

Inhaled Iloprost To Treat Severe Pulmonary Hypertension

An Uncontrolled Trial

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Background: Inhaled aerosolized iloprost, a stable prostacyclin analogue, has been considered a selective pulmonary vasodilator in the management of pulmonary hypertension.

Objective: To assess the efficacy of inhaled iloprost in the treatment of life-threatening pulmonary hypertension.

Design: Open, uncontrolled, multicenter study.

Setting: Intensive care units and pulmonary hypertension clinics at six university hospitals in Germany.

Patients: 19 patients who had progressive right-heart failure despite receiving maximum conventional therapy (12 with primary pulmonary hypertension, 3 with pulmonary hypertension related to collagen vascular disease without lung fibrosis, and 4 with secondary pulmonary hypertension).

Intervention: Inhaled iloprost, 6 to 12 times daily (50 to 200 $\mu\text{g}/\text{d}$).

Measurements: Right-heart catheterization and distance walked in 6 minutes at baseline and after 3 months of therapy.

Results: During the first 3 months of therapy, New York Heart Association functional class improved in 8 patients and was unchanged in 7 patients. Four patients died, 3 of right-heart failure and 1 of sepsis. The acute hemodynamic response to inhaled iloprost was predominant pulmonary vasodilatation with little systemic effect at baseline and at 3 months (data available for 12 patients). Hemodynamic variables were improved at 3 months, and the distance walked in 6 minutes improved by 148 m (95% CI, 4.5 to 282 m; $P = 0.048$). Of the 15 patients who continued to use inhaled iloprost, 8 stopped: Four had lung transplantation, 1 switched to intravenous prostacyclin therapy, and 3 died. Seven patients are still receiving inhaled iloprost (mean \pm SD) duration of therapy, 536 ± 309 days; mean dosage, 164 ± 38 $\mu\text{g}/\text{d}$).

Conclusions: Inhaled iloprost may offer a new therapeutic option for improvement of hemodynamics and physical function in patients with life-threatening pulmonary hypertension and progressive right-heart failure that is refractory to conventional therapy.

Progressive right-heart failure is the ultimate cause of death for most patients with primary pulmonary hypertension. The prognosis is particularly poor for patients with New York Heart Association functional class IV disease and severely increased central venous pressure (1). Prostacyclin was the first drug shown to be life-saving in a controlled study of primary pulmonary hypertension (2). However, the lack of pulmonary selectivity of the vasodilatory effect and consequent systemic side effects limit the usefulness of prostacyclin (3). Patients with severe arterial hypotension and preexistent shunt areas in the lung often cannot tolerate intravenous prostacyclin (4–6). Inhaled nitric oxide has pulmonary selectivity, but its vasodilatory potency in the pulmonary vasculature is lower than that of prostacyclin (7, 8). Because nitric oxide has a short half-life, interruption of nitric oxide inhalation may provoke an immediate rebound hypertensive crisis (9, 10).

In patients with severe primary or secondary pulmonary hypertension, we recently demonstrated that inhalation of aerosolized iloprost, the stable analogue of prostacyclin, substantially decreases pulmonary artery pressure and resistance and increases cardiac output without a significant decrease in systemic artery pressure and ventilation–perfusion mismatch (11, 12). This observation was consistent with previous findings in mechanically ventilated patients with acute respiratory failure, in whom aerosolized vasodilatory prostanoids effected selective pulmonary vasodilatation and preferential distribution of the nebulized vasodilator to the best-ventilated lung areas, with improvement of ventilation–perfusion matching (5, 12–18). We also reported on a patient with circulatory shock and right ventricular decompensation due to severe primary pulmonary hypertension (4) and a patient with decompensating right-heart failure due to collagen vascular disease–induced lung fibrosis (5). Both conditions were refractory to maximum conventional therapy; inhaled

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iloprost, however, seemed to improve hemodynamics and long-term survival. We extended these findings in an open, uncontrolled trial of 19 patients with primary or secondary pulmonary hypertension, all of whom presented with life-threatening pulmonary hypertension and progressive right-heart failure.

Methods

Patients

Between May 1995 and May 1998, we enrolled 19 patients with severe pulmonary hypertension from six university hospitals in Germany. Eighty-seven patients were eligible for therapy with inhaled iloprost, but we enrolled only patients who met criteria for clinical instability. Clinical instability was defined as the occurrence of at least one of the following: 1) rapid deterioration of exercise tolerance, as indicated by a decrease of more than 30% in the distance walked in 6 minutes in the past 1 to 2 months; 2) central venous pressure of 17 mm Hg or higher during physical rest with adequate diuretic therapy; 3) cardiogenic edema that was refractory to intravenous diuretic therapy; 4) cardiogenic ascites or pleural effusion that was refractory to diuretic therapy; 5) hepatic failure, indicated by an increase in bilirubin level above 86 $\mu\text{mol/L}$ (5 mg/dL) or aminotransferase levels more than three times the upper limit of normal; 6) renal failure, as indicated by a creatinine concentration greater than 159 $\mu\text{mol/L}$ (1.8 mg/dL) or oligoanuria; or 7) cardiogenic somnolence.

Severe pulmonary hypertension was diagnosed in all patients before study entry. Diagnostic procedures included transthoracic and, in most cases, transesophageal echocardiography; chest radiography; high-resolution computed tomography of the lung; spirometry; measurement of carbon monoxide diffusion capacity; electrocardiography; and laboratory measurements, including thyroid hormones, antinuclear antibodies, and extractable nuclear antigens. Ventilation and perfusion scanning of the lung and spiral computed tomography or pulmonary angiography were done if pulmonary embolism was suspected.

