

Short-term and long-term epoprostenol (prostacyclin) therapy in pulmonary hypertension secondary to connective tissue diseases: results of a pilot study

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ABSTRACT: Continuous intravenous epoprostenol improves exercise capacity, haemodynamics, and survival in severe primary pulmonary hypertension. Pulmonary hypertension can also be life-threatening in patients with connective tissue diseases.

In a prospective open monocentre uncontrolled study, the effects of epoprostenol were evaluated in patients with severe pulmonary hypertension secondary to connective tissue diseases who were unresponsive to oral vasodilators (including calcium channel blockers) and continued to be in the New York Heart Association (NYHA) functional class III or IV despite conventional medical therapy. Seventeen patients received epoprostenol administered by a portable infusion pump associated with conventional therapy (oral anticoagulants, diuretics, supplemental oxygen).

During the first six weeks of therapy, two (12%) patients died, of pulmonary oedema (n=1) and severe sepsis (n=1). In the fifteen remaining subjects, clinical and haemodynamic parameters improved significantly at six weeks. These patients were subsequently monitored for 80±48 (range 14–154) weeks after initiation of epoprostenol. Five (33%) patients died, of right heart failure (n=2), severe sepsis (n=2) or syncope (n=1) and two patients were successfully transplanted 24 and 52 weeks after initiation of epoprostenol. Seven of the remaining eight patients had a persistent clinical improvement.

Short-term epoprostenol therapy is effective in some patients with connective tissue diseases as demonstrated by better clinical status and haemodynamics at six weeks. However, this study reports several cases of early and late major complications including severe sepsis and pulmonary oedema. Additional information is needed to evaluate the benefit: risk ratio of long-term epoprostenol therapy in pulmonary hypertension secondary to connective tissue diseases.

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Epoprostenol (prostaglandin I₂, prostacyclin) is a potent vasodilator and inhibitor of platelet aggregation produced by vascular endothelium [1]. Epoprostenol reduces pulmonary vascular resistance and increases cardiac output and oxygen delivery when administered acutely to some patients with primary pulmonary hypertension (PPH) [1]. Moreover, continuous intravenous epoprostenol produces substantial and sustained haemodynamic and symptomatic responses as well as improving survival in severe PPH refractory to conventional medical therapy [2–6].

Pulmonary hypertension is an uncommon but well recognized complication of connective tissue diseases (CTD) such as scleroderma, mixed connective tissue disease, and systemic lupus erythematosus [7–14]. In CTD the cause of vascular involvement is unknown, pathological changes are often those of pulmonary hypertensive arteriopathy similar to those observed in PPH, exercise capacity is greatly affected, and the prognosis of pulmonary hypertension is poor [7–15]. This study has therefore attempted to evaluate the effects of the continuous intravenous infusion of epoprostenol on exercise capacity, haemody-

namics, and survival in patients with severe pulmonary hypertension secondary to CTD who were unresponsive to oral vasodilators (including calcium channel blockers) and continued to be in the New York Heart Association (NYHA) functional class III or IV despite conventional therapy, which consisted of the administration of oral anticoagulants, diuretics, and supplemental oxygen.

Methods

Patient population

From October 1993 to December 1997, seventeen patients referred to the authors' institution for severe pulmonary hypertension secondary to CTD entered this study. The clinical and demographic characteristics of these subjects are shown in table 1. The diagnosis of pulmonary hypertension was established by right heart catheterization. Secondary causes of pulmonary hypertension other than CTD were eliminated by perfusion lung scanning

Table 1. – Clinical details of patients (baseline)

