Electromechanical Modeling of the Infarct Injured Failing Ovine Heart

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INTRODUCTION

Heart ischemia can lead to extensive damage of the myocardium, causing cell death and extensive fibrosis in the region of the injury. As the heart is a largely non-regenerative organ, this damage can cause progressive changes to heart function and shape, eventually leading to heart failure. One key target for research in breaking this downward spiral of function after a myocardial infarct is the infarct border zone, where observed elevated stress and strain may create biochemical and mechanical signals that lead to continued pathological remodeling of the ventricle. In order to better understand the electromechanical nature of injured ventricle and the dysfunction of the border zone, a fully coupled finite element model of myocardial electromechanics - consisting of an advanced cellular physiological model, a bidomain electrical diffusion solver, and a non-linear mechanics solver was fit to the MRI measured geometry and fiber orientations of an ovine left ventricle suffering from a surgically induced antero apical infarct. This model was then cycled through the complete cardiac loop of inflation, isovolumic contraction, ejection, and isovolumic relaxation to simulate electromechanical dynamics. The addition of stretch activated channels provided mechanoelectric feedback to help understand how these injuries can lead to electrical and mechanical dysfunction.

METHODS

Mathematical Model

Using the finite element (FE) method and an operator splitting technique, a coupled system of mathematical expressions describing the passive mechanics as well as the cell mediated generation of active force and electrical diffusion were solved throughout the simulated cardiac cycle.[1-3]

Mechanical Model

$$\nabla \cdot (FS) = 0$$

$$F = I + \nabla u$$

$$\lambda = F_{11}$$

$$S = S^p + S^a(s, \lambda, \frac{\partial \lambda}{\partial t})$$

$$S^p = \partial \Psi / \partial E$$

$$\Psi = \frac{1}{2} K(e^W - 1) + C_{compr}(J \ln J - J + 1)$$

$$W = b_{ff} E_{ff}^2 + b_{xx}(E_{nn}^2 + E_{ss}^2 + E_{sn}^2 + E_{ns}^2) + b_{fx}(E_{fn}^2 + E_{nf}^2 + E_{fs}^2 + E_{sf}^2)$$

Cell ODE Model

$$f\left(\frac{\partial s}{\partial t}, s, v, \lambda, \frac{\partial \lambda}{\partial t}\right) = 0$$

Bidomain Model

$$\frac{\partial v}{\partial t} + I_{\text{ion}}(v, s, \lambda) = \nabla \cdot (M_i \nabla v) + \nabla \cdot (M_i \nabla u_e)$$

$$0 = \nabla \cdot (M_i \nabla v) + \nabla \cdot ((M_i + M_e) \nabla u_e)$$

Geometric Mesh

A 12x18x1 (circumferential x longitudinal x transmural) mesh of tri-quadratic 27-node elements was constructed in Cartesian coordinates from a series of long and short axis tagged-MRI images and an adult sheep which had a surgically induced antero apical infarct and a fully developed transmural aneurysm.[4] Epicardial and endocardial surfaces were contoured at the beginning of diastole to create the undeformed mesh, and fiber fields were assigned at nodes from diffusion tensor MRI (DT-MRI) measurements of the explanted ventricles. Cardiac mechanics were solved on this 2739 node mesh, with cell models and the bidomain diffusion solved on a 2x refined mesh of 130,041 nodes

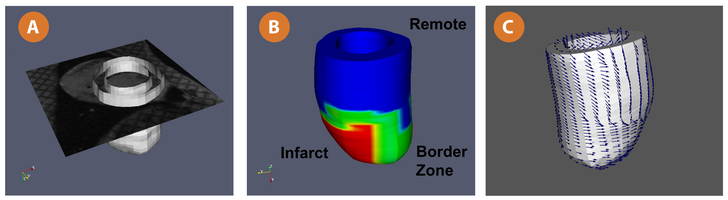


Figure 1 Depiction of contouring process from MRI images (A), along with final mesh (B) depicting zones of remote myocardium, infarct, and border zone. Fiber fields (C) are assigned at nodes from DT-MRI images and are set to circumferential orientation in the in the infarct.

RESULTS

Mechanical Dysfunction of the Infarct Injured Heart

Meshes were inflated to ED pressure and then activated through an electrical stimulation to the endocardium, which propagated through the myocardium. This signal elicited changes in the cell models and resulted in active force generation. Changes in volume during ejection were computed through a 2 element Windkessel model.

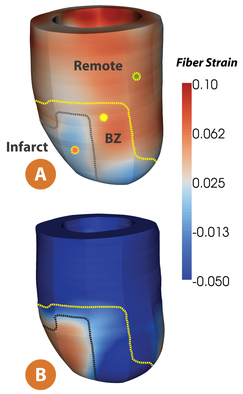


Figure 2 Depiction of the mesh at ED (A) and ES (B) with accompanying Green strain in the local fiber direction. Elevated strains can be observed in the border zone at ES relative to the remote myocardium.