We excluded patients with fresh lung embolism or chronic lung embolism of central or segmental vessels and patients with active interstitial lung disease requiring high-dose steroids or immunosuppressant therapy. Patients with disorders of the left ventricle, mitral or aortic valve disease, severe liver disease, or hemorrhagic diathesis were not eligible. All patients gave written informed consent. The study was approved by the local ethics committees of all participating centers.

Intervention

Iloprost (Ilomedin, Schering AG, Berlin, Germany) was diluted in 0.9% saline (10 $\mu\text{g/mL}$), jet-nebulized with room air at a pressure of 80 kPa (fluid flux, 0.07 mL/min; mass median aerodynamic diameter of particles, 3.2 μm ; geometric SD, 1.8 as determined by impactor technique) and delivered to a spacer connected to the afferent limb of a Y-valve mouthpiece for 12 to 15 minutes (total nebulized dose, 8.4 to 10.5 μg). Patients inhaled 6 to 12 times daily after the baseline examination was performed. The frequency of inhalations was adjusted as necessary according to decreasing physical capacity or anginal symptoms between doses. The single dose was reduced if adverse effects (such as nausea) occurred during inhalation of the full dose. Patients were taught how to prepare the inhalation device and administer the drug by hospital staff.

Study Protocol

Before therapy with inhaled iloprost was started, a fiberoptic thermodilution pulmonary artery catheter was used to measure central venous pressure, pulmonary artery pressure, pulmonary artery wedge pressure, cardiac output, and central venous oxygen saturation (SvO_2); a femoral artery catheter was used to measure systemic arterial pressure and systemic arterial oxygen saturation (SaO_2). The test trial included inhaled nitric oxide, 20 to 40 parts per million, and aerosolized iloprost as described above. Catheter studies were repeated after 3 months of therapy with inhaled iloprost. One patient (patient 17) entered the study 48 hours after start of therapy with intravenous prostacyclin for decompensating right-heart failure. On initiation of therapy with inhaled iloprost, the dose of intravenous prostacyclin was reduced in a stepwise manner from 20 ng/kg of body weight per minute to 0 within 1 week. In this patient, no baseline test with inhaled iloprost and nitric oxide was performed. The time from the diagnosis of clinical instability to the start of therapy was no more than 2 weeks. After hospital discharge, the investigators who performed the baseline measurements saw the patients every 4 weeks. At these visits, lung function tests and blood gas analysis were performed and patients were asked about adverse effects. Between study visits, patients were managed by their own physicians but could call the investigator if any problems occurred.

The primary outcome of the study was the change in physical capacity in 3 months, assessed by the distance walked in 6 minutes. In addition, we monitored hemodynamic changes during short-term and long-term therapy with inhaled iloprost and followed patients until death, transplantation, or any other cause of cessation of therapy.

Table 1. Patient Characteristics at Baseline and 3 Months*

Patient	Inclusion Criterion†	Sex	Diagnosis	Age	Height	Weight	Pulmonary Vascular Resistance	Central Venous Pressure	New York Heart Association Functional Class‡	3-Month Survival	3-Month Recatheterization
				y	cm	kg	kPa · L ⁻¹ · s	mm Hg			
1	1, 2, 3, 5	Female	CREST	53	166	54	2616	17	IV	No	No
2	1, 2, 3, 4, acral necrosis	Female	Lung fibrosis	26	164	65	1952	18	IV	Yes	Yes
3	1, 3, 4, 5, 6, 7, 8, hypotension	Female	PPH	46	163	58	1953	11	IV	Yes	Yes
4	1	Male	Lung fibrosis	35	161	57	1397	8	IV	Yes	Yes
5	1	Male	Lung embolism	40	180	100	1767	10	III	Yes	Yes
6	1	Male	PPH	17	180	59	1970	4	III	Yes	Yes
7	1, 2, 3, 4, 7, 8, hypotension	Female	PPH	32	163	66	1824	19	IV	Yes	No
8	2, 3, hypotension	Male	PPH	32	180	75	2387	22	III	Yes	Yes
9	1, 2, hypotension	Female	PPH	32	170	62	2444	19	IV	Yes	Yes
10	1, 2, 3, 4	Female	CREST	49	165	53	1350	21	IV	No	No
11	1, 2, 3, 8	Female	PPH	31	161	56	2911	17	IV	Yes	Yes
12	1, heart size	Female	PPH	27	157	49	1582	8	IV	Yes	Yes
13	1	Female	PPH	24	170	53	1622	7.5	IV	Yes	Yes
14	1, 3, heart size	Female	Lung embolism	58	170	58	2000	15	IV	Yes	Yes
15	1, 2, 3, hypotension	Female	PPH	57	158	97	1095	19	IV	No	No
16	1, 2, 3	Male	PPH	48	182	70	2109	21	IV	Yes	Yes
17	2, 3, 5, 8, hypoxemia	Female	CREST	71	160	77	1935	23	IV	Yes	Yes
18	1, 4	Female	PPH	32	162	75	1305	14	IV	No	No
19	1	Female	PPH	28	163	71	1000	11	III	Yes	No
Mean ± SD				38.8 ± 14.1	167 ± 8	66 ± 14	1854 ± 509	15.0 ± 5.7			

* CREST = the syndrome of calcinosis cutis, the Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia; PPH = primary pulmonary hypertension.

