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Review

Epoprostenol Therapy for Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is characterized by elevation of pulmonary artery pressure caused by pulmonary vasoconstriction and vascular remodeling, which leads to right heart failure and death. Epoprostenol (prostaglandin I_2) has a potent short-acting vasodilator property, and intravenous continuous epoprostenol is therefore used for treatment of PAH. Here we review evidence for the usefulness of intravenous continuous epoprostenol therapy in patients with PAH. Epoprostenol therapy is effective in idiopathic PAH patients and in patients with PAH associated with connective tissue disease, portal hypertension or congenital heart diseases, but it is not effective in patients with pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis. High-dose epoprostenol therapy markedly improved hemodynamics in some patients with PAH, possibly due to reverse remodeling of pulmonary arteries. This therapy has several side effects and complications such as headache, hypotension and catheter-related infections. Intravenous continuous epoprostenol is an effective treatment, but there are still some problems to be resolved.

Key words: pulmonary arterial hypertension, epoprostenol, high-dose, complications, side effects

Pulmonary arterial hypertension (PAH) is characterized by elevation of pulmonary artery pressure (PAP), which leads to right heart failure and death. Its definition is mean PAP (mPAP) ≥ 25 mmHg and pulmonary artery wedge pressure ≤ 15 mmHg by right heart catheterization [1]. PAH occurs due to vasoconstriction and vascular remodeling caused by intimal and medial hypertrophy. An imbalance between the release of thromboxane A_2 and that of prostaglandin I_2 (PGI_2) leads to excess vasoconstriction in PAH [2]. PGI_2 is a physiological vasodilator in humans that was discovered by Vane *et al.* in 1976 [3]. Arachidonic acid is released from phospholipids. Cyclooxygenase converts arachidonic acid to prostaglandin H_2, and PGI_2 synthase converts prostaglandin H_2 to PGI_2. PGI_2 released from endothelial cells acts on a specific cell-surface receptor (IP receptor) on vascular smooth muscle cells and platelets. In pulmonary circulation, the binding of PGI_2 to IP receptors on pulmonary artery smooth muscle cells (PASMCs) triggers the activation of adenylate cyclase and increases intracellular cyclic AMP, which induces pulmonary vasodilatation. In platelets, PGI_2 inhibits platelet aggregation. Since PGI_2 is decreased in patients with PAH,

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therapy to supply PGI_2 has been developed.

A synthetic PGI_2, epoprostenol, and synthetic PGI_2 analogues, iloprost and treprostinil, are currently used to treat patients with PAH. Epoprostenol is continuously delivered intravenously via a central venous catheter with an infusion pump because of its short half-life. Patients with PAH must dissolve epoprostenol in a diluent themselves. Although epoprostenol therapy is cumbersome, its efficacy for PAH has been confirmed in various trials. In this review, we focus on the effects and side effects of epoprostenol therapy in patients with PAH.

Epoprostenol Therapy for Idiopathic/heritable PAH

We summarized studies in PAH patients treated with epoprostenol in Table 1. In 1990, Rubin *et al.* conducted a randomized control study to examine the effect of epoprostenol therapy in patients with primary pulmonary hypertension (nowadays called idiopathic PAH) [4]. Twenty-four patients were enrolled and 19 patients completed the study; 4 patients died and one patient stopped epoprostenol therapy because of an adverse event. Ten patients were assigned to the epoprostenol therapy group, and 9 patients were treated with anticoagulants, oral vasodilators, and diuretics. After 8 weeks, total pulmonary vascular resistance (PVR) had decreased from 21.6 Wood units to 7.9 Wood units in the epoprostenol therapy group. Six of the 10 patients in the epoprostenol therapy group had reductions in mPAP of more than 10 mm Hg. In 1996, Barst *et al.* conducted a 12-week prospective, randomized, multicenter trial to compare the effects of epoprostenol plus conventional therapy with the effects of conventional therapy alone in 81 patients with severe primary pulmonary hypertension [5]. The primary endpoint was six-minute walk distance (6MWD). In 12 weeks the 6MWD increased from 315 meters to 362 meters in the epoprostenol therapy group, while it decreased from 270 meters to 201 meters in the conventional therapy group. The patients treated with epoprostenol showed a significant improvement of mPAP (8 percent reduction). These results showed the short-term efficacy of epoprostenol therapy in patients with idiopathic PAH.

