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Losartan diminishes the expression of TGF-beta and improves cardiomyopathy in mice with Marfan syndrome

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Introduction: Marfan syndrome (MFS) is caused by mutations in the fibrillin-1 gene, leading to abnormal signaling of the transforming growth factor beta (TGF-ß). This results in aortic root dilation, dissection and rupture, which are the main causes of morbidity and mortality of MFS patients. Current treatment with losartan, an angiotensin-II receptor-1 blocker, has shown beneficial effect on aortic disease in MFS murine models. However, the mechanisms whereby the treatment with losartan improves cardiac remodeling and function of the left ventricle (LV) in MFS are still unknown.

Purpose: To investigate the effects of losartan on mechanisms of the cardiomyopathy in mice with MFS.

Methods: mg?loxPneo MFS murine model from C129/sv background was utilized in this study. To evaluate the e?ect of the treatment with losartan on the LV of MFS and wild-type mice, animals were allocated in 2 groups of treatments: Losartan group: mice were kept with water supplemented with losartan (0.6g/L); Untreated control group: mice were kept with water only. The animals received treatment from 1 month of age until completing 6 months. After five months of treatment, LV echocardiography was performed, and fragments of LV tissue were analyzed by morphometry and protein expression analysis by Western blot.

Results: Losartan MFS mice showed decrease in interventricular septum and posterior wall thickness and LV mass. Furthermore, losartan prevented aortic and mitral regurgitation, arrhythmia, bradycardia, septal hypokinesia and pulmonary hypertension when compared with control MFS mice. Systolic and diastolic LV function were not di?erent between groups. Collagen volume fraction and the disorganization and disruptions of the elastic ?bers in coronary arteries were lower in losartan treatment than in controls. The protein expression of pro-apoptotic factors (BAX/Bcl-2 and caspase 3 and 9), proliferating cell nuclear antigen and hypoxia-inducible factor 1 and 2a were lower in losartan treatment, whereas the expression of vascular endothelial growth factor was increased in losartan group when compared with control MFS mice. Moreover, the treatment with losartan strongly reduced the TGF-ß, ERK and p38MAPK protein expression compared to controls.

Conclusion: In this murine model of MFS, losartan treatment has the ability to change several pathophysiological mechanisms related with the fibrillin-1 mutation, by decreasing apoptosis, cell proliferation and increasing angiogenesis. Overall, the treatment resulted in improved structural rearrangement and attenuation of the rupture of elastic fibers in the coronary arteries, of the cardiac hypertrophy and myocardial fibrosis. These effects were possibly related with the decreased TGF-ß expression by ERK and p38MAPK signaling pathways by losartan. Our findings shed a new light on the mechanisms of action of losartan on MFS cardiomyopathy.