Epoprostenol in chronic thromboembolic pulmonary hypertension with distal lesions

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Background. **Although patients with primary pulmonary hypertension and patients with chronic thromboembolic pulmonary hypertension with distal lesions may share similar pathophysiological characteristics, scarce information is available on the usefulness of epoprostenol in this form of secondary pulmonary hypertension. The aim of this study was to evaluate the feasibility, safety and efficacy of epoprostenol therapy in surgically untreatable patients with chronic thromboembolic pulmonary hypertension.**

Methods. **Continuous infusive therapy with epoprostenol was undertaken in 16 patients with primary pulmonary hypertension and in 11 surgically untreatable thromboembolic pulmonary hypertension patients. The median follow-up was 12.4 months (range 6-23 months). Patients underwent clinical, echocardiographic and hemodynamic evaluation at baseline and a 6-min walk test every 3 months after beginning epoprostenol; ultrasound evaluations were repeated in a subgroup of patients.**

Results. **Epoprostenol therapy improved the clinical status, exercise tolerance and NYHA functional class. A greater left ventricular end-diastolic volume was recorded at echocardiography in both groups.**

Conclusions. **Epoprostenol therapy may be feasible, safe and clinically effective in patients with surgically untreatable chronic thromboembolic pulmonary hypertension.**

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Introduction

The first randomized study to demonstrate a clinical and hemodynamic improvement as well as an increased survival with epoprostenol (the stable derivative of prostacyclin) in patients with primary pulmonary hypertension (PPH) has been published in 1996[1]. On the basis of this study, epoprostenol has been approved by the United States Food and Drug Administration for the treatment of severe pulmonary hypertension. Similar to endogenous prostaglandins, epoprostenol is a potent vasodilator of the pulmonary arteries and inhibits platelet aggregation. It also has antiproliferative and cytoprotective properties[2-4]. An important part of its action is associated with remodeling of the pulmonary vascular bed due to a reduction in endothelial cell injury[5]. Continuous intravenous infusion of epoprostenol has been shown to improve hemodynamics, to improve exercise tolerance and to prolong survival in severe PPH[6,7].

Pulmonary thromboendarterectomy is the elective treatment for the majority of patients with chronic thromboembolic pulmonary hypertension (CTEPH), in particular for patients with pulmonary hypertension who have persistent thrombi in the major, lobar and segmental branches despite 6 months of anticoagulation[8,9]. On the contrary, there is no specific treatment for patients with distal chronic embolic occlusion of the pulmonary vascular beds, namely patients with lesions only at the level of the segmental or subsegmental pulmonary branches[9]. These patients receive conventional medical therapy based on oral anticoagulants, diuretics and digoxin as necessary and calcium-channel blockers when indicated; supplementary oxygen is rarely of benefit unless a patient has hypoxemia at rest[10]. Since these patients cannot undergo surgery, lung transplantation is the only therapeutic possibility if medical therapy fails[11]. Although PPH and distal CTEPH may share similar pathophysiological characteristics, scarce information is available on the efficacy of epoprostenol in such patients and only few patients with thromboembolic pulmonary hypertension have been enrolled in pharmacological trials[12,13].

In view of this, we undertook an observational study to investigate the safety and efficacy of epoprostenol in patients with distal CTEPH.

Methods

Patients. Between January 1998 and October 2002, epoprostenol therapy via a Groshong catheter or a port-a-cath infusion system was initiated in 16 PPH patients (mean age 51 ± 15 years, 4 out of 16 male patients, mean duration of symptoms 4.7 ± 2.1 months) and in 11 distal CTEPH patients (mean age 50 ± 11 years, 6 out of 11 male patients, mean duration of symptoms 4.4 ± 3.6 months). These patients form part of a larger population of patients admitted to our hospital because of symptomatic pulmonary hypertension during this period of time. Among CTEPH patients, 80 underwent pulmonary thromboendarterectomy, 5 underwent heart transplantation, and 43 were not considered for epoprostenol because they were in NYHA class I or II; among PPH patients, 3 underwent heart transplantation and 18 were not considered for epoprostenol because of a NYHA class I or II. The diagnosis of PPH was made after having ruled out the most common etiologies of pulmonary hypertension[14]. CTEPH was diagnosed when typical pulmonary angiographic findings were present at pulmonary angiography[15]. Patients with angiographic distal embolic occlusion of the pulmonary vascular beds (lesions only at the level of the subsegmental pulmonary branches) were defined as having distal CTEPH. All patients underwent a complete ultrasound examination and right heart catheterization before starting therapy with epoprostenol; 16 patients underwent ultrasound examination and 6 underwent right heart catheterization during follow-up.