† Inclusion criteria were as follows: 1, rapid deterioration; 2, central venous pressure ≥ 17 mm Hg; 3, refractory edema; 4, ascites; 5, pleural effusion; 6, liver failure; 7, renal failure; 8, somnolence.

‡ New York Heart Association functional class was applied according to the recommendations of the PPH World Conference in Évian, France, 1998.

Statistical Analysis

Data are presented as the mean (±SD) unless otherwise noted. The exact Wilcoxon matched-pair signed-rank test was used to assess the acute effects of inhaled iloprost (comparison of mean values before and after inhaled iloprost application) and the changes during 3 months of therapy (comparison of mean values at baseline and at 3 months) in the 12 patients for whom complete hemodynamic measurements at baseline and 3 months were available. Changes were assessed by using the Hodges–Lehmann point estimate, and the corresponding exact 95% CIs were calculated. For the 6-minute walk test, we assigned a value of 0 m to patients who had died in the 3 months from the start of iloprost therapy instead of doing a last-observation-carried-forward analysis. To calculate the Hodges–Lehmann point estimate and the 95% CIs, only the valid pairs were used: that is, patients who could not walk at baseline or at 3 months were excluded from analysis. A *P* value less than 0.05 was considered statistically significant.

Role of the Funding Source

The preparation and evaluation of data in this multicenter study was supported by PPH e.V., a German nonprofit patient self-care organization, and by the Deutsche Forschungsgemeinschaft. The

conduct and reporting of the trial were not influenced by these organizations.

Results

Patient Characteristics

All patients had clinical instability (**Table 1**). Seventeen patients had rapid deterioration; 12 had refractory edema, ascites, or pleural effusion; and 4 had commencing organ failure. Underlying disease was primary pulmonary hypertension in 12 patients, pulmonary hypertension associated with the CREST syndrome (calcinosis cutis, the Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) without pulmonary fibrosis (“isolated pulmonary hypertension”) in 3 patients, chronic peripheral lung embolism in 2 patients, and lung fibrosis in 2 patients. No patient had taken anorexigens, and none had liver cirrhosis or HIV infection.

Concomitant therapy included diuretics and anti-coagulant agents in every patient. Seven patients were receiving long-term therapy with calcium antagonists before catheterization and continued to take these agents during therapy with inhaled iloprost. No patient began taking a calcium antagonist along with inhaled iloprost. Only one patient

Table 2. Acute Vasodilator Response, Treatment, and Outcome

Patient	Pulmonary Vascular Resistance		Calcium Antagonist Therapy Continued	Status of Intravenous Prostacyclin Therapy	Inhaled Iloprost				Days of Inhaled Iloprost Therapy	Reason for Discontinuation of Inhaled Iloprost Therapy
	Response to Nitric Oxide*	Response to Inhaled Iloprost†			Starting Dosage		Last Dosage			
					$\mu\text{g/d}$	inhalation/d	$\mu\text{g/d}$	inhalation/d		
1	-26	-42	No	Never given	100	6	100	6	51	Chronic right-heart failure, death
2	-74	-67	No	Not tolerated	100	6	200	12	1137	Did not discontinue
3	-16	-29	No	Not tolerated	150	12	200	12	878	Lung transplantation
4	-39	-60	Yes	Never given	100	6	100	6	141	Lung transplantation
5	3	-25	No	Never given	100	6	100	6	456	Lung transplantation
6	-19	-30	Yes	Changed‡	100	6	100	6	586	Intravenous prostacyclin
7	-8	-29	No	Added	100	6	100	6	131	Chronic right-heart failure, death
8	-6	-23	No	Never given	150	9	150	9	690	Did not discontinue
9	-61	-73	No	Never given	100	9	150	12	564	Did not discontinue
10	md	-43	Yes	Never given	100	6	100	6	42	Sepsis, death
11	-29	-47	No	Not tolerated	100	12	150	12	481	Did not discontinue
12	-18	-16	Yes	Not tolerated	100	6	150	12	176	Multiorgan failure, death
13	-35	-52	No	Never given	150	9	200	12	283	Did not discontinue
14	-3	-20	Yes	Never given	100	6	100	6	369	Did not discontinue
15	1	-27	No	Not tolerated	100	6	100	6	50	Chronic right-heart failure, death
16	-42	-51	No	Stopped§	150	9	200	12	231	Did not discontinue
17	md	md	No	Never given	100	6	100	6	179	Myocardial infarction, death
18	md	-5	Yes	Never given	100	6	100	6	59	Acute right-heart failure, death
19	md	-10	Yes	Never given	50	6	75	6	110	Lung transplantation
Mean \pm SD	-25 \pm 23	-36 \pm 19			108 \pm 25	7.3 \pm 2.1	130 \pm 43	8.4 \pm 2.9	348 \pm 310	

* 20–40 parts per million.

† 8.4–10.5 μg delivered within 12 to 15 minutes.

‡ Therapy with inhaled iloprost was changed to continuous therapy with intravenous prostacyclin because of deterioration.

§ Changed to inhaled iloprost at study entry.

(patient 17) previously received intravenous prostanooids; this patient had received intravenous prostacyclin 48 hours before therapy with inhaled iloprost was started.

The mean age of the patients was 39 ± 14 years (Table 1). Patients with the CREST syndrome were, on average, older than those with primary pulmonary hypertension (58 ± 12 years compared with 34 ± 11 years).