McLaughlin *et al.* reported the long-term efficacy of epoprostenol therapy in 162 patients with primary pulmonary hypertension [6]. After 17 months, mPAP had decreased from 61 ± 13 mmHg to 53 ± 13 mmHg in patients treated with epoprostenol at a dose of 34.5 ± 30 ng/kg/min. Observed survival rates with epoprostenol therapy at 1, 2 and 3 years were 87.8%, 76.3% and 62.8%, respectively, which were significantly greater than the expected survival rates of 58.9%, 46.3% and 35.4% based on historical data. Sitbon *et al.* reported the long-term efficacy of epoprostenol therapy in 178 patients with primary pulmonary hypertension [7]. After one year, mPAP had decreased from 68 ± 14 mmHg to 60 ± 12 mmHg. Overall survival rates at 1, 2, 3 and 5 years were 85%, 70%, 63% and 55%, respectively. These results showed the long-term efficacy of epoprostenol therapy in patients with idiopathic PAH.

Epoprostenol Therapy for Pulmonary Arterial Hypertension Associated with Connective Tissue Disease (CTD)

In 2000, Badesch *et al.* conducted a 12-week prospective, randomized, multicenter trial to compare the effects of epoprostenol plus conventional therapy with the effects of conventional therapy alone in 111 patients with PAH associated with scleroderma [8]. The primary endpoint was 6MWD. 6MWD increased from 270 to 316 meters in the epoprostenol therapy group, while it decreased from 240 to 192 meters in the conventional therapy group. The changes in mPAP for the epoprostenol and conventional therapy groups were −5.0 and 0.9 mmHg, respectively. The authors reported the results of a 3-year extension study following an initial study in 2009 [9]. The survival rates during the first and second years for all patients treated with epoprostenol were 71% and 52%, respectively. Humbert *et al.* reported the effects of epoprostenol therapy in a prospective single-center uncontrolled study conducted in 1999 that enrolled 17 patients with connective tissue disease (CTD), including 3 with mixed connective tissue disease, 6 with CREST syndrome, 5 with systemic lupus erythematosus (SLE), 2 with scleroderma, and 1 with Sjogren syndrome [10]. After 6 weeks, mPAP, cardiac index, and PVR were significantly decreased in patients treated with epoprostenol at a dose of 11 ± 2 ng/kg/min. During long-term observation, 7 patients died and 2 patients received lung transplantation. In 2003,

Table 1 Summary of studies in PAH patients treated with epoprostenol

Author	Reference number	Diagnosis	Patient No.	Study design	Duration	Final dose of Epo	Pre mPAP	Post mPAP
Rubin	4	IPAH	24	RCT	8 weeks	7.9 ± 2.7	58.6	49.3
Barst	5	IPAH	41	RCT	12 weeks	9.2 ± 0.5	61 ± 2	−2.4*
McLaughlin	6	IPAH	115	O	17 months	34.5 ± 30	61 ± 13	53 ± 13
Sitbon	7	IPAH	107	O	12 months	21 ± 7	68 ± 14	60 ± 12
Akagi	26	IPAH	14	O	3.7 years	107 ± 40	66 ± 16	47 ± 12
Badesch	8	SSc-PAH	56	RCT	12 weeks	11.2	51 ± 11	−5.0*
Badesch	9	SSc-PAH	102	O	3 years	−	−	−
Humbert	10	CTD-PH	17	O	6 weeks	11 ± 2	52 ± 9	46 ± 10
Kuhn	11	SSc-PAH	19	O	12 weeks	−	55 ± 13	47 ± 8
Kuhn	11	SLE-PAH	5	O	12 weeks	−	54 ± 6	41 ± 2
Sirai	12	CTE-PAH	16	O	6 months	23 ± 4	56 ± 9	−
Kuo	13	PoPH	4	O	6–14 months	10–28	53–63	35–43
Kwroka	14	PoPH	10	O	8 days–30 months	6–48	37–86	28–72
Fix	15	PoPH	19	O	15 months	29	48	36
Rosenzweig	16	CHD-PAH	20	O	12 months	82 ± 37	77 ± 20	61 ± 15
Ogawa	17	PVOD, PCH	8	O	12 months	55 ± 11	62 ± 8	62 ± 4
Cabrol	24	CTEPH	27	O	3 months	16 ± 2	56 ± 9	51 ± 8

