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Ventricular dysfunction and fibrosis precedes atrial fibrillation in JDP2 overexpression mice

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Introduction: JDP2 (Jun Dimerization Protein 2) was recently characterized as potential prognostic marker for progression of heart failure after myocardial infarction. Furthermore, persistent cardiac-specific JDP2 overexpression provokes ventricular dysfunction, atrial dilatation and atrial fibrillation.

Purpose: In this study we investigated, if ventricular dysfunction is predisposed to atrial fibrillation. Therefore, we analyzed ventricular function in mice with 1 and 5 weeks of JDP2 overexpression and compared gene expression in ventricular and atrial tissues at these time points.

Methods: JDP2 expression was under control of a Tet-off system. Therefore, JDP2 overexpression was started by withdrawal of doxycycline diet in 4-week-old mice. After 1 or 5 weeks, cardiac function was determined by echocardiography. mRNA expression was analyzed by real-time RT-PCR and protein expression in western blots.

Results: After 1 or 5 weeks, JDP2 mRNA levels were increased in ventricular and atrial tissues of JDP2 mice. Already after 1 week ventricular dysfunction emerged in JDP2 mice: Ejection fraction decreased from 64.6 ± 10.4 % in WT to 58.8 ± 9.3 % in JDP2 mice, fractional shortening from 38.3 ± 7.9 % in WT to 27.4 ± 4.8 % in JDP -mice, and cardiac output from 23.0 ± 4.7 ml/min in WT to 19.4 ± 3.3 ml/min in JDP2 mice (n=11-16, p<0.05). Furthermore, contractile function of isolated ventricular cardiomyocytes of one week JDP2 overexpressing mice was reduced, as determined by relative cell shortening, (dL/L: 11.3 ± 3.4 % in JDP2 vs. 12.2 ± 3.4 % in WT cells, n=100 cells, p=0.05), and contraction velocity (292 ± 107 µm/s in JDP2- vs. 332 ± 130 µm/s in WT-cells, n=100, p=0.05). In ventricular tissues, elastin mRNA expression increased, and the calcium handling protein SERCA decreased within one week of JDP2 overexpression (n=6, p<0.05 vs. WT). After 5 weeks of JDP2 overexpression ventricular dysfunction became even stronger with a cardiac output of 13.6 ± 2.5 ml/min (n=11, p<0.05 vs. WT). Still reduction in SERCA protein was observed, and increased mRNA levels of fibrotic marker genes were detected, as well as contractile function of isolated cardiomyocytes of JDP2 mice continued to decline. In atrial tissue, besides the 3.6 times increase of JDP2 mRNA, no changes could be detected within one week. Atrial dilatation became evident only after 5 weeks of JDP2 overexpression. At this time, mRNA of the calcium-handling proteins PLB, NCX and SERCA, and of the fibrotic marker genes collagen I, fibronectin and elastin were dramatically reduced in atrial tissue of JDP2 compared to WT mice (n=6, p<0.05), and may be functionally involved in atrial fibrillation.

Conclusion: Enhanced expression of JDP2 provokes ventricular dysfunction and fibrosis within one week, whereas changes in the atrial tissue occur later and seem to be a secondary effect that is provoked by the pre-existing ventricular dysfunction.
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