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Effects of combined angiotensin II receptor antagonism and neprilysin inhibition in experimental pulmonary hypertension and right ventricular failure

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Background: Combined angiotensin II receptor antagonism and neprilysin inhibition by LCZ696 reduces morbidity and mortality in heart failure patients and works by reducing RAAS activity and increasing cGMP levels. This study aims to evaluate the effects of LCZ696 in rats with pulmonary hypertension and right ventricular (RV) failure.

Methods and results: Pulmonary hypertension was induced in rats ($n = 34$) by combined exposure to the vascular endothelial growth factor-receptor antagonist SU5416 and hypoxia (SuHx). To distinguish pulmonary vascular from cardiac effects, isolated RV failure was induced by pulmonary trunk banding (PTB) in another group of rats ($n = 40$). In both models, the development of RV dysfunction was verified before randomization to treatment with LCZ696 (60 mg/kg/day) or vehicle for five weeks. Hemodynamic effects were evaluated by echocardiography, MRI scans, and invasive pressure-volume measurements, while pulmonary vascular and RV remodeling was evaluated by stereology.

In the SuHx rats, LCZ696 treatment reduced the increase in RV pressure and the development of RV hypertrophy and RV dilatation compared with vehicle treatment. LCZ696 also reduced remodeling of the smaller pulmonary arteries. In the PTB rats, LCZ696 treatment did not have any effects on RV hypertrophy or function.

Conclusions: Combined angiotensin II receptor antagonism and neprilysin inhibition reduced RV systolic pressure, hypertrophy and dilatation in rats with pulmonary hypertension. These effects seem secondary to pulmonary vascular changes, including reduced pulmonary vascular remodeling, as similar effects were not seen in rats with isolated RV failure.