Echocardiographic and Doppler study. A complete M-mode, two-dimensional and Doppler study was performed using standard parasternal, apical and subcostal approaches[16]. The right ventricular end-diastolic diameter and the thickness of the right ventricular free wall were determined in the parasternal view. The end-diastolic and end-systolic right ventricular areas were measured in the apical view and the fractional area change was calculated as end-diastolic area minus end-systolic area divided by end-diastolic area, × 100. The systolic displacement of the lateral segment of the tricuspid annular plane was measured on the M-mode tracing under two-dimensional echo guidance. The diameter of the inferior vena cava was measured from the subcostal approach and its inspiratory collapsibility evaluated; the peak systolic pulmonary artery pressure was calculated by adding a right atrial pressure estimate to the systolic transtricuspid pressure gradient. Echocardiographic data were averaged over 3 beats.

Right heart catheterization. The procedure has been previously described in detail[17]. Briefly, a modified Swan-Ganz thermodilution catheter with a rapid response thermistor (93A-431H-7F, American Edwards Laboratories, Irvine, CA, USA) was inserted transcutaneously via the right internal jugular vein. The thermistor was connected to a dedicated computer (REF-1 Ejection Fraction/Cardiac Output Computer, American Edwards Laboratories) to display on-line the cardiac output and the right ventricular ejection fraction. The following hemodynamic parameters were measured or calculated: systemic blood pressure (arm-cuff sphygmomanometer), right atrial pressure, pulmonary artery pressure (systolic, diastolic and mean) and pulmonary wedge pressure, right ventricular ejection fraction, cardiac output, cardiac index, systemic vascular resistance, and pulmonary vascular resistance. All thermodilution measurements were obtained in triplicate.

Functional and clinical evaluation. The clinical status was followed using the NYHA functional class and signs of right ventricular heart failure such as peripheral edema, ascites, hepatomegaly, positive hepatojugular reflux, jugular vein turgor, and an S3 gallop. The disappearance of clinical signs of congestive heart failure was considered as clinical improvement. The 6-min walk test was performed before epoprostenol and every 3 months during epoprostenol infusion in accordance with the guidelines for the 6-min walk test of the American Thoracic Society[18].

Statistical analysis. Continuous variables were described using the mean and SD or the median and interquartile range if skewed. Categorical variables were reported as absolute frequencies and as percentages. The baseline characteristics of the diagnostic groups were compared using the Student's t-test and the Fisher exact test for continuous or categorical variables respectively. The mean changes between baseline and follow-up were calculated for continuous variables together with their 95% confidence intervals. Regression models (linear and logistic for continuous and binary dependent variables, respectively) were fitted for each diagnostic group to compare values before and after therapy. Huber-White robust standard errors were computed to account for intra-patient correlation. Stata 7 was used for computation. A two-sided p value < 0.05 was considered as statistically significant.

Results

Study population. Baseline therapy was similar in the PPH and CTEPH groups and, in particular, it included oral anticoagulants in all patients. All patients with distal CTEPH were in NYHA class III and 11 of 16 patients with PPH were in NYHA class III and 5 in NYHA class IV. Six of 16 patients with PPH and 6 of 11 patients with distal CTEPH showed clinical signs of right ventricular heart failure such as peripheral edema, ascites,

hepatomegaly, positive hepatojugular reflux, jugular vein turgor, and an S3 gallop. Exercise tolerance was poor in most patients: the average distance walked during the 6-min walk test was 293 ± 104 m in the PPH group and 253 ± 51 m in the distal CTEPH group. The baseline echocardiographic and hemodynamic parameters are shown in tables I and II.

Table I. Echocardiographic parameters at baseline.

