Effects of Iloprost Inhalation on Exercise Capacity and Ventilatory Efficiency in Patients With Primary Pulmonary Hypertension

Roland Wensel, MD; Christian F. Opitz, MD; Ralf Ewert, MD; Leonhard Bruch, MD; Franz X. Kleber, MD

Background—The continuous infusion of prostacyclin has been shown to improve exercise capacity and survival in patients with primary pulmonary hypertension (PPH). Inhalation of iloprost, a stable analog of prostacyclin, might be an alternative therapy for PPH, selectively acting on the pulmonary vascular bed through ventilation-matched alveolar deposition of the drug. We investigated the short-term effects of iloprost inhalation on exercise capacity and gas exchange in patients with PPH.

Methods and Results—In 11 patients with PPH, we performed 2 consecutive cardiopulmonary exercise tests before and after the inhalation of 17 μg of iloprost. Patients had marked pulmonary hypertension (mean pulmonary artery pressure 65 mm Hg), and inhalation resulted in a decrease in pulmonary vascular resistance (1509 versus 1175 dyne \( \cdot \) s \(^{-1} \) \( \cdot \) cm\(^{-5} \), \( P < 0.05 \)). Arterial blood gases remained unchanged (Pa O\(_2\) 69.3 versus 66.8 mm Hg; Pa CO\(_2\) 29.6 versus 28.8 mm Hg). Iloprost significantly (\( P < 0.05 \)) improved exercise duration (379 versus 438 seconds), peak oxygen uptake (12.8 versus 14.2 mL \( \cdot \) kg\(^{-1} \) \( \cdot \) min\(^{-1} \)), and V\(_{E}\)-versus-V\(_{CO_2}\) slope (58 versus 51.4).

Conclusions—The present data show that iloprost inhalation exerts pulmonary vasodilatation and improves symptoms and exercise capacity in patients with PPH. The data also suggest that iloprost inhalation is a suitable treatment for PPH. Whether these effects are maintained during long-term treatment and are paralleled by improvement in prognosis remains to be determined. (Circulation. 2000;101:2388-2392.)

Key Words: iloprost ■ pulmonary heart disease ■ hypertension, pulmonary ■ exercise ■ lung

Primary pulmonary hypertension (PPH) is a rapidly progressive disease of the pulmonary vasculature with consequent right heart failure.\(^1\)-\(^3\) Because pulmonary vasoconstriction is a major pathogenic component in the disease process, pulmonary vasodilatation is a major aim in the treatment of these patients.\(^3\)-\(^5\) Unfortunately, only a few vasodilator agents sufficiently lower pulmonary vascular resistance without the side effects of systemic hypotension or negative inotropic activity.\(^5\)-\(^9\)

The continuous infusion of prostacyclin has been shown to decrease pulmonary vascular resistance and to significantly reduce mortality rates from PPH, an effect thought to arise not only from pulmonary vasodilatation but also potentially from its antiproliferative activity.\(^9\)-\(^12\) In addition to reduced mortality rates, significant improvements in symptoms and exercise tolerance have been reported.

However, the side effects of intravenous prostacyclin, which include catheter infection, flush, jaw pain, arterial hypoxemia, and systemic hypotension, can limit sufficient dose adjustment of the drug.\(^9\),\(^10\) Furthermore, pharmacological tolerance with the need for steady dose increments during long-term treatment is commonly observed.\(^11\)

The inhalative application of prostacyclin causes pulmonary vasodilatation without the negative side effects on gas exchange and systemic blood pressure that result from ventilation-matched deposition of the drug in the alveoli, thereby causing pulmonary vasodilatation matched to ventilated areas.\(^13\)-\(^15\) A steady concentration gradient from the site of deposition to downstream resistance vessels accounts for marked pulmonary vasodilatation without pronounced systemic vasodilatation. However, the short half-life of prostacyclin limits its use to monitored short-term treatment, as in adult respiratory distress syndrome. Olschewski et al\(^16\) showed that the inhalation of iloprost, a more stable analog of prostacyclin, exerts equivalent effects that last for \( \approx \) 60 to 120 minutes, which makes outpatient treatment feasible.

