Influence of Injectable Hyaluronic Acid Hydrogel Degradation Behavior on Myocardial Infarct Repair

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Statement of Purpose: Recently, acellular injectable biomaterials have been shown to attenuate left ventricular remodeling after myocardial infarction by reducing stresses in the heart wall. Although studies have shown that the mechanics of the material plays a role in altering geometry changes that contribute to maladaptive remodeling, few studies have been able to systematically evaluate both the network mechanics and degradation of injectable hydrogels. This is the focus of the present study, in order to gain insight into material design.

Hyaluronic acid (HA), is a native extracellular matrix molecule that can be functionalized to be either primarily enzymatically degradable (addition of a methacrylate, MeHA) or both enzymatically and hydrolytically degradable (addition of a hydroxy ethyl methacrylate, HeMA) and can be injectable via a radical polymerization (e.g., APS/TEMED redox initiators). In this work, we investigated gels in both in vitro studies and in an ovine infarct model with initial moduli of either approximate that of native myocardium or 4-fold higher that exhibit a range of degradation (~3 weeks and up to little mass loss after 8 weeks).

Methods: Briefly, MeHA (Figure 1) was synthesized by reacting HA (LifeCore, 66 kDa) with methacrylic anhydride and dialyzing. HeMA-HA (Figure 1) was synthesized by reacting HeMA-COOH and HA with 4-dimethylaminopyridine and diterbutyl dicarbonate (BOC₂O) at 45°C for 21 hours, dialyzing against DI-H₂O for 15 hours, and precipitating in acetone. Methacrylation was adjusted by varying HeMA-COOH and BOC₂O or methacrylic anhydride allowed for changes in HeMA-HA or MeHA modification, respectively. This study focused on four macromers (low MeHA: 7.7 kPa, high MeHA: 43.0 kPa, low HeMA-HA: 7.2 kPa, high HeMA-HA: 32.5 kPa) each exhibiting unique mass loss profiles and mechanical changes with time (Figure 1). In general, lower modification resulted in a faster degradation rate and decrease in mechanics. Furthermore, functionalization with HeMA leads to more significant changes in degradation and mechanics with time than MeHA. It is important to tailor these properties with the biological and mechanical trends found after infarction.

Results: Varying the concentration of HeMA-COOH and BOC₂O or methacrylic anhydride allowed for changes in HeMA-HA or MeHA modification, respectively. This study focused on four macromers (low MeHA: 7.7 kPa, high MeHA: 43.0 kPa, low HeMA-HA: 7.2 kPa, high HeMA-HA: 32.5 kPa) each exhibiting unique mass loss profiles and mechanical changes with time (Figure 1). In general, lower modification resulted in a faster degradation rate and decrease in mechanics. Furthermore, functionalization with HeMA leads to more significant changes in degradation and mechanics with time than MeHA. It is important to tailor these properties with the biological and mechanical trends found after infarction.

Conclusions: We have successfully designed an injectable hydrogel system with tunable mechanics and degradation. This system can be used to systematically evaluate the efficacy of biodegradable HA in attenuating left ventricular remodeling, through timing of various cues (e.g., magnitude of stress reduction) following injury. These results show that a quickly-degrading material can be as effective as a slowly-degrading material with the same initial mechanics. Evaluation of our high therapy animals will provide additional insight regarding the role of material degradation as well as the mechanical effects over time on ventricular remodeling.