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Regional matrix metalloproteinase activation correlates with microstructure diffusion tensor indices post myocardial infarction

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Introduction

Post myocardial infarction (MI) activated matrix metalloproteinases (MMPs) degrade the extracellular matrix (ECM) and alter the tissue microstructure (TMS). Diffusion Tensor MRI (DT-MRI) yields diffusivity and anisotropy indices that characterize the TMS. Our previous studies in pigs post-MI have showed that gross spatial and temporal changes in mean diffusivity () and fractional anisotropy (FA) correlate with MMP activation assessed with a 99 mTc-labeled radiotracer (RP805) targeted at activated MMPs.

Purpose

To determine the correlation between regional MMP activation defined by RP805 with alterations in, FA and a new coefficient of anisotropy, the toroidal curvature (TC).

Methods

Correlation between regional MMP activation using RP805 and DT-MRI was assessed in 3 infarcted porcine hearts at 2- and 4-week post-MI. Two hours prior to euthanasia, RP805 (28 ± 3 mCi) was injected. Each heart was then excised and placed in a container and filled with Fomblin. DT-MRI was performed on a 3.0 T scanner (Siemens, Erlangen, Germany) using a segmented EPI sequence, 6 gradient directions; b-values = 0 (T2-weighted) and 600 s/mm2; voxel-size = 2 × 2 × 2 mm3; slices = 50; TR/TE = 5400/84 ms; 40 averages (EPI-factor = 7). Following MR imaging hearts were sliced (5 mm), cut in 8 radial pies and divided into endocardial and epicardial segments for gamma-well-counting for determination of RP805 activity, expressed as percent of injected dose/gram of tissue (%ID/g). Similarly, T2-weighted images were segmented using the same anatomical landmarks and used to classify tissue as infarcted (I) or non-infarcted (NI). TC is defined as the maximum Gaussian curvature of the toroid-based representation of the DT. Figure 1 displays an example of the, FA and TC maps used in quantification compared with RP805 and morphology.

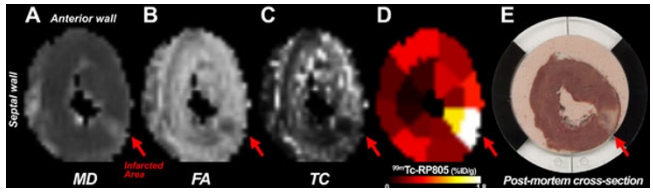

Figure 1
Mid-ventricular cross-section of MD (A), FA (B), TC (C), and RP805 (D) maps, as well as the relative post mortem slice (E) for a 2-week post-MI porcine heart. Figure shows the spatial correlation between the infacted area (red arrow) and the increse in MD and RP805 and the decrease in FA and TC.

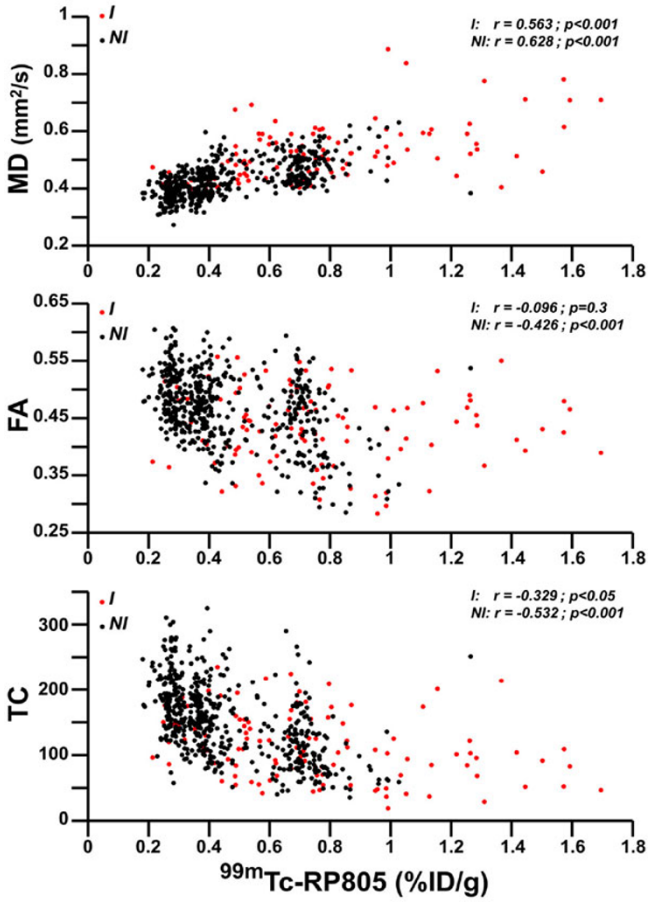

Figure 2
Scatter diagrams showing the correlation between RP805 and MD (A), FA (B), and TC (C) respectively with I (red dots) and NI (black dots) for all animales. The correlation coefficient ***r*** and the relative ***p*** values are indicated in the upper right corner of each panel.

Results

Figure 2 illustrates the positive correlation between regional RP805 activity and for both I ($r = 0.563$, $p < 0.001$) and NI ($r = 0.628$, $p < 0.001$). There was an inverse correlation between RP805 activity and FA ($r = -0.426$, $p < 0.001$) within NI regions, although no correlation within I regions ($r = -0.096$, $p = 0.3$). There were inverse correlations between RP805 activity and TC for both NI ($r = -0.532$, $p < 0.001$) and I ($r = -0.329$, $p < 0.05$) regions. The average (I = 0.52 ± 0.10 mm2/s; NI = 0.43 ± 0.06 mm2/s), FA (I = 0.44 ± 0.06; NI = 0.47 ± 0.06), TC (I = 113.55 ± 39.64, NI = 152.44 ± 45.98) and RP805 activity (I = 0.75 ± 0.34; NI = 0.46 ± 0.19) were all significantly ($p < 0.001$) different between I and NI regions.

Conclusion

Therefore, MMP-mediated degradation of the ECM post-MI was associated with increased water diffusivity as reflected by and reduced anisotropy by a decrease in FA and TC. Hence, evaluation of regional DT-MRI indices of microstructure in combination with evaluation of MMP activation may provide new insight in the remodeling process post-MI.