11-7-2017

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HHS Public Access

Author manuscript

J Biomech. Author manuscript; available in PMC 2018 November 07.

Published in final edited form as:

J Biomech. 2017 November 07; 64: 231–235. doi:10.1016/j.jbiomech.2017.08.024.

Computational Sensitivity Investigation of Hydrogel Injection Characteristics for Myocardial Support

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Abstract

Biomaterial injection is a potential new therapy for augmenting ventricular mechanics after myocardial infarction (MI). Recent in vivo studies have demonstrated that hydrogel injections can mitigate the adverse remodeling due to MI. More importantly, the material properties of these injections influence the efficacy of the therapy. The goal of the current study is to explore the interrelated effects of injection stiffness and injection volume on diastolic ventricular wall stress and thickness. To achieve this, finite element models were constructed with different hydrogel injection volumes (150 μL and 300 μL), where the modulus was assessed over a range of 0.1 kPa to 100 kPa (based on experimental measurements). The results indicate that a larger injection volume and higher stiffness reduce diastolic myofiber stress the most, by maintaining the wall thickness during loading. Interestingly, the efficacy begins to taper after the hydrogel injection stiffness reaches a value of 50kPa. This computational approach could be used in the future to evaluate the optimal properties of the hydrogel.

Keywords

Finite Element Modeling; Biomaterial; Left Ventricular Remodeling

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Conflict of Interest Statement

None of the authors have any commercial or other interest that are in conflict with the integrity of this work.

1. Introduction

According to the American Heart Association, cardiovascular disease is the leading cause of death worldwide, accounting for more than 17.3 million deaths per year, and is projected to increase to more than 23.6 million by 2030 (Mozaffarian et al., 2016). Roughly 785,000 people in the United States have a myocardial infarction (MI) each year, which can eventually lead to chronic heart failure due to adverse remodeling of the heart wall (Mozaffarian et al., 2016). As such, the material properties of myocardium are an important determinant of global left ventricular (LV) function in both health and disease. One potential treatment strategy being investigated is the use of biocompatible injectable materials as a means of alleviating adverse remodeling. Several formulations of injectable biomaterials have been studied in order to evaluate the impact on wall thickness and global LV function (Dorsey et al., 2015; Ifkovits et al., 2010; Morita et al., 2011; Tous et al., 2011). These in vivo studies have demonstrated that injectable hydrogel injections can mitigate the adverse effects of MI (Dorsey et al., 2015; Rodell et al., 2016).

Interestingly, the stiffness of these injections can be tuned to minimize wall thinning and ventricular dilation. Specifically, experimental studies with large animal models were conducted to investigate different hydrogel injections with altered stiffness characteristics, namely, one with a higher stiffness and another with a lower stiffness (Ifkovits et al., 2010; Rodell et al., 2016). The results showed a better ability to limit infarct expansion and remodeling with the higher stiffness hydrogel injection. Inspired by these studies, the current investigation combines experimental data and finite element (FE) modeling to better understand how hydrogel injection stiffness and volume influence myocardial wall stress and wall thickness. This was accomplished by using previously measured MRI data from explanted ovine LVs, which were injected with an array of hydrogel, in order to assess in vivo injection geometry. FE models were then constructed to represent various combinations of injection volume within the LV wall, over a range of hydrogel elastic moduli.

2. Methods

2.1 Finite Element Model

In order to evaluate the effects of various hydrogels, FE models of the LV with two different injection volumes (150 μL and 300 μL) were generated, as well as a control model with no injections. The reference configuration of each model was chosen to represent early diastole, since the stress in the LV is at a minimum. The LV FE meshes were produced using tri-linear hexahedral brick elements (TrueGrid; XYZ Scientific, Inc., Livemore, CA). The size and shape of the hydrogel injections (Figure 1, Table 1) were based on MRI reconstruction of injected explant tissue from a previous study. For more detail related to that experimental data, please see the Supplemental Material section in (Rodell et al., 2016). The geometry of the LV wall was based on experimental measurements from ovine hearts (Rodell et al., 2016). For the control case, the undeformed wall thickness was approximately 1.3cm, the inner diameter of the endocardial wall near the equator was 4 cm, and the distance from base to apex was 6.4 cm.

