Acute Hemorrhagic Myocardial Infarction Leads to Localized Chronic Iron Deposition: A CMR Study

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Target Audience – Scientists and clinicians studying myocardial ischemia-reperfusion injury

Purpose – Reperfusion into severely ischemic myocardium leads to intramyocardial hemorrhage (IMH). However, the long-term fate of IMH is largely unexplored. We investigated whether acute IMH, secondary to reperfused myocardial infarctions (MIs), leads to localized chronic iron deposition within infarcted territories in a pilot patient population and a proof-of-concept canine model.

Methods - *Patient Studies*: Patients (n=15; mean age=58±8 years; 3 women) with first STEMI, who underwent successful PCI (luminal stenosis reduced to 20% of residual stenosis), underwent CMR (1.5T) at 3 days (acute) and 6 months (chronic) post-PCI. 2D T2* maps (6 TEs=2.6ms–13.7ms; ΔTE=2.2ms) and Late Gadolinium Enhancement (LGE) of the entire LV were acquired. ***Animal Studies:*** Eleven canines were subjected to 3 hours of LAD occlusion followed by reperfusion (Infarct group), while three canines were sham-operated (Sham group). The Infarct group underwent CMR (1.5T) at 3 days (acute) and 56 days (chronic) post-reperfusion, while the Sham group underwent CMR at matched time points. In-vivo 2D T2* maps (6 TEs=3.4–18.4ms; ΔTE=3.0ms) and LGE images of the entire LV were acquired. Commonly used imaging parameters were slice thickness=8mm and in-plane resolution=1.3x1.3mm^2. The animals were euthanized, hearts were excised and sliced, and ex-vivo 2D T2* maps and LGE images of the slices were acquired. Samples of hemorrhagic (Hemo+), non-hemorrhagic (Hemo-), remote and Sham myocardium were isolated. The extent of iron deposition ([Fe]) within each sample was measured using mass spectrometry. Histology was performed on representative samples. ***Image Analysis:*** Remote myocardium was defined as the region with no Gadolinium hyperintensity on LGE images. Infarcted myocardium was defined on LGE images as the region with mean signal intensity (SI) at least 5 standard deviations (SDs) above that of a reference ROI drawn in remote myocardium[1]. Hemorrhagic (Hemo+) myocardium was defined on T2*-weighted images as the region with mean SI at least 2 SDs below that of the same reference ROI[2]. Non-hemorrhagic (Hemo-) myocardium was defined as infarcted myocardium that did not show any T2* losses as detected by the Mean-2SD criterion on the corresponding T2*-weighted images.

Results – *Patients:* Patients who sustained acute Hemo+ infarctions (defined by T2* losses on day 3 T2* maps) had persistent T2* losses within infarcted territories even at 6 months post-PCI. Mean T2* of Hemo+ was 40% lower than those of remote myocardium and non-hemorrhagic infarctions (Hemo-) at both acute and chronic phases (p<0.001). However, no difference was observed between T2* measures obtained from remote myocardium and non-hemorrhagic (Hemo-) infarctions in both acute and chronic phases (p=0.14). ***Animals:*** Consistent with the patient studies, canines with acute Hemo+ infarctions (defined by T2* losses on day 3 T2* maps) had persistent T2* losses within infarcted even at 56 days post-reperfusion. Mean in-vivo T2* of Hemo+ myocardium was 40% lower than those of control tissues (remote, sham and Hemo- myocardium) at both 3 days and 56 days post-reperfusion (p<0.001), while no differences were found among the in-vivo T2* of control tissues (p=0.71). Mean ex-vivo T2* of Hemo+ myocardium was also 40% lower than those of control tissues (p<0.001), while no difference was found among control tissues (p=0.43). Perl's stain confirmed localized iron deposition only with Hemo+ myocardium. Mass spectrometry showed that Hemo+ myocardium had 10-fold higher iron content than control tissues (p<0.001). There was a strong linear relationship between log(ex-vivo T2*) and –log([Fe]) (R^2=0.7, p<0.001).