The physical capacity of the patients was severely restricted. Fifteen patients (79%) had New York Heart Association functional class IV disease and 4 had class III disease. Among the patients with class IV disease, 5 were completely confined to bed with resting dyspnea, commencing organ failure syncope at rest, or a combination of these conditions. At baseline, the mean pulmonary artery pressure was 66 ± 17 mm Hg, the cardiac index was 1.59 ± 0.31 $\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, the pulmonary vascular resistance was 1854 ± 509 $\text{kPa} \cdot \text{L}^{-1} \cdot \text{s}$, and the systemic vascular resistance was 2067 ± 623 $\text{kPa} \cdot \text{L}^{-1} \cdot \text{s}$. The mean central venous pressure was 15.0 ± 5.7 mm Hg, and the pulmonary artery wedge pressure ranged at low normal values (6 ± 4 mm Hg). The heart rate at baseline was 97 min^{-1} . The systemic artery pressure was 84 ± 17 mm Hg, and the ratio of pulmonary vascular resistance to systemic vascular resistance

was increased to 0.93 ± 0.31 . Responses to inhaled nitric oxide and inhaled iloprost were available in 15 and 18 patients, respectively (Table 2).

Three-Month Observation Period

Treatment and Outcome

The overall daily dose of iloprost was 50 to 150 μg (mean dose, 108 ± 25 μg) at the start of long-term therapy with inhaled iloprost. The dose was adjusted to the patients' needs and tolerability. Some adverse effects occurred, such as coughing, headache, and flush, but they were slight to moderate, were mostly transient, and did not lead to cessation of therapy. The single doses of inhaled iloprost had to be reduced by 50% in patients 9 and 12 because of nausea associated with the inhalation procedure, but the total daily dose remained constant because the frequency of inhalation was increased. After 12 weeks, the mean dosage was an average of 120 $\mu\text{g/d}$.

During the 3-month observation period, four patients died (Table 1). Patients 1 and 15 died of chronic progressive right-heart failure despite having received the maximum conservative therapy, including dobutamine and intravenous prostacyclin. These therapies were started because of the pa-

tients' progressive deterioration; however, they did not provide substantial benefit over that obtained with aerosolized iloprost. One patient died suddenly, presumably of acute right-heart failure, and one patient who had the CREST syndrome and was receiving low-dose steroids died of pneumogenic sepsis (Table 2). All of the deaths seemed to result from the disease processes rather than therapy with inhaled iloprost.

Hemodynamics and Gas Exchange

Repeated measurements of the hemodynamic response to inhaled iloprost at baseline and 3 months were available in 12 patients. The other patients were lost because of death ($n = 4$), refusal to undergo recatheterization ($n = 2$), and lack of baseline vasoreactivity testing ($n = 1$). In the remaining 12 patients, the following results were obtained (Figure 1).

The acute response to iloprost was maintained. The mean pulmonary artery pressure decreased by 11.5 mm Hg (95% CI, 7.5 to 19.0 mm Hg) at baseline and by 9.5 mm Hg (CI, 6.5 to 18 mm Hg) after 3 months, and pulmonary vascular resistance

decreased by 815 $\text{kPa} \cdot \text{L}^{-1} \cdot \text{s}$ (CI, 481 to 1189 $\text{kPa} \cdot \text{L}^{-1} \cdot \text{s}$) at baseline and by 689 $\text{kPa} \cdot \text{L}^{-1} \cdot \text{s}$ (CI, 424 to 975 $\text{kPa} \cdot \text{L}^{-1} \cdot \text{s}$) after 3 months, corresponding to a 41% decline. Mean values at 3 months improved from the values obtained at baseline, before therapy was begun ($P < 0.01$) (Figure).

At 3 months, pulmonary artery pressure was decreased by 7.5 mm Hg (CI, 3 to 10.5 mm Hg), pulmonary vascular resistance was decreased by 295 $\text{kPa} \cdot \text{L}^{-1} \cdot \text{s}$ (CI, 113 to 485 $\text{kPa} \cdot \text{L}^{-1} \cdot \text{s}$), central venous pressure was decreased by 5.5 mm Hg (CI, 2.5 to 8.3 mm Hg), and the cardiac index was increased by 0.24 $\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ (CI, 0.07 to 0.46 $\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$). All of these changes were statistically significant ($P < 0.05$ for all comparisons).

Compared with baseline values, post-irradiation hemodynamics after 3 months of therapy with inhaled iloprost were markedly improved: Pulmonary artery pressure decreased by 16 mm Hg (CI, 10.5 to 23 mm Hg); pulmonary vascular resistance decreased by 980 $\text{kPa} \cdot \text{L}^{-1} \cdot \text{s}$ (CI, 609 to 1349 $\text{kPa} \cdot \text{L}^{-1} \cdot \text{s}$); central venous pressure decreased by 9.8 mm Hg (CI, 4.5 to 15.0 mm Hg); and cardiac