Patient No.	Age yrs	Sex	Collagen vascular disease	6MWT m	NYHA functional class	mRAP mmHg	mPAP mmHg	mPCWP mmHg	CI L·min·m ⁻²	PVR U·m ⁻²	S _v O ₂ %
1	29	F	MCTD	350	III	6	51	6	2.07	24.5	64
2	48	F	CREST	320	III	4	49	5	2.28	21.3	71
3	35	F	SLE	320	III	20	53	4	1.27	42.0	35
4	65	F	CREST	145	IV	15	55	10	2.32	23.9	27
5	62	M	CREST	350	III	5	50	6	2.52	20.0	64
6	54	F	CREST	125	IV	20	59	10	1.79	33.1	51
7	45	F	SS	295	IV	20	53	12	2.05	25.7	38
8	41	F	PGS	450	III	14	49	5	2.01	24.2	58
9	49	F	SLE	240	III	9	43	7	2.69	16.0	55
10	60	F	MCTD	395	III	16	58	12	2.17	26.9	46
11	43	F	SS	0	IV	10	43	6	1.94	22.3	53
12	63	F	CREST	90	IV	10	49	10	2.75	17.8	66
13	27	F	SLE	350	III	16	73	10	2.54	38.9	46
14	34	F	SLE	100	IV	3	42	4	1.60	26.3	27
15	24	F	SLE	0	IV	20	65	4	1.53	42.3	37
16	34	F	MCTD	240	IV	19	40	10	2.04	19.6	49
17	64	F	CREST	185	IV	15	59	7	1.78	33.1	50
Mean	46	-	-	233	-	13	52	8	2.08	26.3	49
±SD	14	-	-	137	-	6	9	3	0.41	7.6	13

F: female; M: male; CI: cardiac index; CREST: CREST syndrome; MCTD: mixed connective tissue disease; mPAP: mean pulmonary artery pressure; mPCWP: mean pulmonary capillary wedge pressure; mRAP: mean right atrial pressure; NYHA: New York Heart Association; PGS: primary Sjögren's syndrome; SLE: systemic lupus erythematosus; SS: systemic sclerosis; S_vO₂: mixed venous oxygen saturation; PVR: pulmonary vascular resistance; 6MWT: 6 minute walk test. (1 mmHg=0.133 kPa.)

and/or pulmonary angiography and echocardiography [16]. No patient had significant interstitial lung disease as demonstrated by pulmonary function tests (total lung capacity of at least 60% of predicted values) and high-resolution computed tomography of the chest (either normal or showing mild interstitial disease). All patients developed severe pulmonary hypertension despite CTD management, including corticosteroids (n=10), cyclophosphamide (n=7), D-penicillamine (n=5), hydroxychloroquine (n=4), methotrexate (n=2), azathioprine (n=1), gold salts (n=1), cyclosporine (n=1), and colchicine (n=3). Patients were in NYHA functional class III or IV despite optimal medical therapy, which consisted of the administration of oral anticoagulants, diuretics, and supplemental oxygen. All patients were referred to the authors' centre because they were unresponsive to the vasodilators commonly used to treat the disease. Some patients were treated with calcium channel blockers before referral to the centre. In this case, calcium channel blockers were stopped because they did not provide clinical or haemodynamic benefits, as demonstrated by the patients' clinical outcome.

Right heart catheterization and exercise capacity

Right heart catheterization was performed on all patients using standard techniques. Mean right atrial pressure, mean pulmonary artery pressure (mPAP), mean pulmonary capillary wedge pressure, cardiac index (CI), mixed venous oxygen saturation (S_vO₂), and pulmonary vascular resistance (PVR) were measured at baseline, and at six weeks after initiation of continuous intravenous epoprostenol in all patients.

Acute vasodilator challenge was performed after stopping all vasodilator therapy (with a wash-out period of at least five half-lives before right-heart catheterization). It has previously been demonstrated that inhaled nitric oxide

at low dose is an effective, safe and reliable substitute for epoprostenol in screening for acute pulmonary vasodilator responsiveness during therapeutic assessment of patients with PPH [17]. Therefore, baseline vasodilator response was tested with a short-term inhalation of an air/nitric oxide (10 parts per million (ppm)) mixture administered through a face mask over a 10-min period, as previously described [17]. Acute vasodilator response was defined by a fall both in mPAP and PVR by >20%. Using these criteria, no patient responded to vasodilator. After initiation of epoprostenol therapy, scheduled visits included right heart catheterization every 3–6 months. Exercise capacity was assessed in parallel with the use of the unencouraged 6-min walk test (6MWT). Patients who were unable to walk because of pulmonary hypertension were assigned a value of 0 m.

