3D High-Resolution Diffusion Tensor Imaging of Heart ex-vivo after Myocardial Infarction in Porcine Model

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INTRODUCTION: High resolution DTI is a promising tool to study myofiber remodeling in different disease models, specifically myocardial infarction (MI). Most studies of microstructure utilize either high field magnets and small animals hearts or pieces of large animal hearts. To our knowledge, this is the first study that incorporates sub-millimeter 3D DTI to study the remodeling process around the infarct area in a large animal model and is suitable for whole human heart imaging [1,3]

PURPOSE: To develop a 3D high resolution DTI imaging sequence to examine cardiac microstructure *ex vivo* in a large animal model using a standard clinical system.

MATERIALS AND METHODS: Under IACUC-approved protocol, the mid–left anterior descending coronary artery of a swine was occluded for 120 min using a balloon angioplasty catheter (2.7 Fr) to create MI (n=3 MI, n=3 control). Eleven months post infarction, the left ventricle function was assessed *in vivo* using CINE, and the infarction was delineated using phase sensitive inversion recovery (PSIR) late Gadolinium enhancement (LGE) imaging. As a gold standard for MI, Gd-DTPA (Magnevist®) was injected (0.2mmol/kg) 20 minutes before sacrifice. The hearts were arrested with KCl and after the excision, the ventricles were filled with rubber (Task5™) to keep the heart in the natural unloaded shape. To avoid sample dehydration and susceptibility artefacts generated from the tissue-air interface, the heart was submerged in perfluorocarbon, (Fluorinert-77, 3M). T1-W GRE MRI was performed (acquired resolution 0.25x0.25x0.50mm, TE=2.3ms, TR=12ms, scan duration: 1hr), and the sample was fixed in 10% buffered formaldehyde for future DTI. A 3D Fast Spin Echo DTI sequence was developed and used on 3T clinical system (Achieva TX, Philips Healthcare, Best, The Netherlands) to image the whole heart *ex vivo* (TE = 63ms, TR=504ms, BW = 290.0Hz, number of echoes: 2, diffusion gradient timing: 22.8/12.6 ms, max gradient strength = 60 mT/m, number of diffusion encoding directions: 15, max b-value = 800 s/mm^2, typical FOV: 110x115x130 mm^3, acquired resolution 0.6x0.6x1.2mm^3, reconstructed resolution: 0.45x0.45x0.45 mm^3 and total scan duration= 42hrs). Image reconstruction was performed offline, using customized MATLAB code, and tensor calculation was done using DTI Studio [2]. The imaging technique and the post processing pipeline were validated using DTI specific fiber phantom and three control heart samples. For the purpose of point-to-point comparison of diffusion properties with respect to the infarct location, T1-W GRE and DTMRI data were registered using affine and nonlinear transformations to correct for the slight shrinkage of the tissue due to fixation. The effect of fractional anisotropy (FA) alteration due to uneven fixation process was minimized by excluding the septal wall, which showed lower FA for healthy myocardium in some samples. Infarct area was defined to be the high intensity voxels on T1-W GRE images (3 SD above the average remote myocardium value). The mid-value voxels at the proximity of the infarction were segmented and labeled as border zone. The global and regional microstructural remodeling was assessed using the reconstructed diffusion tensor field. In addition to conventional DTI measures (FA and apparent diffusion coefficient, ADC), an inter-voxel gradient metric was defined to represent the extent of fiber variation around the infarct.

RESULTS: The myocardial SNR, the ratio of the mean signal to the Gaussian converted (x0.65) standard deviation of the background noise at b0 image, was >100 for all acquisitions. All chronic MI hearts showed significant wall thinning at the apical and mid-wall anterior and septal wall as well as a significant reduction in function (Ejection Fraction (EF) = 0.25, N=2). Fig. 1 compares infarcted regions in representative in-vivo PSIR images to its corresponding high-resolution ex-vivo images. The remodeling at the infarcted area is clearly shown via the FA map, and the myofiber disorganization is delineated by the primary eigenvector map and the elevated gradient metric. Fig. 2 shows the comparison of FA and ADC for a control and MI group. The infarcted area shows a significantly lower average FA and higher ADC with respect to the remote zone while the border zone takes mid-range values in most of the cases. The baseline for remote values of FA and ADC, obtained from healthy myocardium excluding the septum, showed a significant change in chronic MI cases comparing to the control group. In general, the thinned wall area of myocardium showed a smaller decrease in FA while having a higher transmural gradient of fiber angles.