	PPH (n=16)	Distal CTEPH (n=11)	p
RVEDD (mm)	38 ± 2	45 ± 3	0.06
RVWT (mm)	8 ± 2	8 ± 2	0.46
TAPSE (mm)	16 ± 5	13 ± 2	0.06
RVEDA (cm^2)	28 ± 6	32 ± 9	0.08
RVFAC (%)	20 ± 9	28 ± 6	0.06
HVd (mm)	8 ± 3	10 ± 1	0.13
IVC (mm)	15 ± 8	19 ± 8	0.26
sPAP (mmHg)	80 ± 20	77 ± 15	0.64
dPAP (mmHg)	27 ± 7	30 ± 14	0.65
ACT (ms)	75 ± 25	71 ± 14	0.61
LVEDV (ml)	55 ± 16	59 ± 35	0.73
LVEF (%)	62 ± 6	57 ± 6	0.07

ACT = acceleration time; CTEPH = chronic thromboembolic pulmonary hypertension; dPAP = diastolic pulmonary arterial pressure; HVd = hepatic vein diameter; IVC = inferior vena cava; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; PPH = primary pulmonary hypertension; RVEDA = right ventricular end-diastolic area; RVEDD = right ventricular end-diastolic diameter; RVFAC = right ventricular fractional area change; RVWT = right ventricular wall thickness; sPAP = systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion.

Table II. Hemodynamic parameters at baseline.

	PPH (n=16)	Distal CTEPH (n=11)	p
HR (b/min)	79 ± 14	79 ± 10	0.43
mSBP (mmHg)	95 ± 9	88 ± 12	0.91
sPAP (mmHg)	92 ± 17	90 ± 25	0.57
dPAP (mmHg)	37 ± 6	34 ± 5	0.89
mPAP (mmHg)	56 ± 8	53 ± 12	0.68
PWP (mmHg)	10 ± 5	13 ± 6	0.09
TPG (mmHg)	45 ± 9	40 ± 12	0.85
CO (l/min)	3 ± 1	4 ± 1	0.12
CI (l/min/m^2)	2 ± 1	2 ± 1	0.20
PVR (UW)	15 ± 6	12 ± 6	0.85
RVEF (%)	18 ± 10	12 ± 5	0.95

CI = cardiac index; CO = cardiac output; CTEPH = chronic thromboembolic pulmonary hypertension; dPAP = diastolic pulmonary arterial pressure; HR = heart rate; mPAP = mean pulmonary arterial pressure; mSBP = mean systolic blood pressure; PPH = primary pulmonary hypertension; PVR = pulmonary vascular resistance; PWP = pulmonary wedge pressure; RVEF = right ventricular ejection fraction; sPAP = systolic pulmonary arterial pressure; TPG = transpulmonary gradient.

Effects of epoprostenol on the patients' clinical conditions. The mean dose of epoprostenol was 15.0 ± 7.2 ng/kg/min in the PPH group and 12.7 ± 6.8 ng/kg/min in the CTEPH group. Epoprostenol improved the clinical status of both patients with PPH and patients with distal CTEPH. The clinical improvement was assessed on the basis of the changes in NYHA functional class, the resolution of clinical signs of right heart failure, the reduction in the dosage of diuretics, and the results of the 6-min walk test.

NYHA functional class. Nine of 16 patients with PPH and 6 of 11 patients with distal CTEPH in NYHA class III improved their status to NYHA class II after 1 year of epoprostenol therapy (p = 0.0001) (Table III). Both patients with PPH and patients with distal CTEPH referred an improvement in their quality of life after the initiation of epoprostenol therapy.

Clinical signs of right heart failure. Six of 16 patients with PPH and 6 of 11 patients with distal CTEPH had clinical signs of right heart failure before epoprostenol such as peripheral edema, ascites, hepatomegaly, positive hepatojugular reflux, jugular vein turgor, and an S3 gallop; only 2 patients with PPH and 1 patient with distal CTEPH still had signs of congestive heart failure (p = 0.0001) (Table III) after 1 year of intravenous epoprostenol. The resolution of the clinical signs of right heart failure was the same in both groups of patients and started just after the initiation of infusion therapy. The dosage of diuretics was changed: before epoprostenol the mean dose of furosemide was 90 ± 34 mg in the PPH group and 92 ± 35 mg in the distal CTEPH group; after epoprostenol the mean dose of furosemide was significantly reduced to 30 ± 11 mg in PPH patients and to 31 ± 11 mg in CTEPH patients (both p = 0.0001).

Exercise tolerance. Exercise tolerance, as evaluated at the 6-min walk test, showed a significant improvement after epoprostenol in both etiologies of pulmonary hypertension (from 293 ± 104 m before epoprostenol to 402 ± 77 m after epoprostenol in PPH patients, p = 0.002; and from 253 ± 51 m before epoprostenol to 352 ± 119 m after epoprostenol in CTEPH patients, p = 0.0006) (Table III).