Treatment

All patients received continuous infusion of epoprostenol (Flolan®) at doses based on clinical signs and symptoms of pulmonary hypertension. They also received oral anticoagulants in doses adjusted to achieve an international normalized ratio (INR) of ~2.0. Adjustments in concomitant medications (diuretics, oxygen) were allowed during the study on the basis of clinical judgement. Venous access for the infusion of epoprostenol was obtained by the insertion of a permanent catheter into a subclavian vein. Epoprostenol was infused continuously with the use of a portable infusion pump (Graseby Medical Ltd., Watford, UK). Before being discharged from the hospital patients were trained in sterile technique, catheter care, and drug preparation and administration. Epoprostenol therapy was initiated at a dose ranging 8–16 ng·kg⁻¹·min⁻¹ (11±2 ng·kg⁻¹·min⁻¹). All patients were evaluated six weeks after initiation of continuous intravenous epoprostenol and visits were scheduled every 3 months.

Statistical analysis

Data were analysed with a Macintosh computer (Apple Company, New York, NY, USA) using the Statview® 4.5 Software (Abacus Concepts Inc., Berkeley, CA, USA). Data are presented as mean±SD. The paired Student's t-test was used for clinical and haemodynamic comparison between baseline values and those obtained after initiation of continuous intravenous epoprostenol.

Results

The baseline demographic, clinical, and haemodynamic characteristics of patients are shown in table 1. Epoprostenol therapy was initiated at a dose ranging 8–16 ng·kg⁻¹·min⁻¹ (11±2 ng·kg⁻¹·min⁻¹). All patients were evaluated at six weeks and 15 patients were subsequently monitored during 80±48 weeks (range 14–154) with scheduled visits every three months. In these patients, epoprostenol therapy was progressively increased to doses ranging 10–26 ng·kg⁻¹·min⁻¹ (17±5 ng·kg⁻¹·min⁻¹) at 6 months, representing an average increase of 1.1 ng·kg⁻¹·min⁻¹ every month. At the last follow-up visit, doses were 12–28 ng·kg⁻¹·min⁻¹ (19±5 ng·kg⁻¹·min⁻¹).

Exercise capacity and NYHA functional class

Results at six weeks. Fifteen patients were evaluated six weeks after initiation of continuous intravenous epoprostenol. Exercise capacity improved in 13 (87%) patients. The mean change in 6MWT from baseline was an increase of 109 m (p=0.01) (fig. 1). NYHA functional class improved in 11 (73%) patients, was unchanged in three (20%), and worsened in one (7%).

Last scheduled visit. Sustained exercise capacity improvement was demonstrated at the last scheduled visit (6MWT: 344±137 m).

Haemodynamical measures

Results at six weeks. mPAP, CI, PVR, and Sv_vO₂ were 6.1±1.3 kPa (46±10 mmHg), 2.65±0.69 L·min⁻¹·m⁻², 18.7±6.5 U·m⁻², and 60±10%, respectively (all p-values <0.05 versus baseline values) (fig. 2).

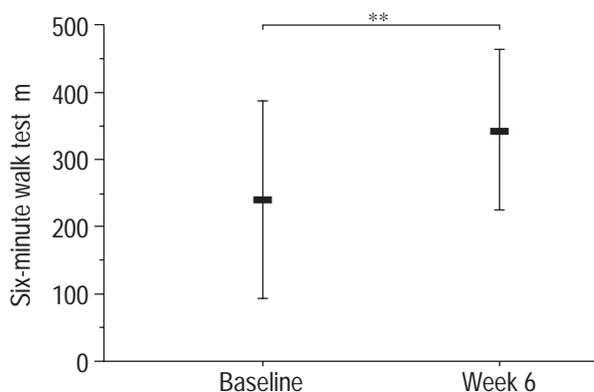


Fig. 1. – Changes in the six-minute walk test from baseline to week 6 after initiation of continuous intravenous epoprostenol. Data are presented as mean±SD. **: p<0.01.

Last scheduled visit. Sustained haemodynamic improvement was demonstrated at the last scheduled visit: mPAP, CI, PVR, and Sv_vO₂ were 6.1±1.6 kPa (46±12 mmHg), 2.43±0.67 L·min⁻¹·m⁻², 21.4±10.1 U·m⁻², and 58±10%, respectively.

Survival

Results at six weeks. During the first six weeks of therapy, two patients (12%) died (severe sepsis (n=1), epoprostenol-induced pulmonary oedema (n=1)) (table 2) (fig. 3).

