We showed previously that ambrisentan, a selective endothelin type A receptor antagonist, and tadalafil, a PDE5 inhibitor, act synergistically to relax endothelin-constricted pulmonary arteries (Liang et al. Hypertension 2012; 59: 705-11). To confirm these findings in an in-vivo model of PAH, we investigated the effect of ambrisentan and tadalafil in combination on hypoxia-induced PAH in rats. Upon exposure to hypoxia (10% O_2), male SD rats were dosed with vehicle, ambrisentan (1 mg/kg, q.d.), tadalafil (10 mg/kg, q.d.) or the combination via oral gavage for 3 weeks. Three weeks of exposure of rats to hypoxia increased mean pulmonary arterial pressure (mPAP) from 10.8 &plusmn0.7 mmHg (normoxic, mean &plusmn SEM, n = 8) to 23.9 &plusmn1.3 mmHg (hypoxic, n = 12, p < 0.01 vs normoxic). Teatments with ambrisentan, tadalafil and the combination reduced mPAP to 20.1 &plusmn0.8 mmHg (n = 12, p < 0.05 vs hypoxic), 20.8 &plusmn1.2 mmHg (n = 11, p < 0.05 vs hypoxic) and 15.9 &plusmn1.0 mmHg (n = 12, p < 0.01 vs hypoxic), respectively. Chronic exposure of rats to hypoxia also increased the ratio of right ventricle weight/ left ventricle weight (RV/LV) from 0.326 &plusmn0.013 (normoxic, n = 8) to 0.602 &plusmn0.019 (hypoxic, n = 12, p < 0.01 vs normoxic). The ratios of RV/LV from hypoxic rats dosed with ambrisentan, tadalafil and the combination were decreased to 0.527 &plusmn0.014 (n = 12, p < 0.05 vs hypoxic), 0.531 &plusmn0.016 (n = 11, p < 0.05 vs hypoxic) and 0.430 &plusmn 0.017 (p < 0.01 vs hypoxic). Consistent with the in-vitro pulmonary artery data, the combination of ambrisentan and tadalafil caused a greater effect than each drug alone or the calculated sum of the individual effects of each drug, suggesting that ambrisentan and tadalafil synergistically attenuate hypoxia-induced PAH in rats.

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Real world experience in the DETECT study for pulmonary artery hypertension associated with systemic sclerosis

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Objectives: The currently ongoing DETECT study, a two-stage, prospective, observational, cohort study in systemic scleroderma (SSc) patients to evaluate screening tests and the incidence of pulmonary arterial hypertension (PAH) and pulmonary hypertension, is attempting to refine the screening process in pulmonary artery hypertension associated with SSc. We adopted the same multiple screening tests forced vital capacity [% predicted]/DLCO [% predicted]; current/past telangiectasias; anti-centromere antibody; N-terminal pro-brain natriuretic peptide; uric acid; right axis deviation on electrocardiography) in patients with SSc in our hospital to evaluate its Method: Date from 21 SSC patients, who had undergone right heart catheterization from 2009 to 2012 in our hospital, were retrospectively analyzed. We compared the result of DETECT screening system to mean pulmonary artery pressure assessed by right heart catheterization. Results: Seventeen SSc patients (80.9%) were categorized as candidates to referral to right heart catheterization in this study. Overall sensitivity was 100% and specificity was 25%. Conclusion: According to the 2012 American College of Rheumatology Annual Meeting, DETECT algorithm was announced that its sensitivity was 96% and specificity was 48%. Therefore, our results indicated that DETECT algorithm had the possibility to overestimate the risk of PAH in SSc patients.

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Reduced circulating endothelin-1 Level in uncorrected ASD patients with severe pulmonary hypertension