Epo, epoprostenol; IPAH, idiopathic pulmonary arterial hypertension; SSc, systemic sclerosis; CTD, connective tissue disease; SLE, systemic lupus erythematosus; PoPH, portopulmonary hypertension; CHD, congenital heart disease; PVOD, pulmonary veno-occlusive diseases; PCH, pulmonary capillary hemangiomatosis; CTEPH, chronic thromboembolic pulmonary hypertension; O, observational study.
*reduction from baseline value.

Kuhn *et al.* reported long-term outcomes in 24 patients with pulmonary hypertension associated with CTD (19 scleroderma, 5 SLE) receiving epoprostenol therapy in 2003 [11]. Epoprostenol therapy tended to decrease mPAP at the one-year follow-up. Survival rates at 1, 2 and 3 years in patients with scleroderma were 58%, 41% and 34%, respectively. In 2013, Shirai *et al.* reported the efficacy of epoprostenol treatment in 16 patients with PAH associated with CTD (6 SLE, 5 mixed connective tissue disease, 4 scleroderma, 1 Sjogren syndrome) [12]. Survival rates at 1, 2 and 3 years were 69%, 69%, and 55%, respectively. These results showed that epoprostenol therapy improved hemodynamics and survival in patients with PAH associated with CTD. However, improvement of survival in patients with PAH associated with scleroderma was less than that in patients with PAH associated with other CTDs (Table 2). Scleroderma frequently coexists with other disorders (interstitial lung diseases and renal failure). Particularly, the coexistence of interstitial lung diseases in patients with scleroderma deteriorated survival [13]. We think that PAH patients with scleroderma, which frequently coexists with other disorders, may not see as significant a survival gain from epoprostenol therapy.

Epoprostenol Therapy for Pulmonary Hypertension Associated with Portal Hypertension

In 1997, Kuo *et al.* reported the efficacy of epoprostenol in 4 patients with pulmonary hypertension associated with portal hypertension in 1997 [14]. Epoprostenol at doses of 10–28 ng/kg/min decreased mPAP by 29–46% and PVR by 25–75% over a period of 6–14 months. Krowka studied 10 consecutive patients with pulmonary hypertension associated with portal hypertension in 1999 [15]. Epoprostenol therapy resulted in significant improvements in PVR and mPAP; however, 6 patients died during follow-up. In 2007, Fix *et al.* conducted a retrospective study on the long-term effects of treatment with ($n = 19$) or without ($n = 17$) epoprostenol on hemodynamics and survival in patients with pulmonary hypertension associated with portal hypertension [16]. There were significant improvements in mPAP (48.4–36.1 mmHg; $p < 0.0001$) after a median period of 15.4 months of epoprostenol treatment. However, survival did not seem to differ between the 2 groups. These results