Follow-up. Patients were monitored for 80±48 weeks (range 14–154) after initiation of epoprostenol. Five patients (33%) died of right heart failure (n=2), severe sepsis (n=2) or syncope (n=1) (table 2). Seven of the remaining eight patients had a persistent clinical and haemodynamic improvement.

Transplantation

Two patients underwent lung transplantation 24 weeks (patient 15) and 52 weeks (patient 6) after initiation of epoprostenol therapy, respectively. Lung pathology showed pulmonary hypertensive arteriopathy similar to that observed in PPH. These patients are now alive and well 46 and 5 months after transplantation.

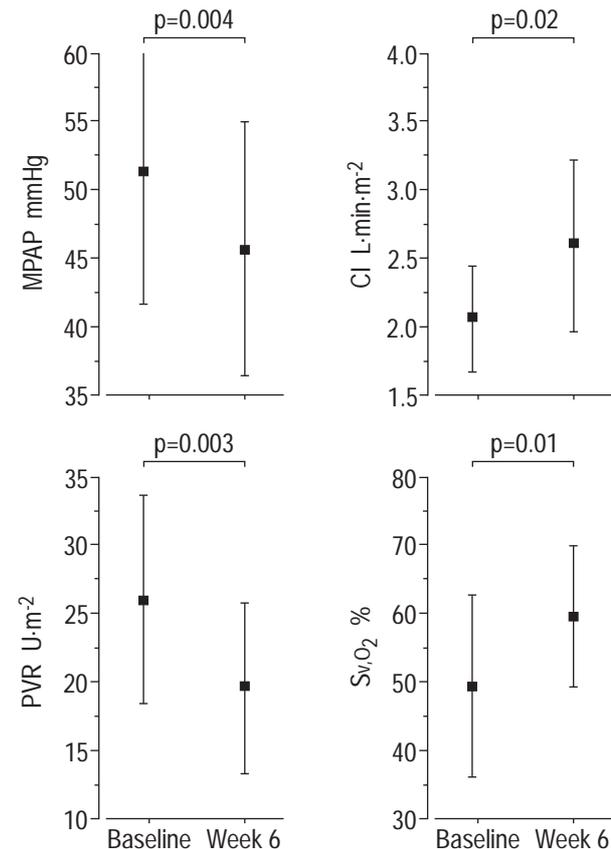


Fig. 2. – Changes in the haemodynamic measures from baseline to week 6 after initiation of continuous intravenous epoprostenol. Data are presented as mean±SD. mPAP: mean pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance; Sv_vO₂: mean venous oxygen saturation. (1 mmHg=0.133 kPa.)

Table 2. – Clinical informations (patients dead at follow-up)

Patient No.	Delay weeks	Last 6MWT m	Last NYHA functional class*	Cause of death
1	121	520	II	Severe sepsis (cutaneous)
3	147	380	III	Right heart failure (syncope)
7	13	380	II	Syncope (drug-delivery system dysfunction?)
10	43	120	IV	Right heart failure (syncope)
14	140	310	III	Severe sepsis (cutaneous); right heart failure (syncope)
16	3	240	IV	Severe sepsis (cutaneous); right heart failure (syncope)
17	6	185	IV	Pulmonary oedema

6MWT: 6-min walk test. *: the results obtained at the last scheduled visit before the death of the patients are indicated. For patients 16 and 17, this corresponded to the baseline visit.

Complications

Minor complications related to the use of epoprostenol were frequent (jaw pain, diarrhoea, flushing, headaches, nausea, and vomiting). Serious complications were linked either to the drug itself (epoprostenol-induced pulmonary oedema, n=1) or to the drug-delivery system (including 15 catheter-related sepsis in seven patients, five catheter-related upper limb deep vein thromboses in three patients, and five catheter-related pneumothorax in five patients). The rate of catheter-related sepsis in the present study population was 0.64 per year and per patient. One unexpected death occurred at home despite dramatic clinical and haemodynamic improvement, suggesting the possibility of a drug-delivery system dysfunction (patient 7, table 2). Additional problems related to the delivery system included irritation or infection at the catheter site requiring simple outpatient care.

Discussion

Pulmonary hypertension is a major disabling and life-threatening complication of CTD [7–14]. In some patients it is associated with mild-to-moderate interstitial disease. In this case the degree of pulmonary hypertension is usually out of proportion with the patients' restrictive pulmonary disease, and it is widely accepted that pulmonary hypertension is not secondary to chronic hypoxaemia or abnormal pulmonary mechanics, but that it is a consequence of an "intrinsic" pulmonary vascular disease [7–14].