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There is increased risk of pulmonary hypertension (PH) in patients with Atrial Septal Defect (ASD), although the factors associated have not been clearly defined. Endothelin-1 (ET-1), a potent vasoconstrictor derived mainly from pulmonary endothelium, has been reported to be elevated in PH associated with congenital heart defect (CHD). However, studies about CHD-related PH included only a small number of ASD-patients and most of them were performed in children. In this study, we aim to measure the circulating ET-1 level in adult patients with uncorrected ASD complicated by severe pulmonary hypertension. Fifty-two newly diagnosed ASD patients were participating in this study, aged 20–79 years old. Measurements of RVSP, characteristics of ASD, remodeling RV were performed using TTE and TEE. The hemodynamic measurement by echo showed significant correlation with right heart catheterization ($r = 0.8; p < 0.0001$). Peripheral blood was withdrawn from brachialis vein and circulating ET-1 was measured using ELISA. Severe PH were defined as RVSP > 60 mmHg. The severe PH group (n = 25) was confirmed by larger RA diameter, larger RV diameter, reduced RV systolic function, and higher tricuspid valve gradient as compared to non-severe PH group (n = 27) (47.6 ± 1.47 vs. 41.2 ± 1.24 mm; $p < 0.01$; 48.6 ± 1.16 vs. 41.2 ± 1.29 mm; $p < 0.001$; 21.9 ± 1.01 vs. 25.9 ± 1.45 mm; $p < 0.0001$; 92 ± 5.5 vs. 33.7 ± 1.88 mmHg; $p < 0.0001$; respectively). There were no differences of age, diameter of the defect, and pulmonary flow ratio in the severe PH group. Interestingly, the circulating plasma ET-1 level was significantly lower in the severe group (6.3 ± 0.48 vs. 4.7 ± 0.32 pg/dl; $p < 0.01$). In conclusion, we reported lower circulating plasma ET-1 in ASD patients with severe PH. Further study should be performed to elucidate the ET-1 level in pulmonary circulation in this disease.

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Current state of medicine usage and the predictor of mortality in pulmonary arterial hypertension in Japan

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Background: Endothelin receptor antagonist (ERA) is recommended for treatment of pulmonary arterial hypertension (PAH). However, recommendation is based on reports of monotherapy. Method: We examined consecutive 112 patients diagnosed with Group 1 and 1' PAHwho visited 14 affiliated hospitals from July 2006 to January 2013. The difference in mortality between monotherapy group and combination therapy group (ERA and other PAH drugs) was compared. Results: There were 41 idiopathic, 43 collagen tissue disease, 24 congenial heart disease and 4 other types of PAH. Mean age was 52.2 years old, female 66.1%, WHO Functional Class1 5.6%, 2 31.5%, 3 53.9%, 4 9.0%, BNP 128 (49.3–406.5) pg/mL, cardiac index 3.4 ± 1.6 (L/kg/m2), mean pulmonary arterial pressure

48.2 ± 19.3 mmHg, and tricuspid regurgitation pressure gradient (TRPG) 57.5 ± 25.2 mmHg. Pericardial effusion was observed in 28%. ERA, prostacyclin, PDE-5 inhibitor and epoprostenol were used in 71.8%, 60.9%, 51.8%, and 18.2%, respectively. There were no significant difference in characteristics between the monotherapy group and the combination therapy group, except for the frequent use of the combination therapy in idiopathic PAH. Although pericardial effusion, cardiac index, and mean right atrial pressure were predictors for mortality in the combination group, there was no difference in mortality between the monotherapy group and the combination group. Conclusion: Combination therapy was frequently used in idiopathic PAH. However, difference in mortality was not apparent between monotherapy and combination therapy with other PAH drugs.

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Clinical effect of ambrisentan in pulmonary hypertension

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Background: A development of the drugs used in pulmonary hypertension (PH) contributes a lot to its clinical improvement. An advent of new endothelin receptor blocker, ambrisentan, has further diversified selection of PH drugs. Purpose: The purpose of this study was to evaluate the efficacy and safety of ambrisentan on PH. Method: Ambrisentan was administered to 26 (50 ± 19 years old, 7 men, 19 women) patients with PH including 11 patients with chronic thromboembolic PH (CTEPH), 5 with Eisenmenger syndrome, 5 with connective tissue disease (CTD) PH and 3 with idiopathic pulmonary arterial hypertension. Ambrisentan was added to the other PH drugs in all the patients. The patients underwent right-side heart catheterization before and after the administration of ambrisentan with measurement of cardiac output (CO), mean right atrial pressure (mRA), mean pulmonary arterial pressure (mPA), pulmonary vascular resistance (PVR). Brain natriuretic peptide (BNP) was also determined. Results: After administration of ambrisentan (the average follow-up period was 168 ± 97 days), mPA (36 ± 9 vs 22 ± 6: $p < 0.01$) and PVR (11 ± 6 vs. 7 ± 4: $p < 0.01$) and CO (4.0 ± 1.5 vs. 4.8 ± 1.8: $p < 0.05$) improved significantly, but BNP, mRA nor heart rate did not. The most frequent adverse reactions was edema with 6 patients, 3 of which abandoned ambrisentan. Conclusions: Ambrisentan is useful for pulmonary hypertension even if added to other PH drugs.

