Inhaled Prostacyclin and Iloprost in Severe Pulmonary Hypertension Secondary to Lung Fibrosis

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Pulmonary hypertension is a life-threatening complication of lung fibrosis. Vasodilator therapy is difficult owing to systemic side effects and pulmonary ventilation–perfusion mismatch. We compared the effects of intravenous prostacyclin and inhaled NO and aerosolized prostacyclin in randomized order and, in addition, tested for effects of oxygen and systemic calcium antagonists (CAAs) in eight patients with lung fibrosis and pulmonary hypertension. Aerosolized prostaglandin (PG)I_2 caused preferential pulmonary vasodilatation with a decrease in mean pulmonary arterial pressure from 44.1 ± 4.2 to 31.6 ± 3.1 mm Hg, and pulmonary vascular resistance (R_L) from 810 ± 226 to 386 ± 69 dyn · s · cm^{-5} ($p < 0.05$, respectively). Systemic arterial pressure, arterial oxygen saturation, and pulmonary right-to-left shunt flow, measured by multiple inert gas analysis, were not significantly changed. Inhaled NO similarly resulted in selective pulmonary vasodilatation, with R_L decreasing from 726 ± 217 to 458 ± 81 dyn · s · cm^{-5}. In contrast, both intravenous PGI_2 and CAAs were not pulmonary selective, resulting in a significant drop in arterial pressure. In addition, PGI_2 infusion caused a marked increase in shunt flow. Long-term therapy with aerosolized iloprost (long-acting PGI_2 analog) resulted in unequivocal clinical improvement from a state of immobilization and severe resting dyspnea in a patient with decompensated right heart failure. We concluded that, in pulmonary hypertension secondary to lung fibrosis, aerosolization of PGI_2 or iloprost causes marked pulmonary vasodilatation with maintenance of gas exchange and systemic arterial pressure. Long-term therapy with inhaled iloprost may be life saving in decompensated right heart failure from pulmonary hypertension secondary to lung fibrosis. Olschewski H, Ghofrani HA, Walmrath D, Schermuly R, Temmesfeld-Wollbrück B, Grimminger F, Seeger W. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis.

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Lung fibrosis of various etiologies is often associated with pulmonary hypertension, which may become a major contributor to morbidity and mortality, or may even represent the major cause of death as in systemic sclerosis (1). In patients suffering from primary pulmonary hypertension (PPH), intravenous prostacyclin has been demonstrated to be a potent pulmonary vasodilator, and long-term infusion of the prostanoid was found to improve exercise tolerance and survival in these patients (2–4). However, in the presence of lung fibrosis, any systemic vasodilator therapy may be hampered by two drawbacks. (*1*) The percentage of increased pulmonary vascular resistance that is due to fibrotic and thus "fixed" remodeling processes, compared with the percentage caused by vasoconstriction, is unknown. Systemic vasodilatation due to medications in the absence of pulmonary vasodilatation may provoke severe systemic hypotension in these patients if cardiac output is not adequately increased. (*2*) Any systemic administration of vasodilators may increase the blood flow to low or nonventilated lung areas by interfering with the physiological hypoxic vasoconstrictor mechanism, thereby worsening preexistent ventilation ($\dot{V}$)/perfusion ($\dot{Q}$) mismatch and shunt (5), resulting in arterial hypoxia and wasting of the small ventilatory reserve of these patients.

Selective pulmonary vasodilatation by inhalation of the vasorelaxant agent is an appealing concept to circumvent some of the hazards inherent in systemic vasodilator therapy in pulmonary hypertension. The feasibility of this concept was demonstrated for inhalation of nitric oxide (NO) by children with persistent pulmonary hypertension of the newborn (6–9), in the adult respiratory distress syndrome (ARDS) (10), and also in scleroderma patients with "isolated" pulmonary hypertension that is characterized by severe pulmonary hypertension without interstitial lung disease (11). By employing an aerosol technique, our group demonstrated that the concept of pulmonary selectivity may be extended to inhalation of aerosolized prostacylin (prostaglandin I_2, PGI_2) (12, 13): in patients with ARDS both intravenous and aerosolized PGI_2 caused pulmonary vasodilatation; however, the former deteriorated whereas the latter improved shunt flow and gas exchange. This corre-

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wherein selective vasodilatation in the pulmonary vascular bed was achieved by aerosolized PGI_2 (14). Subsequent studies in patients with ARDS and severe pneumonia demonstrated that inhalation of NO and aerosolized PGI_2 resulted in comparable hemodynamic and gas exchange effects (15, 16).

