Journal of Cardiology Cases 9 (2014) 177–178

Contents lists available at www.sciencedirect.com

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase

Editorial: Could reverse remodeling be a novel treatment goal of pulmonary hypertension?

Keywords:
PGI_2
Apoptosis
Pulmonary artery smooth muscle cells
Vascular remodeling

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by vascular remodeling of small- to medium-sized pulmonary arteries, resulting in elevated pulmonary arterial pressure (PAP) and ultimately in right heart failure and death. Advanced PAH is characterized by arteriopathy, which includes muscularization of distal pulmonary arterioles, concentric intimal thickening, and obstruction of the vascular lumen by proliferating endothelial cells, resulting in plexiform lesions [1]. Pulmonary vasoconstriction and vascular remodeling are associated with substantial number of molecules and cellular substrates, a concept referred to as the "multiple-hit-theory" [2] (Fig. 1).

Prostacyclin (PGI_2) is one of the most potent intrinsic vasodilators with anti-proliferative effects and is produced by endothelial cells. A classically known signaling pathway of PGI_2 is activated by the rhodopsin type G protein-coupled cell surface receptor termed IP. Its effectiveness in the treatment of PAH, a condition in which patients have reduced IP receptor expression in the remodeled pulmonary arterial smooth muscle cells (PASMCs), has been firmly established in various clinical conditions [3]. IP receptor deficient mice exhibit more severe vascular remodeling in response to hypoxia, and are more susceptible to thrombosis, suggesting that the beneficial effects of PGI_2 in the treatment of PAH might be exerted via activation of the IP receptor signaling pathway. Transgenic mice with selective pulmonary overexpression of the PGI_2 synthase gene were protected against the development of hypoxia-induced pulmonary hypertension. Moreover, PGI_2 and its analogs had also been reported to prevent pressure overload-induced cardiac hypertrophy [4], and to reduce cardiac ischemia/reperfusion injury via the membrane receptor IP [5].

Previously, a novel signaling pathway of PGI_2 and its analogs through peroxisome proliferator-activated receptor (PPAR)δ had been demonstrated in adipocytes, lung fibroblasts, and uterine cells at the site of implantation. We demonstrated for the first time that $cPGI_2$, a PGI_2 analog, induces expression of an enzyme involved in mitochondrial fatty acid β-oxidation in cardiomyocytes via PPARδ [6].

Intravenous PGI_2 is the first drug to provide appreciable benefits in patients with idiopathic PAH (IPAH). The treatment algorithm of PAH was updated at the 5th World Symposium on Pulmonary Hypertension held in Nice, France, in February/March 2013, and the conclusion of each task force was published in the *Journal of the American College of Cardiology* in December 2013. Intravenous epoprostenol (EPO) is recommended as Class I and Level A in World Health Organization functional class III and IV PAH patients in the most current treatment algorithm [7]. In addition, EPO and macitentan were highlighted because morbidity and mortality were applied as primary end-point in randomized controlled studies of these drugs [7].

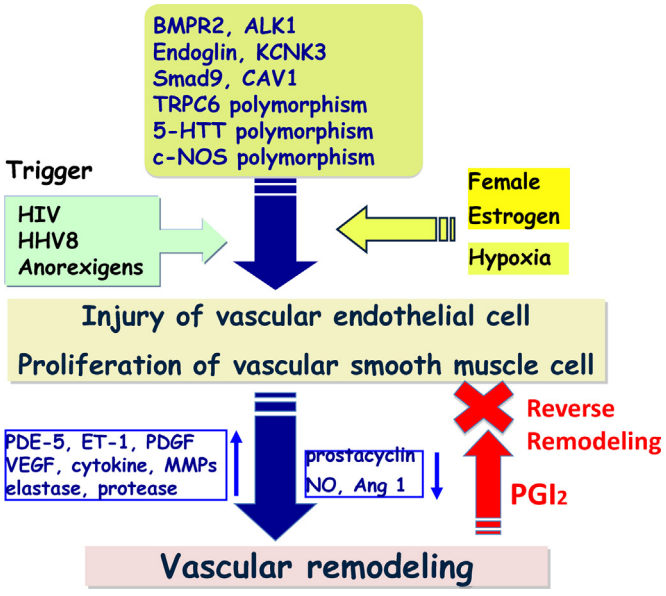

Fig. 1. Multiple-hits-theory and vascular remodeling.

