Cardiovascular phenotyping of the mouse heart using 4-dimensional radial acquisition and liposomal Gd-DTPA

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Introduction

Magnetic Resonance Imaging (MRI) has become an important tool in evaluating cardiovascular phenotypes in the mouse [1]. MRI has the capability of acquiring longitudinal studies of the mouse in a non-invasive manner. Previous studies use slice-selective techniques for evaluating important cardiac functional parameters, but are limited to a Z resolution of 1mm [2,3]. To address the spatial resolution limitations, we have developed a 3D plus time radial MRI pulse sequence that allows rapid acquisition (16 minutes) of high-resolution cine 87 x 87 x 348 μm^3 volumetric images with 9.6 ms temporal resolution. High-resolution images allow for more sensitive calucation of functional cardiac parameters such as ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV), and stroke volume (SV) by reducing partial volume effects. Rapid data acquistion allows for high-throughput imaging without sacrificing spatial or temporal resolution. The 4D MRI technique has been applied to 3 populations of mice with 4 mice in each group: C57BL/6J mice, DBA/2J mice, and DBA/2J CSQ+ mice. Left ventricular volumes for each population of mice were analyzed to determine how genotype affects functional cardiac phenotype.

Methods

12 mice (4 of each: C57BL/6J, DBA/2J, and DBA/2J CSQ+) of approximately equal weight and age were anesthetized with isoflourane and given a tail vein injection of liposomal Gd [4] at a dose of 0.2 mmol/kg resulting in an average injection of 0.10 mL for a 21-gram mouse. Animals were free-breathing and maintained under anesthesia through the use of an isoflourane nose cone. Temperature, heart rate, and breathing rate were continuously monitored with ECG and ventilatory equipment from SA instruments Inc (Edison, NJ USA). Isoflourane was adjusted to keep physiological parameters as consistent as possible throughout the scan.

A 4D radial MRI pulse sequence was designed and implemented on a 7T magnet using a GE EXCITE console. Echo time (TE) was minimized to 300 µs and repetition time (TR) was minimized to 2.4 ms to increase temporal resolution and reduce scan time; complete technical detail is provided elsewhere [5]. Ten phases of the heart cycle were acquired at a temporal resolution of 9.6 ms at a spatial resolution of 87 x 87 x 348 μm^3 with an acquisition time of 16 minutes for all phases of the heart cycle. Images were imported into ImageJ and the left ventricle was segmented out using a semi-automated procedure to calculate the values for EDV, ESV, SV, and EF.

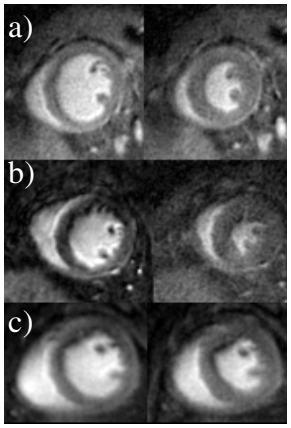

Figure 1: *Diastole (left column) and systole (right column for a representative short axis view of a C57BL/6J mouse (a), a DBA/2J mouse (b) and a DBA/2J CSQ+ mouse (c).*

Results and Discussion

Figure 1 displays the mid-ventricular short-axis slice for one C57BL/6J mouse (a), one DBA/2J mouse (b), and one DBA/2J CSQ+(c) mouse used in this study. The left column shows diastole for each, while the right column shows systole. The 4D datasets generally produced 20 slices through the left ventricle for every phase of the heart cycle. Notice the large size of the DBA/2J CSQ+ heart (c) compared to the DBA/2J heart (b) and the qualitative differences in heart size and ejection fraction between both of the wild types: the C57BL/6J (a) has a large heart size relative to the DBA/2J (b) for the same size mouse. Reported values for EDV, ESV, SV, and EF are shown in the table. ANOVA analysis was performed resulting in a statistical difference between all three populations for EDV, ESV, and EF with a $p<0.0001$. SV was not statistically different for the three populations of mice. Given the non-invasive nature of MR imaging, combined with the fast scan times of 16 minutes, this technique has been shown to be an effective tool for cardiovascular phenotyping of the mouse and has significant promise in its application to high-throughput, longitudinal studies.

Strain	N	Weight (g)	EDV (µL)	ESV (µL)	SV (µL)	EF (%)
C57BL/6J	4	22.0 ± 1.2	54.37 ± 6.33	20.83 ± 2.63	33.56 ± 3.78	61.74 ± 0.77
DBA/2J	4	21.3 ± 0.5	38.06 ± 5.92	11.49 ± 2.27	26.57 ± 4.30	69.80 ± 3.26
DBA/2J CSQ+	4	22.0 ± 3.6	70.56 ± 6.90	39.39 ± 5.77	31.17 ± 3.58	44.27 ± 4.59

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