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

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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 (PGL2) is one of the most potent intrinsic vasodilators with anti-proliferative effects and is produced by endothelial cells. A classically known signaling pathway of PGL2 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 PGL2 in the treatment of PAH might be exerted via activation of the IP receptor signaling pathway. Transgenic mice with selective pulmonary overexpression of the PGL2 synthase gene were protected against the development of hypoxia-induced pulmonary hypertension. Moreover, PGL2 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 PGL2 and its analogs through peroxisome proliferator-activated receptor (PPAR)β had been demonstrated in adipocytes, lung fibroblasts, and uterine cells at the site of implantation. We demonstrated for the first time that cPGL2, a PGL2 analog, induces expression of an enzyme involved in mitochondrial fatty acid β-oxidation in cardiomyocytes via PPARβ [6].

Intravenous PGL2 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 mafenidate were highlighted because morbidity and mortality were applied as primary end-point in randomized controlled studies of these drugs [7].

In 2010, there was an interesting report that IPAH patients receiving high-dose PGL2 showed marked hemodynamic improvement [8]. They were treated with $107 \pm 40$ ng/kg/min EPO for $1355 \pm 627$ days, and subsequently mean PAP decreased from $66 \pm 16$ to $47 \pm 12$ 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.

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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 (SvO2) 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/m² 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 imatinib 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 imatinib 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, PGI2 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 PGI2 but not with low-dose PGI2. An IP receptor antagonist inhibited the induction of apoptosis, elevation of cyclic AMP, and upregulation of Fas ligand induced by high-dose PGI2, 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 PGI2 dose in PGI2-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 PGI2 [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 PGI2. However, the mean PAP was markedly improved in this patient, whereas it was unchanged in the patient who was not treated with PGI2. 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 PGI2 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 PGI2 will strongly encourage future exploration of effective treatment options for managing patients with severe PAH.

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