Table 2 Survival rate

Author	Reference number	Diagnosis	Survival rate (%)			
			1 year	2 year	3 year	5 year
Rubin	4	IPAH	–	–	–	–
Barst	5	IPAH	–	–	–	–
McLaughlin	6	IPAH	87.8	76.3	62.8	–
Sitbon	7	IPAH	85.0	70.0	63.0	55.0
Akagi	26	IPAH	–	–	–	–
Badesch	8	SSc-PAH	–	–	–	–
Badesch	9	SSc-PAH	71.0	52.0	–	–
Humbert	10	CTD-PH	–	–	–	–
Kuhn	11	SSc-PAH	58.0	41.0	34.0	–
Kuhn	11	SLE-PAH	–	–	–	–
Sirai	12	CTE-PAH	69.0	69.0	55.0	–
Kuo	13	PoPH	–	–	–	–
Kwroka	14	PoPH	–	–	–	–
Fix	15	PoPH	–	–	–	–
Rosenzweig	16	CHD-PAH	–	–	–	–
Ogawa	17	PVOD, PCH	–	–	–	–
Cabrol	24	CTEPH	73.0	59.0	41.0	–

showed that epoprostenol therapy improved hemodynamics in patients with pulmonary hypertension associated with portal hypertension but did not improve long-term survival. Epoprostenol therapy improved the pulmonary hypertension but not the portal hypertension, which was caused by liver dysfunction. Liver dysfunction progresses and sometimes leads to death and requires liver transplantation in PAH patients with portal hypertension. We think that liver dysfunction diminishes the survival benefit of epoprostenol therapy in PAH patients associated with portal hypertension.

Epoprostenol Therapy for Pulmonary Hypertension Associated with Congenital Heart Disease

Rosenzweig *et al.* reported the effects of long-term epoprostenol therapy in patients with pulmonary hypertension associated with congenital heart diseases [17]. Twenty patients (11 patients with previous cardiac surgery, 11 patients with residual systemic to pulmonary shunt) were treated with epoprostneol, and in 1 year, a mean epoprostenol dose of 82 ± 37 ng/kg/min decreased mPAP from 77 ± 20 to 61 ± 15 mmHg.

Epoprostenol Therapy for Pulmonary Veno-occlusive Disease (PVOD)/Pulmonary Capillary Hemangiomatosis (PCH)

PVOD and PCH are rare diseases that are classified as a subgroup of PAH. PVOD is histologically characterized by intimal fibrosis that narrows and occludes pulmonary veins [18]. PCH is histologically characterized by localized capillary proliferation within the lung, in which capillaries invade the pulmonary interstitium and vessels [19]. Although a few cases of PVOD patients in whom epoprostenol therapy ameliorated hemodynamics and exercise capacity have been reported [20, 21], some reports have warned that epoprostenol can cause massive pulmonary edema in patients with PVOD or PCH [22, 23]. Ogawa reported the long-term effects of epoprostenol therapy in 8 patients with PVOD and PCH [24]. With careful management, epoprostenol therapy significantly improved 6MWD but did not significantly reduce mPAP. Epoprostenol therapy acted as a bridge to lung transplantation in 4 patients. Careful application of epoprostenol might be considered as a bridge to lung transplantation.

Epoprostenol Therapy for Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Although CTEPH is not PAH, Cabrol *et al.* reported the results of a retrospective analysis of 27 consecutive patients with inoperable CTEPH treated with long-term intravenous epoprostenol [25]. Long-term epoprostenol therapy at a dose of 16 ng/kg/min reduced mPAP values by 56 to 51 mmHg and increased cardiac indexes by 1.9 to 2.4. However, survival rates at 1, 2 and 3 years were 73%, 59% and 41%, respectively. The above-described studies are summarized in a Table.

Dose of Epoprostenol

The dose of epoprostenol is adjusted upward on the basis of symptoms and side-effects of the drug. The appropriate dose range of epoprostenol is thought to be 25 to 40 ng/kg/min [26]; however, the optimal dose of epoprostenol has been uncertain and the efficacy of treatment with epoprostenol at a dose greater than 40 ng/kg/min was not known. We previously reported 14 patients with severe idiopathic PAH who received high-dose epoprostenol monotherapy (>40 ng/kg/min) [27]. The mean dose of epoprostenol was 107 ± 40 ng/kg/min and the mean duration of treatment was $1,355 \pm 627$ days. High-dose epoprostenol therapy reduced mPAP by 30% and PVR by 68% compared with the baseline state. In previous studies, long-term epoprostenol therapy reduced mPAP by 12% to 22% and reduced PVR by 32% to 53% compared with baseline values [6, 7, 28]. High-dose epoprostenol monotherapy dramatically reduced mPAP and PVR. A significant exponential relationship was observed between the dose of epoprostenol and the PVR ratio after epoprostenol therapy [29].