Effects of epoprostenol on echocardiographic parameters. The baseline echocardiographic characteristics of the patients with PPH and of those with distal CTEPH are shown in table I. Only 9 PPH patients and 7 CTEPH patients were re-evaluated after a median follow-up of 10 months (4-24 months); the mean dose of epoprostenol in these patients was 15 ± 7 ng/kg/min in the PPH group and 13 ± 7 ng/kg/min in the CTEPH group. The echocardiographic parameters were not significantly different in the two groups of patients at baseline and after epoprostenol therapy, with the only

Table III. Changes in clinical parameters after epoprostenol (epo).

	PPH (n=16)					Distal CTEPH (n=11)				
	Before epo		After epo		p	Before epo		After epo		p
NYHA	II	III-IV	II	III-IV	0.0001	II	III-IV	II	III-IV	0.0001
	0%	100%	56%	44%		0%	100%	55%	45%	
RHFcs	37%		12%		0.0001	54%		9%		0.0001
6MWT (m)	293 ± 104		402 ± 77		0.002	253 ± 51		352 ± 119		0.0006

CTEPH = chronic thromboembolic pulmonary hypertension; PPH = primary pulmonary hypertension; RHFcs = clinical signs of right heart failure; 6MWT = 6-min walk test.

exception of the left ventricular end-diastolic volume, which was significantly greater after epoprostenol in both groups (in the PPH group it increased from 53 ± 11 to 58 ± 25 ml, p = 0.046; in the distal CTEPH group it increased from 63 ± 36 to 80 ± 29 ml, p = 0.038) (Table IV).

Safety of epoprostenol. Epoprostenol therapy turned out to be feasible and safe in both groups of patients. During epoprostenol titration, the reduction in the systolic blood pressure was small and in all cases well tolerated. At the beginning of therapy, systemic systolic blood pressure was 120 ± 18 mmHg in PPH patients, and 133 ± 6 mmHg in distal CTEPH patients. After epoprostenol, systemic systolic blood pressure was 110 ± 6 mmHg in PPH patients and 105 ± 46 mmHg in distal CTEPH patients (p = 0.28, p = 0.09). No episodes of symptomatic arterial hypotension were observed. Systemic infections occurred in 3 patients with PPH and in 3 patients with CTEPH; in all patients, the infusion system had to be removed and it was replaced on the contralateral side without major problems. Two patients died during follow-up. One patient with PPH died of severe pulmonary hemorrhage after 2 years of epoprostenol; the other patient, affected by CTEPH, died of postoperative hemorrhage following abdominal surgery. In both groups, minor hemorrhagic events were uncommon.

Discussion

Conventional medical therapy and lung transplantation constitute the only therapeutic possibilities for patients affected by distal CTEPH. Scarce information is available on the use of epoprostenol in inoperable patients since only few patients with thromboembolic disease have been enrolled in pharmacological trials[12,13]. Recently, Nagaya et al.[19] analyzed the effects of epoprostenol infusion in the preoperative period of pul-

Table IV. Changes in echocardiographic parameters after epoprostenol.

	Overall (n=16) (relative mean change 95% CI)	p^1	PPH (n=9) (relative mean change 95% CI)	Distal CTEPH (n=7) (relative mean change 95% CI)	p^2
RVEDD	-3 (-7 to 2)	0.15	-6 (-12 to -0.09)	1.3 (-6 to 8.4)	0.44
RVWT	-3 (-14 to 9)	0.22	-6 (-17 to 50)	0.9 (-25 to 27)	0.82
TAPSE	-0.7 (-13 to 11)	0.56	-5 (-27 to 17)	5 (-6 to 15)	0.5
RVEDA	8 (0.1 to 18)	0.09	18 (7 to 30)	-3 (-13 to 7)	0.12
RVFAC	36 (-30 to 102)	0.27	65 (-60 to 200)	-1 (-28 to 26)	0.22
HVd	-9 (-26 to 8)	0.24	-13 (-37 to 10)	-4 (-37 to 30)	0.65
IVC	0.4 (-32 to 33)	0.61	-8 (-36 to 20)	10 (-66 to 86)	0.70
sPAP	2 (-7 to 13)	0.82	6 (-80 to 21)	-1 (-18 to 15)	0.56
dPAP	9 (-15 to 35)	0.65	14 (-50 to 76)	6 (-30 to 41)	0.64
ACT	-6 (-20 to 60)	0.23	-10 (-27 to 67)	-2 (-30 to 23)	0.58
LVEDV	22 (1.7 to 43)	0.05	11 (-22 to 44)	37 (10 to 63)	0.52
LVEF	-3 (-14 to 70)	0.41	-11 (-26 to 50)	6 (-8 to 21)	0.08

