Magnetization transfer encoded steady state cardiac imaging of fibrotic development in mice

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Introduction. The emergence of fibrotic tissue in the heart typically occurs either following myocardial infarction (MI) or accompanying heart failure. MR imaging of fibrotic scar tissue or dense fibrosis with gadolinium is well established, and recently, MR based methods using an infusion of gadolinium with R1 mapping have been applied to identification of diffuse fibrosis. Fibrotic collagen generates significant magnetization transfer (MT) effects across a broad frequency range with surrounding water molecules. We sought to exploit the MT properties of collagen in order to quantitatively and non-invasively image fibrotic scar formation following MI in mice. **Methods.** A free-breathing retrospectively cardio-respiratory gated MT-encoded steady state cardiac cine pulse sequence (described in detail in abstract control #2986) was used to generate a series of MT-encoded cine images of the mouse heart. Specific parameters were FOV=2.56x2.56cm, Matrix = 256x128, slices = 1, and slice thickness = 1mm. Briefly, spectra of the heart were obtained by applying a saturation pulse train module (Gaussian, flip angle = 270°, bandwidth = 200Hz, duration = 13.7 ms, number of pulses = 28) prior to a constant TR gradient echo readout module (TR/TE = 10.2/3.5 ms, flip angle = 10°, number of acquisitions = 100). The total number of sequence repetitions (saturation and readout modules) was 128. Offset frequencies of -12, -9, -6, -4, -2, -1, 0, 1, 2, 4, 6, 9, 12 ppm for saturation pulses were used in order to obtain spectra, and a separate reference scan (offset = -12ppm and saturation flip angle = 1°) was acquired for signal normalization (Fig A). Afterwards, delayed contrast enhanced (DCE) images were acquired following intraperitoneal injection of gadolinium-DTPA (0.1 mmol/kg body weight) via an indwelling intraperitoneal line. T1-weighted DCE images were acquired using a cine imaging sequence with identical spatial parameters and flip angle = 25°. Image analysis was performed on end diastolic images by defining infarct (hyper-intense), border (5 pixels away from infarct zone circumferentially), and remote (remainder) myocardial zones based on signal enhancement of DCE images. Spectra were obtained by normalizing signal intensity for each ROI to the corresponding reference scan signal intensity. For each data set, spectra from infarct and border zone ROIs were modeled as the convolution of remote zone spectra with a Lorentzian function that describes the line broadening and MT effects of fibrosis (Fig A). The values of A and γ were optimized via RMS minimization, and from this the fibrotic score was calculated as F.S. = $(1/A_{ROI}-1)*100$. All imaging was performed on a 9.4T Bruker Biospec (Ettlingen, Germany) scanner using a cylindrical volume coil for excitation and a single element surface coil for reception. MI was surgically induced via permanent ligation of the left anterior descending (LAD) coronary artery in C57B6 male mice (n = 7) at 8 weeks of age. Mice were imaged at 1, 7, 10, 14 and 21 days after MI. At the conclusion of imaging at 21 days after MI, hearts were isolated, fixed, sectioned, and stained for collagen using Masson's Trichrome staining. **Results** Representative images acquired 14 days post-MI demonstrate decreased signal in infarct zone (blue arrows) myocardium following off-resonant saturation. At day 1 post-MI, the border and infarct zone spectra were similar to remote zone spectra. By day 10 post-MI, the development of scar tissue resulted in significant MT effects at off-resonant frequencies in infarct zone myocardium, with an intermediate effect in border zone tissue (Fig B). The fibrotic score measured in infarct and border zone myocardium demonstrated a significant increase between 7-10 days post-MI (Fig B). **Discussion** In this study we utilized the MT effects of collagen to image the dynamics of scar formation following MI. The temporal characteristics of the fibrotic index in the infarct zone tissue paralleled the known time-course of scar formation following permanent ligation of the LAD [1]. Since the spatial characteristics of the fibrotic score were confirmed by collagen staining at 21 days post-MI, the decline in the fibrotic score in border zone tissue likely reflects shifting of the border zone into non-infarcted tissue as a result of infarct extension. This method can be easily translated to clinical use, where accelerated imaging schemes and lower heart rates in patients would enable rapid spectral acquisition. Importantly, this could serve as an avenue for completely non-invasive imaging of cardiac fibrosis in patients.

Acknowledgements Whitaker Postdoctoral Fellowship to MHV, R01 CA75334 US National Cancer Institute, European Commission 7th Framework Integrated Project ENCITE, and European Research Council Advanced grant 232640-IMAGO to MN. **References** [1] Vandervelde et al. Cardiovascular Pathology; 2005.

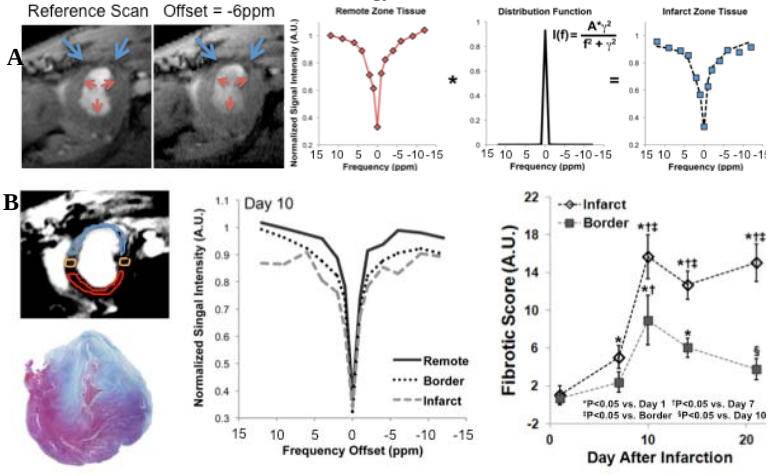

Figure. (A) Representative reference and MT-encoded images acquired 14 days after MI. Corresponding spectra in infarct zone tissue (blue arrows, squares) were modeled as the remote zone spectra (red arrows, line) convolved with a Lorentzian distribution function which describes the MT effects of collagen. **(B)** A representative cardiac DCE image (left, top) acquired 21 days after MI was used to define regions of interest for the infarct (blue), border (yellow), and remote (red) zones based upon enhancement patterns. These zones agreed with areas of scar and healthy tissue as shown by Masson's trichrome staining (bottom). (Middle) Representative spectra for regions of interest at Day 10 post-MI revealed significant MT effects in infarct zone tissue, and moderate MT effects in border zone tissue. (Right) The Fibrotic Score paralleled the time-course of scar formation in mice [1].