Reverse Remodeling Effects by High-dose Epoprostenol Therapy

We studied why high-dose epoprostenol therapy markedly improved hemodynamics using PASMCs or lung tissues obtained from patients with PAH. Epoprostenol induced apoptosis of PASMCs from patients with PAH (Fig. 1) [30]. The tunica media of pulmonary arteries were thin and apoptotic cells were detected in patients who had received high-dose epoprostenol therapy [31]. Thus, high-dose epoprostenol therapy has the potential for reverse pulmonary artery remodeling by induction of PASMCs apoptosis in patients with PAH.

Complications and Side Effects of Epoprostenol Therapy

Epoprostenol therapy has several complications. The most important and serious complication is catheter-related infection. The catheter infection rate was reported to be 0.26 per 1,000 catheter days in PAH patients treated with epoprostenol [32]. Catheter-related infections were divided into 2 groups: catheter-related bloodstream infection (CRSBI) and tunnel infection. CRBSI could be caused by bacterial invasion through the catheter connection. Tunnel infection could be caused by direct bacterial invasion through the catheter insertion site. The catheter hub was the most important source of CRBSI; therefore, we used a closed-hub system for PAH patients treated with epoprostenol to prevent bacterial invasion from the catheter hub. The incidence of CRBSI significantly decreased with the use of a closed-hub system [33].

Epoprostenol is a potent systemic and pulmonary vasodilator and often affects the systemic vascular bed more than it does the pulmonary vascular bed. Initiation of epoprostenol therapy can cause severe systemic hypotension, which leads to hemodynamic collapse in vulnerable patients with WHO-FC IV. Thus, it is important to initiate epoprostenol therapy while preventing hemodynamic instability to the greatest extent possible. We have used dobutamine and/or dopamine as first-line inotropic agents at the initiation of epoprostenol therapy in patients with PAH when inotropic agent support is required. Neither dobutamine nor dopamine use was an independent risk factor for short-term or long-term mortality [34]. Thus, temporary use of dobutamine and dopamine appears to be safe for hemodynamic support at the initiation of epoprostenol therapy for patients with severe PAH.

High-dose epoprostenol therapy is effective but increases side effects related to systemic vasodilatation (headache, flushing, leg pain and jaw pain). We thought that the addition of other types of PAH-