For the models with hydrogel injections, the control model was modified to include a 4 × 4 pattern of 16 injections within the myocardium and the spacing between injections was assumed to be 1.5 cm from center to center (Figure 2a) (Rodell et al., 2016; Rodell et al., 2015; Ryan et al., 2009). Since the injections remain as discrete plugs in the LV wall, rather than diffusing into the tissue, the total volume of myocardium must be conserved. This was accomplished by increasing the wall thickness in the injection region within each FE model. For the case of 300 μL injections, the wall thickness was increased by 1.5 mm to account for the volume added to the wall (Figure 2b). For the case of 150 μL injections, the wall thickness was increased by 0.5 mm (Figure 2c). The LV wall away from the injections, and the longitudinal dimensions, were unaltered relative to the control case. The myofiber orientation was assigned to vary linearly from epicardium to endocardium using the angle of −37 degrees to 83 degrees, respectively (McGarvey et al., 2015). A pressure of 10 mmHg was assigned as a boundary condition on the endocardial surface in each of the FE models, in order to simulate end-diastole.

2.2 Material response

The material response of the myocardium was represented using a nearly incompressible, transversely isotropic, hyperelastic constitutive law, which was defined using the following strain energy function (Guccione et al., 1991):

$$W_{myocardium}=\frac{C}{2}\left(e^{b_f E_{ff}^2+b_t(E_{SS}^2+E_{nn}^2+E_{ns}^2+E_{sn}^2)+b_{fs}\left(E_{fS}^2+E_{sf}^2+E_{fn}^2+E_{nf}^2\right)}-1\right)+\frac{\kappa}{2}(J-1)^2 \quad (1)$$

where E_{ij} are the deviatoric components of the Green-Lagrange strain tensor relative to the myofiber coordinate system (f = fiber direction, s = cross-fiber in-plane direction, n = transverse-fiber direction) and J is the determinant of the deformation gradient. The diastolic material parameters were assigned to be C=0.51 kPa, b_f=22.84, b_t=3.45, and b_{fs}=12 (Rodell et al., 2016), while the bulk modulus was κ = 1e10^3 kPa. Since the model was meant to mimic the initial time frame after infarction, is was assumed that 30 minutes post-MI the myocardial properties around the injections would be roughly unchanged (Holmes et al., 2005).

The material response of the hydrogel injections was represented using a nearly incompressible, isotropic, hyperelastic constitutive law, which was defined using the following strain energy function:

$$W_{injection}=\frac{E}{2(1+\nu)}\,\mathrm{tr}(\mathbf{E}^2)+\frac{E}{6(1-2\nu)}\ln(J)^2 \quad (2)$$

where **E** is the deviatoric Green-Lagrange strain tensor, tr( ) is the trace operator, and ln( ) is the natural log operator. The material parameters for Young's modulus (E) were assigned in a range between 0.1 kPa to 100 kPa, while the Poison ratio (ν) was assigned a value of 0.499. The range for Young's modulus was based on measurements by Rodell et al. (Rodell

et al., 2016), where two formulations with a modulus of 0.8 kPa and 40 kPa were injected into an ovine model of MI.

