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Telmisartan improves RV function and hypertrophy by modulating processes of fibrosis and autophagy in PA banded rat

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Introduction: RV failure is a significant complication in patients with congenital heart disease with right-sided obstructive lesions, and PH. Effective medical treatment for decompensated RV remains to be elucidated. While ARBs are known to reduce mortality in patients with left side heart failure by inhibiting cardiac remodeling, their effects for RV failure are unknown. Pressure overload stress induces a robust autophagic response and hypertrophic changes in cardiomyocytes. However, previous studies showed conflicting results with regards to whether induction of autophagy was adaptive or maladaptive in overloaded ventricle.
Method: RV failure model rats were surgically generated by pulmonary artery banding using SD rats. Those rats were treated with oral telmisartan (T group: 5mg/kg/day n=24) or water as control (n=12) for 4 weeks. RV-PV loops were examined using a micro catheter. For histological analysis of cardiac muscles remodeling, Masson's trichrome staining and electron microscopy were performed to obtain the view of morphological changes of cardiomyocytes. The level of LC3A/B, and p62 were measured by Western blotting.
Results: Median survival time for the T group was significantly longer than the control rats. There were significant increases in RV cardiac output ($P < 0.01$), RV EDP, end-systolic elastance, and end-diastolic elastance ($p < 0.05$) derived from RV PV loop in the T group. RV/LV+S was decreased significantly in the T group ($P < 0.01$). Quantitative analysis for autophagy showed significant reduction of the number of autophagosome in the T group. Both LC3A/B and p62 expressions were reduced in the T group compared with control. The rate of fibrosis in RV was significantly lower in the T group ($p < 0.01$) as well as mRNA expression of Pro-collagen 3, CTGF, and periostin.
Conclusions: In PA banded rats, telmisartan had effects to improve RV cardiac output and to decrease mortality without reduction of RV pressure by inhibiting cardiac fibrosis, autophagy and RV hypertrophy. Decreased expressions of LC3A/B and p62 indicated that the reduction of autophagy was induced by mitochondria dysfunction. These results suggest that telmisartan prohibit overload-dependent RV failure and fibrosis by blocking mitochondrial dysfunction and telmisartan may be an effective treatment option for RV failure.