Despite rare reports of clinical and haemodynamic improvement with corticosteroids and/or immunosuppressants [18, 19], clinicians are usually unable to control or prevent the occurrence of severe pulmonary hypertension. In the present study, all patients presented with NYHA functional class III or IV despite the use of corticosteroids and immunosuppressants, and failed to acutely respond to inhaled nitric oxide, epoprostenol, and oral calcium channel blockers [20]. There is a strong demand for new vasodilator therapy in this population which has an extremely poor prognosis [7, 12]. Reports of short- and long-term epoprostenol therapy in PPH [1–6] led the authors to propose this drug to patients with CTD. DE LA MATTA *et al.* [21] have recently reported their experience with iloprost, a prostacyclin analogue, in three patients with pulmonary hypertension secondary to systemic sclerosis. In these patients there was some dis-

crepancy between improved NYHA functional class, better quality of life, and the lack of objective haemodynamic amelioration [21]. In the present study, clinical and haemodynamic improvement was demonstrated in most patients six weeks after initiation of epoprostenol. Interestingly, the benefits of epoprostenol in CTD was not restricted to scleroderma, but to all CTD studied, including systemic lupus erythematosus and primary Sjögren's syndrome. Sustained beneficial effects on haemodynamics and exercise capacity in some patients supports the

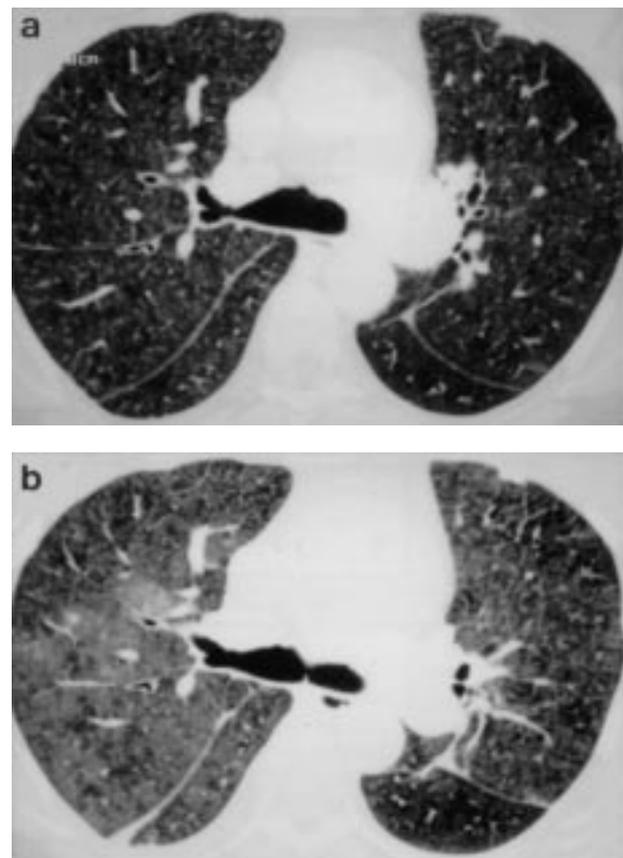


Fig. 3. – Epoprostenol-induced pulmonary oedema in severe pulmonary hypertension secondary to systemic sclerosis (patient 17). a) High-resolution computed tomography of the chest prior to epoprostenol therapy showing mild nodular interstitial opacities. b) High-resolution computed tomography of the chest 3 weeks after initiation of epoprostenol therapy showing worsened interstitial opacities, and right pleural effusion.

concept that epoprostenol might be used as a primary mode of therapy or as a bridge to transplantation for severe pulmonary hypertension complicating the course of CTD, as already shown in PPH [4–6]. However, it is important to point out that long-term epoprostenol therapy in CTD seemed to be less effective and safe than that reported by McLAUGHLIN *et al.* [6] in PPH.