3. Results

End-diastolic myofiber stress was assessed along the transmural direction, in between injections, for the different stiffness cases. Figure 3a shows that when the injection stiffness is 0.1 kPa the transmural distribution of stress is nearly unchanged compared to the untreated control. For a hydrogel stiffness of 25 kPa, the 150 μL injection reduced the myofiber stress by roughly 18.9% at the epicardium, 0% at mid-myocardium, and 21.6% at endocardium compared to the control (Figure 3b). However, the 300 μL injection reduced the myofiber stress by roughly 31% at the epicardium, 10.6% at the mid-myocardium, and 34.7% at the endocardium compared to the control (Figure 3b). For a hydrogel stiffness of 100 kPa, the 150 μL injection reduced the myofiber stress by roughly 39.2% at the epicardium, 18.3% at mid-myocardium, and 38.7% at the endocardium compared to the control (Figure 3c). However, the 300 μL injection reduced the myofiber stress by roughly 56.8% at the epicardium, 36.5% at the mid-myocardium, and 55.2% at the endocardium compared to the control (Figure 3c).

Additionally, the average myofiber stress in the myocardium surrounding the 150 μL and 300 μL injections, using different hydrogel stiffness values, is shown in Figure 4. When the injection stiffness is increased, the myofiber stress was decreased. It should be noted that the influence of stiffness begins to taper after 50 kPa. Figure 5 shows the average wall thickness as a function of injection stiffness. When the injection stiffness increased, the wall thickness was increased. The average wall thickness at end-diastole for the control was approximately 1cm, while the thickness for the 150 μL injection with 25 kPa stiffness was 1.1cm and 300 μL was 1.2cm. For the case of 150 μL injection with 100 kPa stiffness, the thickness was 1.2cm, while 300 μL was 1.3cm. This is primarily driven by the fact that the stiffer injections maintained their original shape during deformation, which allows the LV wall to remain thick (Figure 6c and 6f). On the other hand, it can be seen that the 0.1 kPa injections effectively collapse in the transmural direction as the LV wall is loaded by the pressure on the endocardium (Figure 6a and 6d). Figure 6 also shows the distribution of end-diastolic myofiber stress throughout the LV wall around the 150 μL injections (Figure 6 a–c) and 300 μL injections (Figure 6 d–f), with stiffness values of 0.1 kPa, 25 kPa and 100 kPa, respectively. It is clear that the myofiber stress showed a greater reduction around the hydrogel injection region when the volume was larger and the stiffness was higher.

Table 2 shows the end-diastolic volume (EDV) in the FE models, using various combinations of injection volume and stiffness. For the case of 150 μL injections, it can be seen that the EDV decreases, relative to the control case, by 0.6%, 2.0%, and 3.5%, using stiffness values of 0.1 kPa, 25 kPa and 100 kPa, respectively. For the case of 300 μL injections, it can be seen that the EDV decreases by 2.5%, 4.8%, and 7.0%, using stiffness values of 0.1 kPa, 25 kPa and 100 kPa, respectively. As noted above, the influence of injection stiffness on myofiber stress tapers after 50 kPa. By using stiffness values below this level, the decrease in EDV would be less than 5.0%.

4. Discussion

The goal of the current study was to assess the effect of different attributes that can be tuned for hydrogel injections. More specifically, this work utilized a combination of previously measured MRI data and FE modeling to investigate how injection stiffness and volume influence myocardial wall stress and wall thickness. The modeling results show a clear reduction of myofiber stress based on the higher hydrogel injection volume. Additionally, by tuning the stiffness of the hydrogel, greater reductions in stress can be achieved. The current results indicated that stiffer hydrogel injections could reduce myofiber stress further. These improvements appear to taper after a stiffness of 50 kPa.

