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Pulmonary Vascular Disease

Favorable Effects of Inhaled Treprostinil in Severe Pulmonary Hypertension

Results From Randomized Controlled Pilot Studies

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OBJECTIVES This study sought to investigate the effects of inhaled treprostinil on pulmonary hemodynamics and gas exchange in severe pulmonary hypertension.

BACKGROUND Inhaled iloprost therapy has a proven clinical efficacy in pulmonary arterial hypertension, but this therapy necessitates 6 to 9 inhalation sessions per day. Treprostinil has a longer plasma half-life and might provide favorable properties when applied by inhalation.

METHODS Three different studies were conducted on a total of 123 patients by means of right heart catheterization: 1) a randomized crossover-design study (44 patients), 2) a dose escalation study (31 patients), and 3) a study of reduction of inhalation time while keeping the dose fixed (48 patients). The primary end point was the change in pulmonary vascular resistance (PVR).

RESULTS The mean pulmonary arterial pressure of the enrolled patients was approximately 50 mm Hg in all studies. In study 1, both treprostinil and iloprost at an inhaled dose of 7.5 μg displayed a comparable PVR decrease, with a significantly different time course ($p < 0.001$), treprostinil showing a more sustained effect on PVR ($p < 0.0001$) and fewer systemic side effects. In study 2, effects of inhalation were observed for 3 h. A near-maximal acute PVR decrease was observed at 30 μg treprostinil. In study 3, treprostinil was inhaled at increasing concentrations with a pulsed ultrasonic nebulizer, mimicking a metered dose inhaler. A dose of 15 μg treprostinil was inhaled with 18, 9, 3, 2 pulses, or 1 pulse, each mode achieving comparable, sustained pulmonary vasodilation without significant side effects.

CONCLUSIONS Inhaled treprostinil exerts sustained pulmonary vasodilation with excellent tolerability at relatively low doses and may be inhaled in a few breaths. (J Am Coll Cardiol 2006;48: 1672–81) © 2006 by the American College of Cardiology Foundation

New therapies for pulmonary arterial hypertension have shown clinical efficacy, but there remains a need for further improvement (1). Continuous intravenous infusion of epoprostenol improves hemodynamics, quality of life, and survival. The stable prostacyclin analog treprostinil might have comparable clinical effects (2–4), but intravenous therapy is prone to catheter-related infections, drug tolerance, and major systemic side effects. The inhalation of iloprost is clinically efficacious in patients with severe pulmonary arterial hypertension (5) and was recently approved for use in Europe, Australia, and the U.S. However, 6 to 9 iloprost inhalation sessions daily with 6- to 12-min inhalation times are recommended, consuming considerable time every day.

The stable prostacyclin analog treprostinil has been approved in the U.S., Israel, Australia, and Canada for treatment of pulmonary arterial hypertension (New York Heart Association functional class II to IV) and by the European Medical Agency for idiopathic PAH (New York Heart Association functional class III) via continuous subcutaneous infusion (6) and continuous intravenous infusion (4). Subcutaneous application circumvents septic events caused by catheter infections related to intravenous infusion; however, local pain and tissue reaction at the infusion site may limit effective dosing and long-term treatment. Treprostinil possesses a longer plasma half-life than iloprost (7) and may show alternative tissue binding characteristics that could result in

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Abbreviations and Acronyms

PVR = pulmonary vascular resistance
AUC = area under the curve
ABC = areas between curves
PAP = pulmonary arterial pressure
SAP = systemic arterial pressure

favorable pharmacodynamic features when delivered via the inhaled route. A recent case report suggests that inhaled treprostinil might be tolerable and efficacious in the long term (8).

We asked whether inhaled treprostinil had acute pulmonary vasodilative properties and whether it might be superior to inhaled iloprost in terms of duration of effect and systemic side effects. We then increased both the total inhaled dose to define a threshold for systemic side effects, and the drug concentration to reduce the inhalation time.

METHODS AND PATIENTS

All studies were approved by the institutional ethics committee of the University of Giessen, and written informed consent was obtained from all 123 enrolled patients. All inhalations were performed with the Optineb ultrasonic nebulizer (Nebutec, Elsenfeld, Germany).

