Magnetic Resonance Imaging of the progression of systolic and diastolic dysfunction in transgenic Tgaq*44 mice in vivo

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Purpose:

The use of Magnetic Resonance Imaging (MRI) is increasing in cardiac measurements and there is a need to develop MR protocols dedicated to heart function of small animals *in vivo*. The aim of this work is to demonstrate the feasibility in monitoring impairment of cardiac dynamics in Tgαq*44 (TG) mice *in vivo* as compared to aged-matched wild-type mice (FVB) using homebuilt, dedicated hardware components for the 4.7T/310 MRI system and subsequent image analysis of the left ventricle slice volume as well as to analyze the progression of systolic and diastolic cardiac dysfunction in this unique model of heart failure.

Subjects and Methods: We used Tgαq* 44 mice with targeted overexpression of activated Gαq (HAαq*) protein in cardiomyocytes that mimics many of the phenotypic characteristics of dilated cardiomyopathy in humans. Cardiac function was measured in Tgαq* 44 mice at the age of 8, 12 and 14-15 months and aged-matched FVB mice. Experiments were performed on a 4.7 T magnet (Bruker) with MARAN DRX (Resonance Instruments) console and the set of built or adapted components consisted of unshielded gradient coils with ID 60 mm, a probehead with an RF birdcage coil, nonmagnetic cradle for positioning and holding anaesthetised mouse, and animal handling system for the anaesthesia, temperature stabilization and ECG monitoring. Investigated mice were placed into an isoflurane anesthesia box and treated with 3% isoflurane to sedation, typically for about 2 minutes. During the experiment sedation was maintained with 1.5-2 % isoflurane *via* nose cone. Animals were positioned supine on the homebuilt cylindrical holder to maintain constant body position throughout the MR study and centered into the transmitter-receiver birdcage coil.

All animal experimental procedures were in accordance with institutional guidelines, given by the Ethic Commission of the Jagiellonian University Medial College. An ECG triggered fast gradient echo (cine-like FLASH with flow-compensation) sequence was used to acquire images through 120% of the cardiac cycle in the short-axis plane at papillary muscles level. The examination started from a sagittal image to locate the position of the heart in the chest. A coronal image was then obtained to visualize a long-axis of the mouse heart. From this view short-axis was defined and MRI data acquisition was performed in the midventricular section of the left ventricle (LV). Left ventricle (LV) slice volumes were evaluated using areas of automatically delineated images of the endocardium. For this task the Aphelion v.3.2 package was used. The image analysis started from the noise reduction and automatic entropy thresholding. Detection of the endocardium took into consideration position, size and shape as well as grey levels distribution within the detected objects. In order to avoid rough errors, the results were verified by a human observer.

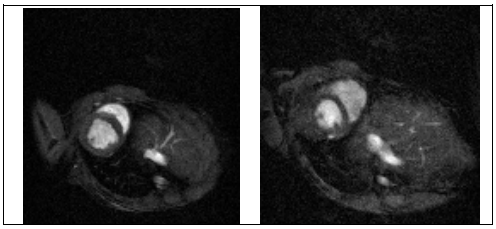

Fig.1 End-diastolic MR images of the LV of the wild-type (left) and TG (right) mouse heart.

Results: The homebuilt hardware components enabled achieving 20-30 frames per cardiac cycle in midventricular short-axis orientation for both FVB and TG mice (corresponding end-diastolic images are shown in Fig.1). An example volume-time curve deriven from corresponding series of images is presented in Fig. 2. Peak ejection rate (ER) given by the maximum slope of the systolic limb of the volume-time curve and peak filling rate (FR) given by the maximum slope of the LV filling curve were calculated for both FVB and TG mice in order to assess dynamics quantitatively. Results are presented in Fig. 3.

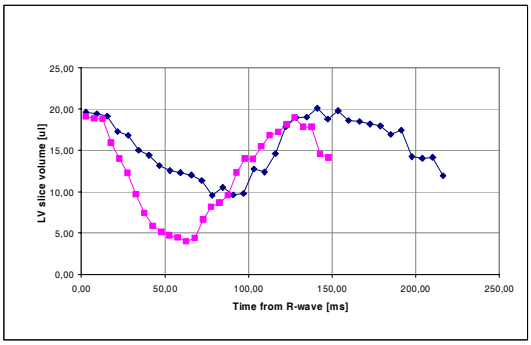

Fig.2 LV slice volume plotted against time of acquisition for TG and FVB mice.

Tgαq*44 mice develop severe end-stage heart failure and died ultimately, because of heart failure at the age of 15-17 months. Using *in vivo* MRI measurements we demonstrated that the impairment of systolic cardiac function was present early during the development of the pathology in Tgaq*44 mice (at 8 months) and remained at approximately the same level till the late phase of the disease. In contrast diastolic cardiac dysfunction was slightly impaired in Tgaq*44 mice at the age of 8 months and progressively deteriorated till the age of 15 months.

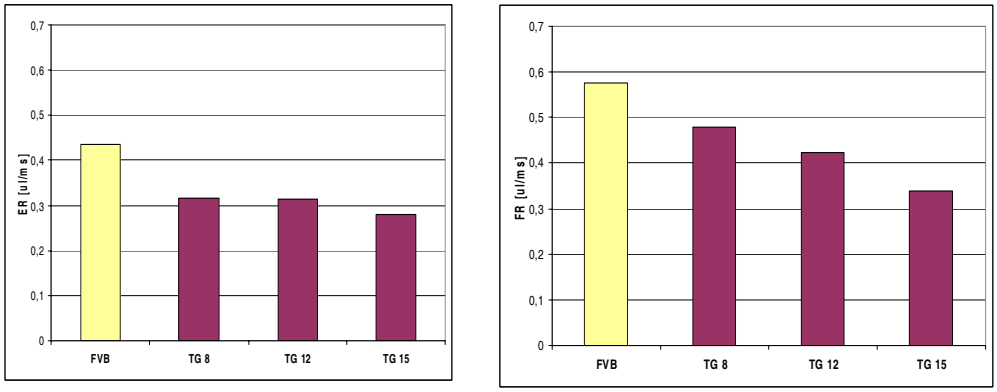

Fig.3. Peak ejection rate (ER) and peak filling (FR) rate for the wild-type FVB (averaged over age) and TG mice (age groups: 8, 12, 15 months).

Conclusion: Application of homebuilt hardware and advanced image analysis allowed for rapid image acquisition and repeatable and fast quantification of cardiac systolic and diastolic dynamics in mice. Using our methodology we were able to demonstrate that the progression of systolic and diastolic cardiac dysfunction in Tgaq*44 mice displays a different pattern. Our results seem to underline the key role of diastolic dysfunction in the development of end-stage heart failure in Tgaq*44 mice.

References: 1. Earls J. P., Ho V. B., et all, Journal of Magnetic Resonance Imaging 16:111-127 (2002) ; 2. Wiessman F., Ruff J., et all, Circ. Res. 2001;88:563-569