Previous studies have used FE modeling to assess the influence of biomaterial injections on LV function and wall stress. Kichula et al. (Kichula et al., 2014) examined the effects of a single hydrogel formulation, which diffused between the tissue, and a single injection volume on LV wall stress. It was found that the injections increased the effective stiffness of the tissue and decreased stress in the wall. Two other studies examined the effects of varying the volume of the injections on wall stress and LV ejection fraction, but did not examine the effects of injection stiffness. Lee et al. (Lee et al., 2014) used a patient-specific FE model to show that increasing the injection volume decreased both the end-diastolic and end-systolic stress in the myocardium. Wise et al. (Wise et al., 2016) used an animal-specific FE model of a rat heart to investigate a wide range of injection volumes in a model of MI. Interestingly, it was found that the beneficial effects of the injection began to diminish once the volume fraction of the injection exceeded 50% of the MI region. It should be noted that the volume fraction of hydrogel injection to treated myocardium in the current study was less than 15%. Also, the results of the current study were consistent with these previous studies, in terms of decreasing myofiber stress with increased injection volume. However, the current study showed the additional benefit of tuning the injection stiffness to reduce stress.

In addition to FE modeling studies, several experimental studies with large animal models have been conducted. Ifkovits et al. found that stiffer hydrogel injections led to a reduction in adverse remodeling in the MI region, i.e., the MI region was smaller in animals treated with stiffer hydrogels, compared with the control infarct group (Ifkovits et al., 2010). In work done by Plotkin et al., it was shown that hydrogels with the highest stiffness exhibited the best rescue of heart function (Plotkin et al., 2014), in terms of ejection fraction. Also, in another previous experimental study, it was shown that the higher stiffness hydrogel injection improved the ejection fraction after 8 weeks but not the lower stiffness hydrogel injection; and LVEDV measured using the higher stiffness hydrogel was smaller than the lower stiffness hydrogel (Rodell et al., 2016). All of these experimental studies showed greater benefit with a higher stiffness hydrogel, in terms of better LV geometry and function. This is consistent with the current FE modeling results, which indicate that the higher stiffness hydrogel injections are more beneficial. Additionally, previous injectable biomaterial studies have demonstrated that injections can increase LV wall thickness and the effective stiffness of the infarct region (Ifkovits et al., 2010; Landa et al., 2008; Morita et al., 2011; Mukherjee et al., 2008; Rane and Christman, 2011; Ryan et al., 2009). This is also

consistent with the current results, in which a higher injection stiffness led to increased wall thickness due to better retention of injection shape.

One limitation of the current study is that it only focused on changes induced during the diastolic phase, due to hydrogel injection. Further studies are needed to assess changes in stress during systolic contraction. Additionally, the residual stresses that are developed during the injection process were not taken into account in the model. Finally, the current work only looked at the acute effects of the hydrogel injection post-MI. Future studies will include experimental data from later time points after the ventricle has been treated.

In conclusion, the current work demonstrated that FE modeling can be used to predict how the LV wall thickness and myofiber stress change as a function of different hydrogel characteristics. This approach could be used as a tool for developing tunable hydrogel injections and predicting stress reduction and heart function post-MI. In the future, this method will be used to examine more optimal injectable biomaterial properties, which would be valuable clinical treatments for myocardial infarction.

Acknowledgments

This study was supported by National Institutes of Health grants R01 HL063954 (R. Gorman) and R01 HL111090 (J. Burdick), as well as a grant from the National Science Foundation CMMI-1538754 (J. Wenk).

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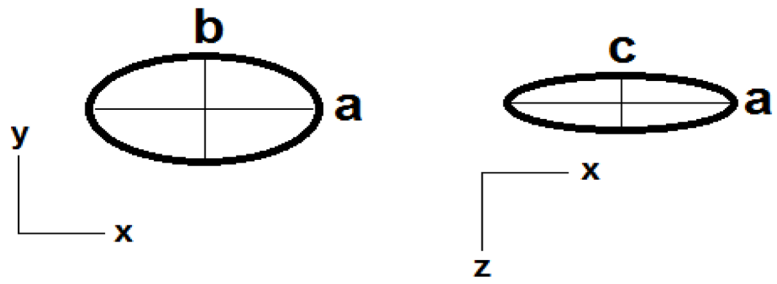

Figure 1.
Hydrogel injections are well retained and can be approximated as an ellipsoid with characteristic dimensions a, b, and c.