By employing this approach in patients with PPH and excessive pulmonary hypertension, we found that aerosolization of PGI_2 or its stable analog, iloprost, effected equipotent pulmonary vasodilatation to the maximum tolerable dose of intravenous prostacyclin, but induced fewer systemic side effects (17). In these patients, prostacyclin appeared to be more potent than NO in decreasing pulmonary resistance, corresponding to other data (18, 19). On the other hand, inhaled NO, owing to its immediate inactivation by hemoglobin binding on entering the intravascular space, is strictly selective to the pulmonary vessels, whereas inhaled prostacyclin will have some systemic effects due to overspill into the systemic circulation. In this study, we examined the effects of the most important systemic and inhalative vasodilators, NO and intravenous and inhaled prostacyclin, in comparison with O_2 and systemic calcium antagonists in patients with severe pulmonary hypertension associated with interstitial lung diseases of differing etiologies.

METHODS

Patients

Eight patients with lung fibrosis and pulmonary hypertension, who were referred to the Division of Pulmonary and Critical Care (Department of Internal Medicine, Justus-Liebig-University, Giessen, Germany) between June 1995 and October 1996, were included in the study. Criteria for entry included a peak systolic pulmonary pressure $>$ 50 mm Hg, as suggested by echocardiography or a resting pulmonary mean pressure $>$ 30 mm Hg as measured by catheter investigation, and the diagnosis of chronic fibrotic lung disease. The underlying diseases included extrinsic allergic alveolitis (two patients), systemic sclerosis, CREST syndrome (calcinosis, the Raynaud phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia), collagen vascular overlap syndrome, bronchopulmonary dysplasia, postradiation lung fibrosis, and idiopathic pulmonary fibrosis (Table 1). The diagnosis of these diseases was based on history, lung function testing, chest X-ray, and high-resolution computed tomography, which demonstrated at least medium-grade bilateral interstitial fibrosis in all patients. Flexible bronchoscopy with biopsy and bronchoalveolar lavage was performed in five patients. All suffered from significant lung restriction or severe restriction in gas exchange capacity, with a mean vital capacity (VC) of 48% and CO-diffusing capacity (D_{CO}) of 26% relative to unaffected control patients. Significant arterial hypoxia under resting conditions was noted in seven patients, and these received long-term oxygen therapy. Seven patients were treated with steroids (mean dose, 21 mg of methylprednisolone per day). Two patients were treated with low-dose calcium antagonists (CAAs): patient B had received felodipine because of a right heart catheterization 7 mo before this study, and had subsequently recovered from a period of right heart decompensation. The other patient (patient H) had received low-dose diltiazem for several years, but validation of this approach had never been performed. None of the patients were anticoagulated or treated with other vasodilatory agents. Underlying causes for pulmonary hypertension other than parenchymal lung diseases were excluded by transthoracic and transesophageal echocardiography (n = 8), ventilation and perfusion pulmonary nuclear scintigraphy (n = 8), and pulmonary angiogram (patient F).

Seven patients were classified as stage III according to the New York Heart Association (NYHA) system of classification. Patient F, who later received long-term iloprost inhalation, presented with decompensating right heart failure, unable to walk despite continuous nasal oxygen. This patient was a 27-yr-old woman with a history of dry cough and intermittent pleurisy for 4 yr. High-titer anti-nuclear, anti-DNA, and anti-skin-sensitizing antibodies, suggested collagen vascular disease resulting in progressive lung fibrosis with continuous reduction of VC and D_{CO}. Exercise tolerance had been declining more rapidly in the previous 12 mo. She had been treated with high-dose corticosteroids and azathioprine, and subsequently with bolus application of cyclophosphamide (two boluses with 1 g/m^2, 4 wk apart) without clinical benefit. Current therapy included high-dose corticosteroids, continuous nasal oxygen, and diuretics.

