

Detecting clinically significant subtle myocardial damage in myocardial infarction using multi-contrast delayed enhancement MRI: correlation with whole-mount heart histology at micron-level resolution

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Introduction: It is very challenging to detect subtle myocardial damage such as papillary muscle (PM) and right ventricular (RV) involvement associated with myocardial infarction (MI) by using non-invasive imaging techniques. However, these subtle myocardial findings may be clinically significant. The PM is an integral component of the mitral valve apparatus and its involvement in MI is a primary factor leading to the occurrence of mitral regurgitation, with associated substantial morbidity and mortality [1]. PM-MI is also a potential source of ventricular arrhythmia in these patients [2]. RV-MI and dysfunction are also independent indicators of poor prognosis in patients with MI [3]. Conventional delayed enhancement magnetic resonance imaging (DE-MRI) using inversion-recovery fast gradient-echo (IR-FGRE) has been used to detect PM and RV involvement associated with MI, but PM-MI detection is limited by poor contrast between left ventricular (LV) blood pool and infarct myocardium and RV-MI detection is limited by the thinned wall and confounded by the pericardial fat tissue. A newly developed multi-contrast delayed enhancement (MCDE) MRI has been proposed for the simultaneous detection of scar tissue and wall motion abnormalities in patients with chronic MI [4]. We hypothesize that this MCDE technique may be a better method to identify subtle myocardial damage such as PM and RV involvement in MI, compared to conventional IR-FGRE imaging.

Materials and Methods: In six Yorkshire pigs (20-30 kg) MI was created by a 90-minute percutaneous balloon occlusion of the left anterior descending coronary artery (LAD) proximal to the right ventricular branch (n=2) or of the mid- to distal left circumflex coronary artery (LCX) (n=4). After reperfusion and full recovery from anesthesia, animals were allowed to survive for three to six weeks.

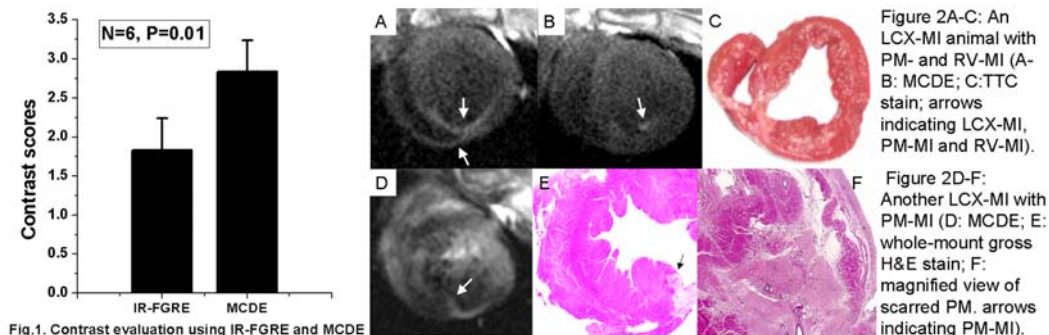
MR studies were conducted on a GE 1.5T Signa Excite system (GE Healthcare, Milwaukee, WI). The MR examination included a steady-state free precession (SSFP) LV function study pre-contrast, and DE-MRI using IR-FGRE and MCDE post-contrast. DE-MRI was performed 10-20 minutes after double-dose bolus injection of Gd-DTPA. Both IR-FGRE and MCDE covered the whole LV in short-axis oblique slices (SAO, slice thickness of 5 mm without gaps) and/or two- or four-chamber views. For IR-FGRE, the TI varied from 200 to 300 ms, depending on the null point of healthy myocardium. For MCDE, a segmented SSFP readout is used following an inversion pulse, providing 20 cardiac-phase-resolved images at varying effective TIs [4]. Axial transverse slices were selectively obtained to better demonstrate RV abnormalities. The in-plane resolution was 1mm x 1mm for both IR-FGRE and MCDE. The contrast between blood pool and hyper-enhanced LV infarct was rated as excellent (3), good (2) or fair (1) based on their differentiation.

