Molecular and Microstructural Changes Accompanying Left Ventricular Hypertrophy Revealed with In-Vivo Diffusion Tensor MRI (DTI) and Molecular Imaging of the Mouse Heart

S. Huang[1], C. Mekkaoui[1], M. Polasek[1], H. H. Chen[1], R. Wang[1], S. Ngoy[2], R. Liao[2], V. J. Wedeen[1], G. Dai[1], P. Caravan[1], and D. E. Sosnovik[1,3]
[1]Martinos Center for Biomedical Imaging, Mass General Hospital, Charlestown, MA, United States, [2]Cardiology, Brigham and Woman's Hospital, Boston, MA, United States, [3]Cardiology, Mass General Hospital, Boston, MA, United States

Introduction: Pressure overload leads to hypertrophy of the myocardium. While initially adaptive, this process ultimately leads to reduced chamber compliance and diastolic heart failure. The transition from adaptive hypertrophy to heart failure, however, is poorly understood and novel tools are sorely needed to better understand and prevent this increasingly common problem. Here, we use molecular MRI of a collagen-binding gadolinium chelate (Gd-Col),[1] and in-vivo diffusion tensor MRI (DTI) of the mouse heart to characterize the microstructural response of the left ventricle (LV) to pressure overload.

Material and Methods: Aortic banding (AB) was performed in 4 C57Bl6 mice. 5 age-matched mice were controls. In vivo MRI was performed 4 weeks after banding on a 9.4T scanner (Bruker Biospin) with a 150 Gauss/cm gradient. 3D DTI was performed in-vivo using a fat-suppressed single-shot spin echo EPI sequence with motion-compensated bipolar diffusion-encoding gradients on either side of the 180° RF pulse (TR/TE: 2000/13.5 ms, b-value 500 - 700 sec/mm^2 with 24 direction encoding, and isotropic resolution of 280 um). An ECG-gated Look-Locker FISP sequence (TR: 3000ms, TE 1.3, MTX: 160 x160, FOV: 2.5 x 2.5 cm^2) was used to measure R1 and the accumulation of Gd-Col in the myocardium.

Results: Hypertrophy of the LV was seen in all the banded mice (Fig 1). However, no mice showed overt signs of heart failure.

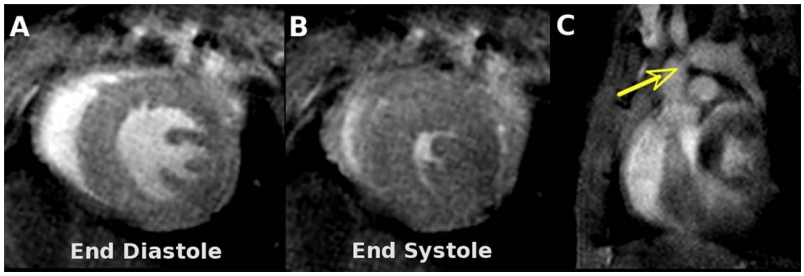

Figure 1: CINE images at end diastole (A) and end systole (B) showing vigorous contraction of the hypertrophied LV in a banded mouse. (C) Banded transverse aorta (arrow).

Myocardial R1 in the banded mice increased significantly after Gd-Col injection and remained elevated 1 hour after injection (Fig 2A). In addition, scattered foci of intense Gd-Col enhancement were seen in the banded mice (Fig 2B). No evidence of Gd-Col retention was seen in the control mice (Fig 2C). 3D DTI revealed a dramatic change in myofiber architecture after aortic banding (Fig 3). Myofibers in the banded mice were more circumferential, showed a positive shift in their helix angles, and had a narrower distribution of helix angles across the myocardial wall (Fig 3).

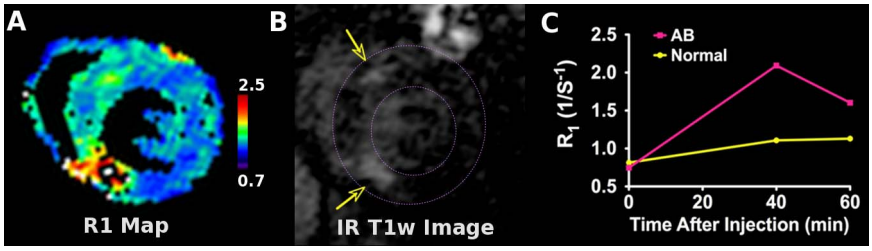

Figure 2: Detection of myocardial fibrosis with a collagen binding Gd chelate (Gd-Col). (A) R1 map in a banded mouse 1 hour after the injection of Gd-Col. A global increase in R1 with significant regional heterogeneity is seen. (B) Inversion recovery image in a banded mouse showing patchy Gd-Col enhancement. (C) Time course of R1 after Gd-Col injections in a banded and a control mouse. Significant retention of Gd-Col is seen in the aortic banded (AB) mouse.

Conclusion: Molecular and microstructural imaging of the heart reveals that exposure to pressure overload results in significant amounts of fibrosis and microstructural remodeling well before the overt transition to diastolic heart failure. The ability to follow these processes serially with noninvasive imaging in-vivo provides a novel and powerful platform to investigate the pathophysiology of LV hypertrophy, hypertension and diastolic heart failure.

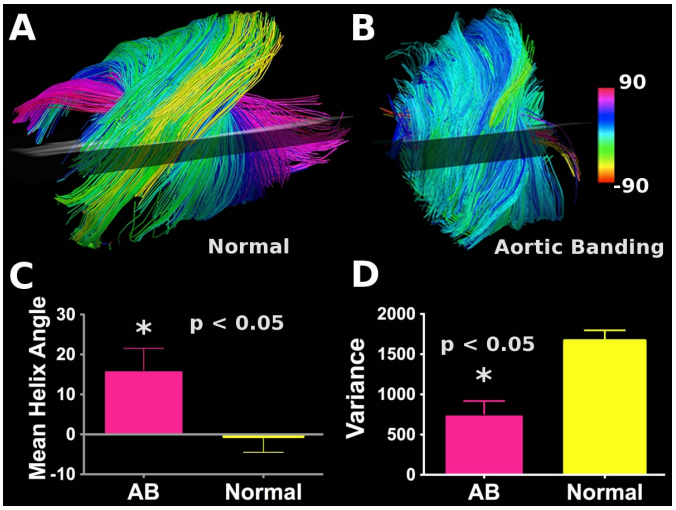

Figure 3: In vivo DTI of normal and aortic banded (AB) mice. Color code = fiber helix angle. (A) Normal mouse: subendocardial fibers have positive helix angles, midmyocardial fibers are circumferential and subepicardial fibers have negative helix angles. (B) Myofibers in the banded mouse are more circumferential. (C) A rightward shift in mean helix angle is seen in the banded mice. (D) The range (variance) in helix angle is also significantly reduced in the banded mice.

References: 1. P. Caravan et al. Angew Chem, 2007. **Funding:** R01 HL093038 (Sosnovik) and NCRR P41RR14075 (Martinos Center)