The hypoxia-mimetic agent cobalt chloride induces the expression of intrinsic BMP antagonist noggin independent of the endothelin pathway

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Background: Mutations in the bone morphogenetic protein type 2 receptor (BMPR2) are responsible for the majority of cases of heritable pulmonary arterial hypertension (PAH). Low penetrance of BMPR2 mutation in heritable PAH, however, suggests the involvement of second-hit elements in the pathogenesis of PAH. We have previously reported that treatment with endothelin-1 induced in vitro increased expression of noggin, an intrinsic bone morphogenetic protein antagonist, in human pulmonary artery smooth muscle cells (PA-SMCs). Moreover, chronic exposure to hypoxia is a well-known inducer of remodeling in pulmonary arteries. However, the potential link between chronic hypoxia exposure and noggin expression has not been elucidated. Aims: We hypothesized that hypoxia could induce, in PA-SMCs, the expression of endothelin-1 which could secondarily result in the upregulation of noggin. Methods and results: Cultured human PA-SMCs were treated for 3, 6, 24, and 48 h with the hypoxia-mimetic agent, cobalt chloride ($CoCl_2$; 100 μM) and gene expressions of preproendothelin-1 (ppET1), endothelin converting enzyme-1 (ECE1) and noggin were then evaluated by QRT-PCR. $CoCl_2$ treatment progressively increased the expressions of ppET1 and noggin, with maximal response after 24 h and 48 h of stimulation respectively. Gene expression of ECE1 was not changed. After pretreatment or not with a non-selective endothelin receptor antagonist (bosentan), we stimulated PA-SMCs with $CoCl_2$ for 5 h. Gene expression of noggin significantly increased after $CoCl_2$ treatment and this reaction was not changed by pretreatment with bosentan. Conclusions: Noggin, an intrinsic bone morphogenetic protein antagonist, was upregulated by $CoCl_2$, independent of hypoxia-induced endothelin-1 pathway at earlier timing (5 h).

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Combination of polymorphisms in angiotensin-converting enzyme and estrogen receptor-alpha genes increases the risk for elevation of arterial stiffness

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Background: Increased arterial stiffness is an independent risk factor for cardiovascular disease. The −401 T/C and insertion/deletion (I/D) polymorphisms of estrogen receptor-alpha and angiotensin-converting enzyme (ACE) genes are associated with arterial stiffness. We examined the effect of this combination of single-nucleotide polymorphisms on the risk for increased arterial stiffness. Methods: Our cross-sectional study comprised 403 middle-aged and older human participants. We determined the genotypes of −401 T/C and I/D single-nucleotide polymorphisms in estrogen receptor-alpha and ACE by TaqMan PCR method. We also measured arterial stiffness by brachial-ankle pulse-wave velocity (baPWV). Subjects were divided into high arterial stiffness and low arterial stiffness groups, with the dividing line set at the median value of baPWV. Results: The odds ratio for the presence of high arterial stiffness in individuals having the TT genotype of estrogen receptor-alpha compared with those having the other genotypes (TC and CC) was 2.46. With regard to the I/D polymorphism in ACE, the odds ratio for the presence of high arterial stiffness in individuals having the II genotype of ACE when compared with those having the other genotypes (ID and DD) was 1.99. Interestingly, the odds ratio was 5.31 for individuals having a combination of the TT genotype of estrogen receptor-alpha and II genotype of ACE when compared with those having a combination of TC and CC genotypes of estrogen receptor-alpha and ID and DD genotypes of ACE. Conclusion: We revealed that a combination of the TT and II polymorphisms in estrogen receptor-alpha and ACE remarkably increased the risk for elevation of arterial stiffness in middle-aged and older humans.