Study Protocol

All patients gave informed written consent to participate in the test protocol, which was approved by the institutional ethics committee of the Justus-Liebig-University. A fiberoptic thermodilution pulmonary artery catheter (Edwards Swan-Ganz, 93A-754H-7.5F; Baxter Healthcare, Irvine, CA) was inserted to measure central venous pressure (Pcv), pulmonary artery pressure (Ppa), pulmonary artery wedge pressure (Ppa,we), cardiac output ($\dot{Q}$; thermodilution technique), right ventricular ejection fraction (RVEF), and central venous oxygen saturation (Sv_{O_2}). A femoral artery catheter was used to assess mean arterial pressure ($\overline{Pa}$) and to draw arterial blood samples. The pulmonary shunt flow was measured by determining the retention and excretion values of sulfur hexafluoride (20) in all patients. In addition, in patient F, the retention and excretion values for ethane, cyclopropane, halothane, diethyl ether, and acetone were used to determine the pattern of ventilation and perfusion distributions (multiple inert gas elimination technique, MIGET) as described in detail by Wagner and co-

TABLE 1

BASELINE CHARACTERISTICS AND LUNG FUNCTION

Patient	Underlying Disease	Sex	Age (*yr*)	Height (*cm*)	Weight (*kg*)	VC		FEV_1 (*L*)	D_{COC} (%)	Po_2 (*mm Hg*)	Pco_2 (*mm Hg*)
						Liters	% pred				
A	EAA	F	30	156	78	1.25	37.1	1.04	25.3	59	37.2
B	SS	M	54	170	51	2.17	51.5	1.68	17.1	60	31.1
C	CREST	M	59	174	70	3.19	71.9	1.96	27.5	58	36.3
D	EAA	M	59	172	76	1.69	40.2	1.52	13	47.9	37.6
E	BPD	F	38	160	40	0.68	20.8	0.66	ND	45	51.6
F	CVOL	F	27	164	65	1.21	32.3	1.16	28.2	49.7	28
G	PRT	F	25	162	74	1.52	41.5	1.12	61.6	75.4	42.6
H	IPF	M	75	180	79	3.92	87.6	2.27	11.8	42	36.7
Mean			45.9	167.3	66.6	2.0	47.9	1.4	26.4	54.6	37.6

Definition of abbreviations: BPD = bronchopulmonary dysplasia after premature birth and long-term ventilation; CREST = calcinosis, the Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia; CVOL = collagen vascular overlap syndrome (*see* text); D_{COC}, diffusion capacity for CO gas, corrected for the actual hemoglobin concentration, given as a percentage of predicted values, corrected for age, sex, and body surface area (single-breath method in patients with VC $>$ 1.5 L and steady state in patients with VC $<$ 1.5 L); EAA = chronic extrinsic allergic alveolitis; F = female; FEV_1 = forced expiratory volume within 1 s; IPF = idiopathic pulmonary fibrosis; M = male; ND = not determined; Po_2 and Pco_2 = resting arterial oxygen and carbon dioxide partial pressure during oxygen pause; PRT = post-radiation therapy presenting with lung fibrosis and lymphocelitis occurring after thoracic radiation during the first year of life and due to

TABLE 2

BASELINE HEMODYNAMICS

	$\dot{Q}$ (*L/min*)	$\overline{Ppa}$ (*mm Hg*)	Ppa,we (*mm Hg*)	R_L [(*dyn · s)/cm^5*]	RVEF (%)	Pcv (*mm Hg*)	HR (*min^{-1}*)	$\overline{Pa}$ (*mm Hg*)	R_L/Rva	Shunt (%)
A	4.6	36	10	457	31	5	55	94	0.292	0.32
B	3.5	30	4	570	9	5	100	68	0.397	4.8
C	3.4	51	12	931	8	11	82	114	0.379	3.6
D	7.5	32	5	288	22	3	84	115	0.241	26.4
E	4.7	50	3	800	30	−3	96	114	0.402	ND
F	2.7	55	6	1,468	7	16	108	117	0.485	3.6
G	4.4	38	11	488	30	5	103	91	0.314	ND
H	7.4	30	5	285	26	−1	112	60	0.410	9.9
Mean	4.8	40.2	7.0	660	20.4	5.1	92.5	96.6	0.365	8.1

