First-pass MRI detects reduced myocardial perfusion reserve in ApoE$^{-/-}$ mice on a high-cholesterol diet

Nivedita K. Naresh[1], Xiao Chen[1], Patrick F. Antkowiak[1], Rene J. Roy[2], and Frederick H. Epstein[1,3]

[1]*Biomedical Engineering, University of Virginia, Charlottesville, VA, United States,* [2]*School of Medicine, University of Virginia, Charlottesville, VA, United States,* [3]*Radiology, University of Virginia, Charlottesville, VA, United States*

Introduction: Atherosclerosis and the associated cardiovascular diseases remain the largest cause of morbidity and mortality in the western world[1]. Transgenic and knockout mice, specifically ApoE$^{-/-}$ mice, are widely used to study atherosclerosis[2]. An emerging concept in cardiology is that coronary vascular dysfunction precedes obstructive atherosclerosis of epicardial coronary arteries and is prognostic of adverse events. Reduced coronary flow reserve is known to be an independent predictor of cardiac mortality in patients with known or suspected coronary artery disease[3]. First pass Gd-enhanced MRI is a well-established non-invasive technique to measure perfusion in humans and has been recently investigated in mice[4-6]. The rapid heart rate and small size of the heart present challenges to performing quantitative first pass imaging in mice. A dual contrast acquisition simplifies the procedure (one Gd injection) and may provide more accurate results than previous methods because the arterial input function (AIF) and tissue function (TF) are acquired under identical conditions. We developed a compressed sensing (CS)-accelerated first pass sequence for mice with a dual contrast acquisition. Using ApoE$^{-/-}$ mice on high cholestoral diet, we sought to establish a mouse model with coronary vascular dysfunction, documented by reduced myocardial perfusion reserve.

Methods: MRI was performed on a 7T system (Bruker, Germany). Wild type C57Bl6 mice (n=5) and ApoE$^{-/-}$ mice (fed on high cholesterol diet for 12 weeks) (n=6) were imaged at rest and with vasodilator Regadenoson (0.1 µg/g body weight). Mice were anesthetized with 1.25 % isoflurane and maintained at 36±0.5 ^{0}C during MRI. During imaging, physiological monitoring and gating of the ECG and respiration were performed using an MRI-compatible system (SAII, Stony Brook, NY). The MR protocol included multi-slice cine imaging to assess ejection fraction (EF), LV end-diastolic (EDV) and end-systolic volumes (ESV), cine DENSE imaging[7] to quantify myocardial strain, and dual contrast first-pass imaging both at rest and with vasodilation to quantify perfusion reserve. A dual contrast saturation-recovery sequence with k_y and time domain undersampling was used to acquire first-pass Gd-enhanced images. Two mid-ventricular slices were acquired within a cardiac cycle, one to obtain the AIF and the other to obtain the TF. For both slices, the center (50%) of k-space was acquired at the Nyquist rate while higher spatial frequencies were randomly undersampled. The acceleration factors for the AIF and TF slices were 6 and 4, respectively. Other imaging parameters were: TE/TR=1.2/2.1ms, FOV=25.6x18mm^2, resolution=200µm^2, matrix=128x74 alpha=15^0, slice thickness=1mm, saturation delay=15/57ms for AIF/TF. A motion-compensated CS algorithm was used to reconstruct the undersampled images[8]. Fermi function deconvolution quantified perfusion[9] in the entire myocardium.

Results: Figure 1 shows example first-pass images obtained from a mouse at rest. Figure 2 summarizes the perfusion results. Perfusion reserve was 1.8±0.4 in wild type mice and 1.1±0.3 in ApoE$^{-/-}$ mice ($p<0.05$ vs. wild type mice). No difference was obtained in the myocardial strain measurements and LV volumes between the wild type and ApoE$^{-/-}$ mice. EDV and ESV indexed by body weight were found to be 1.3±0.2 and 0.4±0.1 in wild type mice and 1.0±0.3 and 0.3±0.1 in ApoE$^{-/-}$ mice respectively. EF was found to be 69.6±8.4 % in wild type mice and 72.1±3.3 % in ApoE$^{-/-}$ mice.

Discussion: Accelerated first-pass MRI using undersampling and CS enables the implementation of a dual-contrast method, which can quantify perfusion and perfusion reserve in the mouse heart. These methods detected reduced perfusion reserve in gene-modified mice. In the future, these methods will enable the investigation of molecular mechanisms that underlie the link between high cholesterol and abnormal coronary vascular function.

Acknowledgements: This work was funded in part by AHA Predoctoral Award 11PRE7440117, NIH R01 EB001763, US-Israel Binational Science Foundation grant 2007290, and AstraZeneca

References: 1) AHA Statistical Update, Circulation 2012; 125: e2-e220. 2) Leitersdorf *et al.*, ATVB 2004; 24: 1006-1014. 3) Murthy *et al.*, Circulation 2011; 124: 2215–2224. 4) Antkowiak *et al.*, JCMR 2010; 14 (Suppl 1): P55. 5) Coolen *et al.,* MRM 2010; 64: 1658–1663. 6) Makowski e*t al,* MRM 2010; 64: 1592–1598. 7) Kim *et al.*, Radiology 2004; 230: 862-871. 8) Chen *et al.*, ISMRM Proceedings 2012. 9) Jerosch-Herold *et al.*, Med Phys, 1998; 25: 73–84.

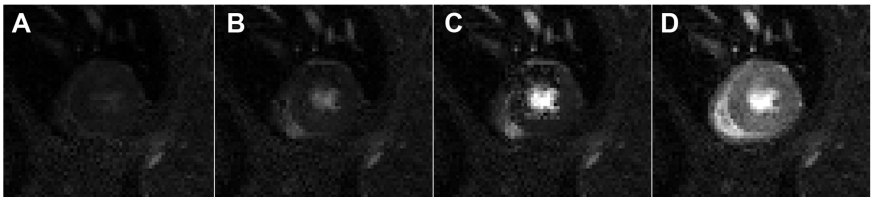

Figure 1: Example first-pass cardiac images obtained from a mouse at rest prior to injection (A), 0.5 s post-injection (B), 1 s post-injection (C) and 5 s post-injection of Magnevist (Gd-DTPA) (D).

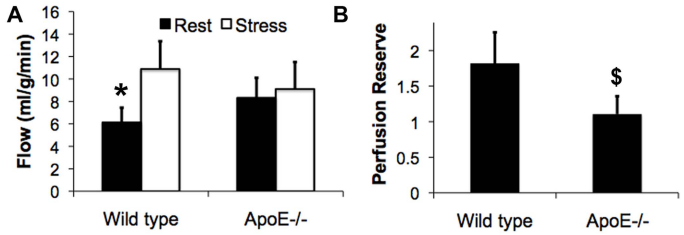

Figure 2 (A): In wild type mice, baseline perfusion was 6.1±1.3 ml/g/min and it increased to 10.9±2.5 ml/g/min with Regadenoson ($p<0.05$ vs. rest). In ApoE$^{-/-}$ mice, baseline perfusion was 8.3±1.8 ml/g/min and it increased to 9.1±2.4 ml/g/min with Regadenoson. (B): Perfusion reserve was 1.8±0.4 in wild type mice and 1.1±0.3 in ApoE$^{-/-}$ mice ($p<0.05$ vs. wild type mice).