Examining the Influence of Injectable Hyaluronic Acid Hydrogels on Myocardial Infarct Repair using MRI

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

[1]Department of Bioengineering, [2]Harrison Department of Surgical Research, University of Pennsylvania, Philadelphia, PA.
[3]Department of Mechanical Engineering, University of Kentucky, Lexington, KY.

Statement of Purpose: Injectable biomaterials have become an attractive therapy to attenuate left ventricular remodeling after myocardial infarction (MI) by providing mechanical stabilization and reducing myocardial wall stress.[1] One such class of materials is hyaluronic acid (HA) hydrogels. HA is a linear polysaccharide found in native cardiac extracellular matrix and can be modified with numerous reactive groups.[2] The addition and amount of these groups enables hydrogel formation and tuning of hydrogel properties (e.g., mechanics, degradation).

Although studies have shown the importance of biomaterial mechanics in attenuating remodeling, the degree and duration of mechanical stabilization necessary to provide benefit remains unclear.[3,4] Imaging modalities, such as MRI, can non-invasively provide mechanistic information over time, which may lead to better design principles for future biomaterial optimization. MRI myocardial tagging enables a highly detailed assessment of myocardial motion as a measure of myocardial strain as an input for theoretical finite element (FE) models.[5] FE models have also illustrated the ability of injectable materials to decrease myocardial stress post MI.[5] In this work, we investigated the mechanical effects of degradable HA hydrogels on myocardial stress and long-term remodeling post MI using MRI and FE modeling.

Methods: Briefly, hydroxyethyl methacrylated HA (HeMA-HA) (Figure 1A) was synthesized by coupling 2-hydroxyethylmethacryl-succinate (HeMA-COOH) to HA-tetrabutylammonium salt using ditertbutyldicarbonate (BOC_2O) and 4-dimethylaminopyridine. [4] Methacrylation was altered by varying the ratio of BOC_2O to HeMA-COOH and quantified with ^{1}H-NMR (Bruker).[4] The macromer was dissolved in PBS and hydrogel crosslinking was initiated using a redox system of APS and TEMED.[4] Gelation onset (*n=3-4*) was quantified with a AR2000ex Rheometer (TA Instruments) by monitoring the storage (G') and loss (G") moduli over time at 37°C under 1% strain and a frequency of 1 Hz in a cone-plate geometry (1°, 20 mm diameter). Compression testing (*n=3-4*) was performed using a Dynamic Mechanical Analyzer (Q800 TA Instruments) at a strain rate of 10%/min. Compressive moduli were calculated from 10-20% strain. Degradation was monitored in PBS at 37°C using an uronic acid assay and mechanical testing.

In vivo function (*n=6/condition*) was assessed in an established porcine infarct model. Posterior infarction was induced by suture ligation of the left circumflex artery and selected obtuse marginal branches. 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 and a histological evaluation was performed.

Results: In addition to being enzymatically degradable, HA functionalization with HeMA enables the resulting hydrogel to be hydrolytically degradable, where properties such as degradation and mechanics are controlled through the extent of HA modification. *In vitro* characterization studies (data not shown) were used to select a single HeMA-HA formulation to apply *in vivo*. The gelation (gel onset of 2.76 min), degradation (Figure 1B), and temporal mechanics (Figure 1C) were characterized *in vitro*. Based on previous studies,[3,4] this formulation was selected due to its anticipated favorable properties: a degradation rate of 9.4 weeks and an initial compressive modulus of 151.7 kPa.

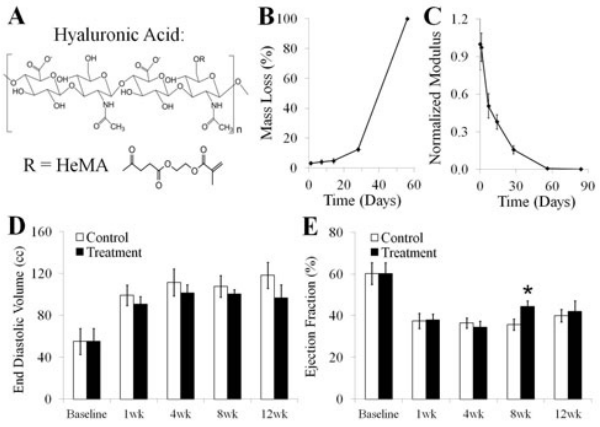

Figure 1: Chemical structure of HeMA-HA (A). Degradation rate (B) and temporal mechanics (C) of selected formulation. EDV (D) and EF (E) over 12 weeks. Data presented as mean ± SD. *$p < 0.05$ vs controls.

MRI was used to assess cardiac structure and function, infarct expansion, and myocardial strain *in vivo*. Structural data (EDV and ESV, data not shown) shows a decrease in ventricular volumes at all time points for the animals that received hydrogel therapy as compared to the controls (Figure 1D). Functional cardiac data (EF and SV, data not shown) shows an improvement at 8 and 12 weeks post MI (Figure 1E). These results imply that a material with high initial compressive mechanics can be effective in improving long-term structural and functional outcomes *in vivo*. Ongoing MRI analysis is being performed to assess infarct expansion and myocardial strain as an input for a FE model.

Conclusions: We have successfully designed an injectable hydrogel system with tunable mechanics and degradation. These results provide insight to both the degree and duration of mechanical stabilization necessary to attenuate chronic remodeling post MI. Evaluation of myocardial stress through our FE model will provide additional insight into the mechanism by which injectable materials attenuate remodeling.

References: [1] Christman, KL. J Am Coll Cardiol 2006;48:907-13. [2] Burdick, JA. Biomacromolecules 2005;6:386-91. [3] Ifkovits, JL. PNAS 2010;107:11507-12. [4] Tous, E. Biomacromolecules 2011;12: 4127-35. [5] Wenk, JF. J Biomech Eng 2009;131:121011-01-07.