Quantitative MRI reveals action of iron chelator in hemorrhagic myocardial infarction

Nilesh R. Ghugre[1], Jennifer Barry[1], John C Wood[2], Alan Moody[3], Bradley H Strauss[4], and Graham A. Wright[1,5]

[1]*Imaging Research, Sunnybrook Research Institute, Toronto, ON, Canada,* [2]*Division of Cardiology, Childrens Hospital Los Angeles, Los Angeles, CA, United States,* [3]*Department of Medical Imaging, Sunnybrook Health Sciences Centre, Toronto, ON, Canada,* [4]*Schulich Heart Program, Sunnybrook Health Sciences Centre, Toronto, ON, Canada,* [5]*Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada*

Introduction: It has been speculated that iron chelation may be beneficial in acute myocardial infarction (AMI) and that early treatment can limit ischemia-reperfusion injury and also reduce infarct size (1,2). However, the role of iron chelation in hemorrhagic myocardial infarction, where it would be most suited, has not yet been explored. Reperfusion hemorrhage results in accumulation of iron degradation products of hemoglobin that may be pro-inflammatory as free iron is toxic in nature. The purpose of the study was to investigate the interaction between the iron chelating agent deferiprone (DFP) and hemorrhage in a porcine model of myocardial infarction and monitor remodeling by quantitative MRI.

Methods: The study involved two groups of animals that were subjected to a 90 min balloon occlusion of the LAD followed by reperfusion – untreated (N=2) and DFP treated (N=2). DFP (ApoPharma Inc., Toronto, ON) was administered (orally) a few hours before the procedure (pre-loading) and treatment was continued with a daily dose of 100 mg/kg. Imaging was performed on a 3T MRI scanner (MR 750, GE Healthcare) pre-AMI (healthy) and from day 2 to week 4 post-AMI. Edema was evaluated by T2 quantification using a T2-prepared spiral sequence and hemorrhage was identified by T2* determined using a multi-echo gradient-echo acquisition (3). Infarct assessment was performed by delayed hyperenhancement (DHE) using an IR-GRE sequence.

Results: Figure 1 demonstrates representative images from the two groups while Fig. 2 shows the cumulative time course of the CMR measurements. In the DFP group, hemorrhage, as indicated by the T2* image (red arrows), was observed only on day 2 and by week 1 it had completely resolved. This was in contrast to the untreated group where resolution of hemorrhage was delayed to week 4. With DFP, inflammation or edema was substantially reduced by week 4 with T2 values approaching control levels. In the untreated group, edema persisted up to week 4. Ejection fraction (EF) was depressed by week 4 in both groups. However, end-diastolic and end-systolic volumes were relatively unchanged in the DFP group while they increased significantly in the untreated group. In both groups, microvascular obstruction (MVO) was seen on day 2 that was partially resolved by week 1.

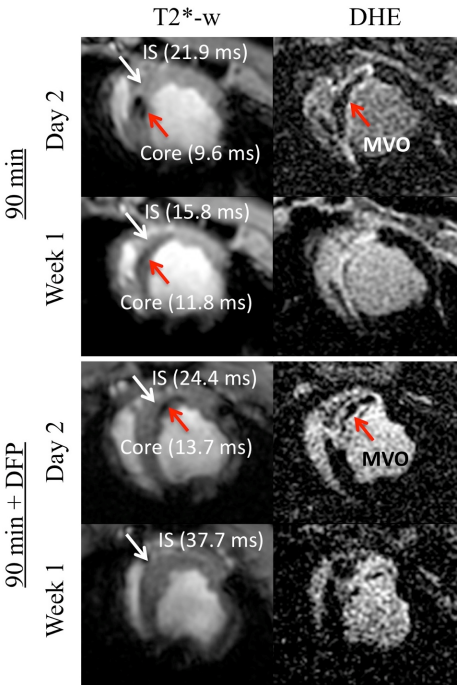

Figure 1: Short axis images from a representative animal subjected to 90-min LAD occlusion without (*top panels*) and with (*bottom panels*) treatment of DFP.

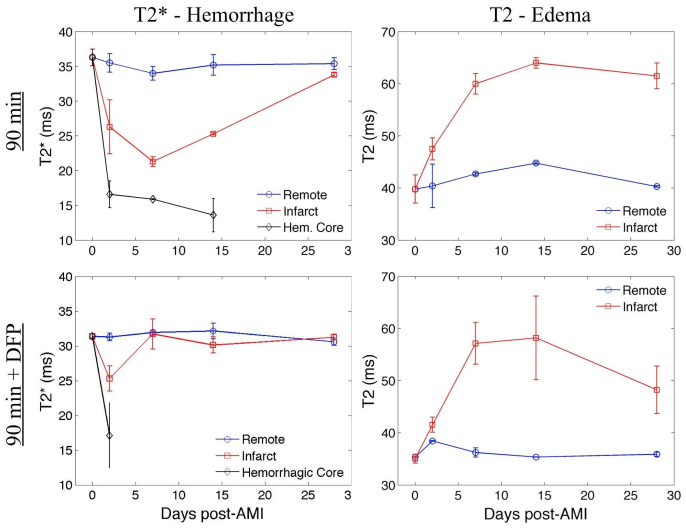

Figure 2: Cumulative time course of T2 and T2* parameters post-AMI pooled across all animals in the 90 min infarct – untreated and treated with deferiprone (DFP); error bars show standard error and day 0 indicates control MRI scans in healthy animals.

Discussion: The presentation of intramyocardial hemorrhage as a consequence of reperfusion injury in AMI has been well documented in both humans (4) and animal models (5). Hemorrhage may be a source of iron toxicity and a mediator of inflammation, directly contributing to adverse remodeling in the setting of AMI. DFP was able to penetrate the infarct zone and was also effective in neutralizing hemorrhagic byproducts. Elimination of hemorrhage resulted in faster resolution of edema and maintenance of normal ventricular volumes, indicating reduced adverse remodeling. The iron neutralizing capacity of DFP in the scenario of hemorrhagic infarction is apparent from this pilot study. Iron chelation could potentially serve as an adjunctive therapy in hemorrhagic AMI.

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