INTRODUCTION
Coronary heart disease (CHD) remains the leading cause of death in the United States, accounting for approximately 26% of the total US deaths in 2006. Myocardial infarction (MI) accounts for approximately half of the CHD cases (1). In the post-MI heart a number of molecular and structural changes are observed, including increased intracellular Ca2+ concentrations in the ischemic peri-infarct zones, and myocardial thinning in the infarcted regions. This study uses molecular MRI contrast agent Mn2+, known to act as a Ca2+ analogue, to assess the molecular changes in Ca2+ handling post-MI surgery in a mouse model, while DTI studies were subsequently performed in the excised heart to evaluate myocardial structural changes. Ultimately this study is designed to examine the relationship between indirect Ca2+ handling and structural modification during the myocardial remodeling process. Results from this study could provide a multiple diagnostic method for monitoring the salvageability of the peri-infarcted zone.

METHODS
Magnetic resonance imaging studies were performed in C57Bl/6 mice (n = 14, average weight = 23.8±2.0g, 9-13 weeks old), as previously described (3). The mice were separated into two groups; a control group undergoing no surgery (n = 6) and a myocardial infarction group (n = 8) where the mice underwent surgical procedures to ligate the left anterior descending coronary artery. In vivo manganese-enhanced MRI (MEMRI) studies were conducted 8±1 days post-surgery. Manganese-Enhanced MRI MEMRI short axis T1 maps were acquired mid-way through the left ventricle, both pre- and post-280 nmoles/g BW MnCl2 infusion, on a 7T Bruker scanner. A Look-Locker pulse sequence was used, as previously described (4): matrix = 128 x 128; TE/TR = 2.5 ms/10 sec; slice thickness = 1.0 mm; FOV = 3.0 x 3.0 cm; NA = 2; inversion time = 9 ms; average echo interval = 138 ms (determined by the average R-R period before acquisition); number of echo images = 50; average flip angle = 11°±1°. A regional analysis was performed in both groups to assess the increase in relaxation rate, (ΔR1 = 1/T1 post – 1/T1 pre-MnCl2 infusion). Following imaging the mice were sacrificed, and the heart was excised as previously described (5).

Diffusion Tensor MRI One day before performing DTI, the post-MI (n = 7) and control (n = 5) fixed hearts were rinsed and suspended in 1X PBS. Diffusion weighted images were acquired on a 9.4T Bruker scanner under room temperature using a spin-echo sequence with a bipolar diffusion gradient. Seven 0.5 mm thick short-axis slices were acquired to cover the whole left ventricle (LV). Imaging parameters were: TE = 34 msec; TR = 2.5 sec; δ = 10 msec; Δ = 20 msec; Diffusion direction = 6; FOV = 1x1 cm2; b = 800 s/mm2; NA = 12; Matrix size = 128x128; Resolution = 78x78 μm2. DTI Data Processing Diffusion tensor matrix and the three corresponding eigenvalues were calculated from diffusion-weighted image sets using an in-house MATLAB-based software. Diffusivity map, defined as the average of the three eigenvalues, was normalized to that of the surrounding PBS solution to minimize the variation in diffusivity caused by temperature fluctuation. Fractional anisotropy (FA) maps were generated to quantify diffusion anisotropy. The infarct area was visually identified as the region with significant LV wall thinning. The remaining myocardium was divided into six equal pieces in circumferential direction. The adjacent, peri-infarct area was defined as the two regions neighboring the infarct zone (Fig 1).

RESULTS
The infarcted regions of the post-MI myocardium exhibited significant reductions in Mn2+ uptake compared to both the healthy, remote tissue, and the myocardial tissue in the control group (p < 0.05) (Fig 2). A radially changing uptake in Mn2+ was similarly observed for the peri-infarct zones.

CONCLUSIONS
A decrease in Mn2+ uptake was observed for the necrotic, infarcted tissue, as well as the ischemic peri-infarct tissue. This is likely caused by changes in Ca2+ handling post-MI, with the contrast agent Mn2+ acting as an indirect molecular predictor for Ca2+ handling. A decrease in diffusivity and an increase in diffusion anisotropy were observed in the infarct hearts, which is consistent with the literature (6). The underlying pathological process may be the formation of granulation tissue, which was more organized in fiber-like structures. The preserved transmural helix and transverse angles suggest that the global fiber structure for both collagen scaffold and myocytes was well preserved in the hearts with myocardial infarction.

REFERENCES