Definition of abbreviations: HR = heart rate; $\overline{Pa}$ = mean systemic arterial pressure; Pcv = central venous pressure; $\overline{Ppa}$ = mean pulmonary artery pressure; Ppa,we = pulmonary artery wedge pressure; $\dot{Q}$ = cardiac output; R_L = pulmonary vascular resistance; R_L/Rva = R_L/Rva (systemic vascular resistance) ratio; RVEF = right ventricular ejection fraction, assessed by thermodilution; Shunt = right-to-left shunt blood flow as a percentage of total pulmonary blood flow, assessed by MIGET analysis.

workers (20). Concerning the patients with long-term CAA therapy, the agent was discontinued 48 h before the test in patient H and continued in patient B, who had suffered from right ventricular decompensation before therapy with felodipine.

Test Procedure

In patients receiving long-term oxygen therapy (seven patients), catheterization was performed with ongoing nasal oxygen. Oxygen delivery was then stopped for 20 min, and baseline values were determined. Next, high-dose oxygen was administered (4–8 L/min) in order to increase arterial oxygen saturation above 95%, and measurements were performed. Subsequently, oxygen supply was titrated to maintain baseline arterial oxygen saturation above 85% (0–4 L/min). This oxygen flow was kept constant throughout the following tests, which were performed in randomized order. Inhaled nitric oxide (15 to 80 ppm; mean, 40 ppm) was titrated to achieve a maximum response of pulmonary artery pressure decrease without decline of arterial oxygen saturation, as assessed by fingertip oximetry. After 5 min on a constant dose, a complete set of hemodynamic measurements was performed. Intravenous prostacyclin (epoprostenol sodium; Wellcome Research Laboratories, Beckenham, Kent, UK) was increased in increments of 2 (ng/kg)/min until patients experienced discomfort (thoracic oppression, heat, headache) or until mean arterial pressure decreased to less than 70 mm Hg. The highest tolerated doses ranged from 5 to 16 (ng/kg)/min, with a mean of 8.0 (ng/kg)/min. Fifteen minutes after finding the highest tolerated dose, during continuous PGI_2 infusion, a complete set of hemodynamic measurements was performed. Aerosolized prostacyclin, diluted in glycine buffer (50 μg/ml), was jet nebulized (Puritan-Bennett raindrop medication nebulizer) with room air at a pressure of 80 kPa (compressor from Pari Boy, Pari, Germany) (fluid flux, 0.09 ml/min; mass median aerodynamic diameter of particles, 3.5 μm; geometric SD of 2.6, ascertained by impactor technique) and delivered to a spacer connected to the afferent limb of a Y-valve mouthpiece. The total inhalation time was 12 to 15 min (total nebulized dose, 54 to 68 μg), depending on systemic pressure and fingertip oximetry. Hemodynamic measurements were performed every 3 min and arterial and central venous blood samples were drawn before and during the last minute of inhalation. After each test, 1 h was allowed to pass to achieve a new baseline. After termination of the randomized trial period, calcium antagonists were given to six patients. Nifedipine, 10 to 20 mg, was administered sublingually (patients A, C, D, E, and F) and hemodynamic measurements were then performed 30 min after ingestion of this dose. In one patient (patient H), instead of nifedipine, diltiazem was applied corresponding to the preceding therapy. Diltiazem, 40 mg, was applied intravenously dur-

TABLE 3

ACUTE RESPONSE OF A PATIENT WITH DECOMPENSATED RIGHT HEART FAILURE TO VASODILATORY THERAPY*

	$\dot{Q}$ (*L/min*)	$\overline{Ppa}$ (*mm Hg*)	R_L [(*dyn · s)/cm^5*]	RVEF (%)	Pcv (*mm Hg*)	HR (*min^{-1}*)	$\overline{Pa}$ (*mm Hg*)	Pa_{O_2} (*mm Hg*)	Shunt (%)
Before NO	2.1	65	2,243	7	18	113	110	69.4	3.6
During NO	5.0	44	774	15	10	90	120	88.6	6.3
Before PGI_2, intravenous	2.4	59	1,789	9	19	111	121	71.9	5.1
During PGI_2, intravenous	6.0	42	470	20	10	102	105	62	23.1
Before PGI_2, aerosolized	2.5	65	2,179	7	18	113	112	74.6	2.4
During PGI_2, aerosolized	4.7	45	644	20.5	9.5	93	113	81.5	5.6
Before nifedipine	2.1	64	2,375	9	19	104	118	70.7	3.4
After nifedipine	3.3	51	955	10	16	108	94	74.5	3.7
After 5 mo									
Before iloprost, aerosolized	2.9	57	1,452	9	12	100	91	66	—
During iloprost, aerosolized	5.3	44	604	24	3	90	84	73	—
After 12 mo									
Before iloprost, aerosolized	2.9	53	1,311	10	9	93	104	53	—
During iloprost, aerosolized	4.1	50	882	19	2	92	97	58	—

