchanged or decreased peak \( \dot{V}_{O_2} \). Although we could find nothing in their initial hemodynamics or exercise tests to suggest which patients would fail to improve their peak \( \dot{V}_{O_2} \), perhaps at least some of the patients were performing greater anaerobic work. This possibility could be evaluated in future study of these patients.

Overall performance in the 6-min walk was positively correlated with peak \( \dot{V}_{O_2} \) and peak work; however, we did not have sufficient data to compare the change in performance in the 6-min walk with changes in gas exchange and cycle ergometry. Further follow-up may allow for correlation between the change in 6-min walk and cycle ergometry.

At the time of the first evaluation, only 3 of the 16 patients had a positive response to \( \text{PGI}_2 \) during acute drug testing, defined by a decrease in mean pulmonary artery pressure of >20% with no decrease in cardiac index.\textsuperscript{10} At retesting, immediately before starting \( \text{PGI}_2 \) therapy, only 1 of the 16 patients remained an acute “responder.” The increase in exercise capacity with long-term \( \text{PGI}_2 \) therapy in the absence of an acute response to \( \text{PGI}_2 \) is an important finding and is consistent with other studies demonstrating that long-term \( \text{PGI}_2 \) may have clinical benefits and improve survival despite lack of an acute response during vasodilator testing.\textsuperscript{4,6,12}

The principal limitation of this observational study was that when receiving a new therapy such as \( \text{PGI}_2 \), the patient’s desire to see improvement and the effort made during testing may affect performance irrespective of hemodynamic change. Although this effect is difficult to control without serial cardiac catheterizations coinciding with each exercise follow-up test, the persistent improvement we observed at up to 27 months’ of follow-up is unlikely to be caused solely by an increase in effort. Of the six patients who failed to increase their exercise capacity at their first follow-up, when an effort effect would be expected to be greatest, four subsequently showed improvement at the 18- to 27-month follow-up study. Furthermore, the similarity of peak heart rates achieved during all periods of follow-up (73 ± 95% of predicted) suggests a relatively consistent effort, albeit a submaximal one, throughout the study period. An additional limitation of this study is that the sense of physical well-being and perceived exercise tolerance of patients with PPH may change from day to day, supported by the observation of spontaneous variability in patients’ pulmonary hemodynamics.\textsuperscript{13}

Although there is a historical control group for survival in patients with PPH,\textsuperscript{16} no similar long-term follow-up is available for exercise testing. Ideally, patients would have been randomized to receive either \( \text{PGI}_2 \) or placebo for the duration of the study; however, \( \text{PGI}_2 \) had already been shown to have beneficial effects with PPH patients.\textsuperscript{4,6} and thus, we chose not to withhold \( \text{PGI}_2 \) therapy from a group of patients who had already failed conventional therapy alone. Almost uniformly, PPH is a progressive disease, and therefore it is unlikely that exercise function in a group of 16 patients would have spontaneously improved or stabilized during the period of follow-up in this study. In addition, the significant deterioration in exercise performance seen in the group before starting \( \text{PGI}_2 \) allowed the patients to function somewhat as their own control group.
In conclusion, exercise capacity, as measured by peak work, peak VO$_2$, and peak O$_2$ pulse, improved in our patients who were treated with continuous IV PGI$_2$. This improvement was seen in patients who had deteriorated while receiving conventional medical therapy and who did not respond to acute PGI$_2$ testing, demonstrating that lack of an acute vasodilator response does not preclude a significant clinical improvement with long-term PGI$_2$ therapy. In patients with PPH, the decision to begin therapy with IV PGI$_2$ is a difficult one. Although for many patients conventional therapy will provide an improved quality of life for years, clinical deterioration may precede an obvious decrease in cardiac function. Performance on standardized exercise tests may help to guide therapy by detecting subtle changes in clinical condition, and patients who deteriorate while receiving optimal conventional therapy should be considered for continuous IV PGI$_2$.

**REFERENCES**