Target Audience: Cardiac MRI researchers and clinicians with a focus on tissue composition.

Purpose: To develop a cardiac MRI (CMR) method to image myocardial fibrosis without the use of gadolinium contrast agents.

Introduction: The development of myocardial fibrosis is increasingly linked to arrhythmia and sudden cardiac death (SCD). Late gadolinium enhanced (LGE) CMR has emerged as a reference standard for in vivo imaging of myocardial fibrosis with excellent prognostic ability, and when combined with a T1-mapping approach, can enable quantitative fibrosis imaging. However, patients with acute and chronic kidney disease are considered contraindicated to LGE-CMR despite being at extremely high risk for cardiac events including SCD. Recently, the magnetization transfer (MT) characteristics of balanced steady state free precession (bSSFP) imaging have been explored for imaging of edema following acute myocardial infarction. We sought to exploit MT from fibrotic collagen to image myocardial fibrosis from pairs of differentially MT-weighted bSSFP cine images as a potential gadolinium-free and endogenous contrast based fibrosis imaging method.

Methods: 15 patients (7 men, 8 women, average age 54 ± 17 years) referred for clinical CMR examination were recruited to participate in the research protocol. All imaging was performed on a 1.5T Siemens Aera scanner (Erlanger, Germany) using a 12 channel chest array coil and an 8 channel spine coil. CMR of ventricular structure and global function was performed using a bSSFP sequence. In each patient, one mid-ventricular slice was selected and a set (Figure 1) of MT-weighted bSSFP cine images were acquired with minimal MT-weighting (excitation flip angle = 5°) and strong MT-weighting (flip angle = 45°). bSSFP imaging used a prospective acquisition with the number of cardiac phases optimized to fill the cardiac cycle. Additional parameters included TR/TE = 35.64/1.25 ms; FOV = 260x260 mm²; Matrix = 256x256; Slice Thickness = 0.8cm; and in-plane spatial resolution was 1mm x 1mm. Maps of myocardial T1-relaxation times were acquired using a 5(3)3 modified Look-Locker imaging sequence (MOLLI) with FOV = 272 x 272mm; Matrix = 256*170; Slice thickness = 0.8cm; and flip angle = 35°. Afterwards, gadolinium-DTPA (0.2mmol/kg) was infused via an indwelling intravenous catheter at an average rate of 4mL/s. After 15 minutes, LGE images were acquired using an inversion recovery pulse sequence (FOV = 260x260mm²; Matrix = 256x192; TR/TE = 796/3.28ms; Averages = 1; Flip Angle = 25°, TI =250-350ms for optimal nulling) followed by post-contrast 4(1)3(1)2 MOLLI imaging. Maps of the MT-ratio (MTR) index were calculated on a pixel-wise basis as MTR Index = (S_MT-S_S)/S_S*100 (%), where S represents the signal intensity of a given voxel. MTR Index measurements over the first 2 and last 2 cardiac phases at end-diastole were averaged. The gadolinium partition coefficient (λ) was calculated from sets of MOLLI images acquired before (pre) and 15 minutes after (post) infusion of gadolinium-DTPA as λ = [(R1_MT-myocardium_post-R1_myocardium_pre)/(R1_blood_post-R1_blood_pre)]. Non-enhanced myocardium was selected on LGE images and fibrotic myocardium was identified as pixels with signal intensity > 2 standard deviations above the un-enhanced mean signal. Myocardial regions of interest in fibrotic and healthy tissue were used to calculate mean MTR Index and mean λ for each patient.

Results: Patterns of fibrosis were detected with LGE-CMR in 8 patients, and were also present as elevated MTR Index in all 8 patients. Fibrosis imaging with MT-weighted bSSFP cine CMR demonstrated strong spatial correlation with patterns of enhancement at LGE-CMR in patients with (Figure 1) and without fibrosis (Figure 2). The average MTR Index was significantly higher in myocardial tissue regions defined as fibrotic at end-diastole compared to healthy tissue (Figure 3). Myocardial tissue with MTR Index > 175% (mean + 2*SD of healthy tissue) demonstrated elevated λ (0.68 ± 0.13 [A.U.]) when compared to myocardium with MTR Index <175% (0.41 ± 0.17 [A.U.], P<0.05).

Discussion: Heightened MTR Index correlated strongly with myocardial fibrosis as identified by enhancement at LGE-CMR, and was further confirmed by quantitative measurement of elevated λ. Maps of MTR Index demonstrated strong spatial correlation with LGE-CMR in patients with non-ischemic dilated cardiomyopathy (Figures 1 and 2), hypertrophic cardiomyopathy, prior myocardial infarction, and left bundle branch block (not shown).

Conclusion: MT-weighted bSSFP enabled rapid and totally non-invasive imaging of left ventricular fibrosis in close agreement with standard of care LGE-CMR and without the use of gadolinium based contrast agents. Although this warrants confirmation in a larger number of patients, this novel technique is ideally suited to enable diagnosis and risk-stratification in large patient populations currently excluded from LGE-CMR but known to be at high risk of SCD, including the increasing number of patients with diabetes and CKD.

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