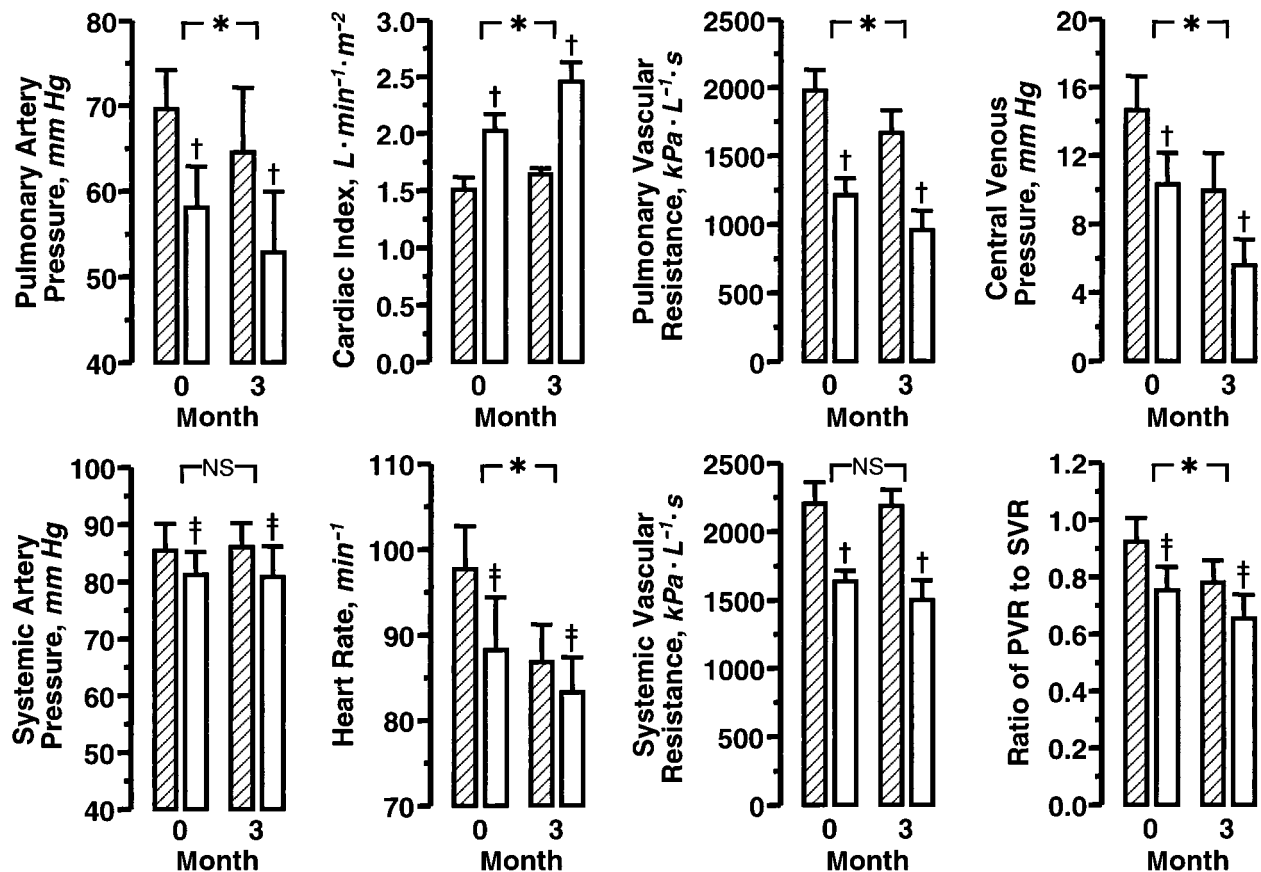


Figure. Hemodynamic response at baseline and after 3 months of therapy with aerosolized iloprost. Pretherapy (striped bars) and post-therapy (white bars) values (+SE) are given for 12 patients for whom complete data were available on hemodynamics at baseline and after 3 months of therapy. A single inhalation of iloprost, 8.4 to 10.5 μg , nebulized within 12 to 15 minutes was given. Mean pulmonary artery pressure, cardiac index, pulmonary vascular resistance, central venous pressure, mean systemic artery pressure, heart rate, systemic vascular resistance, and the ratio of pulmonary vascular resistance (PVR) to systemic vascular resistance ratio (SVR) were significantly changed by inhalation of iloprost * $P < 0.05$ for differences in values from baseline to 3 months; † $P < 0.001$; ‡ $P < 0.01$, by exact Wilcoxon matched-pair signed-rank test. NS = not significant.

Table 3. Change in the Distance Walked in 6 Minutes

Patient*	Distance Walked in 6 Minutes		
	Baseline	3 Months	Difference
	←-----m----->		
1	0	0†	
2	0	224	224
3	0	0	
4	0	0	
7	0	0	
8	249	349	100
9	0	439	439
10	50	0†	-50
11	0	400	400
12	308	466	158
13	287	508	221
14	120	405	285
15	70	0†	-70
16	0	345	345
17	0	125	125
18	116	0†	-116
19	310	0	-310
Hodges-Lehmann estimate (95% CI)			148 (4.5-282)‡
P value			0.048

* 17 patients were requested to perform the test. Patients 5 and 6 were tested on a cycle ergometer (data not included).

† The distance was set to zero because this patient died before the end of the 3 months.

‡ Based on data from valid pairs ($n = 13$).

index was increased by $0.77 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ (CI, 0.55 to $1.37 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$), a 51% increase.

Mean systemic artery pressure (-1 mm Hg [CI, -4.5 to 5.0 mm Hg]) and systemic vascular resistance ($-78 \text{ kPa} \cdot \text{L}^{-1} \cdot \text{s}$ [CI, -290 to $152 \text{ kPa} \cdot \text{L}^{-1} \cdot \text{s}$]) had not changed significantly at 3 months. The SvO_2 increased by 4.5% (CI, -2.1% to 11.9%) but SaO_2 did not change (-0.2% [CI, -2.6% to 1.9%]). The PCO_2 (0.35 mm Hg [CI, -1.35 to 2.15 mm Hg]) and PO_2 (-7.9 mm Hg [CI, -26.5 to 4.2 mm Hg]) were not changed significantly at 3 months.