Study 1 was a randomized, open-label, single-blind crossover study. The primary objective was to compare the acute hemodynamic effects and the systemic side effects of inhaled treprostinil with inhaled iloprost at comparable doses. A total number of 44 patients with moderate to severe precapillary pulmonary hypertension were enrolled. Patient characteristics and hemodynamic as well as gas exchange parameters are outlined in Table 1.

Each patient underwent right heart catheterization and inhaled both iloprost and treprostinil on the same day during hemodynamic monitoring. The drugs were administered consecutively with a 1-h interval between the drug administrations. One-half of the study patients initially inhaled treprostinil and then inhaled iloprost (n = 22), and the other half initially inhaled iloprost and then inhaled treprostinil (n = 22). Patients were randomized to 1 of the 2 groups and blinded regarding the sequence of the study drugs. Drug effects were monitored for 60 min after each inhalation session. Iloprost was inhaled at a concentration of 4 μg/ml (6 min inhalation time; n = 44) and treprostinil was inhaled at concentrations of 4 μg/ml (6 min inhalation; n = 14), 8 μg/ml (6 min inhalation; n = 14) or 16 μg/ml (3 min inhalation; n = 16). Based on previous biophysical characterization of the ultrasonic device with iloprost and treprostinil solution, this corresponds to total inhaled doses of 7.5 μg iloprost and treprostinil (4 μg/ml) and 15 μg treprostinil (8 μg/ml and 16 μg/ml), respectively.

Study 2 was a randomized, open-label, single-blind, placebo-controlled study. The primary objectives were to

Table 1. Patient Characteristics, Hemodynamic Parameters, and Gas Exchange Values at Baseline, Before Challenge With Inhalative Prostanoids

Study Group	n	Age (yrs)	Gender Female/Male	Etiology i/o/t/f	PAP (mm Hg)	PVR (dyn · s · cm^{-5})	SAP (mm Hg)	CVP (mm Hg)	PAWP (mm Hg)	CO (l/min)	SaO_2 (%)	SvO_2 (%)
1a	14	55.1 ± 4.8	11/3	4/4/2/4	53.8 ± 3.1	911 ± 102	95.4 ± 3.6	7.4 ± 1	8.0 ± 0.8	4.3 ± 0.4	93.8 ± 2	63.9 ± 2.4
1b	14	54.1 ± 3.3	10/4	1/6/5/2	47.4 ± 3.8	716 ± 80	90.6 ± 3.3	5.9 ± 1.4	6.4 ± 0.7	4.7 ± 0.4	92 ± 1	64.4 ± 2.3
1c	16	56 ± 2.9	7/9	6/3/6/1	47.5 ± 4.5	777 ± 102	92 ± 4.5	8.3 ± 1.4	8.6 ± 1.4	4.4 ± 0.5	91.4 ± 0.9	59.8 ± 2.6
2a	8	60.8 ± 4	4/4	2/2/3/1	51.9 ± 4.9	849 ± 152	95.9 ± 4.8	7.6 ± 1.4	11.1 ± 1.7	4.4 ± 0.6	89.6 ± 2.8	60.1 ± 2.8
2b	8	52.8 ± 6.6	6/2	1/3/3/1	49 ± 4	902 ± 189	92.4 ± 2.4	4.8 ± 1.1	7.2 ± 1.3	4.0 ± 0.4	92.4 ± 2.4	62.5 ± 1.7
2c	6	56.8 ± 5.9	4/2	0/2/2/2	44.2 ± 3.5	856 ± 123	96.3 ± 3.9	5 ± 1.1	6 ± 1	3.8 ± 0.3	92.8 ± 1.5	63.6 ± 1.8
2d	6	51.2 ± 3.8	4/2	2/2/2/0	55.5 ± 4.9	940 ± 110	91.2 ± 8.1	11.2 ± 1.2	10 ± 0.7	3.9 ± 0.4	92 ± 1.9	62 ± 5.8
2e	3	57.3 ± 9.1	1/2	0/1/0/2	45.3 ± 5.2	769 ± 267	99 ± 3.2	5 ± 2.1	9 ± 0.6	4.5 ± 0.6	94.2 ± 1.3	66.3 ± 1.5
3a	6	52.7 ± 6.6	4/2	2/4/0/0	53.8 ± 6.7	928 ± 145	92.7 ± 7.9	8.7 ± 2.7	8.8 ± 1.3	4.2 ± 0.6	90.4 ± 2.8	64.8 ± 4.3
3b	6	58.3 ± 3.5	4/2	3/1/1/1	54.2 ± 6.1	808 ± 156	94.3 ± 2.8	7 ± 1.4	10 ± 1.3	5 ± 0.7	91.9 ± 0.7	63.5 ± 2.9
3c	21	57.4 ± 5.6	8/3	7/7/6/1	46.1 ± 2.5	900 ± 99	88 ± 2.8	9 ± 1.4	9.2 ± 0.5	3.7 ± 0.3	91.7 ± 0.5	59.7 ± 2
3d	7	55.6 ± 5.8	3/4	0/4/3/0	53.1 ± 7.1	732 ± 123	91.4 ± 5.6	7.9 ± 3.1	8.6 ± 1.3	5 ± 0.4	90.7 ± 1.4	61.3 ± 3.7
3e	8	59 ± 5.2	7/1	0/4/4/0	45.1 ± 3.9	733 ± 114	92.8 ± 6.8	4.6 ± 0.8	8.1 ± 1.1	4.3 ± 0.2	90.7 ± 0.8	66.3 ± 2.8