Definition of abbreviations: *see* Tables 1 and 2.

* Response to NO, intravenous PGI_2, aerosolized PGI_2, and nifedipine during the first test trial and after 5 and 12 mo of iloprost inhala-

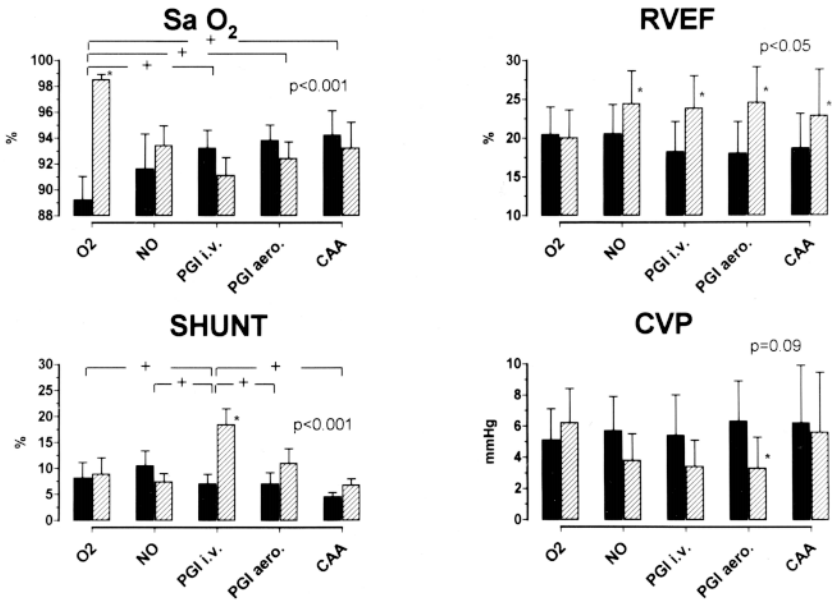

Figure 1. Acute responses to oxygen, NO, intravenously administered and inhaled prostacyclin (PGI i.v. and PGI aero, respectively) in eight patients, and to calcium antagonists (CAAs) in six patients. *Dark columns* and *light columns* give mean values ± SE before and after drug administration, respectively, for arterial oxygen saturation (Sa_{O_2}), right-to-left shunt flow (as a percentage of pulmonary blood flow; SHUNT), right ventricular ejection fraction (RVEF), and central venous pressure (CVP). p = significance level for differences in the responses to the various agents (ANOVA for the intrapair differences); * = significant difference pre- and postapplication, $p < 0.05$; + = significant linear contrast between responses to different agents (Scheffé test, $p < 0.05$).

ing a 30-min infusion period. Measurements were performed 15 min after the end of infusion. Patient G refused to take calcium antagonists owing to intolerance during preceding episodes of treatment with these drugs, and patient B was not included owing to continuous felodipine therapy.

Statistics

One-way analysis of variance (ANOVA) was employed to evaluate changes in parameters during exposure to the different agents (pre- and postexposure percent differences for $\dot{Q}$, pulmonary vascular resistance [R_L], and systemic vascular resistance [Rva] and numerical differences for other parameters) and the Scheffé test was used as an a posteriori test for linear contrasts between these differences. The response to an agent was considered significant if the 95% confidence interval ($p < 0.05$) or the 99% confidence interval ($p < 0.01$) of the pre- and postexposure difference did not overlap with zero. The significance level for the Scheffé test was set at $p = 0.05$.