There are no consensus guidelines for epoprostenol dose adjustments in PPH. McLAUGHLIN *et al.* [6] recently published their experience: after baseline evaluation epoprostenol therapy was increased to the maximum tolerated dose over a period of 7 days and subsequently increased by 2 ng·kg⁻¹·min⁻¹ every month if side-effects permitted or whenever the patient reported an increase in dyspnoea or fatigue that was attributed to PPH. After 16.7±5.2 months, they reached a dose of 40±15 ng·kg⁻¹·min⁻¹ representing a mean increase of 2.4 ng·kg⁻¹·min⁻¹ every month. Since 1992, the authors' regularly used epoprostenol in PPH with a slower amount of increase in doses. In 81 PPH patients, the authors' have recently reported that the mean doses of epoprostenol at 12 months were 16±5 ng·kg⁻¹·min⁻¹, representing a mean increase of <1 ng·kg⁻¹·min⁻¹ every month. In the present study, from week 2 to week 24, the epoprostenol doses were increased by 1.1 ng·kg⁻¹·min⁻¹ every month, in general because patients reported an increase in dyspnoea or fatigue attributed to pulmonary hypertension. Such an increase is more important than in the previous large PPH cohort [22], presumably reflecting a poorer disease control in pulmonary hypertension secondary to CTD.

Patients with a relative degree of immunosuppression due to CTD and its medical management are at risk of infections. Catheter-related sepsis was a major problem in this study leading to unscheduled emergency hospitalizations (0.64 catheter-related infections per patient and per year). This rate of septic complications is high but comparable to that observed in PPH in most institutions [6]. There was no relation between the use of steroids and immunosuppressants and the development of sepsis in the present patient population. In addition to catheter-related infections, severe sepsis unrelated to the drug-delivery system were also observed in this study including three cases (18%) of fatal cutaneous infections (two patients with severe Raynaud's phenomenon and one patient with digital necrosis complicating the course of systemic lupus erythematosus). This rate of fatal infections is uncommon in PPH [6]. In addition, the risk of catheter-related thrombosis is high in this population, especially in patients with antiphospholipid antibody. Four out of 17 patients (24%) were anticardiolipid-positive with no history of thromboembolic disease. These patients received oral anticoagulants in doses adjusted to achieve an INR of ~2.0. Two patients developed sepsis-related thrombosis after initiation of epoprostenol and were subsequently advised to increase their doses to achieve an INR between 3.0 and 3.5, as previously recommended [23]. This high complication rate underscores the need for an improved delivery system of epoprostenol or its analogues (*i.e.* subcutaneous, aerosolized or oral) [24, 25].

Severe pulmonary oedema rapidly complicating continuous intravenous epoprostenol was observed in a patient with systemic sclerosis. It is known that epoprostenol can promote pulmonary oedema in pulmonary veno-occlusive disease or pulmonary capillary haemangiomatosis

presumably because of increased pulmonary perfusion in the presence of downstream vascular obstruction [2, 26]. Interestingly, significant venous involvement has been demonstrated in some patients with pulmonary hypertension secondary to systemic sclerosis [27, 28] and might therefore explain the occurrence of pulmonary oedema in the present patient who unfortunately could not undergo necropsy. In the light of this recent experience it is now recommended to systematically perform high-resolution computed tomography of the chest before initiating vasodilator therapy in patients with pulmonary hypertension and to repeat this procedure in case of subsequent clinical deterioration with epoprostenol. Lung biopsy should be discussed in cases of significant abnormalities in order to avoid clinical deterioration with vasodilator therapy.

Intravenous infusion of iloprost has been showed to improve Raynaud's phenomenon in some patients with systemic sclerosis [29]. In the present series, 13 (76%) patients displayed severe Raynaud's phenomenon at baseline. Two (15%) patients subjectively described an improvement with epoprostenol and 11 (85%) reported it was stable. No objective measurement of digital blood flow was analysed.

In conclusion, this open monocentre uncontrolled study indicates that short-term continuous intravenous epoprostenol plus conventional therapy is effective in a majority of patients with connective tissue diseases, as demonstrated by the better New York Heart Association functional class, exercise tolerance, and haemodynamics at six weeks. However, this study reports several cases of major complications including severe sepsis and pulmonary oedema, and long-term results are still uncertain. Additional information is needed to evaluate the benefit: risk ratio of long-term epoprostenol therapy in pulmonary hypertension secondary to connective tissue diseases.

Acknowledgements. The authors wish to dedicate this work to F. Brenot[†] (1955–1996).

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