Group 1 corresponds to study 1, randomized crossover study comparing inhaled iloprost (ILO) and inhaled treprostinil (TRE): a = 7.5 μg TRE, b = 7.5 μg ILO versus 7.5 μg TRE (6-min inhalation time), c = 7.5 μg ILO versus 15 μg TRE (3-min inhalation time). Group 2 corresponds to study 2; evaluation of maximal tolerated dose of TRE: a = placebo inhalation, b = 30 μg TRE, c = 60 μg TRE, d = 90 μg TRE, e = 120 μg TRE. Group 3 corresponds to study 3; reduction of inhalation time by increase of TRE concentration, aiming at a total inhaled dose of 15 μg: a = 18 pulses of 100 μg/ml TRE, b = 9 pulses of 200 μg/ml TRE, c = 3 pulses of 600 μg/ml TRE, d = 2 pulses of 1,000 μg/ml TRE, e = 1 pulse of 2,000 μg/ml TRE. Etiology of pulmonary hypertension was classified as idiopathic pulmonary arterial hypertension (i), pulmonary arterial hypertension of other causes (o), chronic thromboembolic pulmonary hypertension (t), and pulmonary fibrosis (f).

CO = cardiac output; CVP = central venous pressure; PAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; SAP = mean systemic arterial pressure; SaO_2 = systemic arterial oxygen saturation; SvO_2 = pulmonary arterial oxygen saturation.

describe the pharmacodynamic and pharmacokinetic effects of inhaled treprostinil at a well-tolerated dose (30 μg) and to explore the highest tolerated single dose. A total number of 31 patients inhaled either placebo or treprostinil; each patient underwent 1 inhalation session. The first 16 patients were randomized to 30 μg treprostinil (16 μg/ml, n = 8) or placebo (stock solution containing the same buffer and preservative concentrations as treprostinil 16 μg/ml). Subsequent patients received 60 μg treprostinil (32 μg/ml; n = 6), 90 μg treprostinil (48 μg/ml; n = 6) and 120 μg treprostinil (64 μg/ml; n = 3). Inhalation time was 6 min for all groups. Hemodynamics, gas exchange, and arterial treprostinil concentrations were recorded for 180 min.

