Potential involvement of functional tricuspid regurgitation in the diagnostic error to assess pulmonary arterial pressure by Doppler echocardiography
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Background: Transthoracic Doppler echocardiography (DE) is useful for the screening of pulmonary hypertension (PH), which is often treated by endothelin antagonist, although recent studies have suggested that estimation of pulmonary artery pressure (PAP) by DE is frequently inaccurate. This study aimed to examine that functional tricuspid regurgitation (TR) with geometric alterations caused by right ventricular dilatation is involved in the diagnostic error of echocardiography for the assessment of PAP. Methods: We conducted a retrospective cohort study of consecutive 127 patients (male, n = 58, mean age of 55 years) who received both echocardiography and right heart catheterization (RHC) during the 2-year period from November 2008 to October 2010. We defined PH as mean PAP > 25 mmHg at rest by RHC and “accurate estimated echocardiographic value” when it remained within 10 mmHg of the invasive measurement. Results: A total of 75 patients (59%) were diagnosed to have PH by RHC. When the patients were divided into 3 groups; accurate (n = 52), over-estimate (n = 63) and under-estimate (n = 12), the diagnosis of PH by RHC was more frequently in accurate (p < 0.0001). Right atrium tended to be larger in both over-estimate and under-estimate groups than accurate group (accurate, 30.0 ± 5.7 mm; over, 35.3 ± 8.6 mm; under, 32.8 ± 5.2 mm, P = 0.002), and the severity of TR was significantly worse in over-estimate group (P < 0.0001). Right atrium tended to be larger in both over-estimate and under-estimate groups than accurate group (accurate, 38.8 ± 5.7 mm; over, 42.6 ± 8.49 mm; under, 42.7 ± 6.2 mm, P = 0.073). Conclusions: Our results indicate that the accuracy of DE is not enough for PH evaluation, particularly in patients with PH associated with increased TR grading and enlarged right heart dimension.

Detection of developing pulmonary vasculopathy with non-invasive cardiopulmonary exercise testing
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Since the discovery of ET-1, over-expression of ET-1 has been demonstrated in patients with pulmonary arterial hypertension (PAH). In contrast to chronic thromboembolic pulmonary hypertension (CTEPH), patients with PAH have pulmonary vasculopathy (PV). PV leads to impaired dilatation of affected pulmonary vessels, impeding the increase of cardiac output (CO) and stroke volume (SV) during exercise. Peak O2 uptake shows CO, and peak O2 pulse shows SV during cardiopulmonary exercise testing (CPX). To investigate the increase of CO during exercise, we performed CPX in 12 patients with PAH and 7 patients with CTEPH. Predicted peak O2 uptake (45.5 ± 8.0 vs. 60.6 ± 13.4%, p < 0.01) and predicted peak O2 pulse (55.6 ± 7.6 vs. 69.1 ± 6.9%, p < 0.01) were significant higher in CTEPH than PAH. Diffusion capacity for carbon monoxide (%DLco: 40.3 ± 13.7 vs. 62.2 ± 13.9%, p < 0.01) was also significantly higher in CTEPH than PAH, however there was no correlation between %DLco and peak O2 uptake or peak O2 pulse. While, there was no difference in mean pulmonary arterial pressure (mPAP: 31 ± 6.8 vs. 30.1 ± 7.0 mmHg, n.s.), cardiac output (CO: 4.1 ± 0.6 vs. 4.4 ± 0.4 L/min, n.s.), and pulmonary vascular resistance (PVR: 5.2 ± 2.0 vs. 5.2 ± 2.8 wood units, n.s.) at rest. Our data indicate that, regardless of hemodynamic, both lower peak O2 uptake and peak O2 pulse show PV impeding the increase of CO during exercise. CPX can predict the onset of PAH by detection of PV in early stage.

Vascular endothelial growth factor (VEGF) and the control of endothelin-1 synthesis by human lung microvascular endothelial cells: A possible pathway for pathogenesis
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Introduction: Increased endothelin-1 (ET-1) is a hallmark of pulmonary arterial hypertension (PAH), and contributes to its pathogenesis. The factors controlling ET-1 in PAH are poorly understood. Vascular endothelial growth factor (VEGF) blockade results in PAH-like lesions in animal models, and has caused PAH in humans. The effects of VEGF on ET-1 production by human lung blood microvascular endothelial cells (HMVEC-LBl) are unknown. Methods: We exposed HMVEC-LBl (Lonza Inc.) in-vitro to human VEGF121 (40 ng/ml) in serum-free medium for 7 h, in the absence or presence of the VEGF receptor antagonist, SU5416 (Cayman Chemical, 3 and 10 μM). ET-1 production was measured in the supernatant. Phosphorylation of VEGF receptor 2 (VEGFR2) was measured by western blotting after exposure to VEGF ± SU5416 for 5 and 10 min. Results: VEGF effectively caused ET-1 production by 16% at 10 min, whereas SU5416 decreased ET-1 production by 29%. In the absence of VEGF, SU5146 decreased VEGFR2 phosphorylation, which was blocked by SU5416. VEGF may promote vascular health by decreasing ET-1 production in small pulmonary arteries, which needs further investigation.

