Diffusion tensor imaging of left ventricular remodeling in response to myocardial infarction in the mouse

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Introduction

The mouse offers a unique platform to study the functional development of the healthy and diseased heart. The cardiac muscle architecture lies at the basis of the mechanical and electrical properties of the heart and dynamic alterations in fiber structure are known to be of prime importance in the healing and remodeling following myocardial infarction. Diffusion tensor imaging (DTI) offers a non-destructive tool to study both myocardial fiber orientations [1-3] as well as to evaluate structural changes of the muscle tissue caused by ischemia [4]. In this study left ventricular remodeling was studied using diffusion tensor imaging (DTI) in a permanent ligation mouse model of ischemic infarction up to 28 days post infarction.

Material and Methods

Mice: In 24 male Swiss mice (age, 10 to 12 weeks; weight, 35-45 grams) myocardial infarction was induced by permanent occlusion of the LAD. The mice were sacrificed 7, 14, and 28 days after induction of the infarction. Five healthy mice that matched the 28 days group were used as a control. The hearts were perfusion fixed with 3.5% formalin and MRI measurements were performed within one week after fixation. After MRI histological characterization was performed using Toluidine Blue or Gomori's trichrome staining.

MRI: DTI experiments were performed on a 6.3 T Bruker MR scanner. The hearts were contained in a plastic tube filled with Fomblin (Ausimont, NJ) for susceptibility matching, and placed in a one turn solenoid sheet RF coil with a diameter of 10 mm and a length of 15 mm. DTI experiments were done using a 3-dimensional fast-spin-echo sequence with twin navigators to correct for phase errors between even and odd echoes [5]. 3D volume images of the hearts were acquired with the following parameters: TE=8 ms, TR=1 s, ETL=2, NSA=2, FOV=15^3 mm^3, matrix=128×96×64 (readout×phase×phase) zero-filled to 128^3, resulting in a voxel size of 117^3 μm^3. Diffusion weighting was introduced by pulsed field gradients around the first 180^o pulse with δ=10 ms, Δ=20 ms, and G_{diff}=0 or 110 mT/m, resulting in b-value=0 or 1442 s/mm^2. Diffusion weighting was applied in 6 non-collinear directions. Total acquisition time was approximately 10 hrs.

Data analysis: Diffusion tensor, eigenvectors and eigenvalues were calculated using Mathematica (Wolfram). Fiber orientations were visualized as a vector field, for the projection of the local fiber orientations on the short-axis plane, and in color-coding, for the out-of-plane component. Myofiber orientations were quantified by the helix and transverse angles. Fiber tracking was performed using a tool by Vilanova et al. [6].

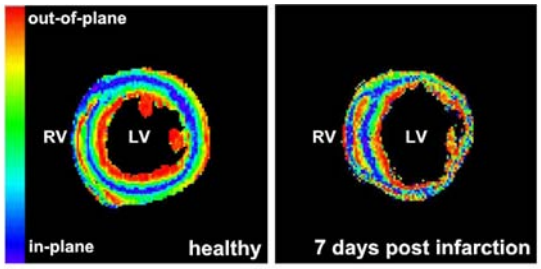

Figure 1: Equatorial slice of a healthy mouse heart (left) and a mouse heart 7 days post LAD ligation (right). The color coding indicates the out-of-plane component of the local myofiber orientation.

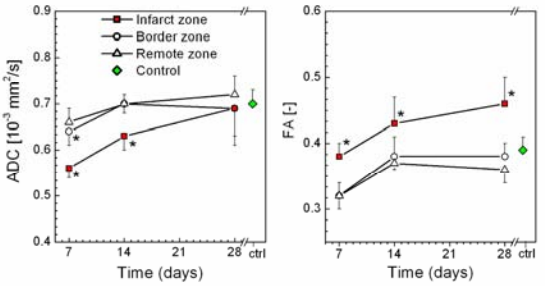

Figure 2: ADC and FA as a function of time post myocardial infarction for infarct, border, and remote zones.

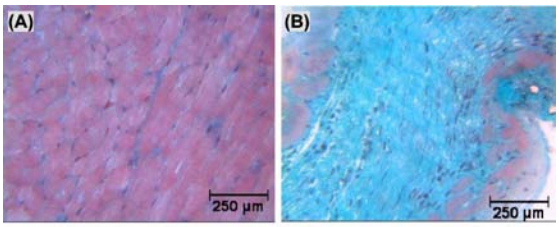

Figure 3: Histology of (A) healthy myocardium and (B) infarct tissue after 28 days, showing a mature scar with cross-linked fibrous collagen.

Results and Discussion

Figure 1 shows a color-coded map of out-of-plane component of the fiber orientations of a slice near the equator of a healthy heart and a heart 7 days post myocardial infarction. The healthy heart displays the well-known helical fiber architecture with a characteristic (blue) ring of midwall fibers that run predominantly in the circumferential direction and axially oriented fibers near the epicardium, the endocardium, and in the papillary muscles. The infarct hearts displayed extreme thinning of the apical myocardial wall. The infarct area expanded throughout almost the entire free wall of the LV to almost two-third of the long axis from apex to base. Fiber orientations were almost completely random in the infarct zone, as can be seen in figure 1 for a heart of a mouse 7 days post infarction. Also the border and remote zones displayed a more random fiber orientation as compared to the healthy mice. Figure 2 shows the time course of the changes in ADC and FA. The ADC in the infarct zone 7 and 14 days post infarction is significantly lower as compared to the border and remote zones, but renormalizes at 28 days. Although fiber orientations are more random in the infarct zones, the FA is higher in the infarct zone as compared to border and remote zones. The FA increases in time following the infarction. Histological analysis showed that the infarct at 7 days consists of unstructured tissue with residual necrosis and infiltration of macrophages and myofibroblasts. At 14 days post infarction the necrotic tissue has disappeared, collagen fibers are starting to appear and myofibroblasts are elongated. At 28 days the infarct has fully developed into a mature scar with cross-linked collagens that clearly have a fiber like structure (Figure 3). We propose that the high FA in combination with somewhat lower ADC in the infarct zone is caused by structured collagen fibers.

Conclusions

We have presented DTI data of myocardial remodeling in mouse following myocardial infarction. These results show that DTI can provide a valuable non-destructive tool for characterizing structural remodeling in diseased myocardium which is of great importance in understanding the healing process following myocardial infarction.

References:

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