Distance Walked in 6 Minutes

Patients 5 and 6 were tested by using cycle ergometry and were not requested to perform a 6-minute walk test; these data were not included in the analysis. Of the remaining patients, nine were confined to bed at baseline and eight patients had a mean distance walked of 189 m. After 3 months, four patients were confined to bed, four had died, and the nine patients had a mean distance walked of 362 m. The increase in the distance walked in the valid pairs ($n = 13$) was 148 m (CI, 4.5 to 282 m) ($P = 0.048$) (Table 3).

Long-Term Follow-up

After the 3-month observation period, all surviving patients continued to receive inhaled iloprost. In one patient, therapy was switched to intravenous prostacyclin after 580 days because of worsening symptoms. Four patients underwent lung transplantation (Table 2). One patient died of refractory arterial hypotension resulting in multiorgan failure after 6 months of therapy with continuous inhaled

iloprost. The remaining seven patients were still receiving nebulized iloprost at the time of completion of this report. After a mean duration of therapy of 536 ± 309 days, the average dosage was $164 \pm 38 \mu\text{g/d}$, divided in 11 ± 2 inhalations per day.

Adverse Effects

The most common adverse effect associated with use of inhaled iloprost was coughing (Table 4). This side effect was definitely ascribed to the iloprost inhalations in two patients. In most of the patients, coughing was transient, occurring only during the first days of therapy. Five of the patients had nausea, which was transient in most patients and did not require a change in therapy; one patient, however, required reduction of the single dose and increased inhalation frequency. Other adverse effects included tongue hypersensitivity, gum swelling, joint pain, dry skin, and retrosternal burning. None of these effects resulted in reduction or cessation of therapy. Death or a life-threatening situation could not be ascribed to the use of inhaled iloprost in any patient.

Discussion

This study corroborates our previous observation that inhalation of aerosolized iloprost is a feasible approach to achieving preferential pulmonary vasodilation in severe pulmonary hypertension; it does not significantly decrease the systemic artery pressure and maintains or slightly improves gas exchange. Our results extend the previous findings of significant improvement in hemodynamics and physical capacity over 3 months of therapy in severely ill patients who had progressive deterioration despite receiving maximum conventional therapy.

Compared with patients in previous studies of vasodilatory agents in severe pulmonary hyperten-

Table 4. Adverse Effects of Inhaled Iloprost

Adverse Effect	Patients with Adverse Effect	Patients Whose Adverse Effect Was Definitely Drug-Related	Patients Whose Adverse Effect Was Transient
Cough	7	2	4
Nausea	5	2	5
Edema	4	0	3
Thoracic pain	3	2	2
Headache	2	0	2
Jaw pain	1	1	1
Other*	6	1	5

* Tongue hypersensitivity (1 patient), joint pain (1 patient), retrosternal burning (1 patient), gum swelling (1 patient with periodontitis), dry skin (1 patient), and suspicion of rebound pulmonary hypertension starting about 1 hour after inhalation (1 patient).

sion (2, 19, 20), the physical status of our patients was exceptionally poor. More than half of the patients were unable to walk at baseline, the mean cardiac index was $1.59 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, and the mean SvO_2 was less than 50%. Our inclusion criteria were chosen to identify patients at very high risk for death from right ventricular failure in the next 3 months. One of the main factors that defines a very short survival time is refractory venous congestion with increased central venous pressure (1). In our setting, obvious organ failure, venous congestion (refractory peripheral edema, ascites, and pleural effusion), or significantly increased central venous pressure was noted in 13 of the 19 patients at baseline catheter investigation, even though maximum intravenous diuretic therapy and physical rest were prescribed before this testing. The remaining 6 patients did not have massive volume overload or overt organ failure. These patients did, however, experience rapid deterioration of symptoms and exercise capacity that could not be explained except by rapid progression of right-heart failure. In our experience, the prognosis of patients whose condition rapidly deteriorates despite maximum conservative therapy, including calcium antagonists, is very poor, even if the central venous pressure values are not yet very high. Against this background, we accepted the finding of rapid deterioration of exercise tolerance ($>30\%$ in 1 to 2 months of repeated measurements) as a criterion for study entry in addition to the criteria for right-heart decompensation and overt organ failure.

The long-term use of high-dose calcium-channel blockers improves survival in up to 25% of patients with primary pulmonary hypertension, particularly those with the most marked and preferential pulmonary vasodilatation (19). Calcium antagonists had already been introduced in seven of our patients; six of these patients were treated with long-term low-dose nifedipine or diltiazem. Patient 12 received felodipine because of the excellent vasoreactivity found in the first catheter investigation, performed 6 months before study entry. Calcium antagonist therapy was not changed during the study, nor was it started in any of the patients. Any confounding influence of calcium antagonist therapy on the results obtained with inhaled iloprost therapy may thus be excluded.