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Long-term advanced therapy with bosentan improves symptoms and the time to clinical worsening in the Japanese patients with inoperable chronic thromboembolic pulmonary hypertension

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Introduction: Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious devastating disease. It is still a challenge to treat some patients who are not eligible for pulmonary endarterectomy. Short-term bosentan or PDE5 inhibitor was significantly improved in symptoms, hemodynamics and exercise capacity in such patients. However, the long-term beneficial effect of advanced pulmonary vasodilating drugs is little understood. Therefore, we investigated the long-term effect of advanced therapy in the patients with inoperable CTEPH retrospectively. Methods and results: All consecutive 7 Japanese patients (5 female, mean age 62.6 ± 6.9 years) treated with bosentan (125–250 mg) for symptomatic inoperable CTEPH were included. The time to clinical worsening (TCW) was examined (mean follow-up period 896 ± 564 days). WHO-FC was significantly improved from 3.1 ± 0.4 to 2.1 ± 0.4 ($p < 0.01$). Pulmonary vascular resistance was significantly decreased from 786.9 ± 300.0 to 352.2 ± 210.7 dyn s cm^{-5} ($p < 0.05$). Mean pulmonary artery pressure and cardiac index were improved from 47.0 ± 7.6 to 43.3 ± 5.0 mmHg and from 2.18 ± 0.39 to 3.02 ± 0.74 l/min/m^2 ($n = 3$, follow-up 651–849 days). Six-minute walk distance was increased from 257.0 ± 151.0 to 369.8 ± 85.7 m ($p = 0.06$, $n = 4$, follow-up 651–931 days). Plasma BNP level was significantly decreased from 1160.0 ± 971.4 to 305.1 ± 285.9 pg/ml ($p < 0.05$). None of them were required hospitalization. Conclusions: Long-term advanced therapy with bosentan improves symptoms, hemodynamics and TCW in CTEPH patients. Advanced therapy is proposed as an essential treatment for the patients with inoperable CTEPH.

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Analysis of ET-1 system in mild and severe pulmonary arterial hypertension in mice

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Background: A recently developed mouse model for PAH combines hypoxia with a VEGF receptor blocker. Herein we aim to describe in detail this model. The TGFβ/Smad3 pathway is a pivotal factor regulating the transcription of the endothelin (ET-1) gene. Besides, interleukin-1β (IL-1β) increases expression of ET-1, and ETA receptor and reduces expression of ETB receptor. Methods and results: We placed 3-week old male SV129 mice under hypoxia ($O_2 = 10\%$) and treated them with a vascular endothelial growth factor receptor blocker (SU5416) (SU mice) (subcutaneous injection three times a week, 20 mg/kg) for 3 weeks. Compared to mice under hypoxia alone (H) and control mice (CTRL), these mice developed severe PAH, characterized by increased right ventricular systolic pressure measured in anesthetized mice by subxiphoid approach (SU: 37 ± 1.7; H: 29 ± 1.4, CTRL: 22.5 ± 1 mmHg), right ventricularhypertrophy (Fulton index: SU: 0.55 ± 0.042; H: 0.4 ± 0.04, CTRL:0.31 ± 0.026) and muscularization of precapillary vessels together with proliferation of endothelial cells of small arterioles (PCNA positive on endothelial layer/arterial section = SU: 2.9 ± 0.25; H: 1 ± 0.13; CTRL: 0.7 ± 0.08), which lead to completely occluded arterioles by von Willebrand factor expressing cells. Increased ET-1 mRNA, ETA receptor mRNA, protein expression and immunostaining signals and reduced ETB receptor mRNA expression were observed in SU mice only. This was associated with an increased abundance of phosphorylated Smad3 and a 9-fold increase of IL-1β expression. TGF-β mRNA in H and SU mice was similar. Conclusion: In severe PAH, Smad3 by potentiating TGF-β and IL-1β might disturb the expression of the ET system and may represent therefore potential therapeutic targets.

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