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Coupled agent-based and finite-element models for predicting scar structure following myocardial infarction

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ABSTRACT

Following myocardial infarction, damaged muscle is gradually replaced by collagenous scar tissue. The structural and mechanical properties of the scar are critical determinants of heart function, as well as the risk of serious post-infarction complications such as infarct rupture, infarct expansion, and progression to dilated heart failure. A number of therapeutic approaches currently under development aim to alter infarct mechanics in order to reduce complications, such as implantation of mechanical restraint devices, polymer injection, and peri-infarct pacing. Because mechanical stimuli regulate scar remodeling, the long-term consequences of therapies that alter infarct mechanics must be carefully considered. Computational models have the potential to greatly improve our ability to understand and predict how such therapies alter heart structure, mechanics, and function over time. Toward this end, we developed a straightforward method for coupling an agent-based model of scar formation to a finite-element model of tissue mechanics, creating a multi-scale model that captures the dynamic interplay between mechanical loading, scar deformation, and scar material properties. The agent-based component of the coupled model predicts how fibroblasts integrate local chemical, structural, and mechanical cues as they deposit and remodel collagen, while the finite-element component predicts local mechanics at any time point given the current collagen fiber structure and applied loads. We used the coupled model to explore the balance between increasing stiffness due to collagen deposition and increasing wall stress due to infarct thinning and left ventricular dilation during the normal time course of healing in myocardial infarcts, as well as the negative feedback between strain anisotropy and the structural anisotropy it promotes in healing scar. The coupled model reproduced the observed evolution of both collagen fiber structure and regional deformation following coronary ligation in the rat, and suggests that fibroblast alignment in the direction of greatest stretch provides negative feedback on the level of anisotropy in a scar forming under load. In the future, this coupled model may prove useful in computational design and screening of novel therapies to influence scar formation in mechanically loaded tissues.

1. Introduction

Following myocardial infarction, damaged muscle is gradually replaced by collagenous scar tissue. The structure and mechanical properties of the healing infarct are critical determinants of how well the damaged left ventricle continues to pump blood (Fomovsky et al., 2011, 2012a), as well as the risk of serious post-infarction complications such as infarct rupture, infarct expansion, and progression to dilated heart failure (Holmes et al., 2005). Accordingly, a number of therapeutic approaches currently under development aim to alter infarct mechanics in order to reduce complications. These include attaching mechanical restraint devices over the infarct region to limit infarct expansion (Kelley et al., 1999; Gorman et al., 2011) or alter infarct mechanical properties (Fomovsky et al., 2011, 2012a), injecting natural and synthetic polymers in order to stiffen the infarct and/or alter its healing (Christman et al., 2004; Dai et al., 2005; Landa et al., 2008; Ifkovits et al., 2010; Rane and Christman, 2011), and manipulating fibroblast migration and proliferation in order to alter scar remodeling and mechanics (Laeremans et al., 2011). In addition, other therapies routinely used in patients with healing myocardial infarctions — such as cardiac resynchronization therapy (CRT) — alter the timing

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and strength of contraction of different regions of the heart, and consequently change regional mechanics (Shuros et al., 2007; Chung et al., 2010).

We recently showed that the pattern of mechanical stretch experienced by healing infarct scars is the primary determinant of their collagen fiber alignment (Fomovsky et al., 2012b), and Zhou et al. showed that mechanically unloading healing infarcts dramatically reduces collagen content (Zhou et al., 2011). Therefore, we expect all of the therapies discussed above to alter infarct collagen content and structure as a side effect of altering infarct mechanics. Such changes are critical to understand and anticipate when developing post-infarction therapies, as evidenced by a disastrous clinical trial of post-infarction steroid administration to reduce infarct size that was halted after several patients died of catastrophic infarct rupture (Roberts et al., 1976); subsequent studies showed that while steroids and other anti-inflammatory drugs do reduce infarct size, they also reduce scar thickness and mechanical strength, increasing the risk of rupture (Brown et al., 1983; Hammerman et al., 1983).

