IN VIVO MAGNETIC RESONANCE MICROSCOPIC IMAGING REVEALS NEONATAL CARDIOMYOPATHY IN A MOUSE MODEL WITH HEY2 GENE-KNOCKOUT

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INTRODUCTION:

The Hey 2 gene is most strongly expressed during the development of cardiac ventricles and great arteries. It was hypothesized that Hey2 may be an important part of the "somitogenesis clock". Mice with homozygous deletion of the Hey2 gene (Hey2 -/-) reveal a severe growth retardation in the neonatal period and frequently die within the first 10 days after birth.

Aim of this study was to use the potential of non-invasive MR microscopic imaging for very early cardiac phenotype characterization in neonatal mice with Hey2 gene knockout.

METHODS:

We studied Hey2 -/- mice (n=9) at a mean age of 9 ± 1days and a mean body weight of 6.2 ± 1.0 g by in vivo MR microscopic imaging in comparison with age and weight matched heterozygous littermates (control, n=9). Experiments were performed on a 300 MHz Bruker system equipped with a microscopy gradient system allowing for max. field strength of 870 mT/m. Mice were anesthetized with inhalative Isoflurane (1.5 Vol% with 1L oxygen flow) via a nose cone and kept normothermic. For signal detection and transmission, a homebuilt 10 rung birdcage coil with inner diameter 16 mm was used. ECG-gated FLASH Cine MRI was performed with following parameters: TE 1.5 ms, TR 4.3 ms, FOV 20 x 20 mm², in-plane resolution 78 x 78 µm², slice thickness 500 µm.

RESULTS:

MRI in newborn Hey2 -/- mice revealed marked dilatation of the LV with an increase in both end-diastolic volume (18.1 ± 5.2 µl vs. control 6.3 ± 2.3 µl) and end-systolic volume (11.3 ± 4.0 µl vs. control 2.5 ± 0.8 µl, $p < 0.05$ each). Ejection fraction was significantly reduced in Hey2 -/- (39.6 ± 5.2 % vs. control 59.6 ± 4.0 %, $p < 0.01$), indicating left ventricular dysfunction. Comparison of heart rate, stroke volume and cardiac output showed no significant differences between Hey2 -/- and control. There was a trend towards an increased LV mass in Hey2 -/- (52.9 ± 7.4 mg vs. control 33.5 ± 13.4 mg) but without reaching statistical significance.

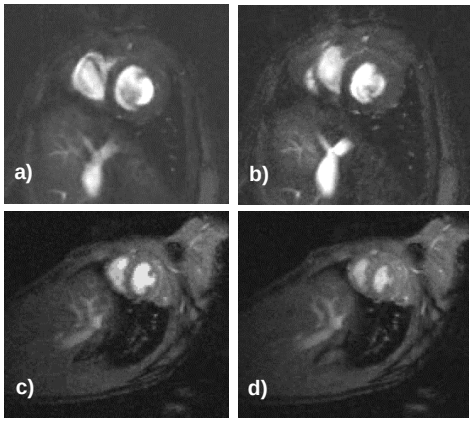

Figure 1: End-diastolic (a) and end-systolic (b) cine magnetic resonance image, acquired in a neonatal Hey2-/- mouse at day 9 after birth. c) and d) show corresponding MR cine frames in a neonatal heterozygous littermate. All images are acquired in a mid-ventricular short axis orientation and are cropped for display purposes. Note the increased LV cavity volume both at diastole (a) and systole (b) in the Hey2-/- mouse, indicating LV dilatation and contractile dysfunction compared to the control mouse (c,d).

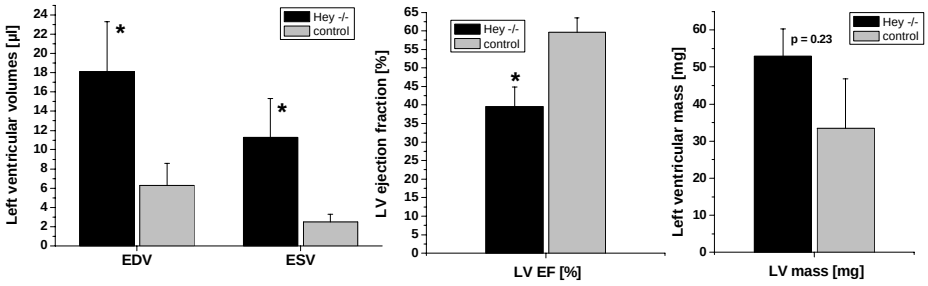

Figure 2: MRI-derived measurements of structural and functional changes in newborn mice (mean age 9 days) with depletion of the Hey2 gene (Hey2 -/-) in comparison to controls. (A) showing increase of left ventricular volumes indicating massive LV dilatation with consecutive decrease in LV EF (B). (C) reveals trend towards higher LV mass in Hey2 -/- indicating commencing left ventricular hypertrophy.

CONCLUSION:

This study demonstrates the feasibility of *in vivo* MR microscopic imaging to non-invasively detect morphologic changes and ventricular dysfunction in a mouse model of neonatal cardiomyopathy. Hence, in murine models with early phenotype or even premature death, MR microimaging allows insights into both the underlying deleterious structural and particularly functional consequences of the genetic defect.