P390 - The impact of Serelaxin on regional myocardial deformation and gene regulation in mice with heart failure

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Background: Recent clinical trials demonstrate that serelaxin, the recombinant form of human gene-2 relaxin, improves long-term survival in acute heart failure patients. However, data directly comparing non-invasive imaging techniques with molecular biology investigating serelaxin’s cardiovascular action is sparse. The aim of this study was to investigate the dynamics of serelaxin in experimental heart failure, using a combinational and comparative approach of serial non-invasive MRI in vivo and molecular biology.

Methods and results: Male C57BL/6J mice were subjected to transverse aortic constriction (TAC) or SHAM surgery and divided into three groups: 1) SHAM-operated/vehicle (veh)-treated, 2) TAC-operated/veh-treated, 3) TAC-operated/serelaxin (0.5 mg/kg BW per day. Novartis, Basel). Echocardiography and serial MRI was done. Gene profiling, cardiac histology, as well as analysis of serum markers were compared to imaging findings. Echocardiography demonstrated that TAC-operated mice suffered from advanced stages of pressure overload-induced cardiac hypertrophy with preserved systolic function (evident by significant increases in pressure gradient and diastolic wall thickness, but unchanged ejection fraction (EF)). Treatment with serelaxin was started at week 10 after TAC surgery and was continued for 4 weeks. MRI revealed a significantly reduced EF after 10 weeks post-TAC, compared to mice undergoing SHAM. EF and stroke volume of TAC-operated mice receiving veh deteriorated significantly, while serelaxin-treatment prevented progression to overt heart failure in TAC-mice (p<0.05). This was accompanied by a significant decrease in perivascular fibrosis and cardiomyocyte hypertrophy in TAC serelaxin mice, compared to Veh treated mice. Furthermore, TAC-surgery increased cardiac BNP and bMHCH mRNA levels, which were significantly decreased by serelaxin. In addition, a gene array based screening approach demonstrated that serelaxin treatment impacted on genes of cardiac remodeling/fibrosis, as well as on the TGF beta/SMAD signaling cascade.

Conclusion: This study demonstrates that serelaxin prevents heart failure progression in TAC-operated mice. Serial in vivo MRI analysis shows that serelaxin impacts on regional myocardial function, accompanied by decreases in cardiac hypertrophy/fibrosis and gene regulation.

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