In 2010, there was an interesting report that IPAH patients receiving high-dose PGI_2 showed marked hemodynamic improvement [8]. They were treated with 107 ± 40 ng/kg/min EPO for 1355 ± 627 days, and subsequently mean PAP decreased from 66 ± 16 to 47 ± 12 mmHg, and more importantly all the patients survived for a period of 3.7 years. The appropriate dose range of EPO is thought to be 25–40 ng/kg/min based on the previous studies [9], and until recently the efficacy of treatment of IPAH patients with EPO >40 ng/kg/min had not been determined. They concluded that for better survival, a treatment with EPO >40 ng/kg/min is required to achieve a marked hemodynamic improvement.

http://dx.doi.org/10.1016/j.jccase.2014.02.004

Hemodynamic parameters are considered to be the gold standard indices of outcome in PAH patients. The National Institutes of Health registry demonstrated that increased mean PAP, increased mean right atrial pressure (RAP), and decreased cardiac index (CI) were associated with an increased mortality. Since then, hemodynamics, specifically, RAP, CI and mixed-venous oxygen saturation (SvO_2) have been confirmed in numerous studies as robust independent prognostic factors [10]. There are still several caveats and limitations in using hemodynamic parameters to assess prognosis. Mean PAP has not been included as a variable to determine response to therapy and prognosis in PAH patients at follow-up period. In addition, even for the CI, there is no strong evidence for the current recommendation of CI >2.5 L/min/m^2 as a hemodynamic goal, as it was derived mainly from studies evaluating patients with left heart failure [11].

PAH is a vascular proliferative disease characterized by abnormal proliferation and impaired apoptosis of PASMCs. The development of medical agents with anti-proliferative and pro-apoptotic effects in PASMCs would provide a novel therapeutic modality for PAH. Evidence from animal models and human disease suggest that platelet-derived growth factor (PDGF) and c-KIT signaling are important in vascular smooth muscle cell (VSMC) proliferation and hyperplasia. Imatinib is an anti-proliferative agent developed to target Bcr-Abl tyrosine kinase in patients with chronic myeloid leukemia. The inhibitory effect of imaninib on PDGF receptors and c-KIT suggests that it may be efficacious in PAH. Imatinib and sorafenib, a multi-kinase inhibitor, are reported to present anti-proliferative effects and induce apoptosis in PDGF stimulated PAH-PASMCs [12] and reverse PAH in an animal model of pulmonary hypertension [13]. However, induction of apoptosis by imatinb is controversial. Furthermore, two randomized controlled trials in PAH patients treated with imatinib have shown positive results on exercise capacity and hemodynamics, in association with increased incidence of subdural hematoma in the patients treated with both imatinib and oral anticoagulants [14].

Recently, Akagi et al. reported [15] that in an in vitro study, PGI_2 induced apoptosis in PASMCs from IPAH patients. They showed that terminal deoxynucleotidyl transferase dUTP nick end labeling-positive, caspase-3 active cells were detected in PASMCs obtained from eight IPAH patients after treatment with high-dose PGI_2 but not with low-dose PGI_2. An IP receptor antagonist inhibited the induction of apoptosis, elevation of cyclic AMP, and upregulation of Fas ligand induced by high-dose PGI_2, and induction of apoptosis was not observed in PASMCs obtained from non-PAH patients. Furthermore, serum Fas ligand level showed a significant positive correlation with PGI_2 dose in PGI_2-treated PAH patients.

In this issue of the *Journal of Cardiology Cases*, Akagi et al. further demonstrated reverse vascular remodeling and apoptotic cells in pulmonary vasculature in lung tissue from an IPAH patient treated with high-dose PGI_2 [16]. This report is a continuation of their previous study, and although a single case, they proposed that reverse remodeling of the pulmonary arteries would be a direct effect of high-dose PGI_2. However, the mean PAP was markedly improved in this patient, whereas it was unchanged in the patient who was not treated with PGI_2. For reverse vascular remodeling in IPAH patients, the significance of lowering PAP is an issue to be considered. In addition, the underlying mechanisms of why only high-dose but not low-dose PGI_2 transduces apoptotic signal in PASMCs have not been clarified to date.

Many medications other than EPO are now available or will be available in the near future, including as a novel endothelin receptor antagonist, soluble guanylate cyclase stimulator, Rho-kinase inhibitor, several growth factors inhibitors, etc. Although the new era is welcomed, we do not yet have a thorough understanding of the usage of new drugs and interactions contributing to improved quality of life and better survival. The evidence of apoptotic cells in pulmonary vasculature in IPAH patients treated with high-dose PGI_2 will strongly encourage future exploration of effective treatment options for managing patients with severe PAH.