In addition to death, exercise capacity is an important clinical parameter in the evaluation of the effectiveness of this therapy in PPH. Continuous prostacyclin therapy improved exercise tolerance in the 6-minute-walk test in patients with PPH.\(^10\)

Cardiopulmonary exercise testing allows a reproducible and less subjective assessment of exercise capacity and
provides valuable information on gas exchange and oxygen consumption (\(V_{\text{O}_2}\)). To determine the short-term effects of inhaled iloprost on exercise capacity and pulmonary gas exchange, we performed serial cardiopulmonary exercise tests on patients with PPH before and after the inhalation of iloprost.

Methods

Patients

The present study consisted of 10 patients with PPH and 1 patient (patient 9) with pulmonary hypertension associated with Osler disease (mean age 41 ± 12 years). The diagnosis of PPH was established on the basis of a mean pulmonary artery pressure of >30 mm Hg and the exclusion of secondary causes of pulmonary hypertension according to the diagnostic criteria reported by Rich et al. All patients had limitation of exercise capacity in accordance with New York Heart Association functional class III. In patient 3, a patent foramen ovale was diagnosed. Long-term medication, which included calcium channel blockers (n=5), oral anticoagulation (n=9), diuretics (n=11), and nasal oxygen therapy (n=3), was kept constant. The study was approved by the institutional ethics board, and written informed consent was given by each patient.

Hemodynamic Measurements

To characterize the hemodynamic response to inhaled iloprost before the initiation of long-term inhalation therapy, patients underwent right heart catheterization. This was performed via the right internal jugular or right subclavian vein, and an 8F Baxter Swan-Ganz catheter (IntelliCath) was used. Monitoring of arterial blood pressure and arterial blood gases was undertaken with an arterial intravenous line (Leader 20-gauge catheter; Vygon) that was inserted into the right radial artery. Cardiac output (Fick method), arterial blood pressure, pulmonary artery pressure, mean right atrial pressure, and pulmonary capillary wedge pressure were measured at baseline and at the end of iloprost inhalation. Iloprost was applied with a jet nebulizer at a concentration of 10 \(\mu\)g/mL. According to an average nebulization rate of 1.7 mL/min, after 10 minutes, a cumulative dose of 17 \(\mu\)g of iloprost had been administered. Measurements were performed within the final minute of inhalation. A cumulative dose of 17 \(\mu\)g was chosen because it had been reported to be safe and effective for the long-term treatment of pulmonary hypertension when used as a single inhalation dose of a daily therapy regimen consisting of 6 inhalations. Patients were started on long-term inhalation of 17 \(\mu\)g of iloprost 6 times daily on the day after catheterization.

Cardiopulmonary Exercise Tests

Within the first week of the initiation of inhalation therapy, patients underwent cardiopulmonary exercise testing. Tests were performed on 2 consecutive days before iloprost inhalation and within 15 minutes after the inhalation of 17 \(\mu\)g of iloprost. The modified Naughton protocol for treadmill exercise testing was used. This is an incremental exercise test with stages of 2 minutes and increments in both slope and velocity of the treadmill that simulate an increment of \(\approx 1\) metabolic equivalent (\(\approx 3.5\) mL \(O_2\) \(\cdot\) kg\(^{-1}\) \(\cdot\) min\(^{-1}\)) per stage. Exercise testing with the use of a cycle ergometer (ER 900; Jaeger) was started at 20 W with a stepwise increment of 16 W/min. Patients were tested with the same exercise protocol (either treadmill or cycle ergometer) for both tests. A Medical Graphics cardiopulmonary exercise system (CPX/D) was used, and gas was sampled through a Rudolph mask. For each type, dead space as specified was corrected individually. The expiratory gas was collected and conveyed to a spirometer as well as to an oxygen and a carbon dioxide detector. \(V_{\text{O}_2}\), carbon dioxide output (\(V_{\text{CO}_2}\)), instantaneous expiratory gas concentrations throughout the respiratory cycle, and minute ventilation (\(V_{\text{E}}\)) were measured continuously on a breath-by-breath basis. Maximal oxygen uptake (\(V_{\text{O}_2\ max}\)) was defined as the peak \(V_{\text{O}_2}\) that was measured, which always occurred well beyond the anaerobic threshold. The \(V_{\text{E}}\) at the gas exchange anaerobic threshold was detected with the V-slope method, \(^{18,19}\) supplemented by the simultaneous observation of end-tidal gas concentrations.

