# Using MRI to Evaluate Injectable Hyaluronic Acid Hydrogel Therapy for Myocardial Infarct Repair

Shauna M. Dorsey[1], Jeremy R. McGarvey[2], Jonathan F. Wenk[3], Leron Arama[1], Joseph H. Gorman III[2], Robert C. Gorman[2], and Jason A. Burdick[1]

[1]Department of Bioengineering, [2]Department of Surgery, University of Pennsylvania, Philadelphia, PA.

[3]Department of Mechanical Engineering, University of Kentucky, Lexington, KY.

**Statement of Purpose:** Injectable biomaterials are an attractive therapy to attenuate left ventricular (LV) remodeling after myocardial infarction (MI) by providing mechanical stabilization and reducing myocardial wall stress.[1] One such biomaterial is hyaluronic acid (HA) hydrogels. HA is a linear polysaccharide found in native cardiac extracellular matrix that can be modified with numerous reactive groups to tune hydrogel properties.[2]

Although studies have shown that injectable HA hydrogels improve cardiac structure and function *in vivo*, the mechanism behind their success remains unclear.[3] Imaging modalities, such as MRI, can noninvasively provide mechanistic information over time. Delayed-contrast enhancement (DCE) MRI enables visualization of infarcted regions to quantify infarct expansion. MRI myocardial SPAMM tagging provides a highly detailed assessment of wall motion as a measure of myocardial strain as an input for theoretical finite element (FE) models.[4] FE models have also illustrated the ability of injectable materials to decrease myocardial stress post MI.[4] In this work, we investigated the effects of degradable HA hydrogels on global LV remodeling, infarct expansion, myocardial wall motion, and myocardial stress post MI using MRI and FE modeling.

**Methods:** Hydroxyethyl methacrylated HA (HeMA-HA) macromers were synthesized and crosslinked into hydrogels using a redox initiator system of APS and TEMED.[3] Gelation, compressive temporal mechanics, and degradation were assessed *in vitro*. *In vivo* function (*n=6/condition*) was assessed in an established porcine posterior infarct model. Thirty minutes post MI, treatment animals underwent an array of twenty 0.3 mL injections of prepolymer solution in the infarct area; controls received saline injections. MRI scans were performed at baseline (i.e. prior to infarction) and at 1, 4, 8 and 12 weeks post MI. Animals were sacrificed at 12 weeks.

LV volume and global function was assessed by segmenting cine MRI images throughout all cardiac phases using ITK-SNAP.[5] Infarct wall thickness was measured in cine MRI images at end diastole from radially-oriented spokes positioned throughout the infarct in ImageJ. Infarct volume was quantified by manually segmenting the infarct and LV in DCE MRI images in MIPAV. Regional systolic and diastolic strain was calculated from 3D SPAMM images using a custom optical flow plug-in for ImageJ to derive 3D displacement flow fields.[6] Using a custom MATLAB code, radial maximum principal strain ($\varepsilon_{max}$) was calculated for the infarct, borderzone, and remote myocardial regions. Diastolic strains were input into a FE model to assess infarct stiffness. LS-OPT commercial optimization software was used to minimize the error between the FE model predicted strain and *in-vivo* MRI measured strain and determine regional stress distributions.

**Results:** Based on *in vitro* characterization (data not shown), a single hydrogel formation was applied *in vivo* (*in vitro* degradation 9.4 weeks, initial compressive modulus 152 kPa). MRI was used to assess cardiac structure and function, infarct expansion, and myocardial wall function. Hydrogel treatment leads to decreased LV volumes and improved ejection fraction (data not shown). Infarct wall thickness is greater with hydrogel therapy than saline, particularly after 1 week (Figure 1A). Infarct volume remains consistent in hydrogel animals due to bulking but decreases in saline controls due to wall thinning (Figure 1B). Regional myocardial wall function was assessed in terms of contractility and passive material properties using systolic and diastolic strain analysis, respectively. Beyond 1 week, systolic borderzone strain is higher with hydrogel therapy than saline, implying preserved borderzone contractility (Figure 1C). Preliminary material parameter optimization, using FE model simulations with diastolic strain inputs, demonstrates hydrogel therapy significantly increases infarct stiffness between 1 and 4 weeks with a slight regression at 8 weeks due to hydrogel degradation whereas saline animal infarcts become progressively less stiff with time (Figure 1D). These results demonstrate that hydrogels with high initial compressive mechanics can limit infarct expansion, maintain borderzone contractility, and increase infarct stiffness to attenuate LV remodeling.

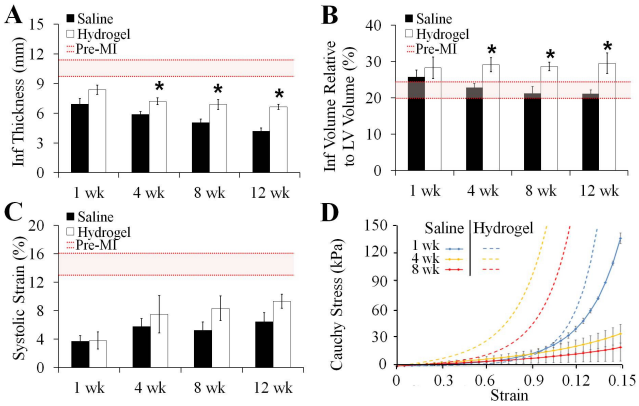


**Figure 1**: Infarct thickness (A) and volume (B). Borderzone systolic radial ($\varepsilon_{max}$) strain (C). Changes in infarct stiffness over time (D). Data presented as mean ± SD. *$p < 0.05$ vs controls.

**Conclusions:** We have successfully applied a tunable, injectable hydrogel system *in vivo* to examine its effect on global remodeling, infarct expansion and myocardial wall function using MRI. Evaluation of myocardial properties through our FE model provides additional insight into the mechanism by which injectable materials improve long-term structural and functional outcomes post MI.

**References:** [1] Christman, KL. J Am Coll Cardiol 2006;48:907-13. [2] Burdick, JA. Biomacromolecules 2005;6:386-91. [3] Tous, E. Biomacromolecules 2011;12: 4127-35. [4] Wenk, JF. J Biomech Eng 2009;131:121011-01-07. [5] Yushkevich, PA. Neuroimage 2006;31:1116-28. [6] Xu, C. J Cardiovasc Magn Reson 2010;12:19.