References

[1] Ravinovich M. Molecular pathogenesis of pulmonary arterial hypertension. J Clin Invest 2013;122:4306–13.
[2] Yuan JX, Rubin LJ. Pathogenesis of pulmonary arterial hypertension: the need for multiple hits. Circulation 2005;111:534–8.
[3] Badesch DB, McLaughlin VV, Delcroix M, Vizza CD, Olschewski H, Sitbon O, Barst RJ. Prostanoid therapy for pulmonary arterial hypertension. J Am Coll Cardiol 2004;43:56S–61S.
[4] Hara A, Yuhki K, Fujino T, Yamada T, Takayama K, Kuriyama S, Takahata O, Karibe H, Okada Y, Xiao CY, Ma H, Narumiya S, Ushikubi F. Augmented cardiac hypertrophy in response to pressure overload in mice lacking the prostaglandin I2 receptor. Circulation 2005;112:84–92.
[5] Xiao CY, Hara A, Yuhki K, Fujino T, Ma H, Okada Y, Takahata O, Yamada T, Murata T, Narumiya S, Ushikubi F. Roles of prostaglandin I(2) and thromboxane A(2) in cardiac ischemia-reperfusion injury: a study using mice lacking their respective receptors. Circulation 2001;104:2210–5.
[6] Kuroda T, Masaki M, Sugiyama S, Hiramoto Y, Fujio Y, Hirota H, Hori M, Yamauchi-Takihara K. Carbacyclin induces carnitine palmitoyltransferase-1 in cardiomyocytes via peroxisome proliferator-activated receptor (PPAR) δ independent of the IP receptor signaling pathway. J Mol Cell Cardiol 2007;43:54–62.
[7] Galiè N, Corris PA, Frost A, Girgis RE, Granton J, Jing ZC, Klepetko W, McGoon MD, McLaughlin VV, Preston IR, Rubin LJ, Sandoval J, Seeger W, Keogh A. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol 2013;62:D60–72.
[8] Akagi S, Nakamura K, Miyaji K, Ogawa A, Kusano KF, Ito H, Matsubara H. Marked hemodynamic improvements by high-dose epoprostenol therapy in patients with idiopathic pulmonary arterial hypertension. Circ J 2010;74:2200–5.
[9] McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002;106:1477–82.
[10] Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. Eur Respir J 2010;35:1079–87.
[11] McLaughlin VV, Gaine SP, Howard LS, Leuchte HH, Mathier MA, Mehta S, Palazzini M, Park MH, Tapson VF, Sitbon O. Treatment goals of pulmonary hypertension. J Am Coll Cardiol 2013;62:D73–81.
[12] Nakamura K, Akagi S, Ogawa A, Kusano KF, Matsubara H, Miura D, Fuke S, Nishii N, Nagase S, Kohno K, Morita H, Oto T, Yamanaka R, Otsuka F, Miura A, et al. Pro-apoptotic effects of imatinib on PDGF-stimulated pulmonary artery smooth muscle cells from patients with idiopathic pulmonary arterial hypertension. Int J Cardiol 2012;159:100–6.
[13] Schermuly RT, Dony E, Ghofrani HA, Pullamsetti S, Savai R, Roth M, Sydykov A, Lai YJ, Weissmann N, Seeger W, Grimminger F. Reversal of experimental pulmonary hypertension by PDGF inhibition. J Clin Invest 2005;115:2811–21.
[14] Hoeper MM, Barst RJ, Bourge RC, Feldman J, Frost AE, Galié N, Gómez-Sánchez MA, Grimminger F, Grünig E, Hassoun PM, Morrell NW, Peacock AJ, Satoh T, Simonneau G, Tapson VF, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation 2013;127:1128–38.
[15] Akagi S, Nakamura K, Matsubara H, Kusano KF, Kataoka N, Oto T, Miyaji K, Miura A, Ogawa A, Yoshida M, Ueda-Ishibashi H, Yutani C, Ito H. Prostaglandin I_2 induces apoptosis via upregulation of Fas ligand in pulmonary artery smooth muscle cells from patients with idiopathic pulmonary arterial hypertension. Int J Cardiol 2013;165:499–505.
[16] Akagi S, Nakamura K, Matsubara H, Ohta-Ogo K, Yutani C, Miyaji K, Ogawa A, Kusano K, Oto T, Ueda-Ishibashi H, Ito H. Reverse remodeling of pulmonary arteries by high-dose prostaglandin I_2 therapy: a case report. J Cardiol Cases 2014;9:173–6.

Keiko Yamauchi-Takihara (MD, PhD, FJCC)*
Health Care Center, Osaka University & Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

* Correspondence to: Health Care Center, Osaka University, 1-17 Machikaneyama Toyonaka, Osaka 560-0043, Japan. Tel.: +81 6 6850 6012; fax: +81 6 6850 6040.
E-mail address: takihara@wellness.hss.osaka-u.ac.jp

14 February 2014