Conclusions – Acute reperfusion IMH leads to localized chronic iron deposition within infarcted territories, which can be reliably assessed with T2* CMR. The impact of the chronic iron deposition following acute reperfusion IMH remains to be investigated.

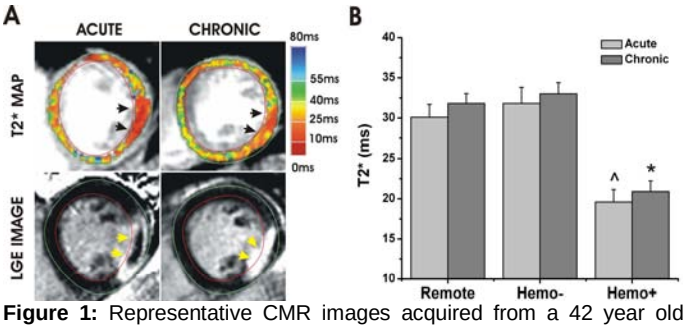

Figure 1: Representative CMR images acquired from a 42 year old patient with first STEMI at 3 days (acute) and 6 months (chronic) post-PCI are shown (**A**). Mean T2* of remote myocardium, and Hemo- and Hemo+ infarctions at both acute and chronic phases are shown (**B**).

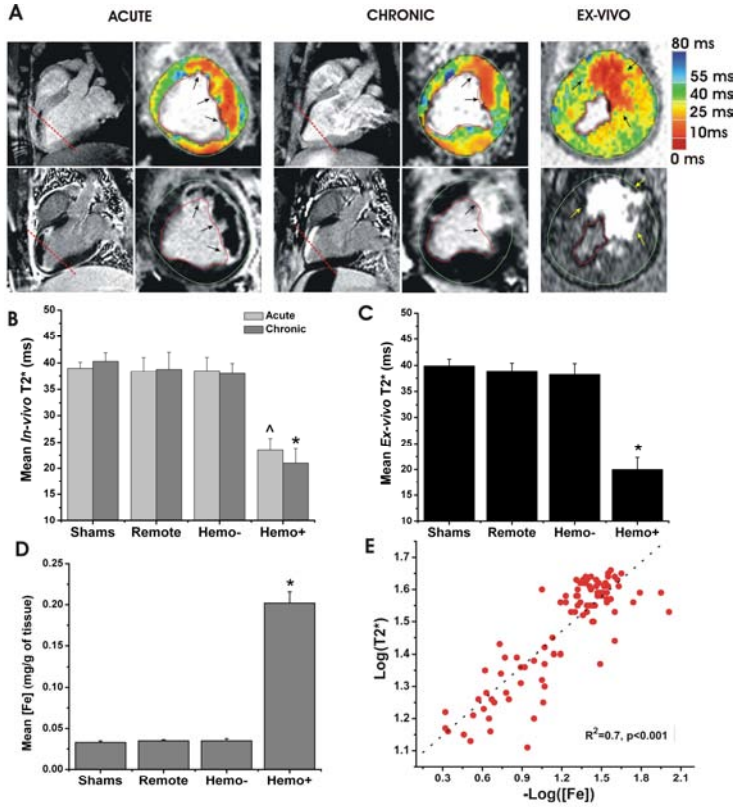

Figure 2: Representative in-vivo CMR images from a canine subjected to ischemia-reperfusion acquired at 3 days (acute) and 56 days (chronic) post-reperfusion, and the corresponding ex-vivo CMR images are shown (**A**). Mean in-vivo T2* (both acute and chronic; **B**), ex-vivo T2* (**C**) and iron content (**D**) of sham, remote, Hemo+ and Hemo- myocardium are shown. Linear relationship between log(ex-vivo T2*) and –log([Fe]) is shown (**E**).

References –

(1) Bondarenko O et al. *J Cardiovasc Magn Reson.* 2005;7(2):481-485; **(2)** Kumar A et al. *JACC Cardiovasc Imaging.* Dec 2011;4(12):1274-1283.