Using Magnanese-Enhanced MRI to Monitor the Efficacy of Angiotensin Converting Enzyme Inhibitor Treatment in a Murine Myocardial Infarction

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Introduction: The ischemically injured myocardium contains a mixture of viable and non-viable tissue post-myocardial infarction (MI); thus, a method to discern the various zones would be of great value in clinical management[1]. The traditional approach in treatment attempts to salvage the viable peri-infarcted areas, by pharmaceutical intervention. A popular route of treatment is providing Angiotensin Converting Enzyme inhibitors (ACEi) to reduce QT dispersion (QTd) following MI. Increased QTd is a marker of electrical instability predisposing to ventricular arrhythmias in the infracted areas. Captopril, an ACEi, is widely used as an effective reducer of mortality and morbidity following MI[2] , primarily due to its ability to improve left ventricular remodeling following the cardiac event[3].The physiological effect of Captopril has on the peri-infarcted regions post- MI has not been well interpreted. Studies show promise in the field of cardiac imaging using manganese as a contrast agent to track changes in tissue viability[4]. In this study we would like to examine, using a murine model: (1) the sensitivity of manganese enhanced MRI (MEMRI) T_1 mapping to detect peri-infarction sites, and (2) the sensitivity to differentiate pre- and post- ACEi treatment. This non-invasive imaging technique could provide a potential diagnostic method to monitor pharmaceutical intervention and therefore improve diagnostic assessment of ischemic damage, thus improving patient care.

Methods: The left anterior descending coronary arteries of male C57B1/6 mice (7-10 weeks old), were ligated to induce MI. One group then received captopril (1 mg/kg BW) administered in their drinking water for 7 days (n=7); comparable to the 65 mg daily dose post-MI administered to clinical patients (7). The other group received no treatment (n=9). $MnCl_2$ (282 nmol/g BW) was infused at a rate of 0.6 ml/hr 7-10 days post-MI. The mice were then imaged in a 7.0 T 20 cm horizontal bore Biospec MRI spectrometer (Bruker Instruments, Billerica, MA) equipped with a micro imaging gradient insert (950 mT/m). A 35 mm inner diameter coil was used to transmit and receive at ^1H frequency. Mn^{2+} signal enhancement was monitored with a T_1-weighted ECG gated Gradient Echo Flow Compensated (GEFC) pulse sequence with the following parameters: matrix= 128x128; TE= 3.5 ms; TR = 35ms; slice thickness= 1.0 mm; FOV= 3.0x3.0 cm; and NA= 6. The short axis T_1-map GEFC images were acquired with an ECG gated, flow compensated Look-Locker pulse sequence with the following parameters: matrix= 128x128; Inter TE/TR= 2.5 ms/10sec; slice thickness= 1.0 mm; FOV= 3.0x3.0 cm; NA= 2; inversion time/interval= 9/150 ms; echo images= 50. The analysis of the resulting images was performed using an in-house computer program (Myoplotter), developed in MATLAB (Natick, MA) that segmented the cardiac image into 24 sectors and reported the T_1 value of each, which has an inverse relationship with the uptake of Mn^{2+}.

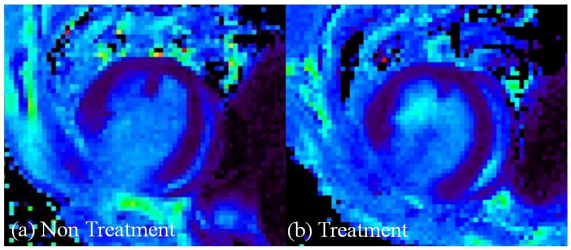

Figure 1: Short axis T_1 MRI maps of mice at the level of the infarction. Areas which have taken up more Mn^{2+} appear darker . Treatment (a) and non treatment (b). The segmentation program imports raw MRI images into 24 equal sectors for analysis. It then provides data on thickness and T_1 value in both graphical sector maps and plain numeric formats.

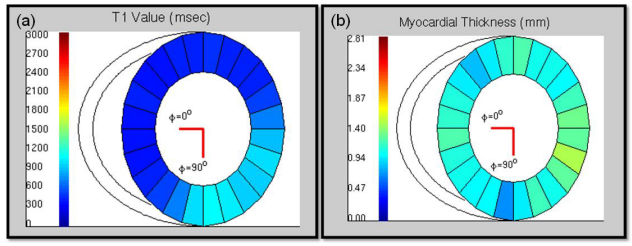

Figure 2: Example Sector maps. Numbering starts at 90º, increasing counterclockwise. Sectors 1-6 and 24 correspond to LAD territory (infarct zone). T_1 values for each sector are generated by averaging the values of pixels within that sector (a).

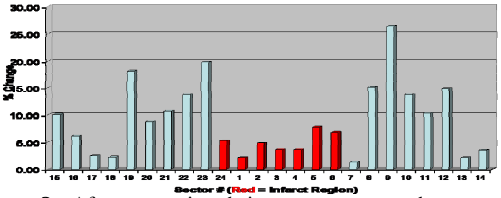

Figure 3: After comparing their sector averages, the percent change in T_1 value at each sector from the non-treatment (control) group versus the treatment group was calculated. Sectors labeled in red were in the approximate infarcted area directly affected by the LAD

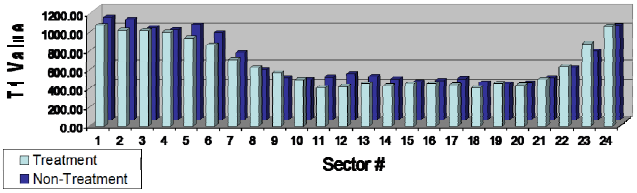

Figure 4: Using the numeric output from Myoplotter, averages were taken of each sector's T_1 value across all treatment and control mice. Higher T_1 indicates less uptake of the Mn^{2+} contrast agent.

Results: Variation in Mn^{2+} uptake due to MI is shown in the myocardium (Figure 1). There is minimal variation between the treatment and the control group within the MI zone (Figure 2); however, the sectors adjacent to the infarct regions showed a higher percent change with and without ACEi treatment (26.5%) in the T_1 values between the groups (Figure 3). The most impacted areas of note were sector #19 (p=0.019) and sector #10 (p=0.066), both within the peri-infarct region.

Conclusion: Differential Mn^{2+} uptake between the experimental and control mice were observed in the peri-infarct regions, indicating the MEMRI with T_1 mapping implementation is sensitive enough to show a difference with and without pharmaceutical intervention by ACEi. This agrees with the idea that the necrotic regions in, and healthy regions far away from, the infarct zone are less likely to be affected by treatment than transitional areas. Further research is warranted on why the Mn^{2+} uptake in peri-infarct regions is different in the treatment group. There is also room to improve the MEMRI T_1 mapping technique, along with histological validation, to be more sensitive in demonstrating preclinical models with potential translational impact.

References:

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