Effect of bosentan on exercise capacity in patients with pulmonary arterial hypertension or inoperable chronic thromboembolic pulmonary hypertension
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Background: Endothelin receptor antagonists (ERA) improve the prognosis of patients with pulmonary arterial hypertension (PAH). However, only limited data are available on the effect of treatment with the ERA bosentan on exercise capacity assessed with cardiopulmonary exercise testing (CPX) in patients with PAH or inoperable chronic thromboembolic pulmonary hypertension (CTEPH). Purpose: To investigate the effect of the oral, dual-ERA bosentan on exercise capacity in patients with PAH or inoperable CTEPH by means of CPX. Methods: Fifteen consecutive PAH (mean age, 47 ± 21 years) and 9 consecutive inoperable CTEPH patients (mean age, 49 ± 12 years) with World Health Organization Functional Class II to IV were treated with bosentan. All patients underwent cardiac catheterization, echocardiography, and CPX at baseline. CPX was performed both prior to initiation of bosentan therapy and after 6 months. Results: In PAH patients, peak VO2 significantly increased from 13.8 ± 6.8 mL/kg/min at baseline to 16.8 ± 7.2 mL/kg/min after 6 months (P < 0.01). Similarly, VE/VO2 slope also significantly decreased from 56.8 ± 22.5 to 48.9 ± 17.5 (P < 0.05). However, in CTEPH patients, there were no significant differences in peak VO2 or VE/VO2 slope between the before and after bosentan therapy values (P = 0.35, P = 0.67, respectively). The medication was well tolerated by all patients, and there was no evidence of drug-related liver dysfunction. Conclusions: Bosentan therapy improves exercise capacity in patients with PAH within a relatively short period. However, the effect is not seen in patients with CTEPH.


Short-term drug interaction of bosentan and sildenafil under the long-term use in patients with pulmonary arterial hypertension
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Background: Bosentan and sildenafil are often administered together for the treatment of PAH. Bosentan is a known inducer of CYP3A4 in chronic use and therefore, the plasma concentration of sildenafil is decreased almost by half when co-administered. In the course of daily life, patients tend to take these medicines at the same time in the morning and the evening. We investigated how the plasma concentration of sildenafil changed when bosentan/sildenafil was taken beforehand with the other. Methods: A randomized, open-label crossover study was conducted in PAH patients of WHO functional class III, who chronically received both bosentan and sildenafil. Patients were randomly assigned to either Pattern 1 or 2, both of which consisted of three phases as follows; phase S: patients take sildenafil 3 h prior to bosentan, phase B: patients take bosentan 3 h prior to sildenafil, and phase C: patients take sildenafil and bosentan simultaneously (control). We collected blood samples on the last day of each phase and measured the plasma concentration of sildenafil using liquid chromatography-tandem mass spectrometry. Results: Six patients entered the study. In sildenafil Cmax, phase S was 72.9 ± 40.9 (ng/ml, mean ± S.D) and it was significantly lower than phase C (P = 0.00215). Phase B was 99.6 ± 33.9 with no significant difference with phase C (P = 0.6173). In sildenafil AUC0-8, phase S was 108.2 ± 126.4 (h/ng/ml, mean ± S.D) and phase B was 240.7 ± 121.8. Neither phase proved significant difference with that of phase C (203.5 ± 81.3, P = 0.3213 and 0.1999, respectively). Conclusion: It is indicated that there is a short-term drug interaction between bosentan and sildenafil which may be relevant to CYP3A4 metabolism.


Chronic treatment with novel endothelin receptor antagonist macitentan improved severe pulmonary arterial hypertension in rats
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Background: Endothelin receptor antagonists (ERA) improve the pulmonary hemodynamic and histopathology in the rat model with established severe PAH. This study investigated the effects of macitentan on pulmonary arteriopathy indistinguishable from that in PAH patients. Method and results: Rats received a single subcutaneous injection of 20 mg/kg SU5416, a VEGF blocker, and then exposed to 3-week hypoxia (10% O2) followed by 5 weeks of normoxia. Eight weeks after the SU5416 injection, in comparison with normal rats, all rats developed severe PH (RV systolic pressure: 23 ± 6 vs. 102 ± 15 mmHg, n = 4 or 5 for each, P < 0.001) with RV hypertrophy (the mass ratio of RV to LV pulse septum: 0.23 ± 0.01 vs. 0.77 ± 0.05, P < 0.001). Five-week treatment with macitentan (30 mg/kg/day, orally, from week 3 to 8) significantly reduced RV systolic pressure (41 ± 5 mmHg, n = 6, P < 0.05) and hypertrophy (0.36 ± 0.03, n = 7, P < 0.005) without decreasing cardiac output. Also, macitentan significantly attenuated the medial wall thickness and complex occlusive lesions in PAH rats by histological examination. Conclusion: Chronic treatment with macitentan markedly hemodynamically and histopathologically improved PAH in SU5416/hypoxia/normoxia-exposed rats. The improvement of arteriopathy may in part contribute to the beneficial effects of macitentan on PH.


Ambrisentan and tadalafil synergistically attenuate chronic hypoxia-induced PAH in rats
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