Study 3 was a randomized, open-label, single-blind study. The primary objective was to explore the shortest possible inhalation time for a 15-μg dose of inhaled treprostinil. A total of 48 patients inhaled 1 dose of treprostinil during hemodynamic monitoring. The drug was applied in 18, 9, 3, 2 or 1 breaths. The aerosol was generated by a pulsed ultrasonic nebulizer (Ventaneb; Nebutec, Elsenfeld, Germany) in cycles consisting of 2-s aerosol production (pulse) and a 4-s pause. The device included an optic-acoustical trigger enabling the patient to synchronize the inspiration to the end of the aerosol pulse, thereby providing exact dosage. The treprostinil dose of 15 μg was either generated during 18 cycles (Optineb filled with 100 μg/ml treprostinil, n = 6), 9 cycles (200 μg/ml treprostinil, n = 6), 3 cycles (600 μg/ml treprostinil, n = 21), 2 cycles (1,000 μg/ml treprostinil, n = 7), or 1 cycle (2,000 μg/ml treprostinil, n = 8). Hemodynamics and gas exchange were recorded for 120 to 180 min.

Treprostinil plasma concentrations were assessed in study 2 at 10, 15, 30, 60, and 120 min after inhalation. Treprostinil quantification was performed by Alta Analytical Laboratory (El Dorado Hills, California) with a validated liquid chromatography atmospheric-pressure ionization tandem mass spectrometry as previously described (9). Mixed venous blood was drawn at 10, 15, 30, 60, 120, and 240 min after inhalation, centrifuged, and the plasma frozen at −80°C until temperature-controlled shipping on dry ice.

Statistics. For statistical analysis of study 1, the repeated pulmonary vascular resistance (PVR) measurements after inhaled iloprost and treprostinil were subjected to a 3-factorial analysis of variance (factors: time [A], drug [B], treprostinil concentration [C]) to avoid multiple testing. The time to maximum PVR decrease after inhalation of iloprost versus treprostinil was compared by paired *t* test. The area under the curve (AUC) was calculated from the start of inhalation until 60 min after inhalation. Means, standard error of the mean, and 95% confidence intervals were calculated. For studies 2 and 3, areas between curves (ABC) were calculated between placebo inhalation (study 2) and the respective treprostinil inhalation until 180 min (study 2) and 120 min (study 3) after the end of inhalation.

RESULTS

The inhalation of both iloprost and treprostinil in study 1 resulted in a rapid decrease in PVR and pulmonary arterial pressure (PAP) (Figs. 1 to 3). No significant differences were observed for the AUC of PVR decrease after inhalation of 7.5 μg treprostinil in 6 min (AUC −12.6 ± 7.0%), 15 μg treprostinil in 6 min (AUC −13.3 ± 3.2%), and 15 μg treprostinil in 3 min (AUC −13.6 ± 4.3%). The AUC for PVR after the inhalation of 7.5 μg iloprost in 6 min was −7.7 ± 3.7% (mean ± 95% confidence interval). An overview of the pooled data of treprostinil inhalation compared with iloprost inhalation is given in Figure 3. The maximum effects of iloprost and treprostinil on PVR were comparable, but this effect was reached significantly later after treprostinil inhalation (18 ± 2 min) compared with iloprost (8 ± 1 min; mean ± SEM, $p < 0.0001$) and lasted