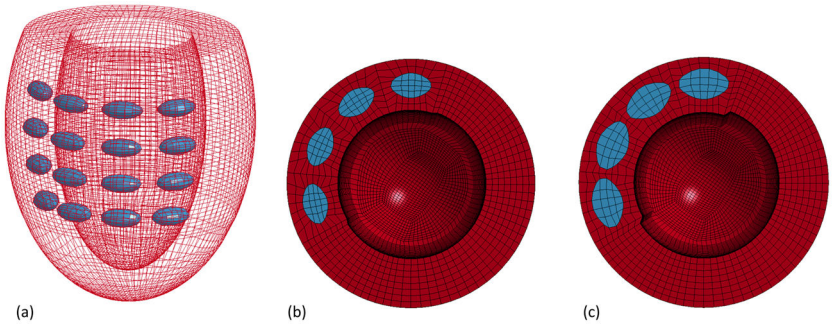

Figure 2.

(a) FE model of an ovine LV with 16 150 μL hydrogel injections. (b) Short axis view of the LV wall with 150 μL hydrogel injections. (c) Short axis view of the LV wall with 300 μL hydrogel injections.

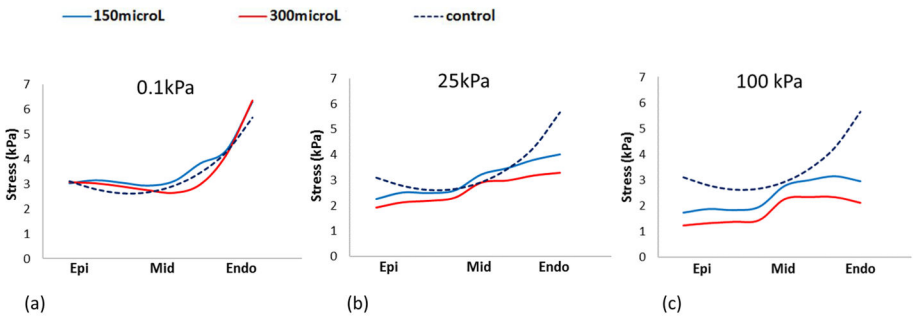

Figure 3.

Transmural distribution of end-diastolic myofiber stress using a stiffness of (a) 0.1 kPa, (b) 25 kPa and (c) 100 kPa, comparing between the control and injection volumes of 150 μL and 300μL. Note: The transmural direction along which the stress was assessed is shown as a thick black line, in between injections, in Figure 6.

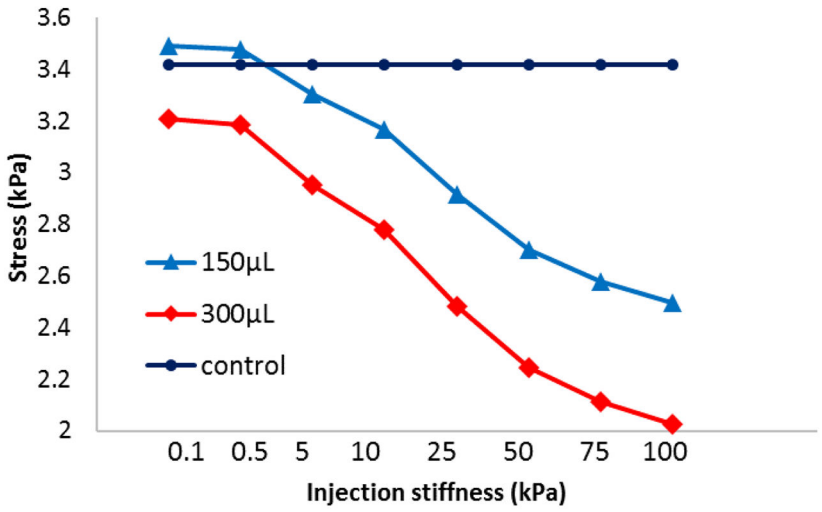

Figure 4.