Upon the completion of MRI examinations all animals were sacrificed. In five animals (3 LCX-MI, 2 LAD-MI) the heart was removed. Two to three whole-mount SAO blocks based on DE-MRI images with 4-5 mm thickness were sliced and kept in a 10% neutral-buffered formalin solution for extended fixation, followed by a long paraffin processing using a non-routine schedule to allow paraffin infiltration [5]. Sections with 4-micron thickness were stained using haematoxylin and eosin (H&E) and/or Masson trichrome methods; these slides were then digitally scanned at a resolution of two to ten microns for further analysis. In one animal (LCX-MI) macroscopic examination and TTC staining were conducted for the excised heart and selected small tissue blocks from suspected PM-MI sent for histology with H&E staining.

Results: Macroscopic examination of the excised heart, TTC staining, and gross whole-mount histology confirmed the presence of LV-MI in all animals, RV involvement in 3 animals (2 LAD-MI plus 1 LCX-MI), and PM involvement in 4 animals (LCX-MI). The gross appearance of chronic MI was gray-white scarring in LV, RV and PM with increased collagen deposition in histology. Gross whole-mount histopathology slides were the best to show the scar tissue and the heterogeneity within the infarct. In animals with PM involvement, the scarred PM demonstrated more heterogeneity with normal islands of myocytes within the scar. Other subtle myocardial findings on whole-mount histology included a long rim of thinned healthy myocardium located in the endo- or epi-myocardial layers and bundles of finger-like cardiac myofibers extending into the scar tissue.

Although IR-FGRE and MCDE determined the presence and extent of LV-MI equally well, better contrast scores were achieved in MCDE (2.8 ± 0.40) compared to IR-FGRE (1.83 ± 0.41 , $P=0.01$, Figure 1). MCDE clearly demonstrated PM-MI in 4 LCX-MI (100%, Figure 2), as verified by partially scarred PM on histology. However, these could not be visualized in the corresponding IR-FGRE images, which displayed poor contrast between the blood pool and infarct myocardium. This also may be related to significant infarct heterogeneity in PM observed from whole-mount histology; there might be less Gd uptake in these more heterogeneous PM regions reducing contrast between the PM and blood pool. The multi-contrast capability of MCDE facilitates an improved differentiation between blood pool and infarct. This is especially important for the detection of PM-MI since a large portion of PM extends within the LV blood pool and does not attach to the solid LV wall [6]. For the detection of RV involvement in 3 animals with histological evidence, IR-FGRE was ineffective, with zero detection rate. MCDE detected RV-MI in two animals but missed one small case of RV involvement in LAD-MI. In one LCX-MI both PM- and RV involvement were identified using MCDE. The presence of pericardial fat tissue and the thinned RV free wall were the primary culprits for poor identification of RV involvement using IR-FGRE [7]. Other subtle histological findings such as normal islands of myocytes within the scar and bundles of finger-like cardiac muscle extending into the infarct cannot be identified easily from visual inspection of original DE-MRI images using either technique due to the limited spatial resolution. However, myocardial T1* mapping based on MCDE imaging can be used to show intermediate contrast between viable myocardium and scar tissue, providing a way to demonstrate the infarct heterogeneity [4].

Conclusions: Compared to conventional DE-MRI, MCDE imaging provides better contrast between blood pool, infarct myocardium, and surrounding pericardial fat, thus improving the determination of clinically significant subtle myocardial damage associated with MI such as PM- and RV-MI. MCDE with higher resolution may be needed to further explore the spatial structure of infarct heterogeneity.



References:

1. DePasquale NP. *Annu Rev Med* 1971; 22:327.
2. Bogun F. *JACC* 2008; 51:1794.
3. Larose E, et al. *JACC* 2007; 49:855.
4. Detsky JS, et al. *MRM* 2007; 58:365.
5. Clarke GM. *Histopathology* 2007; 50:232.
6. Axel L. *Circulation* 2004; 109:3145.
7. Yang Y, et al. *JCMR* 2008; 10(suppl 1): A359.