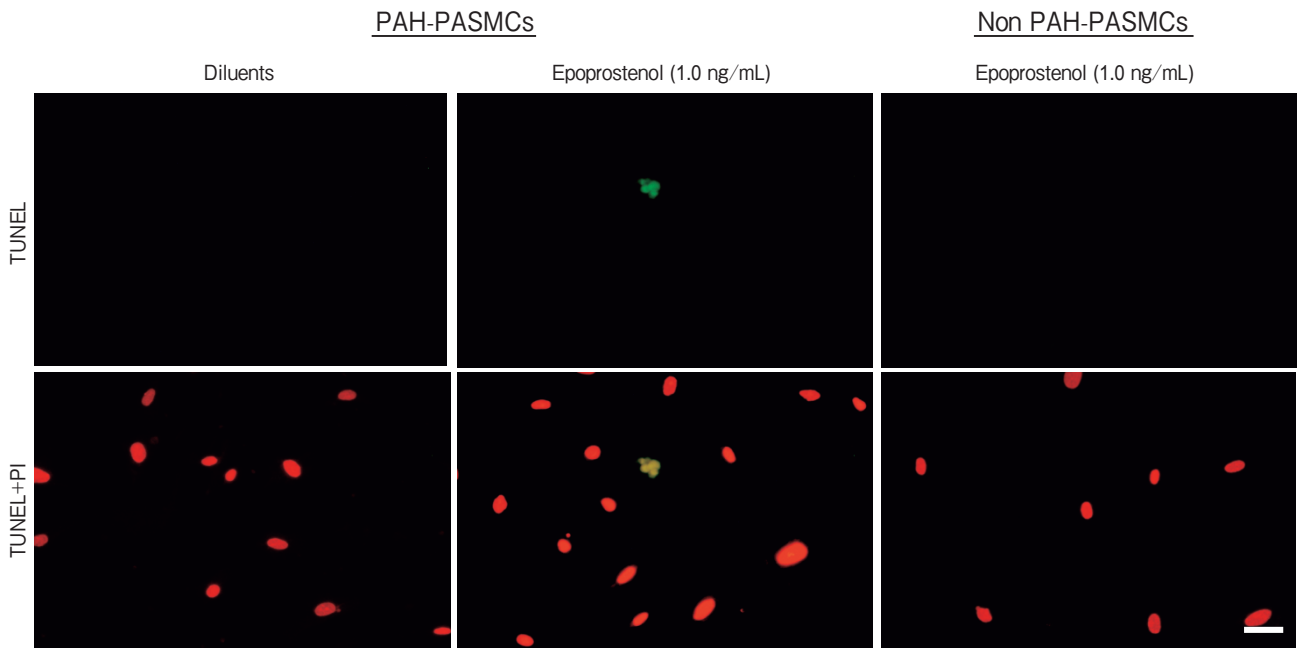

Fig. 1 Representative images reflecting findings of induction of apoptosis. For IPAH experiments, pulmonary artery samples were obtained from patients with idiopathic PAH at lung transplantation. For non-PAH experiments, non-PAH-PASMCs were obtained from patients with lung cancer at lung lobectomy. Peripheral pulmonary arteries smaller than 1 mm in outer diameter were disaggregated with collagenase. The adventitia and intima were removed and isolated arteries were cut into 2-mm-long sections. The cut arteries were placed in a 6-well plate and cultured. We constructed a flow circuit and administered epoprostenol or its diluents using the flow circuit for 24 hours in PAH-PASMCs and non-PAH-PASMCs. A TUNEL assay was performed using an ApopTag fluorescein *in situ* apoptosis detection kit (Chemicon International Inc.) to assess apoptosis of PASMCs. Nuclear morphology was examined by labeling with prodium iodium (PI, red). PAH-PASMCs treated with epoprostenol at a high concentration (1.0 ng/mL) showed TUNEL-positive nuclei (green). TUNEL-positive nuclei were not observed in PAH-PASMCs treated with only diluents and non-PAH-PASMCs treated with epoprostenol. Bar = 20 μm.

specific drugs might help to reduce side effects caused by high-dose epoprostenol while maintaining hemodynamic improvement. We evaluated the additional effects of bosentan in IPAH patients already treated with high-dose epoprostenol [35]. Since a remarkable elevation of cardiac output was observed at the initiation of bosentan, we reduced the dose of epoprostenol (from 99.6 ± 43.4 to 82.8 ± 31.3 ng/kg/min) while maintaining the cardiac output at the initial value. As a result, side effects were relieved while the hemodynamic improvement caused by high-dose epoprostenol was maintained.

Anticoagulation therapy is recommended and has a survival benefit in patients with PAH. However, many hemorrhagic complications occur in patients with IPAH who receive both anticoagulation and epoprostenol, because epoprostenol itself has a potent antiplatelet activity [36]. Patients who received dosages less than 28 ng/kg/min did not experience any bleeding episodes. Thus, discontinuation of anticoagulation should be considered if the dose of epoprostenol exceeds 25 ng/kg/min.

Conclusion

Epoprostenol therapy is effective for patients with severe PAH, but there remain several problems to be solved. It is important to address these problems in the next stage of clinical research.

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