RESULTS

Baseline Data

Values of $\overline{Ppa}$ and R_L for all patients were significantly elevated and scattered over a wide range (Table 2). Ppa,we was in the normal range, excluding left heart failure as the underlying cause of the pulmonary hypertension. $\dot{Q}$ values were in the normal or lower normal range in all patients, except in patient F, who presented with low-output syndrome and decompensated right heart failure, and had elevated Pcv (Table 3). The R_L/Rva ratio was increased and RVEF was decreased in all. Shunt flow was increased with great differences between individuals. Seven patients presented with significant arterial hypoxemia, whereas P_{CO_2} values were slightly elevated in only

Oxygen

During high-dose oxygen inhalation, Pa_{O_2} increased to an average of 125 mm Hg ($p < 0.01$), with a corresponding increase in Sa_{O_2} (Figure 1). Heart rate decreased significantly from 92.5 ± 6.1 to 85.3 ± 6.3 min^{-1} ($p < 0.05$) and $\overline{Ppa}$ decreased from 40.1 ± 3.4 to 37.5 ± 3.9 mm Hg ($p < 0.05$; Figure 2). All other hemodynamic and gas exchange variables were not significantly altered. Continuous low-flow nasal oxygen was then administered to maintain baseline Sa_{O_2} values above 85% (*see* increased baseline Sa_{O_2} data in the following tests).

NO

Inhaled NO significantly decreased $\overline{Ppa}$ from 39.8 ± 4.3 to 31.9 ± 3.2 mm Hg ($p < 0.01$), R_L from 726 ± 217 to 458 ± 81 dyn · s · cm^{-5} ($p < 0.05$), and the R_L/Rva ratio from 0.389 ± 0.026 to 0.289 ± 0.030 ($p < 0.05$). RVEF was increased from 20.5 ± 3.9 to 24.4 ± 4.4% ($p < 0.05$). All other hemodynamic and gas exchange variables were not significantly altered (*see* Figures 1 and 2).

Intravenous PGI_2

Prostacyclin infusion increased $\dot{Q}$ from 4.9 ± 0.7 to 7.1 ± 1.0 L/min ($p < 0.01$) and significantly decreased both $\overline{Ppa}$ from 39.6 ± 4.9 to 33.6 ± 3.0 and $\overline{Pa}$ from 93.1 ± 7.3 to 81.6 ± 8.1 mm Hg ($p < 0.05$, respectively). Correspondingly, both R_L and Rva were decreased by an average of 40%, resulting in an unchanged R_L/Rva ratio. RVEF increased significantly from 18.2 ± 3.9 to 24.5 ± 4.2%. A more than 2.5-fold increase in pulmonary shunt flow occurred, from an average of 7.0 ± 1.9 to 18.4 ± 3.1% (*see* Figures 1 and 2). Owing to the increased central venous oxygen saturation (data not given), which reflected $\dot{Q}$ increase, this marked augmentation of shunt flow

