Serial assessment of hyperintense post-infarct myocardial edema in mice by T2-weighted MRI

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Introduction: Following reperfused coronary occlusion, a need exists to quickly and reliably differentiate acute myocardial infarct (MI) from the surrounding salvaged area (SA) of myocardium that together defines the area at risk (AAR) [1]. T2-weighted cardiac MRI (T2w CMR) noninvasively detects the edematous region that delineates the AAR by increased signal intensity, while separately, late gadolinium-enhanced (LGE) CMR quantifies the necrotic MI region. The size difference between the AAR and MI determines the salvaged area (SA) made possible by reperfusion and has prognostic value [2]. Past T2w CMR studies have been performed in larger mammals, including canine, swine, and humans, but not in mice [3]. Furthermore, these past studies applied T2w CMR at inconsistent time-points that did not track the time-course of hyperintense edema. The goal of this study was to serially apply, in post-MI mice, T2w CMR to noninvasively quantify the hyperintense edematous AAR, along with LGE CMR to measure MI size, in order to characterize the AAR, MI, and SA size relationships over a 9-day period following MI.

Methods: We developed a T2w CMR sequence, based on T2 prep with multislice gradient echo readout, specifically for mice, to run on a Bruker 7 T ClinScan. We imaged 4 healthy mice (for baseline) and 23 post-MI mice as early as hour 3 through day 9 (D9) at multiple time points. MI was achieved by a surgical 20 to 30-minute coronary occlusion of the left anterior descending artery, followed by reperfusion. Multislice scans were performed to cover the entire heart with 6-7 contiguous short axis slices. On D1, after T2w CMR was completed, LGE CMR was also performed to measure MI size, using intraperitoneal infused gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA), followed ten minutes later by multislice inversion-recovery imaging. T2w CMR parameters included: TR = 3 sec, TE = 60 ms, FOV = 25 x 25 mm, slice thickness = 1 mm, matrix = 128 x 128, BW = 520 Hz/pixel, averages = 2. Image analysis via Matlab included selecting the necessary regions of total myocardium and a "normal" myocardium subregion in each slice. This allowed for per-slice statistical threshold segmentation of the hyperintense AAR and MI regions and subsequent calculation of whole-heart relationships as: AAR as percent LV mass, MI as percent LV mass, MI as percent AAR, and the salvaged area (SA) as percent of AAR.

Results: The earliest T2w edema images, collected 3-5 hours post-reperfusion, gave a hyperintensity contrast to noise ratio (CNR) of 29.7 ± 2.1 (mean ± SEM) above normal myocardium. All 23 post-MI mice had a T2w hyperintense AAR sizes larger than the MI size. Figure 1A-D compares same-slice, long and short axis sets of T2w AAR (top row) and LGE MI (bottom row), which show good spatial agreement of AAR and MI, and the MI lies within the AAR. Figure 2 presents the 9-day serial study results for the edematous signal CNR. The healthy mice provided the Day 0 (D0) point with no edema. The CNR peaked at D2 with CNR = 43.7 ± 3.4, then resolved by D9 to 18.3 ± 3.4. Also tracked over the 9 days (graphs not presented here) were the changes in LV mass, AAR as % LV mass, and MI as % AAR. At D2 (peak signal), the AAR size was 34.0 ± 2.8 % LV mass, while MI size was 18.7 ± 2.4 % LV mass. Therefore, the MI as % AAR was 53.6 ± 4.8 %, thus defining the salvaged area (SA) as 46.4 ± 4.8 % AAR. The CNR pattern in Figure 2, combined with the rise-and-fall of LV mass during the same period, coincide with inflammatory cell response as reported in previous studies [4], and substantiate an increase in interstitial water content.

Conclusions: By T2w CMR, this study noninvasively tracked for 9 days the hyperintense region resulting from post-MI edema as AAR, and combined LGE MI results, to characterize the AAR, MI, and SA relationships. The peak hyperintense CNR at D2 suggests, at least in mice, that D2 is the best time to quantify the post-MI AAR. These MRI methods may be useful for investigating pharmaceutical strategies for increasing the SA after MI. Furthermore, the mouse model, with genetic manipulations, may be used to identify individual genes and biological pathways that may influence the AAR, MI, and SA outcome. Finally, these same MRI methods provide for both short-term acute MI and long-term LV remodeling studies to be conducted within the same cohort of mice.

References: [1] Abdel-Aty, *et al*, "Edema as a Very Early Marker…", JACC, 53:14, 2009; [2] Friedrich, "Myocardial edema – a new clinical entity?", Nat Rev Cardiol, 7, 2010; [3] O'Regan, *et al*, "Cardiac MRI of myocardial salvage…", Am J Phys Heart Circ Phys, 297, 2009; [4] Vandervelde, *et al*, "Increased inflammatory response…", Cardio Path, 15:2, 2006.

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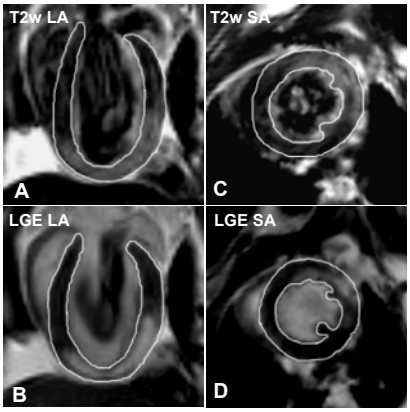

Fig 1. CMR comparing AAR (top) to same-slice MI (bottom) shows spatial agreement and MI within the AAR.

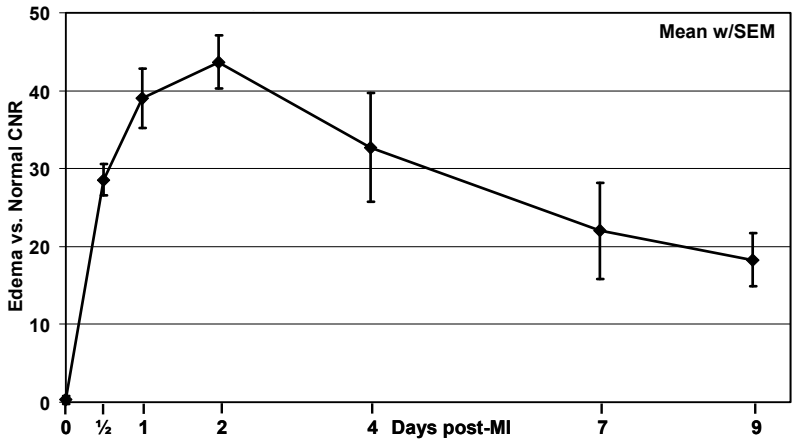

Fig 2. CNR of hyperintense edema tracked by T2w CMR for 9 days including: healthy mice at D0, peak edema CNR at D2, and partial signal resolve by D9.