CONCLUSION: DTI has been shown to be a promising tool to study the cardiac microstructural remodeling non-destructively *ex vivo* [1,3,4]. It has previously been shown that the tensor calculation results can be highly biased at lower SNRs [6] with the FA value and the fiber variation inversely related to SNR. We incorporated the high SNR and low artefact characteristics of 3D spin echo to develop a 3D DTMRI sequence that could be used in large animal and human models to study the remodeling after myocardial infarction at the sub-millimeter resolution. Our preliminary results from hearts harvested from swine 11 months post MI show the global and regional remodeling after the MI and show consistency with previous studies in the reduction of FA and increase in ADC [1,3,4]. However, unlike [1], the mean FA for the remote zone of the diseased hearts showed reduction when compared to the control cases in this study. This could be secondary to heart failure developed 11 months post MI (EF = 0.25, N=2). The higher variability of these measures, and the elevated fiber variation metric imply for tissue heterogeneity inside and around the scar. The mid FA values for border zone area could reflect the co-existence of scar and viable myocardium in this region. The extent of microstructural remodeling illustrated by sub-millimeter DTI maybe of great importance in studying the pathophysiology of infarct in both humans and animals, and might be used to predict further electromechanical dysfunction developed after MI.

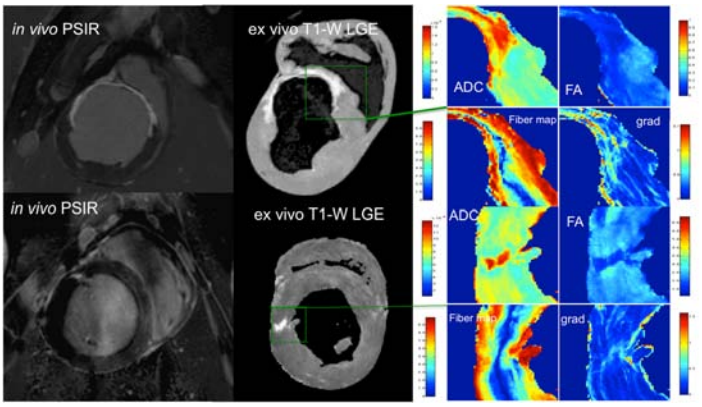

Figure 1: visualization of infarction in two chronic MI hearts using in-vivo PSIR LGE (left), *ex vivo* LGE image (middle) and DTI maps (right): a) ADC b) FA c) out of plane component of primary eigenvector (blue represents the in-plane orientation) and d) gradient magnitude of fiber field reflecting higher variation around infarct.

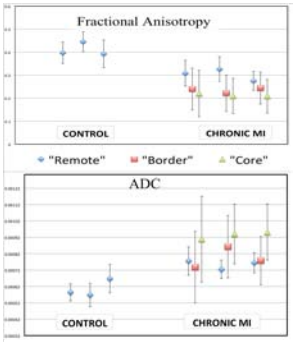

Figure 2: FA and ADC measurements for three control and three 11mo chronic MIs

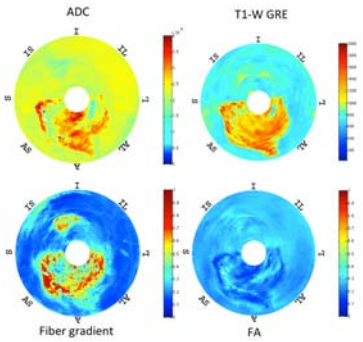

Figure 3: Bulls eye plot representation of the second MI case in the Fig.1, using T1-W GRE and DTI

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