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

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Abstract: 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 (CoCl2; 100 μM) and gene expressions of preproendothelin-1 (ppET1), endothelin converting enzyme-1 (ECE1) and noggin were then evaluated by QRT-PCR. CoCl2 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 CoCl2 for 5 h. Gene expression of noggin significantly increased after CoCl2 treatment and this reaction was not changed by pretreatment with bosentan. Conclusions: Noggin, an intrinsic bone morphogenetic protein antagonist, was upregulated by CoCl2, independent of hypoxia-induced endothelin-1 pathway at earlier timing (5 h).


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

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


The impact of RV/LV volume ratio on biventricular function

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Abstract: 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-dimensional trans-thoracic 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/m2), end systolic volume index (ml/m2), stroke volume index (ml/m2) and ejection fractions (EF) were measured with 3-dimensional trans-thoracic 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/m2 and 53.0 ± 10.1 ml/m2, 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 volume ratio and RVEF (R = 0.518). On the other hand, the degree of PS didn’t correlate with biventricular volume and function. Conclusions: LV EF may be affected rather by RV/LV volume ratio and RVEF in the patients with c-ToF.


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

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