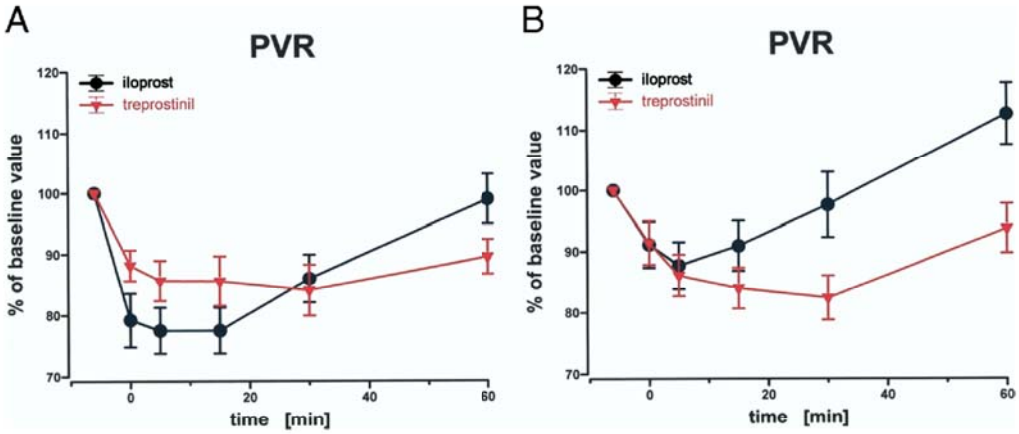

Figure 1. Response of pulmonary vascular resistance (PVR) to inhaled treprostinil versus iloprost: period effects. **(A)** First inhalation session with treprostinil (n = 22) versus first inhalation session with iloprost (n = 22). **(B)** Second inhalation session with treprostinil (n = 22) versus second inhalation session with iloprost (n = 22). The PVR decrease with treprostinil was delayed and prolonged compared with that for iloprost. Because of carryover effects from the first period, in the second period, the effects of both drugs appeared shortened. Data are shown as percent of baseline values (mean ± 95% confidence interval).