Values are expressed as percentages. ACT = acceleration time; CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; dPAP = diastolic pulmonary arterial pressure; HVd = hepatic vein diameter; IVC = inferior vena cava; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; PPH = primary pulmonary hypertension; RVEDA = right ventricular end-diastolic area; RVEDD = right ventricular end-diastolic diameter; RVFAC = right ventricular fractional area change; RVWT = right ventricular wall thickness; sPAP = systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion. p^1 = p value for paired Student's t-test (before/after epoprostenol); p^2 = p value for unpaired Student's t-test (comparing PPH vs CPTEH).

monary thromboendarterectomy. The results of this experience were positive: a better postoperative trend was observed in treated patients, most likely due to the hemodynamic improvements achieved during the preoperative period with epoprostenol. Our experience shows that in patients affected by distal CTEPH, continuous epoprostenol infusion is feasible and safe: the number of complications was similar to that observed in patients affected by PPH. The efficacy of epoprostenol was demonstrated by the improvement in the NYHA functional class and in exercise tolerance as assessed by means of the 6-min walk test.

Clinical improvement with epoprostenol. Even during the initial phases of epoprostenol titration the patients affected by PPH and those with distal CTEPH reported a significant clinical improvement: a decrease in NYHA functional class and an increase in exercise tolerance during the 6-min walk test, an improvement or complete resolution of the signs of congestive heart failure and a reduced dose of diuretics to maintain a stable hemodynamic status. The reduction in heart rate at rest and during exertion may also be considered as a sign of clinical stabilization. The clinical benefits induced by infusion therapy with epoprostenol in distal CTEPH could be explained by the fact that the multiple pharmacological properties of prostacyclin such as the antiplatelet effects and the antiproliferative and cytoprotective properties, in addition to pulmonary vasodilation, may be advantageous even in patients with distal CTEPH.

Echocardiographic changes. We did not observe any statistically significant improvements in the echocardiographic parameters of patients treated with epoprostenol, with the only exception of an increase in the left ventricular end-diastolic volume which reflects a reduced compression exerted by the right ventricle. It is important to note that the doses of epoprostenol used in previous studies which demonstrated hemodynamic improvement were substantially higher than those used in the present study. This is most likely the consequence of the conservative clinical approach we used: in fact, the titration of epoprostenol was stopped when patients showed clinical improvement, rather than continued until a hemodynamic improvement could be demonstrated.

Safety of epoprostenol. In no case was it necessary to suspend epoprostenol infusion because of symptomatic arterial hypotension. A slight reduction in blood pressure was observed in most cases at the beginning of epoprostenol therapy, but it was transitory, resolving after a few days of continuous therapy. Infections were similarly frequent in the two groups and were successfully managed with the removal of the infected infusive system and the positioning of a new system after antibiotic therapy. The low incidence of local and systemic infectious episodes is likely due to the exclusion from our population of patients with connective tissue disease or HIV infected patients, in whom the incidence may be higher. It is known that the bleeding risk in patients treated with epoprostenol and oral anticoagulant therapy is higher than in other patients. In our population, episodes of minor bleeding were rare and well controlled; 2 patients died after major bleeding episodes.

Limitations of the study. We acknowledge that data obtained in an observational, non-blinded study such as the present one are exposed to the risk of bias. However, we also believe that the present results strongly suggest the need of randomized studies to assess the potential efficacy of epoprostenol in patients with distal CTEPH.

The small number of repeated right heart catheterizations and echocardiographic evaluations during follow-up render any definite conclusions on the hemodynamic effects of epoprostenol impossible. This limitation, however, does not preclude the possibility of establishing the clinical efficacy of this therapy: nowadays, the distance walked during the 6-min walk test is in fact an accepted surrogate endpoint for mortality not only in PPH but also in several forms of non-PPH[1,20,21].

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