Inhaled nitric oxide, a selective pulmonary vasodilator that is effective in primary pulmonary hypertension (21), isolated pulmonary hypertension (22), and secondary pulmonary hypertension (5), has been suggested as a bridge to transplantation (23) and for long-term therapy in patients with primary pulmonary hypertension (24). In addition, inhaled nitric oxide is used as a screening agent to predict the response to calcium antagonists (25, 26). How-

ever, rebound pulmonary hypertension (9, 10) and toxicologic problems (7) may limit the long-term use of this agent. During baseline catheterization, the acute response to inhaled nitric oxide was tested in most of our severely ill patients, and the reduction of pulmonary vascular resistance was less prominent with this agent than with inhaled aerosolized iloprost (mean reduction, -25% compared with -36%). These findings compare favorably with our previous results (11) and those of other investigators (7, 8). Another report from our group addressed this issue in a larger number of patients with primary pulmonary hypertension (27).

A significant increase in cardiac output, a decrease in central venous pressure, and an increase in SvO_2 were observed during catheterization in response to therapy with inhaled iloprost. The efficacy of iloprost in the currently studied patients with life-threatening pulmonary hypertension and mostly overt right-heart decompensation thus corresponds well to that described in patients with compensated right ventricular function (11) (mean reduction in pulmonary vascular resistance, approximately 36% in our study and approximately 41% in the previous study). Beyond characterization of the acute hemodynamic effects of iloprost nebulization, we focused on whether a regimen of daily repeated iloprost inhalation might act as "rescue" therapy in patients with life-threatening end-stage pulmonary hypertension. After 3 months of therapy, four patients (two with primary pulmonary hypertension and two with isolated pulmonary hypertension) had died, three of them of right-heart failure. These patients were somewhat older than the mean age of the group, all had New York Heart Association class IV disease at baseline, and the criteria for right-heart decompensation (central venous pressure values and fluid accumulation) were more prominent than those in the average patient. One patient died of pneumonia in the 3-month observation period. This patient had the CREST syndrome and was receiving low-dose steroid therapy, which may have enhanced the risk for infectious complications. In three of four patients (the fourth died of right-heart failure), we tried to change therapy to intravenous prostacyclin (which is not approved in Germany) because of deterioration during ongoing iloprost inhalation. However, intravenous prostanoid therapy was not tolerated because worsening of arterial hypotension (two patients) or death occurred despite the infusion. The mortality rate in the present study cannot be compared with the data from the study by Barst and colleagues (2), in which none of the patients treated with intravenous prostacyclin died within the first 3 months of therapy, for two reasons. First, our patients had significantly greater decompensation at study entry, as shown by the mean distance walked

in 6 minutes (189 m compared with 294 m in Barst and colleagues' study) and the SvO₂ (46.9% compared with 60.5%). Second, we included patients with secondary pulmonary hypertension; two of the early deaths (50%) occurred in this group.

In our study, 12 of 19 patients had significant and, in some cases, impressive improvement in hemodynamics (pulmonary artery pressure, pulmonary vascular resistance, cardiac index, and central venous pressure) and exercise capacity in response to long-term iloprost inhalation. In long-term follow-up, 4 patients had elective lung or heart-lung transplantation, 3 patients died, and 1 patient was switched to intravenous prostacyclin. One of the deaths could be ascribed to myocardial infarction due to coronary heart disease (patient 17). The other patients were receiving prostanoid therapy at completion of this report, with only a moderate increase in dosage to a mean of 164 µg/d after 1.5 years of therapy. The therapy was generally well tolerated; side effects, such as coughing or facial flush or headache after inhalation, were minor and mostly transient.

Our study had several limitations. First, the study was uncontrolled, and a direct comparison of exercise capacity and survival data in a nontreated control group may not be undertaken. Moreover, no variable reliably predicts survival time in patients with decompensation (28). In light of our previous experience with inhaled iloprost therapy and worldwide experience with intravenous prostacyclin therapy (2, 3, 20, 29, 30), we felt that withholding prostanoid therapy in patients with acutely life-threatening pulmonary hypertension would not be ethical. Second, we included patients with primary pulmonary hypertension (the predominant group) and those with secondary pulmonary hypertension of different cause (the CREST syndrome, lung fibrosis, and chronic peripheral lung embolism), thereby possibly mixing groups with different degrees of responsiveness. Detailed analysis of the data of the different subgroups did not, however, show obvious differences in the response to iloprost inhalation including outcome between patients with primary and those with secondary pulmonary hypertension. Third, no systematic comparison with continuous intravenous prostacyclin infusion, shown to have life-saving efficacy in patients with primary pulmonary hypertension (2, 3, 20, 29, 30), was undertaken.

In conclusion, nebulized iloprost was associated with acute preferential pulmonary vasodilatation and improvement of right ventricular function in patients with primary pulmonary hypertension or secondary pulmonary hypertension who had life-threatening progressive right-heart failure, in most cases associated with refractory venous congestion. Fifteen of 19 patients who received repeated daily

doses of inhaled iloprost survived the 3-month observation period and had substantial improvement in exercise capacity and hemodynamics. In view of the extremely poor prognosis of patients with pulmonary hypertension and right-heart decompensation that is refractory to conventional therapy, we suggest consideration of inhalation of iloprost as a rescue strategy in these patients.

