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Changes of gene expressions in pulmonary arterial hypertension rat models after ambrisentan treatment.

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Introduction: Pulmonary arterial hypertension (PAH) causes right ventricular failure due to a gradual increase in pulmonary vascular resistance. Ambrisentan is an oral, once-daily, endothelin (ET) A - selective endothelin receptor antagonist (ERA) for the treatment of PAH. The purpose of this study was to investigate the effect of ambrisentan on right ventricular (RV) pressure, lung pathology and gene expressions.

Methods: The rats were grouped as follows: the control (C) group; the M group, monocrotaline (MCT) 60 mg/kg, sc); the A group (MCT + ambrisentan 3 mg/kg/day by gavage feeding). Hemodynamic study was performed by catheterization into the external jugular vein and pathological changes were investigated by Victoria blue staining in the lung tissues. Changes of protein expression levels of ET-1, ERA, endothelial nitric oxide (eNOS) and NADPH oxidase (NOX) 4 were confirmed by western blot analysis.

Results: The mean RV pressure was significantly reduced in the A group at weeks 2 (M vs. A, 27.00 ± 1.47 mmHg vs. 16.60 ± 0.40 mmHg) and 4 (M vs. A, 32.40 ± 0.76 mmHg vs. 14.67 ± 0.80 mmHg). LV +septum/RV ratio was significantly reduced in the A group at week 4. Reduced medial wall thickness in the pulmonary arteriole was noted in the A group at week 4. Reduction in number of intra-acinar muscular pulmonary arteries was observed in the A group at week 4. Protein expression level of ET-1 significantly decreased in the A group at week 2. Protein expression level of ERA significantly decreased in the A group at weeks 2 and 4. Protein expression level of NOX4 significantly increased in the M group compared with the C group, but there was no difference between the M group and the A group. Protein expression level of eNOS significantly increased in the A group at weeks 2 and 4.

Conclusion: There was significant improvement of mean RV pressure, RV hypertrophy and pulmonary pathology after ambrisentan treatment. Significant reduction in ET-1 and ERA protein expressions and an increase of eNOS protein expressions were also detected.