Ventilatory efficiency on exercise was measured by plotting VE against \(V_{\text{CO}_2}\). This plot revealed a linear relationship (r = 0.98 to 0.99). The ventilatory efficiency on exercise is represented by the slope of all VE/\(V_{\text{CO}_2}\) values for 1 person during incremental exercise. The nonlinear portion of this relationship after the onset of acidotic drive to ventilation\(^{20}\) was excluded. The parameters that we used to determine exercise capacity were \(V_{\text{O}_2\ max}\), oxygen uptake at the ventilatory anaerobic threshold, and exercise duration. Pulmonary gas exchange was assessed with the ratio of \(V_{\text{E}}/V_{\text{CO}_2}\), the slope of this ratio on exercise, the end-tidal partial pressure of carbon dioxide (\(P_{\text{ET CO}_2}\)) at rest, and percutaneous oxygen saturation.

Statistical Analysis

Values are given as mean ± SD. Changes in exercise parameters before and after iloprost inhalation were analyzed with the paired t test or Wilcoxon signed rank test.

Results

Hemodynamics

Baseline hemodynamic profiles of the patients and the acute effects of inhaled Iloprost are shown in the Table. All patients had marked pulmonary hypertension, with increased right atrial pressure in 6 patients. The inhalation of 17 \(\mu\)g of iloprost led to a significant decrease in pulmonary vascular resistance, which resulted in an increase in cardiac output and decreased pulmonary artery and right atrial pressures. No significant changes occurred in arterial oxygen saturation (92.3% versus 92.7%), arterial partial pressure of oxygen (\(P_{\text{AO}_2}\)) (69.3 versus 66.8 mm Hg), and arterial partial pressure of carbon dioxide (\(P_{\text{ACO}_2}\)) (29.6 versus 28.8 mm Hg).

No serious side effects or adverse drug reactions were observed during short-term testing or on the next days.

Cardiopulmonary Exercise Tests

Exercise testing was performed with a treadmill (n = 7) or cycle ergometer (n = 4). All patients tested with treadmill exercise reported dyspnea as the limiting symptom at the end of exercise, whereas 3 of 4 patients tested with the cycle ergometer reported both dyspnea and muscular weakness. There was no change in these symptoms when exercise testing was compared before and after the inhalation of iloprost.

The inhalation of iloprost resulted in a significant increase in exercise duration (379 versus 438 seconds, \(P<0.05\)) and \(V_{\text{O}_2\ max}\) (12.8 versus 14.2 mL \(\cdot\) kg\(^{-1}\) \(\cdot\) min\(^{-1}\), \(P<0.05\), Figures 1 and 2). Furthermore, we observed a significant improvement (ie, a decrease) in the \(V_{\text{E}}/V_{\text{CO}_2}\) slope on exercise (58 versus 51.4, \(P<0.05\), Figure 3), whereas resting \(P_{\text{ET CO}_2}\) (24.5 versus 24.7 mm Hg), resting \(V_{\text{E}}/V_{\text{CO}_2}\) (58.4 versus 56.3), percutaneous oxygen saturation at rest (93.5% versus 94.4%), and peak exercise levels (88.5% versus 89.2%) remained unchanged.

Discussion

PPH is a progressive and fatal disease with a median survival time of 2.8 years after diagnosis.\(^{21}\) Hemodynamically, it is characterized by increased pulmonary vascular resistance that leads to an elevation in pulmonary artery pressure and consequent right heart failure. Among the various pharmaco-
logical agents used to influence the clinical course of the disease, prostacyclin has shown the most promising results. In a randomized study, the continuous intravenous application resulted in long-term reduction in pulmonary vascular resistance and, more importantly, improved survival times.9 –11 Furthermore, hemodynamic and prognostic improvement correlated with an increased exercise tolerance on the 6-minute-walk test.

Recently, Olschewski et al16 reported that the inhalation of prostacyclin can exert effects on the pulmonary vascular resistance that are the equivalent of intravenous application and that the prostacyclin analog iloprost can produce comparable acute effects that last from 60 to 120 minutes. Iloprost inhalation might therefore represent a long-term therapy for patients with PPH. However, the effects of iloprost inhalation on cardiopulmonary exercise capacity, which is one of the most sensitive and objective parameters to describe functional impairment from pulmonary hypertension, have not been described yet.

