Early detection of pulmonary arterial hypertension by the exercise echocardiography in patients with connective tissue diseases
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Objective: To detect an early stage of pulmonary arterial hypertension (PAH) in patients with connective tissue diseases (CTD) who do not show the significant rise of tricuspid valve pressure gradient (TRPG) by echocardiography in rest, using the exercise echocardiography. Patients and methods: 27 patients with systemic sclerosis (SSc), 13 patients with mixed connective tissue disease (MCTD), 8 patients with systemic lupus erythematosus (SLE), and 30 healthy controls (HC). To these patients, exercise echocardiography was performed. CTD patients whose TRPG in rest was 31 mmHg or less were enrolled for this study from September 2010 to June 2012. The patients included were when TRPG on exercise went up by 35 mmHg or more from that in rest, right heart catheterization (RHC) was conducted, if the patient’s written informed consent was obtained. Result: The average increase of TRPG caused by exercise (delta TRPG) in SSc patients was higher than that in HC (both p < 0.05). Although, there was no SLE patients whose delta TRPG was 35 mmHg or more, 5 SSc patients and 3 MCTD patients showed 35 mmHg or more delta TRPG. Among these 8 patients, RHC was carried out for two SSc patients and two MCTD patients who have agreed with implementation of RHC. Three patients out of four were diagnosed as PAH by RHC. Conclusion: In CTD patients, exercise echocardiography is a useful tool to detect early stage of PAH patients who do not show the significant rise of TRPG in rest.


Why are endothelin antagonists effective in pulmonary arterial hypertension with right ventricular dysfunction?
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In pulmonary arterial hypertension (PAH), increases in endothelin-1 (ET-1) contribute to elevated pulmonary vascular resistance which ultimately causes death by right ventricular heart failure. ET antagonists are effective in treating PAH but in marked contrast, lack efficacy in treating left ventricular heart failure. The aim of the study was to use radioligand binding assays to quantify the density of ETA and ETB in human heart from patients with PAH and in an established model of PAH, the monocrotaline (MCT) rat. This model recapitulates some of the pathophysiological features of the human condition, including increase in right ventricle systolic pressure and hypertrophy. In the right ventricles of PAH hearts, there was a significant increase in the ratio of ETA receptors (n = 12) but a decrease in ETB ratio compared with normal hearts. There was no change in ratio in the left ventricle. In the MCT rat (n = 8), receptor density was also significantly different in the right ventricle compared with vehicle control but with ETA downregulation and ETB upregulation. There was no change in the left ventricle. In both human PAH and MCT model, ET receptor density changes in the right ventricle although the ratio was reversed in the rat. We have previously shown that ETA receptors in the failing left ventricle of patients with ischaemic heart disease are also significantly increased. Endothelin is a potent positive inotropic agent. In heart failure, increased receptor density may be an adaptive response to increase beneficial cardiac contractility. In PAH, the main benefit of ET antagonists may be in blocking deleterious vascular effects rather than improving cardiac function.


Endothelin-1 induces down-regulation of IP receptor in pulmonary artery smooth muscle cells obtained from patients with pulmonary arterial hypertension
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Background: We previously reported that addition of bosentan in pulmonary arterial hypertension (PAH) patients treated with high-dose intravenous prostaglandin I2 (PGI2) decreased not only pulmonary artery pressure but also reduced the dosage of PGI2. IP receptor, a PGI2 receptor, plays an important role in the treatment of PGI2. However the relation of IP receptor and endothelin-1 is unknown. Methods: Effects of PGI2 and endothelin-1 on IP receptor expression was examined by qRT-PCR in pulmonary artery smooth muscle cells (PASMCs) obtained from six patients with PAH. Results: PGI2 induced time and dose-related down-regulation of IP receptor expression in PAH-PASMCs. Expression levels of IP receptor

Efficacy of oral triple upfront combination therapy (long-acting prostacyclin analogue, endothelin receptor antagonist, phosphodiesterase 5 inhibitor) in the patients with idiopathic/heritable pulmonary arterial hypertension
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Background: The efficacy of oral triple upfront combination therapy for severe idiopathic /heritable pulmonary arterial hypertension (I/HPAH) in long-term has not been established. Patients & methods: We retrospectively reviewed three patients in WHO-FC III who received oral triple upfront combination therapy (oral long-acting