MR imaging of Hypertrophy and Cardiac Recovery in the Mouse Aorta and Heart

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Introduction: Cardiac loading, induced e.g. by aortic valve stenosis or dilated cardiomyopathy, can initiate hypertrophy and cellular remodeling. However, the factors identifying patients who benefit from a load removal provided e.g. by a valve implant or ventricular assist device are still not fully understood [1]. Therefore, the causes and the mechanisms of remodeling after cardiac unloading are of high interest for therapeutic intervention adapted to the individual patient. In this context, mouse models of experimentally increased cardiac loading and mechanical unloading [2] can provide an important tool to investigate cardiac remodeling and recovery. To monitor global and regional cardiovascular function during these, ultra-high field small animal MRI has proven to be a useful tool for the detailed evaluation of a wide spectrum of functional parameters [3]. Therefore, the aim of this work was to detect and monitor changes in aortic diameter and regional cardiac function during remodeling and recovery after experimental myocardial loading by aortic stenosis using MRI in comparison with ultrasound.

Methods: A thoracotomy was performed in three male C57BL/6 mice. A 7-0 prolene thread was applied around the aortic arch between the brachiocephalic trunk and the left carotid artery to introduce a stenosis approximately 300-400µm in internal diameter. Three weeks after the application of the stenosis, the thread was removed by a second thoracotomy**.** As shown in Fig. 1, MRI was performed to monitor progression of disease (development of left ventricular (LV) hypertrophy due to the stenosis, 3 weeks post stenosis placement) and cardiac recovery (weeks 1 and 7 after stenosis removal). Two additional healthy control mice were also included in the study. All mice were anaesthetized for the MRI scans with isoflurane in 100% O_2 and buprenorphine analgesia, then intubated and ventilated at 250µl stroke volume and 150 strokes/min.

MRI measurements were performed on a 9.4T system (Bruker, BioSpin, Germany) using a quadrature coil. Three short axis views (base, mid, apex) were acquired with prospectively ECG-triggered and respiratory-gated CINE FLASH sequence with a temporal resolution of 10ms and a spatial resolution of 130x150µm^2 (matrix 192x192, 0.7mm slice thickness, 15° flip angle, 6 averages). Furthermore, ECG-triggered FLASH images were acquired to depict the complete aortic arch as well as a set of images perpendicular to the aortic arch at the site of the stenosis (see Fig. 2) with a spatial resolution of 110x120µm^2 mm (matrix 256 x 256, 0.4 mm slice thickness, 30° flip angle, 4 averages). MRI data analysis included the myocardial contour segmentation followed by the calculation of an approximated ejection fraction (EF) using the three acquired short axis views. Further, the global and regional wall thickening according to the AHA 16-segment model was determined. Moreover, ultrasound measurements were performed within the same timeline using a Vivid 7 Dimension echocardiograph and a 14 MHz transducer (GE Healthcare, München, Germany)**.** LV systolic and diastolic anterior and posterior myocardial wall thickness was determined as well as the EF by applying the Teichholz formula and values were compared to the MRI results.

Results: Exemplary images of the stenotic aorta as well as a diastolic frame are shown in Fig. 2. Similar image quality was achieved for all measurements. In all animals, the aortic stenosis could be clearly identified and an obvious reopening of the aortic lumen after stenosis removal was confirmed by aortic arch MRI. Global wall thickening (averaged over all 16 segments) in Fig. 3 reveals a fast recovery of cardiac function already 1 week after cardiac unloading which remains constant 7 weeks after unloading, comparable to the control subjects. A similar behavior can be observed for the segmental analysis in Fig. 4 as well as for the EF in table 1. Slightly lower values for the EF are obtained by the MRI analysis compared to Ultrasound which might be due to the approximated calculation based on the echo data. A good agreement between MRI and echo is obtained for systolic and diastolic regional wall thickness in basal anterior and posterior segments.

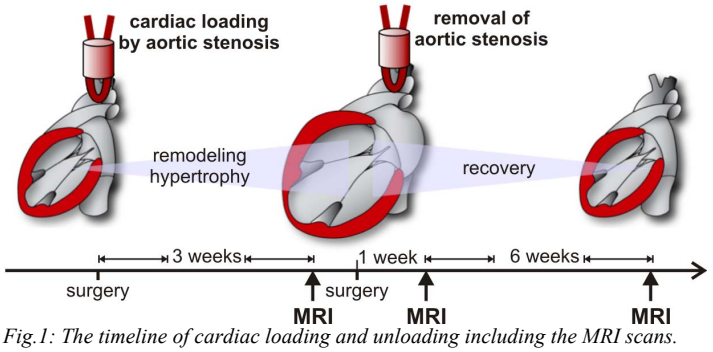

Fig.1: The timeline of cardiac loading and unloading including the MRI scans.