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The impact of RV/LV volume ratio on biventricular function

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Background: Right ventricular (RV) dilation and dysfunction after corrected tetralogy of Fallot (c-ToF) is associated with their prognosis. In contrast, left ventricular (LV) function has been focused as a novel determinant of prognosis in patients with c-ToF. We aimed to assess RV and LV volume in consideration of interaction with biventricular EF. Methods: We studied 45 patients with repaired ToF (23 males, 20.8 yrs, range 7–49 yrs). We examined 2-dimensional and 3-dimensinoal transthoracic echocardiography. To determine the severity of pulmonary stenosis (PS), we recorded the maximum flow velocity through the pulmonary valve obtained from continuous wave Doppler measurement by 2-dimensional echocardiography. The pressure gradients were calculated from this velocity using a simplified Bernoulli's equation. RV and LV end diastolic volume index (EDVI, ml/m^2), end systolic volume index (ml/m^2), stroke volume index (ml/m^2) and ejection fractions (EF) were measured with 3-dimensional transthoracic echocardiographic system (RV; Tomtec imaging systems, LV; 4D auto LVQ. GE Vivid E9, Japan). Results: RVEDVi and LVEDVi measured were 80.2 ± 22.6 ml/m^2 and 53.0 ± 10.1 ml/m^2, respectively. RV/LV EDVI ratio (1.57 ± 0.59) was negatively correlated with RVEF ($r = -0.350$, $p = 0.021$). In the multivariate stepwise analysis, LVEF was associated with RV/LV EDVI ratio and RVEF ($R = 0.518$). On the other hand, the degree of PS didn't correlate with biventricular volume and function. Conclusions: LVEF may be affected rather by RV/LV volume ratio and RVEF in the patients with c-ToF.

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Immediate improvement of pulmonary hypertension with out-of-proportion physiology after percutaneous coronary intervention for ischemic heart disease

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Introduction: Pulmonary hypertension (PH) due to left heart disease is common, and associated with increased left atrial pressure. In some patients with PH caused by left heart failure, there is entity called 'PH with out of proportion' (further increase of the pulmonary artery pressure evoked by elevated precapillary pulmonary vasoconstriction and vascular remodelling). The treatment of this clinical condition is often difficult. We report a markedly improved case of PH with left ventricular dysfunction caused by coronary artery disease (CAD) which was treated by percutaneous coronary intervention (PCI). Case presentation: A 68-year-old man was admitted to our hospital for the purpose of detailed examination about CAD. Outpatient examinations including echocardiogram, treadmill exercise test and coronary computed-tomography angiography suggested that he had systolic and diastolic left heart failure because of CAD. Severe pulmonary arterial hypertension without significant valvular disease was also observed by echocardiography and his systolic right ventricular pressure was estimated to be 80 mm Hg. Coronary angiography showed significant stenosis of right coronary artery (diffuse in mid to distal portion) and left anterior descending artery (proximal portion). Right heart catheterization was performed before percutaneous coronary intervention and revealed severe PH with out-of-proportion physiology. He underwent elective percutaneous coronary intervention for these two vessels. After these interventions, pulmonary wedge pressure, pulmonary artery pressure, and pulmonary vascular resistance were apparently improved, even though in and out valance was almost equal during procedure. Conclusion: Ischemic left ventricular diastolic dysfunction showed an important impact to the severe pulmonary resistance elevation. Coronary revascularization would be the first line therapy for PH patients with CAD.

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Diabetes and obesity are significant risks of morning hypertension. From large scale home BP study: Ibaraki Hypertension Assessment Trial (I-HAT)

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Background: Morning hypertension (HT) has been identified as a major cardiovascular risk, however, the population susceptible to morning hypertension is unknown. This study aimed to clarify the relationship between morning hypertension and diabetes or obesity in a large scale population. Methods and results: A total of 2554 outpatients with hypertension at 101 clinics or hospitals were enrolled. Their clinic blood pressures (BPs) and 2-week awakening BPs were recorded. The mean office BP >140/90 mm Hg or awakening BP >135/85 mm Hg was considered as HT. Subjects were classified into four groups on the basis of office BP and home BP, normal BP, white coat HT, masked HT and sustained HT. The morning BP (mm Hg) elevated significantly and progressively in the order of normal glucose tolerance (134.1 ± 12.2), impaired glucose tolerance (135.4 ± 13.1), and diabetic patients (137.5 ± 11.5) ($P < 0.0001$). Incidence of morning HT also increased significantly and progressively in the same order (53.4%, 55.6%, 66.4%, $P < 0.0001$). Moreover, the morning BP of obese diabetic patients was significantly higher than that of non-obese and non-diabetic patients (138.8 ± 10.5, 133.1 ± 11.9, $P < 0.0001$). In addition, the incidence of morning HT in obese diabetic patients was significantly higher than the others (73.0%, 49.9%, $P < 0.0001$). Conclusion: Morning hypertension is frequent in diabetic or obese patients.

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