We recently took a significant step towards predicting the long-term consequences of therapies that alter infarct mechanics by developing and validating an agent-based model (ABM) of scar formation after myocardial infarction that reproduced the variety of collagen fiber orientation distributions previously reported in different animal models (Rouillard and Holmes, 2012). However, in our original model, we simply prescribed experimentally measured strains in the infarct as one of several inputs sensed and integrated by fibroblasts to determine their orientation and the orientation of collagen they deposit. This approach is clearly inadequate for predicting responses to novel therapies, since any therapy that alters scar structure, scar mechanics, or ventricular mechanics will also alter strains in the healing infarct, which in turn feed back to influence ongoing scar remodeling. Accordingly, we sought to develop a straightforward method for coupling our agent-based model of scar formation to finite-element models of tissue mechanics, creating a multi-scale model that represents the dynamic interplay between mechanical loading, scar deformation, and scar material properties. Rather than specialize the presentation to a finite-element model of the infarcted left ventricle, we present here the more general case of a mechanically loaded 'slab' of tissue that should be easily adaptable to model scar formation not only in heart but also in skin, tendon, and other mechanically loaded tissues.

Moving forward, we expect models such as the one presented here to make several important contributions to the treatment of myocardial infarction and post-infarction complications. First, once models that predict long-term effects of altered mechanics on scar healing are validated, they can be used to computationally screen therapies such as polymer injection or CRT for unexpected side effects on infarct healing. Next, such models can be used prospectively to design novel mechanical interventions that expressly aim to modulate infarct healing. Finally, extending multiscale models such as the one presented here to include network models of fibroblast signaling will enable better understanding of drug–device interactions in post-infarction patients and design of therapeutic approaches that take appropriate advantage of pharmacologic approaches, device-based approaches, and their synergies.

2. Methods

2.1. Agent-based model

The agent-based model of infarct healing described previously (Rouillard and Holmes, 2012) was utilized for the present study with some minor modifications as described below. Briefly, fibroblasts were modeled as circular discs free to move in a square, two-dimensional space. The space was divided into square patches, which stored information about the local extracellular matrix structure, chemokine concentration, and mechanical strains. The extracellular matrix structure was described using collagen and non-collagen fiber orientation distributions at each patch. Fibroblasts could migrate, proliferate, undergo apoptosis, and remodel the local extracellular matrix. Fibroblast orientation was determined by structural, chemical, and mechanical guidance cues. The guidance cues were modeled as vectors, where the magnitude of each vector indicated the strength of each cue. The strength and orientation of the structural guidance cue were determined by the strength of alignment and mean orientation of extracellular matrix fibers in the local region around the cell. The strength and orientation of the chemical guidance cue were determined by the magnitude and orientation of the chemokine concentration gradient in the local region around the cell. The strength and orientation of the mechanical guidance cue were determined by the magnitude of strain anisotropy (difference between principal strains) and orientation of greatest strain acting on the cell. Integration of multiple guidance cues by a cell was simulated by computing a weighted average of the individual cue vectors and randomly selecting an orientation from a probability distribution determined by the length and orientation of the average vector. Migration speed and proliferation rate depended on the local chemokine concentration. Fibroblasts remodeled the local extracellular matrix by degrading existing extracellular matrix fibers and by depositing new collagen fibers along the current orientation axis of the fibroblast (aligned deposition). The model simulated a six week time course of healing after infarction, where at each half-hour time step, each fibroblast updated its orientation according to the local guidance cues, remodeled the local extracellular matrix, migrated, and underwent mitosis or apoptosis if the time was appropriate according to the internal clock of the cell.

In the present work, we made several minor modifications to the previously published model, in order to focus our simulations on the interaction between mechanical loading, strain, and collagen fiber orientation. In the published model, we found that predicted long-term collagen structures were insensitive to the rate of migration of fibroblasts into the infarct, the effects of a separate persistence cue, and chemokine gradients across the physiologically plausible range of migration speeds and infarct shapes. Therefore, in this study we modeled the center of the infarct with a spatially uniform concentration of chemokines and with fibroblasts already distributed throughout the infarct, and we eliminated the separate persistence guidance cue. We also replaced an arbitrary equation governing the relationship between strain anisotropy and the resulting strength of cell alignment with a function derived from published experimental data. The derivation of this curve is provided in the Supplemental Methods.

2.2. Finite element model

2.2.1. Geometry, boundary conditions, and mesh

The finite-element model (FEM) was constructed in FEBio (version 1.5.0), a publicly available software program developed by the University of Utah (Maas et al., 2012). The model represented a slice of the anterior wall of the left ventricle cut parallel to the epicardial surface at 50% transmural depth as a thin, square slab of material, with the x-axis corresponding to the circumferential direction in the left ventricle, the y-axis to the longitudinal direction, and the z-axis to the transmural direction (Fig. 1A). Circumferential and longitudinal wall stresses were applied to the side faces of the slab. Six nodal displacements at four corners of the slab were fixed