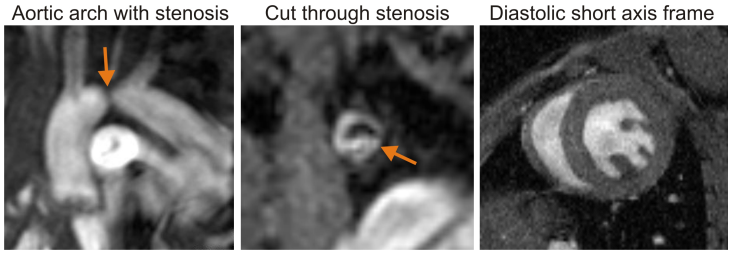

Fig.2: MR images showing the aortic arch after the creation of the stenosis (left, arrow). A transversal imaging plane through the stenosis showed some signal voids due to the accelerated and complex stenotic blood flow (mid). Right: a short axis frame during diastole shows a mild hypertrophy of the left ventricle.

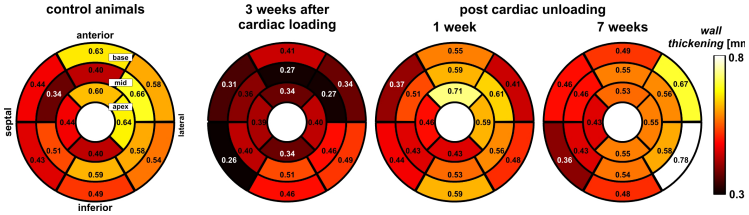

Fig.4: Bulls-eye plots (AHA 16-segment model) of the LV summarizing the regional LV contractility in mice during cardiac loading and post unloading and compared to control animals. Values in each segment represent average regional wall thickening over n=3 mice which underwent surgery and follow up according to fig.1 and n=2 normal control animals. Impaired LV performance (reduced segmental thickening) during cardiac loading compared to the normal mouse heart is clearly evident. Cardiac unloading resulted in improved regional LV function in all segments even 1 week after surgery and further improved wall thickening 7 weeks after removing the stenosis.

Discussion: The results of this study illustrate the potential ultra-high field small animal MRI to assess and monitor vascular geometry and regional cardiac function whereas ultrasound was limited to certain LV regions. The impaired LV performance after cardiac loading and recovery of LV function after unloading could be clearly demonstrated by MRI. Future studies should include a larger number of mice to allow for statistical analysis of parameters describing the cardiac remodeling. In addition, the acquisition of further functional parameters such as aortic flow or myocardial velocities is of high interest.

Acknowledgements: Bundesministerium für Bildung und Forschung (BMBF), Grant # 01EV0706. **References:** [1] Albes JM. *Thorac Cardiovasc Surg* 2010;58:61-8. [2] Gao et al. *Am J Physiol Heart Circ Physiol* 288: H2702–07, 2005. [3] Ruff et al. *Magn Reson Med* 1998;40:43-8.

			Regional wall thickenss [mm]							
time	EF [%]		Anterior, diastole		Anterior, systole		Posterior, diastole		Posterior, systole	
point	MRI	Echo	MRI	Echo	MRI	Echo	MRI	Echo	MRI	Echo
1	40 ± 4	54 ± 4	0.9 ± 0.1	1.0 ± 0.2	1.3 ± 0.1	1.3 ± 0.2	1.0 ± 0.3	1.0 ± 0.3	1.5 ± 0.4	1.0 ± 0.3
2	51 ± 6	63 ± 5	0.8 ± 0.1	0.8 ± 0.2	1.3 ± 0.2	1.2 ± 0.1	1.0 ± 0.2	0.9 ± 0.1	1.6 ± 0.2	1.3 ± 0.1
3	55 ± 1	66 ± 2	0.8 ± 0.2	0.8 ± 0.1	1.3 ± 0.4	1.2 ± 0.2	0.8 ± 0.1	1.0 ± 0.1	1.3 ± 0.1	1.3 ± 0.1
controls	64 ± 2	66 ± 1	0.6 ± 0.1	0.8 ± 0.1	1.3 ± 0.1	1.1 ± 0.1	0.6 ± 0.1	0.8 ± 0.1	1.0 ± 0.1	1.1 ± 0.1

Table 1: Comparison of global and regional LV function parameters from MRI and echocardiography.

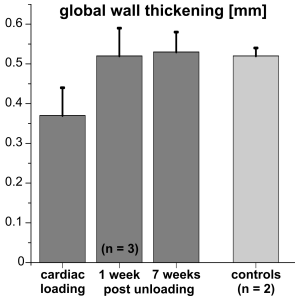

Fig. 3 (right): Global wall thickening (average over all 16 segments of the AHA model) indicating fast recovery of cardiac function already 1 week after cardiac unloading.