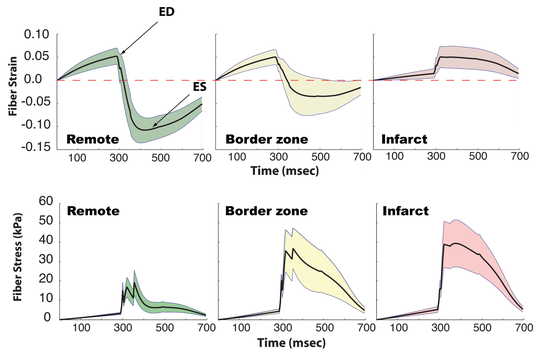


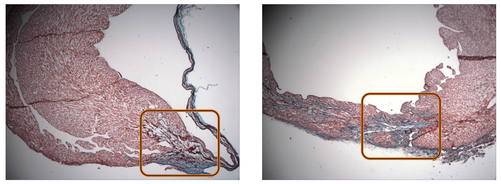
Figure 3 Mechanical dysfunction observed in the simulations. Fiber strain (top) average (solid line) and standard deviation (colored region) for the three discreet zones. Elevated strain is seen after ED in the border zone with some elements remaining in extension throughout the cardiac cycle. Stress (bottom) plots show similar dysfunction, with substantially increased stress throughout the border zone, especially at and after ED.

Mechano-electric Feedback and Stretch Activated Channels.

In order to examine electromechanical feedback, stretch activated channels (SACs) were added to the cell model. These had the form: $I = g_{SAC}(V_{mem} - E_{SAC})$ where g_{SAC} is a linear function of the primary fiber stretch ratio (lambda, λ). We scaled the linear effect of g_{SAC} from 0 - 5x published values[5] to examine the trends of their inclusion in the model.

In addition simulations were also run with reduced electrical connectivity in the border zone to simulate the effect of fibrosis and other damage in this region.

Figure 4 Examples of fibrosis and other disorganization in the border zone region of a developed anuerysm. H & E stained histology sections taken from LVs of mice with a generated infarct.



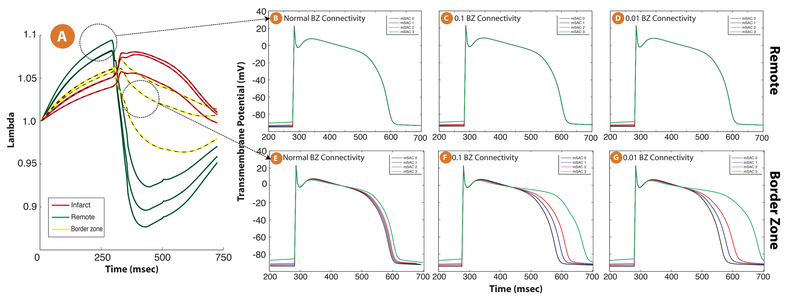


Figure 5 Electromechanical effect of increasing magnitude of SACs and decreasing border zone bidomain connectivity. Example fiber stretch ratio plots for remote, border zone and infarct regions (A), with effect on cell model APs in the remote (B-D) and border zone (E-F) areas. Heterogeneous APs are only observed with decreased border zone connectivity.

RESULTS

Electromechanical feedback on simulated Action Potentials.

Feedback in the form of SACs and as well as decreased border zone electrical connectivity altered the action potential dynamics of the entire mesh (~80,000 remote nodes and ~10,000 border zone nodes)

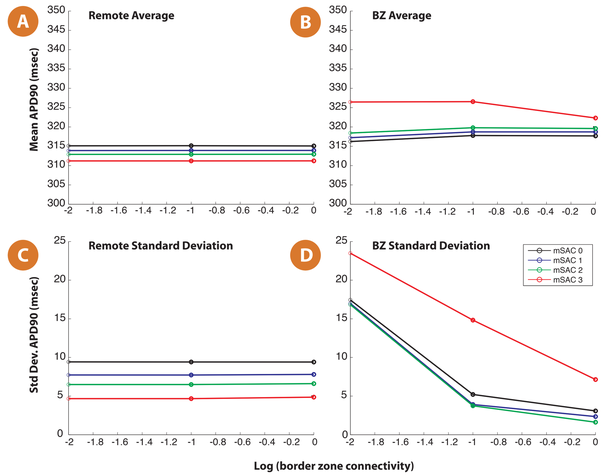


Figure 6 Global effect of increasing SAC magnitude and decreased border zone electrical connectivity. SACs reduce mean time to 90% repolarization (ADP90) in the remote region (A) while increase it in the BZ (B). Heterogeneity decreases in the remote region with SACs (C), while increasing in the border zone. Decreasing BZ connectivity increases AP90 heterogeneity in both the remote (C) and BZ (D) while changing mean values little.

CONCLUSIONS

- A method of strongly coupling cardiac mechanics with cell behavior and electrical diffusion was used to realistically simulate an injured left ventricle built from biological data.
- Substantial mechanical dysfunction was observed in the resulting model, with elevated stress and strain in the infarct border zone region. Some active regions in direct proximity to the infarct remained in extension throughout the cardiac cycle
- Mechanoelectric feedback in the form of SACs could introduce heterogeneity in the cell model APs, but only in the presence of reduced connectivity in the infarct border zone.

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