Unlooked-for Significance of Cardiac Versus Vascular Effects of Endothelin-1 in the Pathophysiology of Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is a progressive and devastating condition that is characterized by pulmonary vascular remodeling resulting in increased pulmonary vascular resistance and raised pulmonary arterial pressure, eventually leading to right ventricular (RV) failure and premature death. PAH carries a poor prognosis. Even in the current treatment era, the average life expectancy of PAH patients after diagnosis is estimated at 5 to 7 years, with significant morbidity.

The pathobiology of PAH remains incompletely understood. The process of pulmonary vascular remodeling involves pathological changes in the intima, media, and adventitial layers of the vessel wall, and each cell type, including endothelial, smooth muscle, and fibroblast, in the pulmonary vascular wall plays a specific role in the pathogenesis. Both vascular endothelial and smooth muscle cells exhibit an abnormal growth phenotype, which is characterized by excess cellular proliferation and apoptosis resistance. Disorganized endothelial cell proliferation leads to the formation of glomeruloid structure known as the plexiform lesions, which are common pathological features of the pulmonary vessels of PAH patients and are not found in the diseases of the systemic circulation. In addition, a characteristic feature of severe pulmonary hypertension is the formation of a layer of myofibroblasts and extracellular matrix between the endothelium and the internal elastic lamina, termed neointima. These abnormalities in resident vascular cells, in concert with vasoconstriction, thrombosis, and inflammation, contribute to physical narrowing of the distal part of the pulmonary arterial tree. Such narrowing results in a remarkable increase in pulmonary vascular resistance, leading ultimately to the chronic and progressive elevation of pulmonary arterial pressure.

Endothelin-1 (ET-1) is a potent vasoconstrictor and mitogen that has been implicated in the pathogenesis and progression of PAH. Patients with idiopathic PAH show higher circulating levels of ET-1 and higher arterial-to-venous ratios of ET-1 than healthy control. This may represent increased production of ET-1 by the lung or reduced clearance of ET-1 by the lung. The lung is an important site of ET-1 production with an mRNA level of ET-1 5 times more abundant than those seen in other organs. Increased lung ET-1 levels have been demonstrated in PAH patients and in animal models of PAH. Consistent with these findings is the observation that immunoreactivity for ET-converting enzyme-1 is augmented in the endothelium of pulmonary arteries from PAH patients. Furthermore, a rise in mRNA levels of 2 ET receptors, ETₐ and ET₆, has been shown in lungs of rats with hypoxia-induced PAH. Therefore, nearly every component of the ET system in lungs seems to be upregulated in PAH.

ET-1 can be involved in the development of lung vascular and interstitial remodeling (Figure). Thus, ET-1 promotes vascular smooth muscle cell proliferation through both ETₐ and ET₆ receptors, stimulates endothelial cell proliferation through ET₆ receptors, and causes fibroblast activation and proliferation through both ETₐ and ET₆ receptors. In rats with monocrotaline-induced PAH, ET receptor antagonists (ERAs) have demonstrated their capacity to cause beneficial remodeling of pulmonary vessels, reduce pulmonary fibrosis, and improve the endothelial dysfunction of pulmonary vessels. Currently, 2 ERAs are available for the treatment of PAH: bosentan, a nonselective ETₐ and ET₆ receptor antagonist; and ambrisentan, a relatively selective antagonist of ET₆ receptors. A third ERA, sitaxsentan, a highly selective ET₆ receptor antagonist, was voluntarily withdrawn from the market due to causes of unpredictable serious liver injury. These ERAs were approved based on results of 12 to 16 week randomized, placebo-controlled trials demonstrating their efficacy in improving exercise capacity. Current treatment guidelines recommend these ERAs, especially for PAH patients in the World Health Organization (WHO) functional class III.

In the current issue of Circulation Research, Nagendran et al demonstrate a compensatory role for the upregulated ET-1 axis to preserve RV contractility in RV hypertrophy. The authors found that bosentan and cyclo(Trp-Asp-Pro-Val-Leu) (ET₆ receptor antagonist) decreased cardiac contractility in hypertrophied, but not normal rat RVs in a concentration-dependent manner. Thus, they proposed that the beneficial effects of ERAs in decreasing the RV afterload, by reversing pulmonary artery vasoconstriction and remodeling, may be limited by a potential negative inotropic effect on the RV, at least in some patients with RV hypertrophy (Figure).

RV dysfunction and failure in patients with PAH is a major contributor to increased morbidity and mortality. Although ERAs show antiproliferative and antifibroblastic effects (Figure) and their effectiveness for the therapy of some forms of chronic PAH has been firmly established, the question remains as to whether ERAs would be beneficial in the therapy of patients...
with heart failure and significant associated PAH. Clinical trials using ERAs in heart failure such as Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure and Research on Endothelin Antagonism in Chronic Heart Failure have suggested no overall benefit in the treatment of subjects with heart failure.27 The effect of bosentan on RV dysfunction in PAH does not reach general agreement, but no significant reduction in RV systolic pressure by bosentan is reported in rats with monocrotaline-induced PAH.21 Furthermore, bosentan fails to improve RV systolic function in the hypoxic rat model of PAH.20 Recent work using rats with secondary PAH induced by ischemic heart failure has also shown that RV dysfunction is not improved by bosentan treatment.22 The study by Nagendran et al26 may partly explain why treatment with bosentan provides no significant improvement of RV dysfunction in PAH observed in those studies.

ERAs may potentially lead to a decrease in RV function in some patients with PAH, blunting any beneficial effects that they may have by the improvement of pulmonary vascular remodeling (Figure). Indeed, a double-blind, controlled trial, which compares the effects of sildenafil and bosentan in patients with PAH, WHO functional class III, failed to improve RV ejection despite the fact that the 2 drugs decrease the pulmonary artery pressure similarly.20 Because RV deterioration is associated with poor outcome in PAH patients, this could be a great challenge in future trials of ERAs for PAH. However, further evaluation needs robust data on impact of existing and new ERAs on long-term outcome and survival in PAH patients.

Sources of Funding
This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science of Technology of Japan.

Disclosures
None.

References


Key Words: endothelin ■ pulmonary hypertension ■ pulmonary vascular remodeling ■ right ventricular failure
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Circ Res. 2013;112:227-229
doi: 10.1161/CIRCRESAHA.112.300623

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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