In the present study, we observed an increased exercise capacity after iloprost inhalation as indicated by an increased exercise time and VO2 max on an incremental exercise protocol. As an indicator of pulmonary vasodilatation, the initial hemodynamic studies revealed a marked decrease in pulmonary vascular resistance. Consequently, right ventricular afterload decreased, which led to a reduction in right atrial pressure and an increase in cardiac output. Due to the heterogeneity of the pulmonary vasodilator response of patients with PPH, the quantitative comparison of different vasodilator strategies between patient groups is rather unreliable. However, inhaled iloprost exerted effects similar to those of intravenous iloprost, as described previously.22

Although hemodynamics were not monitored during exercise, we suggest that an increased cardiac output secondary to

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APm indicates mean arterial blood pressure; PAPm, mean pulmonary artery pressure; PCWPm, mean pulmonary capillary wedge pressure; RAm, mean right atrial pressure; CO, cardiac output; SVR, systemic vascular resistance; and PVR, pulmonary vascular resistance.

*P < 0.05 compared with baseline.
†Patients receiving long-term medication with calcium channel blockers.

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Figure 1. Effects of iloprost inhalation on exercise duration.

Figure 2. Effects of iloprost inhalation on VO2 max.
decreased right ventricular afterload accounts for the observed effects on exercise capacity. Iloprost affected neither arterial oxygenation nor the pronounced hyperventilation with decreased PaCO₂, as is usually observed in patients with PPH. Interestingly, in patient 3, the VE-versus-VCO₂ slope increased steadily during exercise, which reflected the ventilatory response to an increasing right-to-left shunt through the patent foramen ovale secondary to a rise in right atrial pressure as right ventricular backward failure deteriorates on patent foramen ovale secondary to a rise in right atrial pressure. In the absence of an intracardiac right-to-left shunt, hyperventilation mainly accounts for the increased VE-to-VCO₂ ratio observed in patients with PPH, because no major abnormalities in pulmonary ventilation/perfusion matching have been reported. Iloprost inhalation did not decrease the VE-to-VCO₂ ratio at rest; however, the VE-versus-VCO₂ slope on exercise did improve after inhalation. We did not measure arterial blood gases on exercise and therefore cannot define whether this effect results from a decreased PaCO₂ set point during exercise. However, stable PaCO₂ and PETCO₂ values at rest make this mechanism rather unlikely. Another mechanism that might explain the change in the VE-versus-VCO₂ slope could be the reduction in functional intrapulmonary right-to-left shunt due to an increased mixed venous oxygen content and reduced carbon dioxide content secondary to an increased cardiac output. Although the exact mechanism remains unclear, the improved ventilatory efficiency reduces the respiratory burden during exercise, and therefore dyspnea, in these patients with PPH. Furthermore, in chronic congestive heart failure, a lower VE-versus-VCO₂ slope has been found to correlate with increased survival time, which is an effect that might be relevant in PPH as well. 

A major limitation of the present study was the lack of a control group to exclude the placebo effect, which was due to the limited number of patients available. This in particular applies to the effects on exercise duration and VO₂ max. However, hemodynamic measurements and ventilatory efficiency are more objective parameters that should not be affected by this phenomenon. Blood gases remained unchanged after iloprost inhalation. A training effect that might have affected our result can be widely ruled out with the short time interval between both exercise tests. An improvement in exercise capacity in a placebo group has been described only at a markedly longer follow-up period. The observed improvements in exercise capacity and ventilatory efficiency show that iloprost inhalation affects not only pulmonary hemodynamics but also symptomatology and possibly survival in these patients. Compared with continuous intravenous prostacyclin therapy, inhalation provides the advantage of noninvasive drug administration, thereby avoiding rare but serious side effects, such as infection and catheter thrombosis. Furthermore, no adverse symptoms were reported during inhalation, which is a major advantage of selective iloprost use.

A potential disadvantage of this therapy is the discontinuous drug application. Despite a markedly prolonged half-life compared with prostacyclin, iloprost does not exert a continuous effect on the pulmonary circulation when administered in a regimen of 6 inhalations/d. Instead, fluctuating drug levels are present for only a few hours during the day with a long drug-free interval during the night. In addition, it is unknown whether the proposed antiproliferative effect of this type of treatment requires a steady dose profile during the day to become fully effective. Therefore, the role of iloprost inhalation in the treatment of patients with PPH and its long-term effects on exercise capacity and survival remain to be investigated in randomized controlled studies.

**References**


![Figure 3. Effects of iloprost inhalation on VE-vs-VCO₂ slope.](image-url)
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