Manganese-Enhanced MRI Combined with Delayed Enhancement MRI Detects Injured Border Zone Myocardium in a Pig Ischemia-Reperfusion Model

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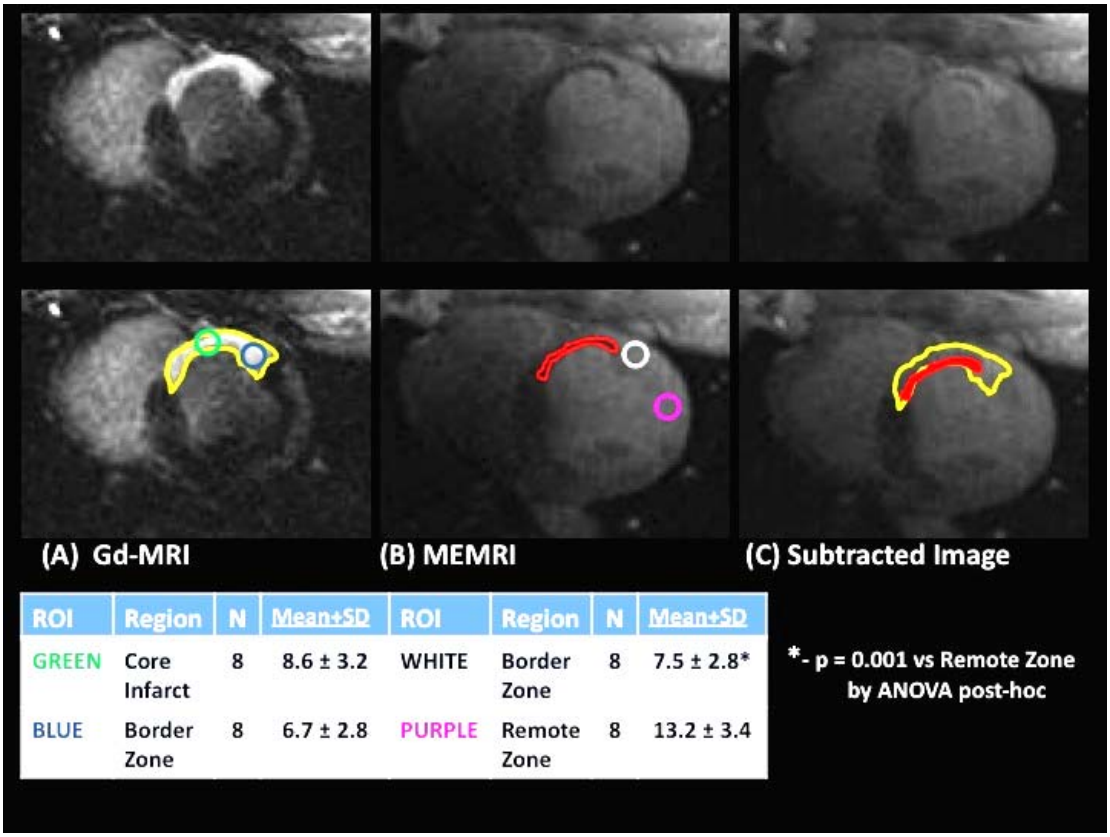
Background: Ischemic heart disease remains a leading cause of death. Improved, non-invasive detection of viable myocardium would lead to more effective therapy for ischemic cardiomyopathy. Delayed enhancement MRI (DE-MRI) with gadolinium (Gd) identifies the scarred, non-viable morphology of the myocardium. This signal does not provide any direct cell viability information. On the other hand, manganese-enhanced MRI (MEMRI) produces a T1-shortening effect like Gd while also detecting specific functional uptake of Mn^{2+} into viable cells via voltage-gated Ca^{2+} channels. Prior work in our lab has demonstrated reliable MEMRI of the viable myocardium. In this study, we generated multi-contrast myocardial assessment by combining 3D DE-MRI and MEMRI in a large animal ischemia-reperfusion (IR) model to delineate peri-infarct border zone *in vivo*.
Hypothesis: Combined MEMRI and DE-MRI will identify viable, injured peri-infarct myocardium after IR injury in pig hearts *in vivo*.
Methods: 60 min IR injury was induced in 6 adult farm pigs (~50kg) using percutaneous balloon occlusion of the proximal left anterior descending coronary artery. 21 days after IR injury, 3 Tesla cardiac MRI was performed (Signa 3T HDx, GE HealthCare, USA) with an 8 channel cardiac coil (3.0T HD Cardiac Array, GE). Functional images were acquired using FIESTA sequences (SSFP: TR 3.8, TE minimum full, flip angle 45, slice thickness 10.0, matrix 224x224, FOV 35.0). In 3 pigs, MEMRI (FGRE-IR: TR 4.7 ms TE 1.3 ms, TI 200 ms, FA 10, ST 10mm matrix 224x192) was obtained 25-40 minutes after a 0.7cc/kg intravenous bolus of manganese chloride solution (Eagle Vision Pharmaceutical Corp., Harrisburgh, PA). Finally, both 2D and 3D myocardial DE-MRI (3D MDE: 3D-FGRE-IR: TR 4.6, TE minimum, flip angle 15, slice thickness 3.0, matrix 256x256, FOV 35.0) were acquired 10-20 min after injection of 0.2 mmol/kg Gd (Magnevist, Bayer HealthCare, Germany). Image analysis was performed on an Advantage Workstation (AW VolumeShare, GE HealthCare, USA) and a public domain Java image processing program (Image-J Ver. 1.42, NIH, USA). The infarct size and LV volumes were determined by tracing the endocardial, epicardial, and infarcted borders manually. The percentage of infarct to normal myocardium was calculated using infarct volume[cm^3]/LV volume[cm^3]. 2,3,5-Triphenyltetrazolium chloride (TTC) histologic stain of the explanted hearts was performed to validate the MRI findings.
Results: Average ejection fraction (%) by MRI quantification demonstrated severely reduced LV systolic function (25±5%, n=6) following IR injury. 3D DE-MRI quantification of scar volume (r^2=0.91, p=0.003) correlated significantly with histopathologic scar volume quantification. MEMRI pattern revealed a significantly (p<0.05) lower scar volume (MEMRI defect area) percentage compared to DE-MRI (6.6±2.5%* vs. 20.4±1.7%,* - p<0.05, n=6). The areas of DE-MRI scar outside of MEMRI defect regions in the peri-infarct border zone demonstrated significant heterogeneity with lower SNR compared to the core areas of DE-MRI located within the corresponding MEMRI defect regions as shown in Figure 1. Similarly, the measurement of MEMRI signal in the peri-infarct border zone also displayed lower SNRs compared to the remote areas of normal myocardium as shown in Figure 1. (see figure). These observations suggest that the viable but injured myocardium exists within these peri-infarct border zones as delineated by the specific, preferential Mn^{2+} uptake in MEMRI.



