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Bioinjection treatment: Effects of post-injection residual stress on left ventricular wall stress

Lik Chuan Lee [a,*], Samuel T. Wall [e], Martin Genet [b,c,d,f], Andy Hinson [g], Julius M. Guccione [b,c,d]

[a] Department of Mechanical Engineering, Michigan State University, MI, USA
[b] Department of Surgery, University of California, San Francisco, CA, USA
[c] Department of Bioengineering, University of California, San Francisco, CA, USA
[d] Department of Medicine, University of California, San Francisco, CA, USA
[e] Simula Research Laboratory, Oslo, Norway
[f] Marie-Curie International Outgoing Fellow, Brussels, Belgium
[g] Lonestar Heart Inc, Oslo, Norway

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ABSTRACT

Injection of biomaterials into diseased myocardium has been associated with decreased myofiber stress, restored left ventricular (LV) geometry and improved LV function. However, its exact mechanism(s) of action remained unclear. In this work, we present the first patient-specific computational model of biomaterial injection that accounts for the possibility of residual strain and stress introduced by this treatment. We show that the presence of residual stress can create more heterogeneous regional myofiber stress and strain fields. Our simulation results show that the treatment generates low stress and stretch areas between injection sites, and high stress and stretch areas between the injections and both the endocardium and epicardium. Globally, these local changes are translated into an increase in average myofiber stress and its standard deviation (from 6.9 ± 4.6 to 11.2 ± 48.8 kPa and 30 ± 15 to 35.1 ± 50.9 kPa at end-diastole and end-systole, respectively). We also show that the myofiber stress field is sensitive to the void-to-size ratio. For a constant void size, the myofiber stress field became less heterogeneous with decreasing injection volume. These results suggest that the residual stress and strain possibly generated by biomaterial injection treatment can have large effects on the regional myocardial stress and strain fields, which may be important in the remodeling process.

1. Introduction

Injection of materials into the myocardium as a treatment for heart diseases has generated considerable interest over recent years. The injection of biomaterials, which range from biological materials e.g., Alginate (Landa et al., 2008) and Fibrin (Christman et al., 2004), to synthetic hydrogels (Jiang et al., 2009), have shown positive outcomes in animal studies. Recently, significant reverse remodeling – 50% reduction in end-diastolic volume (EDV) and end-systolic volume (ESV) – in patients suffering from dilated cardiomyopathy was observed as early as 3 months after injection of Algiysl-LVR^{TM} (a calcium–sodium alginate hydrogel) and Coronary Artery Bypass Grafting (Lee et al., 2013a).

Despite these favorable outcomes, the exact mechanism(s) of action of the injection treatment remain(s) unclear. While the treatment's primary rationale is to provide support to the diseased myocardium to reduce ventricular wall stress (widely believed to be responsible for adverse cardiac remodeling), there are also suggestions that these injected biomaterials can create a "healthier micro-environment through stress shielding" that increases capillary and arteriole densities (Nelson et al., 2011). Thus, the effects of this treatment need to be better understood, especially because of its potential as an effective treatment for heart diseases.

Computational modeling has been used to better understand the effects of injecting material into the myocardium (Kortsmit et al., 2012; Wall et al., 2006; Wenk et al., 2009). These modeling studies generally support the primary rationale of the injection treatment: helping to provide support to the myocardium through thickening of the ventricular wall to reduce ventricular wall stress. However, these studies did not include the possible effects of residual stress that could occur when injections are introduced into the myocardium. The effects of residual stresses that were imparted to the myocardium after implantation of other treatment

* Corresponding author at: Department of Mechanical Engineering, Michigan State University, 2445 Engineering Building, East Lansing, MI 48824-1226, USA.
E-mail address: lclee@egr.msu.edu (L.C. Lee).

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devices into the heart has been considered in other analyses (Carrick et al., 2012; Lee et al., 2014).

Injectable biomaterials usually begin in a viscous liquid that solidifies though chemical changes *in situ* to form a solid hydrogel (Christman et al., 2004; Lee et al., 2013b). When injected, these liquids are forced into the myocardium, creating new space to accommodate the bleb of material. As such, residual stress can be introduced during this process, especially when the void that accommodates the injection has an initial volume smaller than the injected volume itself. Although the myocardial extracellular space ($\sim$ 24% of the tissue space) consists of about 6% "empty" space devoid of any structural components (Frank and Langer, 1974)—about 2.7 ml for a left ventricular (LV) wall volume of 190 ml in the patient-specific model described here, they are interspersed within the myocardium and the local "empty" space is substantially smaller. Hence, it is likely that residual stress could be present when the injection volume$\sim$0.3 ml (Lee et al., 2013a) is greater than the local "empty" or void space.

The primary aims of this paper are twofold: first, to describe a methodology to model the effects of post-injection residual stress, and second, to highlight the possible effects of residual stress on local myofiber stress and stretch fields.

2. Methods and results

2.1. Finite element model of the LV

A patient-specific finite element (FE) model of the LV was constructed based on the baseline magnetic resonance (MR) images of patient 1 described in Lee et al. (2013a). The patient was diagnosed with NYHA class III heart failure and had ischemic cardiomyopathy, hypertension, hyperlipidemia and renal insufficiency. The LV was modeled using 110,976 trilinear hexahedral elements and the FE mesh was graded so that its mesh density was 4 times higher at the mid-LV (where the injections are located) (Fig. 1a).

Nearly incompressible and transversely isotropic hyperelastic material laws for the passive (Guccione et al., 1991) and active myocardium (Guccione et al., 1993) were used to model the mechanical behavior of the LV during a cardiac cycle. The material passive stiffness (C) and the tissue contractility (T_{max}) were chosen so that the predicted LV volumes (without injection) matched the corresponding EDV (197 ml) and ESV (122 ml) measured from the MR images. All other parameters had values equal to those used in large animal studies (Sun et al., 2009) and human study (Wenk et al., 2012).

