Non-contrast MRI for Assessing Myocardial Fibrosis: Initial Study in a Canine model of Myocardial Reperfusion after Drug Treatments

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Target Audience Radiologist, cardiologist, MRI physicist, and the professionals involved with patient care for myocardial ischemia and heart failure.

Purpose Cardiac magnetic resonance (CMR) T1 mapping techniques allows quantification of fibrosis.[1-2] However, this T1 mapping requires the administration of gadolinium contrast agent to obtain pre- and post-contrast T1 maps, which may be contraindicated to some cardiac patients who have severe renal deficiency, e.g., heart failure, diabetes, etc. In this project, a non-contrast CMR approach for the fibrosis detection was developed and the feasibility was tested in a canine model of myocardial reperfusion with and without a human recombinant apyrase treatment.

Methods

Imaging Methods: A newly developed cardiac spin-locking T1ρ mapping sequence was used in this study.[3] Three T1ρ-weighted images at times of spin-locking (TSL) of 10, 30, and 50 msec were acquired in a single breath-hold, at spin-locking frequency (SLF) ω_1 of 0 and 510 Hz. The R1ρ (= 1/ T1ρ) can be expressed: $R1_\rho(\omega_1) = R1_\rho(0) + FI(\omega_1, [collagen])$ (1)

FI is a fibrosis index that can be quantified by following approach

$S = S_0 e^{-TSL \times R1_\rho}$ (2); Then, $\frac{S(\omega_1)}{S(0)} = e^{-TSL \times (R1_\rho(\omega_1) - R1_\rho(0))} = e^{-TSL \times FI}$ (3)

FI and its map can be calculated from the Eq. (3), by nonlinear curve fitting with three different TSL. Higher FI indicates more fibrosis.

Experiments: This project was in conjunction with an ongoing study to evaluate anti-bleeding effect of APT102 (APT Therapeutics, St. Louis, MO) after coronary reperfusion, in comparison with Clopidogrel treatment (a standard clinical treatment). APT102 is a human recombinant apyrase, which degrades circulating ATP and ADP causing inhibition of platelet activation and generation of cardioprotective adenosine.[4] It was also tested in other animal studies for its anti-fibrosis effect. Six mongrel dogs in two groups had coronary thrombotic occlusion induced by electrical current followed by fibrinolysis. Animals received either Clopidogrel (4 mg/kg, n= 3) or APT102 (1.0 mg/kg, n = 3), and then daily Clopidogrel (1 mg/kg) for 7 days. CMR study was performed baseline, 24 hours, and 7 days after fibrinolysis (n = 1 for each groups). Masson's trichrom stain was used in the last two dogs after sacrifice for the determination of fibrosis.

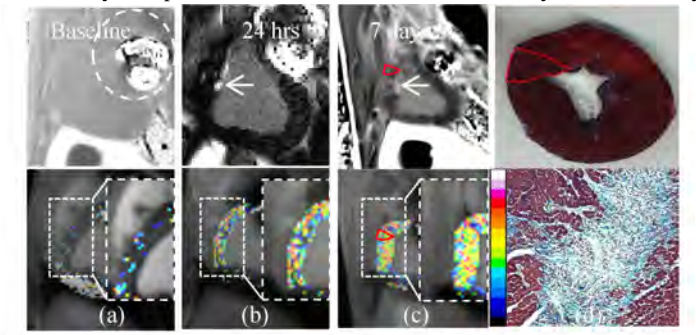

Figure 1. Short-axial myocardial MR images of LGE (top row) and fibrosis index maps (bottom row) at baseline (a), 24 hrs after reperfusion (b), and 7 days after fibrinolysis (c). The dog received Clopidogrel (control) treatment. The dashed circle in the anterior-lateral wall indicates image artifacts induced by the metal electrode. Only the septal region was free from artifacts. The white arrows in top row point to the small endocardial infarction in the septum. The infarction was more apparent at 7 days than at 24 hours. The enhanced area in the septum on fibrosis index map at 7 days was more spread-out (see insert enlarged images in bottom row). The trichrome-stained histopathological images from the anterior septum (red triangle) at 7 days (d) shows moderate collagen deposit (blue) with abundant inflammatory cells (d, bottom). The color bar scale for fibrosis index map is 0-100 (arbitrary unit).

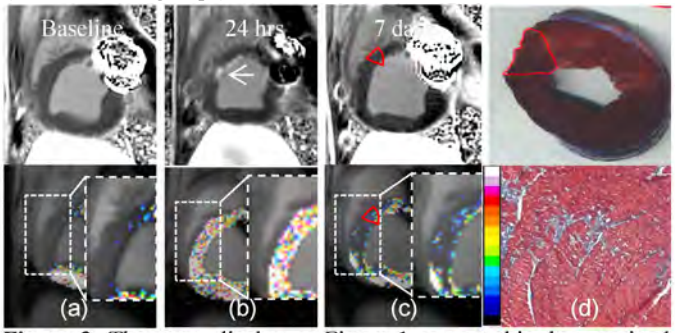

Figure 2. The same display as Figure 1, except this dog received experimental drug APT102 treatment – possibly anti-fibrotic and anti-inflammatory treatment. The endocardial region of anterior septum (white arrow in b, top) shows a LGE enhancement at 24 hrs and no LGE signals at 7 days (c, top). The signals in the septum on fibrosis index map (see insert enlarged images in bottom row) was elevated at 24 hrs (b, bottom) and then diminished at 7 days (c, bottom). The trichrome-stained histopathological image from the anterior septum (red triangle) at 7 days shows small and focal collagen deposit (blue) with much less cytoarchitecture (d, bottom).

CMR: CMR protocol included pre-contrast T1ρ imaging at SLF of 0 and 510 Hz and post-contrast late gadolinium enhancement (LGE) imaging after an administration of 0.15 mmol/kg Multihance (Bracco Diagnostics Inc, Monroe Township, NJ), for the detection of myocardial infarction.

Results **Figure 1 and 2** demonstrate the changes in FI maps at baseline, 24 hours, and 7 days after fibrinolysis in dogs treated by Clopidogrel and APT102, respectively. The LGE images were also shown as a comparison. The averaged FI changes in two groups were: (Clopidogrel) 44.7 ± 7.2 (baseline), 56.6 ± 13.2 (24 hrs), **50 (7 d)**; (APT102) 46.6 ± 20.9 (baseline), 54.9 ± 22.1 (24 hrs), **26.4 (7 d)**. No statistical difference was noted between Clopidogrel and APT102 treatments in FI at baseline and 24 hours, but FI decreased 50% at 7 days in one dog after APT102 treatment.

Conclusion This is the first study to apply a non-contrast fibrosis index to assess myocardial fibrosis changes during a drug treatment. Although the dog number was limited, the imaging study shows the potential of this fibrosis index to quantitatively monitor myocardial remodeling without the use of any MRI contrast media. This may has important clinical implication for the management of cardiac patients with heart failure and diabetes when their renal functions are limited.

References [1] Broberg CS,, et al, Circ Cardiovasc Imaging. 2010;3:727-734; [2] :64-122. [2] Miller CA, et al, Circ Cardiovasc Imaging. 2013;6: 373-383. [3] McCommis KS, et al, Magn Reson Med, 2010; 63: 1442-1447. [4] Moeckel D, et al. Sci Transl Med. 2014; 6.