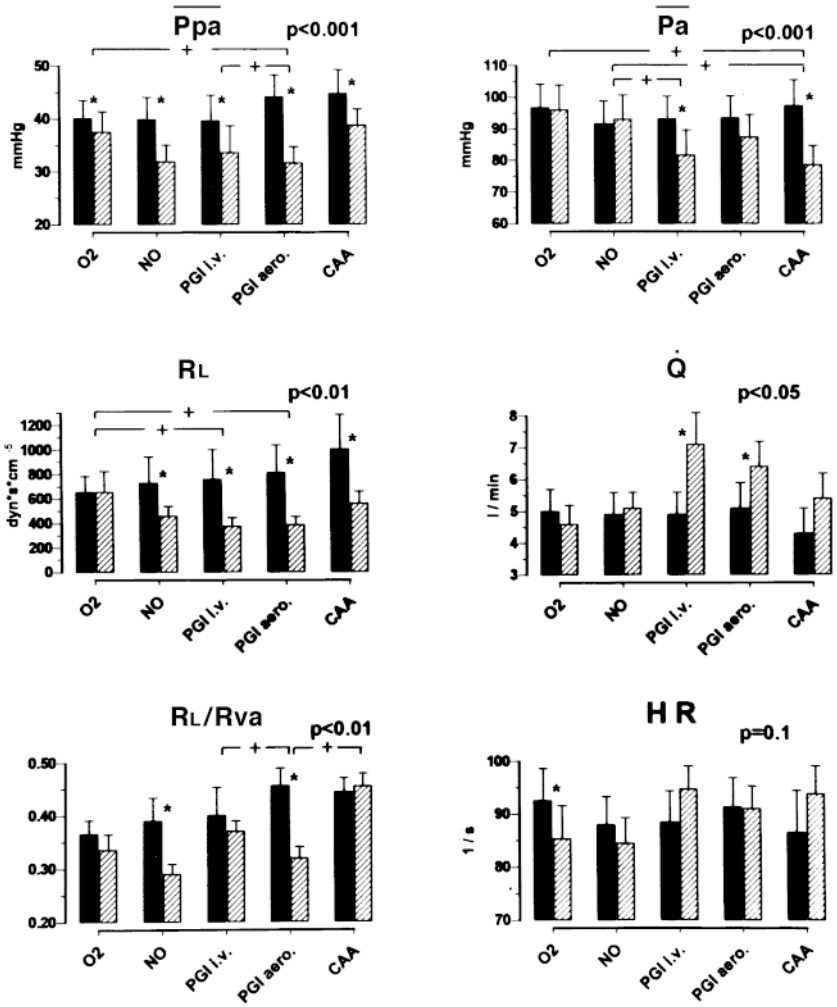

Figure 2. Acute responses to oxygen, NO, intravenously administered and inhaled prostacyclin (PGI i.v. and PGI aero, respectively), and calcium antagonists (CAAs). *Dark columns* and *light columns* give mean values ± SE before and after drug administration, respectively, for mean pulmonary artery pressure ($\overline{Ppa}$), pulmonary vascular resistance (R_L), ratio of pulmonary to systemic vascular resistance (R_L/Rva), mean systemic arterial pressure ($\overline{Pa}$), cardiac output ($\dot{Q}$), and heart rate (HR). For statistics *see* Figure 1.

Inhaled PGI_2

Aerosolized PGI_2 markedly decreased the pulmonary artery pressure from 44.1 ± 4.2 to 31.6 ± 3.1 mm Hg. This response was significantly greater than the response to intravenous PGI_2 (Scheffé test). Most of the difference in these responses, however, resulted from increased preinhalation rather than decreased postinhalation pressures. In contrast, Pa values were not significantly reduced. $\dot{Q}$ increased from 5.1 ± 0.8 to 6.4 ± 0.8 L/min. Correspondingly, the R_L values were reduced by about 50% (from 810 ± 226 to 386 ± 69) and the R_L/Rva ratio was significantly decreased (from 0.456 ± 0.034 to 0.319 ± 0.022). RVEF was increased from 18 ± 4.0 to 24.6 ± 4.6%, and Pcv was significantly lowered from 6.3 ± 2.6 to 3.4 ± 2.0 mm Hg. Shunt flow and heart rate did not change significantly.

Calcium Antagonists

Calcium antagonists significantly decreased Ppa and, more impressively, Pa values. $\dot{Q}$ increased from 4.3 ± 0.8 to 5.4 ± 0.8 L/min and RVEF was increased from 18.6 ± 4.5 to 22.8 ± 5.9%, on average ($p < 0.05$, respectively). Correspondingly, R_L/Rva ratio. Shunt flow and arterial oxygenation were not significantly altered.

Long-term Therapy

On the basis of the results of the test trial, in three patients (A, C, and E), in whom nifedipine resulted in a substantial decrease in Ppa and R_L without systemic side effects, treatment with calcium antagonists was started and in patient H the CAA was withdrawn owing to decreased arterial oxygen pressure after the test dose. In the patient with immobilization due to decompensated right heart failure (patient F), calcium antagonists were not tolerated. This may be related to a negative inotropic effect of the calcium antagonist suggested by the moderate Pcv decrease from 19 to 16 mm Hg despite an afterload reduction > 50% (*see* Table 3) in this patient; long-term therapy with repetitive aerosolization of iloprost, the stable analog of prostacyclin, was started. This decision was based on the fact that both PGI_2 infusion and PGI_2 inhalation markedly decreased the excessively high Ppa and R_L values, with approximate doubling of $\dot{Q}$, but intravenous PGI_2 drastically increased the shunt flow in this patient (Figure 3), with concom-

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