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References

1. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med.* 1991;115:343-9.
2. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med.* 1996;334:296-301.
3. Barst RJ, Rubin LJ, McGoon MD, Caldwell EJ, Long WA, Levy PS. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. *Ann Intern Med.* 1994;121:409-15.
4. Olschewski H, Ghofrani HA, Walmrath D, Temmesfeld-Wollbrück B, Grimminger F, Seeger W. Recovery from circulatory shock in severe primary pulmonary hypertension (PPH) with aerosolization of iloprost. *Intensive Care Med.* 1998;24:631-4.
5. Olschewski H, Ghofrani HA, Walmrath D, Schermuly R, Temmesfeld-Wollbrück B, Grimminger F, et al. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. *Am J Respir Crit Care Med.* 1999;160:600-7.
6. Agustí AG, Rodríguez-Roisin R. Effect of pulmonary hypertension on gas exchange. *Eur Respir J.* 1993;6:1371-7.
7. Warren JB, Higenbottam T. Caution with use of inhaled nitric oxide. *Lancet.* 1996;348:629-30.
8. Mikhail G, Gibbs J, Richardson M, Wright G, Khaghani A, Banner N, et al. An evaluation of nebulized prostacyclin in patients with primary and secondary pulmonary hypertension. *Eur Heart J.* 1997;18:1499-504.
9. Miller OI, Tang SF, Keech A, Celemajer DS. Rebound pulmonary hypertension on withdrawal from inhaled nitric oxide. *Lancet.* 1995;346:51-2.
10. Cueto E, Lopez-Herce J, Sanchez A, Carrillo A. Life-threatening effects of discontinuing inhaled nitric oxide in children. *Acta Paediatr.* 1997;86:1337-9.
11. Olschewski H, Walmrath D, Schermuly R, Ghofrani A, Grimminger F, Seeger W. Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. *Ann Intern Med.* 1996;124:820-4.
12. Walmrath D, Schneider T, Pilch J, Grimminger F, Seeger W. Aerosolized prostacyclin in adult respiratory distress syndrome. *Lancet.* 1993;342:961-2.
13. Walmrath D, Schneider T, Pilch J, Schermuly R, Grimminger F, Seeger W. Effects of aerosolized prostacyclin in severe pneumonia. Impact of fibrosis. *Am J Respir Crit Care Med.* 1995;151:724-30.
14. Walmrath D, Schneider T, Schermuly R, Olschewski H, Grimminger F, Seeger W. Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1996;153:991-6.
15. Zwissler B, Kemming G, Habler O, Kleen M, Merkel M, Haller M, et al. Inhaled prostacyclin (PGI₂) versus inhaled nitric oxide in adult respiratory distress syndrome. *Am J Respir Crit Care Med.* 1996;154:1671-7.
16. Eichelbronner O, Reinelt H, Wiedeck H, Mezody M, Roissant R, Georgieff M, et al. Aerosolized prostacyclin and inhaled nitric oxide in septic shock—different effects on splanchnic oxygenation? *Intensive Care Med.* 1996;22:880-7.
17. Putensen C, Hormann C, Kleinsasser A, Putensen-Himmer G. Cardiopulmonary effects of aerosolized prostaglandin E₁ and nitric oxide inhalation in patients with acute respiratory distress syndrome. *Am J Respir Care Med.* 1998;157:1743-7.
18. De Jaegere AP, van den Anker JN. Endotracheal instillation of prostacyclin in preterm infants with persistent pulmonary hypertension. *Eur Respir J.* 1998;12:932-4.
19. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med.* 1992;327:76-81.
20. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med.* 1998;338:273-7.
21. Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT, Stone D, Wallwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. *Lancet.* 1991;338:1173-4.
22. Williamson DJ, Hayward C, Rogers P, Wallman LL, Sturgess AD, Penny R, et al. Acute hemodynamic responses to inhaled nitric oxide in patients with limited scleroderma and isolated pulmonary hypertension. *Circulation.* 1996;94:477-82.
23. Snell GI, Salamonsen RF, Bergin P, Esmore DS, Khan S, Williams TJ. Inhaled nitric oxide used as a bridge to heart-lung transplantation in a patient with end-stage pulmonary hypertension. *Am J Respir Crit Care Med.* 1995;151:1263-6.
24. Channick RN, Newhart JW, Johnson FW, Williams PJ, Auger WR, Fedullo PF, et al. Pulsed delivery of inhaled nitric oxide to patients with primary pulmonary hypertension: an ambulatory delivery system and initial clinical tests. *Chest.* 1996;109:1545-9.
25. Sitbon O, Brenot F, Denjean A, Bergeron A, Parent F, Azarian R, et al. Inhaled nitric oxide as a screening vasodilator agent in primary pulmonary hypertension. A dose-response study and comparison with prostacyclin. *Am J Respir Crit Care Med.* 1995;151:384-9.
26. Ricciardi MJ, Knight BP, Martinez FJ, Rubenfire M. Inhaled nitric oxide in primary pulmonary hypertension: a safe and effective agent for predicting response to nifedipine. *J Am Coll Cardiol.* 1998;32:1068-73.
27. Höper MM, Olschewski H, Ghofrani HA, Wilkens H, Winkler J, Borst MM, et al. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. *J Am Coll Cardiol.* [In press].
28. Sandoval J, Bauerle O, Palomar A, Gomez A, Martinez-Guerra ML, Beltran M, et al. Survival in primary pulmonary hypertension. Validation of a prognostic equation. *Circulation.* 1994;89:1733-44.
29. Higenbottam TW, Spiegelhalter D, Scott JP, Fuster V, Dinh-Xuan AT, Caine N, et al. Prostacyclin (epoprostenol) and heart-lung transplantation as treatments for severe pulmonary hypertension. *Br Heart J.* 1993;70:366-70.
30. Higenbottam TW, Butt AY, McMahon A, Westerbeck R, Sharples L. Long-term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. *Heart.* 1998;80:151-5.