Local fiber direction was defined on the local tangent plane by prescribing a fiber angle taken with respect to the local circumferential vector running counter-clockwise when viewed in the base-to-apex direction. In the entire LV, the fiber angle varied linearly from the endocardium (60°) to the epicardium (-60°) (Streeter et al., 1969) (Fig. 1b). The epicardial-base edge was fixed, whereas the base displacement was constrained in the out-of-plane direction.

Three simulation cases, namely, BASELINE, RESIDUAL and NO-RESIDUAL were performed. BASELINE was defined to be the case before injections. RESIDUAL and NO-RESIDUAL corresponded to the post-injection cases with and without the effects of residual stress, respectively.

2.2. Modeling injections in the LV

The LV wall was meshed with spherical voids at the mid-LV (halfway between the base and the apex) and the voids were filled with hexahedral elements. The finite element meshes of the voids and the LV wall have matching nodes at their common interface. There were a total of 12 voids, each with an arbitrarily prescribed radius of 1 mm (Fig. 1c).

To model the effects arising from post-injection residual stress (RESIDUAL), the hexahedral elements in the void were first prescribed with a dummy material law and a spherical displacement field was then imposed to dilate each void to an arbitrary prescribed injection volume of 0.02 ml. Thereafter, stresses were initialized to zero in the elements defining the void and these elements were prescribed with a material law describing the hydrogel injections. In other words, the elements within the void now define the injected hydrogel. The hydrogel injections were modeled using nearly incompressible Mooney–Rivlin material law with previously obtained parameters (Wenk et al., 2009) from alginate experiments. Then, the spherical displacement field was removed to allow the injections and the LV to deform until a force-equilibrium was reached (Fig. 1d). This resultant configuration is defined to be the unloaded (but not stress-free) configuration. In NO-RESIDUAL, stresses of both the injections and LV wall were initialized to zero from the unloaded configuration of the RESIDUAL case.

End-diastole (ED) and end-systole (ES) were simulated in all 3 cases by imposing a pressure boundary condition of 20 and 125 mm Hg at the endocardial wall in the unloaded configuration, respectively. All simulations were performed using LS-DYNA (Livermore Software Technology Corporation, Livermore, CA) with the passive and active myocardial material law implemented as a user-defined material subroutine.

2.3. Effects on global stretch and stress in the myofiber and cross-myofiber directions

Stretch and stress in both the myofiber and cross-myofiber directions were averaged over the entire LV at ED and ES for BASELINE, RESIDUAL and NO-RESIDUAL (Table 1). The average stress and stretch (at ES and ED) were not very different between BASELINE and NO-RESIDUAL in both the myofiber and cross-myofiber directions. However, the average ED myofiber stress of RESIDUAL (11.2 ± 48.8 kPa) was nearly twice as large as that of BASELINE (6.9 ± 4.6 kPa), whereas the average ES myofiber stress of RESIDUAL (35.1 ± 50.9 kPa) was 17% higher than that of BASELINE (30 ± 15 kPa). Similar trend was also observed for the cross-myofiber stress of RESIDUAL, which was higher than BASELINE. The average ED and ES stretch of RESIDUAL was not very different from that of BASELINE in both the myofiber and cross-myofiber directions. In general, both ES and ED stress and stretch in RESIDUAL had larger values of standard deviation than BASELINE and NO-RESIDUAL.

2.4. Effect on local myofiber stretch and stress

The substantially larger standard deviation found in RESIDUAL suggests that the myofiber stress and stretch were more heterogeneous than the other 2 cases. Moreover, the significantly larger change in fiber stress than in fiber stretch indicates that out-of-fiber-direction tensions and shear-stress components must be activated.

Closer inspection of the myofiber stretch and stress fields reveals an organized pattern in the injection region, particularly in RESIDUAL when compared to NO-RESIDUAL (Figs. 2 and 3). In RESIDUAL, the myofiber stretch was substantially decreased and was less than unity at the mid-wall between injections at both ED and ES. At ES, the myofiber stretch was elevated in the transmural direction between the injections and the endocardium, as well as between the injections and the epicardium. The ES myofiber stress field displayed similar pattern as that of the ES myofiber stretch. Contrastingly, ED myofiber stress did not decrease substantially between the injections that were located at the mid-wall and was elevated in the transmural direction between the injections and both the epicardium and the endocardium.

Without residual stress (NO-RESIDUAL), the myofiber stretch and stress fields at the injection region were largely similar to those in BASELINE, with the exception that the ED and ES myofiber stress between injections was slightly lower than in BASELINE (Fig. 3).

2.5. Effect of void-to-injection size ratio on myofiber stress

The myofiber stress is also sensitive to the void-to-injection size ratio. By keeping the void size constant, both global ES and ED average myofiber stress decreases with decreasing injection volume (Fig. 4a). In addition, the standard deviation of the myofiber stress also decreased substantially with decreasing injection volume and approaches the values in NO-RESIDUAL. Correspondingly, the myofiber stress field became more homogeneous near the injection sites (Fig. 4b).

2.6. Effect on ventricular volume

The injections had little effects on both EDV and ESV in RESIDUAL and NO-RESIDUAL. Only in RESIDUAL was the EDV slightly smaller (198 ml) than BASELINE (201 ml).

3. Discussions

3.1. Myofiber stretch and stress heterogeneity

Although the inclusion of residual stress in our simulations led to elevated global averaged myofiber stress when material was added to the myocardium, this increase was associated with a greater increase in its standard deviation due to a resulting complex pattern of loading and unloading. As such, the principal finding of our simulation is that residual stress can dramatically