Valsartan protects non-infarcted left ventricle tissue and prevents left atrium enlargement in a mouse model of myocardial infarction.

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ABSTRACT

Purpose: Post-infarction cardiac remodeling affects the entire left ventricle (LV), with progressive architecture alterations in both infarcted and non-infarcted regions, and the left atrium (LA), which increases its size to maintain adequate LV filling, reflecting the severity of diastolic dysfunction. Pharmacological modulation of heart remodeling is aimed at preventing progressive functional deterioration leading to heart failure. Clinical trials demonstrated that long-term administration of renin-angiotensin-aldosterone-system (RAAS) blockers, decreasing LV preload and afterload, has beneficial effects in post-myocardial infarction (MI) LV remodeling reducing cardiovascular mortality and morbidity. Here we evaluated the effect of valsartan, a RAAS blocker, on LV and LA remodeling after MI.

Methods: MI was induced by LAD ligation in thirty C57BL/6N female mice. They were divided into two experimental groups: infarcted untreated mice (MI-vehicle, n=15), and infarcted treated daily with Valsartan 1 mg/Kg/die in drinking water (MI-Valsa, n=15). All mice underwent cardiac magnetic resonance (CMR) and echocardiography in order to obtain LA, LV global and regional parameters at different time points: baseline, and 1, 7 and 28 days after surgery. After the last echocardiogram, mice were sacrificed and the hearts treated for histological and whole-genome gene expression analysis.

Results: Analyses were made 28 days after MI. Valsartan showed a protective effect on LV mass (128±50mg *vs.* 178±53mg, $p<0.01$) and infarct size (39±4% *vs.* 50±10%, $p<0.05$). LV regional function (RFAC%), performed with CMR and visualized in bull's eye format, showed better contractility associated to reduced thickness of posterior non-infarcted wall in MI-Valsa compared to MI-vehicle group. Microarray analysis, performed on LV non-infarcted myocardium, reinforced these findings showing a favorable modulation of genes involved in extracellular matrix deposition, cell proliferation and apoptosis. Echocardiographic analysis revealed that LA maximum (4.67±0.89µl *vs.* 10.71±4.16µl, $p<0.05$) and minimum volumes (1.98±0.47µl *vs.* 6.65±3.4µl, $p<0.05$), left appendage (LAA) length (3.9±0.59mm *vs.* 4.7±0.54mm, $p<0.05$) and LAA contractility (41.8±5% *vs.* 22.3±7%, $p<0.01$) were also preserved by the pharmacological treatment.

Conclusion: Valsartan protective actions affect the function of the whole heart. It has an anti-fibrotic effect on scar tissue and preserves LV regional contractility, possibly modulating gene expression on non-infarcted tissue. In addition, LA and LAA dimensions are preserved.