ROI	Region	N	Mean+SD	ROI	Region	N	Mean+SD
GREEN	Core Infarct	8	8.6 ± 3.2	WHITE	Border Zone	8	7.5 ± 2.8*
BLUE	Border Zone	8	6.7 ± 2.8	PURPLE	Remote Zone	8	13.2 ± 3.4

*- p = 0.001 vs Remote Zone by ANOVA post-hoc

Figure 1. First Row: Representative short-axis images showing the differing infarct patterns of Gadolinium DE-MRI (Gd-MRI, left column) and MEMRI (middle column). Subtracted image (right column) shows the pattern mismatch of the two techniques. Second Row: the area of DE-MRI (yellow tracing) is visibly greater than the MEMRI defect area (red tracing). Colored circles reflect regions of interest (ROI) with respective SNR calculations noted in lower panel. SNR from the border zone of DE-MRI region (blue ROI) trends lower than the core zone of DE-MRI region (green ROI). The corresponding region on MEMRI is bright (white ROI), indicating Mn^{2+} uptake. However, the SNR of this region is significantly less than the SNR of a remote region on MEMRI (purple ROI). These findings indicate demarcation of injury in the border zone using the combined contrast technique. N=8 sets of SNRs from 8 matched DE-MRI and MEMRI slices across 3 pig hearts.

Conclusions: MEMRI infarct patterns exhibit a smaller zone of non-viable tissue than the DE-MRI infarct patterns. This signal difference delineates the peri-infarct border zone suggesting that 'at-risk' myocardium may be detectable using this novel combined contrast method, which enables both morphological and functional assessment of the myocardial tissue. SNR heterogeneity in the border zone areas demonstrated by combined MEMRI and DE-MRI may indicate gradations of tissue viability or injury in these regions. Further evaluation of the nature of this heterogeneous signal is required.