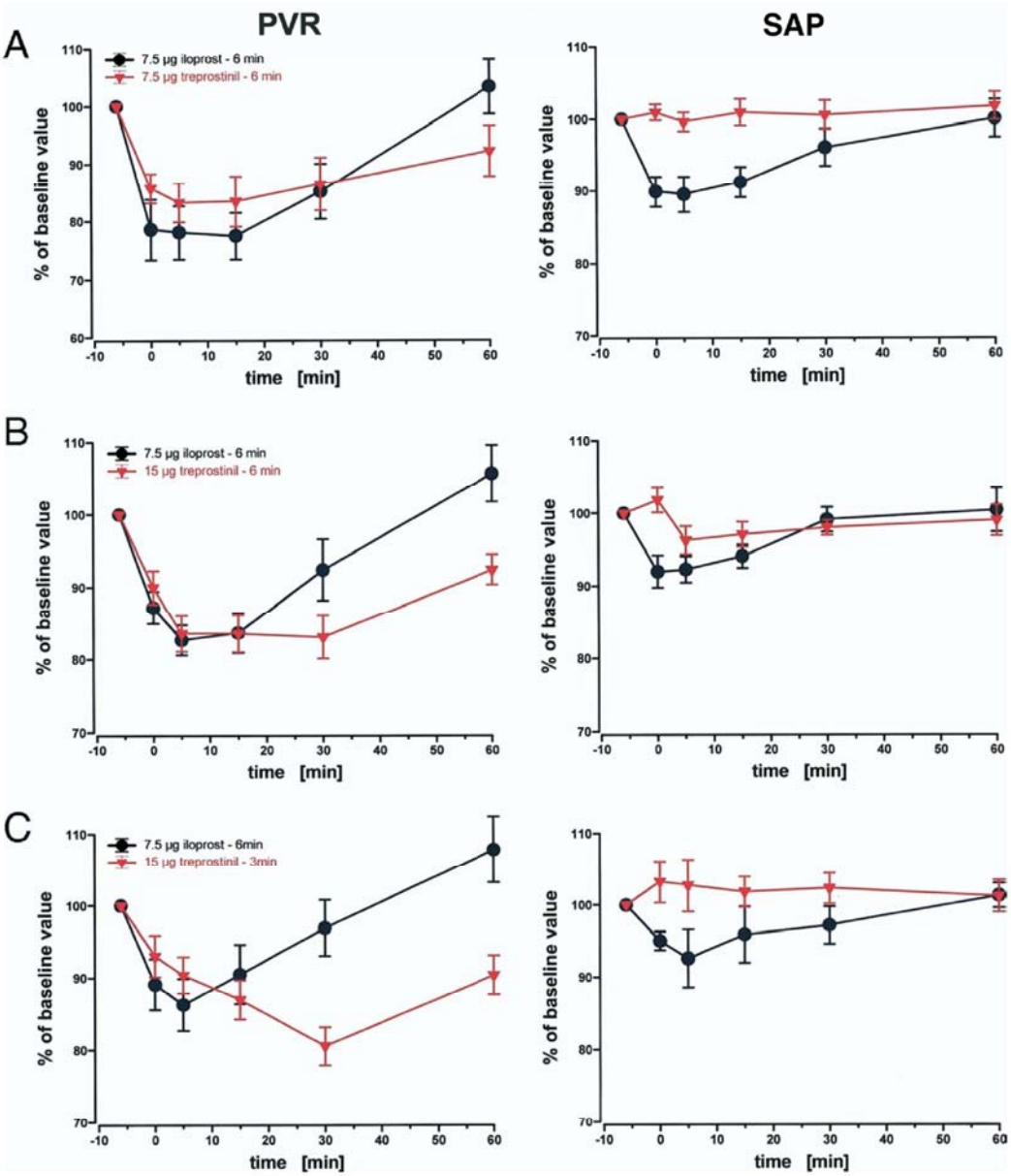

Figure 2. Response of pulmonary vascular resistance (PVR) and systemic arterial pressure (SAP) to inhalation of treprostinil versus iloprost: dose effects. **(A)** Inhalation of 7.5 µg iloprost (in 6 min) versus 7.5 µg treprostinil (6 min) (n = 14, in randomized order). **(B)** Inhalation of 7.5 µg iloprost (6 min) versus 15 µg treprostinil (6 min) (n = 14, in randomized order). **(C)** Inhalation of 7.5 µg iloprost (6 min) versus 15 µg treprostinil (3 min) (n = 16, in randomized order). Data are shown as percent of baseline values (mean ± 95% confidence interval). **Circles** = iloprost; **triangles** = treprostinil.

considerably longer (after 60 min, PVR values in the treprostinil group had not yet returned to baseline). The increase in cardiac output was less brisk but more sustained after treprostinil inhalation. Systemic arterial pressure (SAP) was unaffected by treprostinil inhalation, whereas a transient decrease was observed after iloprost inhalation. Neither iloprost nor treprostinil affected gas exchange. Three-factorial analysis of variance for PVR showed a significant difference between repeated measurements after inhalation ($p[A] < 0.0001$), no significant difference between drugs ($p[B] = 0.1$), no difference between treprostinil concentrations ($p[C] = 0.74$), and a significant drug × time interaction ($p[A \times B] < 0.0001$). This translates into a significant effect of both drugs on PVR with comparable drug potency, but a prolonged drug effect of treprostinil compared with iloprost.

In study 1, mild side effects were observed in some patients with iloprost inhalation at the 7.5-µg dose (transient flush, headache) but were not observed with inhaled treprostinil at 7.5 or 15 µg. Bad taste was reported by most of the patients after inhalation of treprostinil. This was subsequently found to be attributable to the metacresol preservative contained in the treprostinil solution, which was then left out in study 3.

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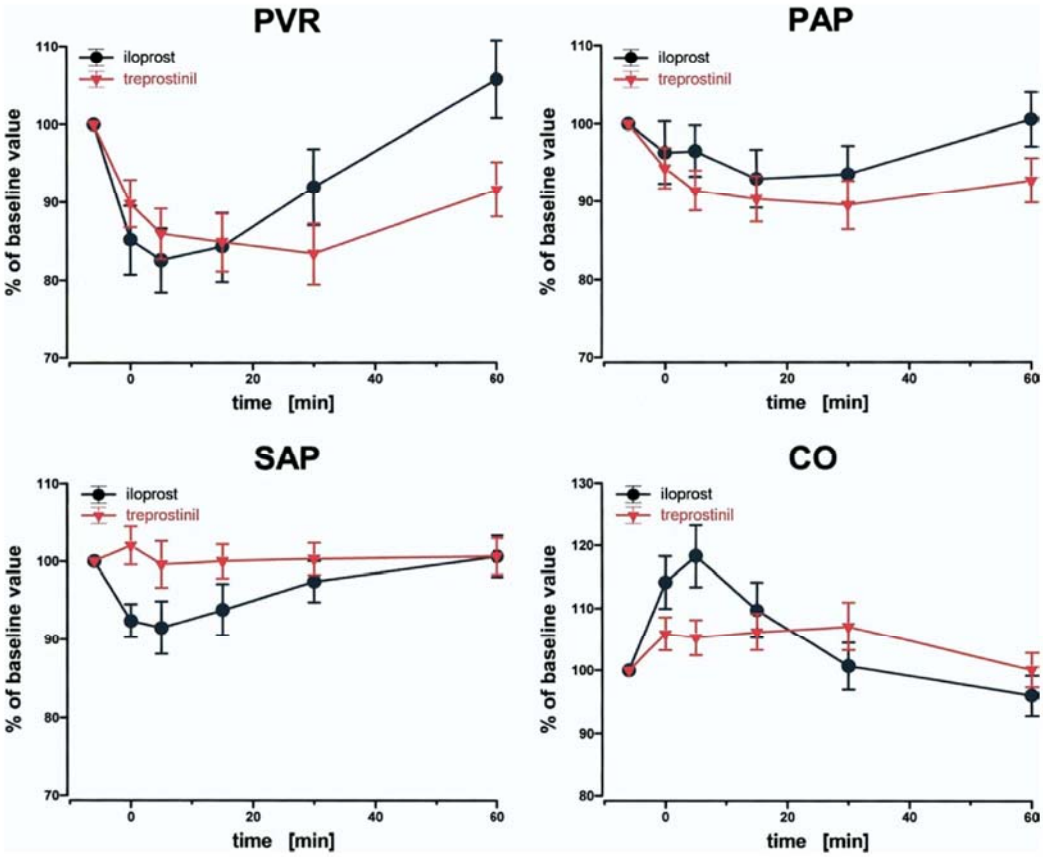