Average end-diastolic myofiber stress surrounding the injection as a function of injection stiffness and volume.

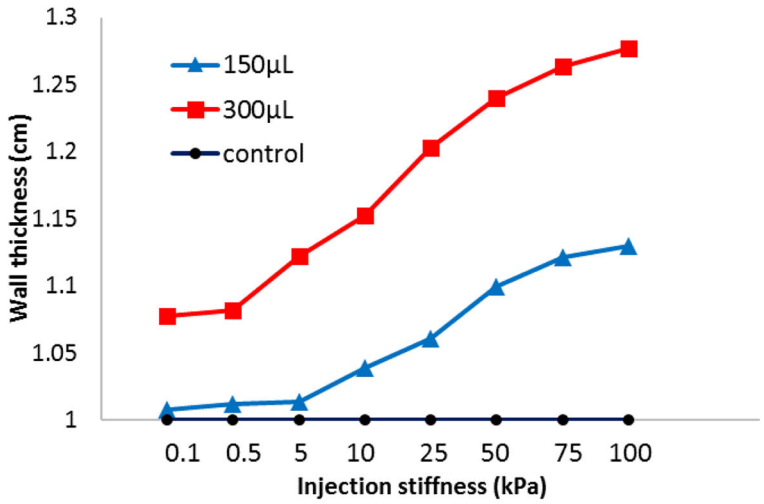

Figure 5.

Average end-diastolic myocardial wall thickness in the injection region as a function of injection stiffness and volume.

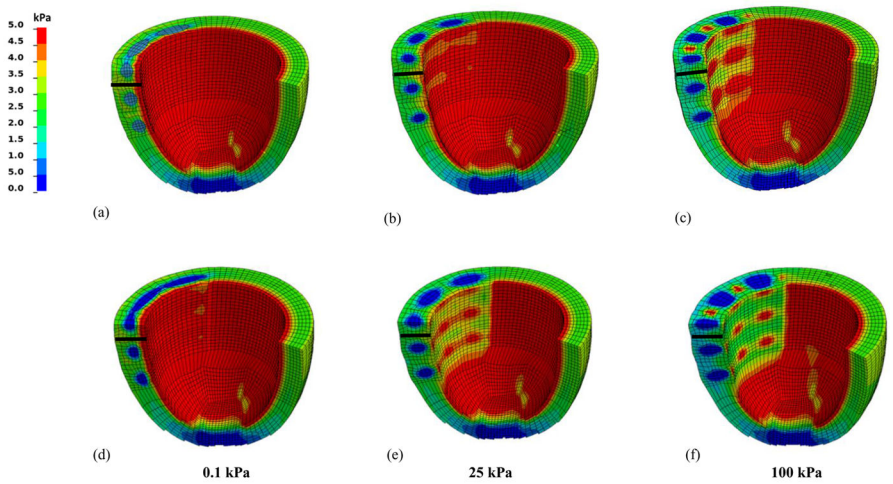

Figure 6.

The LV end-diastolic myofiber stress distribution around (a–c) 150 μL injections and (d–f) 300 μL injections with stiffness values of 0.1 kPa, 25 kPa and 100 kPa, respectively.

Table 1

Ellipsoidal dimensions of the 150 μL hydrogel injection and 300 μL hydrogel injection, based on MRI data (Rodell et al., 2015).

	150 μL	**300 μL**
a	5.50 mm	6.60 mm
b	3.15 mm	3.94 mm
c	2.40 mm	2.73 mm

Table 2

End-diastolic volume in the FE model for different combinations of injection stiffness and volume. Note: The control end-diastolic volume is 110.1 mL.

	150 μL	**300 μL**
0.1 kPa	109.4 mL	107.3 mL
25 kPa	107.9 mL	104.8 mL
100 kPa	106.3 mL	102.4 mL