Figure 3. Hemodynamic response to inhalation of treprostinil versus iloprost. Data from 44 patients who inhaled both drugs in randomized order, shown as percent of baseline values (mean ± 95% confidence interval). Abbreviations as in Table 1.

In study 2, the pharmacodynamics of inhaled placebo or treprostinil were observed for 180 min. Placebo inhalation was followed by a gradual increase in PVR over the entire observation time. Because of reduced patient numbers in the 120-μg treprostinil group (because of side effects, see below), the hemodynamic values for this group were not included in the graphs of this study (Figs. 4 and 5). All treprostinil doses led to comparable maximal decreases of PVR to 76.5 ± 4.7% (30 μg), 73.7 ± 5.8% (60 μg), 73.3 ± 4.3% (90 μg), and 65.4 ± 4.1% (120 μg) of baseline values. An extended duration of pulmonary vasodilation was noted, surpassing the 3-h observation period for the 60-μg and 90-μg (and 120-μg) treprostinil doses, whereas in the 30-μg dose group the hemodynamic changes had returned to baseline by the end of this period. Even at the highest doses, treprostinil had only minor effects on SAP (Fig. 4). Maximal cardiac output was 106.8 ± 3.2% (30 μg), 122.9 ± 4.3% (60 μg), 114.3 ± 4.8% (90 μg) and 111.3 ± 3.9% (120 μg) of baseline values. The areas between the response curves after placebo versus treprostinil inhalation were calculated for PVR, PAP, systemic vascular resistance, and SAP (Fig. 5). A nearly maximal effect on PVR was already observed with 30 μg treprostinil, and areas between the curves for PVR were not significantly different for 30, 60, and 90 μg treprostinil. Effects on PAP and SAP were small and did not show a dose-response relationship. Gas exchange was not affected at doses up to 90 μg treprostinil, but arterial oxygen saturation was significantly decreased at a dose of 120 μg treprostinil in all 3 patients. Further dose increments above 120 μg were not performed because of this desaturation and a severe headache in 1 patient.

Bad taste of the treprostinil aerosol was again reported by most patients. Other side effects were flushing (n = 1; 30 μg), mild transient cough (n = 3; 60 μg), mild transient bronchoconstriction that resolved after fenoterol administration (n = 1; 30 μg), and moderate bronchoconstriction that resolved after fenoterol administration (n = 1; 120 μg). The bad taste, the bronchoconstriction, and the decrease in Sa_{O_2} was attributed to metacresol contained in the original treprostinil solution. With the use of a metacresol-free solution of treprostinil (University Hospital Giessen, Germany; produced according to the manufacturer's protocol) in the subsequent study, these side effects no longer occurred.

Study 3 was performed with metacresol-free treprostinil solution, which was tasteless and odorless. A total of 48 patients were enrolled. This study aimed at the reduction of inhalation time and aerosol volume needed for pulmonary drug delivery. A modified Optineb (Nebutec, Elsenfeld, Germany) inhalation device was programmed to produce a constant amount of aerosol during

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