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Cardiac Defibrillation and the Role of Mechanoelectric Feedback in Postshock Arrhythmogenesis

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Abstract

Ventricular dilatation increases the defibrillation threshold (DFT). In order to elucidate the mechanisms responsible for this increase, the present article investigates changes in the postshock behavior of the myocardium upon stretch. A two-dimensional electro-mechanical model of cardiac tissue incorporating heterogeneous fiber orientation was used to explore the effect of sustained stretch on postshock behavior via (a) recruitment of mechanosensitive channels (MSC) and (b) tissue deformation and concomitant changes in tissue conductivities. Recruitment of MSC had no influence on vulnerability to electric shocks as compared to control, but increased the complexity of postshock VF patterns. Stretch-induced deformation and changes in tissue conductivities resulted in a decrease in vulnerability to electric shocks.

Keywords

defibrillation; mechanoelectric feedback; reentry; myocardial stretch; bidomain model

INTRODUCTION

Strong electrical shocks are commonly used to terminate ventricular fibrillation (VF). The understanding of defibrillation mechanisms and factors influencing defibrillation efficacy is essential to the improvement of existing and development of new defibrillation techniques. Together with other factors influencing defibrillation efficacy, such as electrophysiological properties of the myocardium,^{1–3} geometry of the heart,⁴ and blood volume,⁵ the mechanical conditions of the ventricles and atrial contraction can play an important role in postshock activity via mechanisms of mechanoelectrical feedback (MEF).^{6–8} Experimental evidence demonstrates that ventricular dilatation, due to increase in ventricular preload⁹ or intracavitary balloon placement,¹⁰ elevates the defibrillation threshold (DFT). It has been speculated that an increase in DFT is due to changes in refractoriness of cardiac tissue. Changes in refractoriness that take place during ventricular dilatation accelerate VF, increase complexity of the VF activation pattern,¹¹ and decrease the current threshold for VF onset.¹² Alterations in preshock state have been shown to change the DFT.¹³

During ventricular dilatation, tissue stretch evokes MEF mechanisms, including activation of mechanosensitive channels (MSC).^{14–18} Heterogeneous fiber structure within the ventricular wall creates regional strain gradients and subsequent inhomogeneous activation of MSC, which may explain stretch-induced heterogeneities in tissue refractoriness.^{12,19–21} Stretch of the myocardium also results in changes in the orientation of myocardial fibers

with respect to the defibrillation electrodes, which may affect postshock behavior. Fiber geometry influences the location and magnitude of shock-induced virtual electrodes^{22,23} and thus shock outcome.

We hypothesize that increased propensity of postshock arrhythmias following stretch of the ventricular wall is due to heterogeneous fiber structure, which results in

1. inhomogeneous activation of MSC, leading to a dispersion of refractoriness and a more complex preshock state, and
2. change in the myocardial fiber angle with respect to defibrillation electrodes, influencing shock-induced virtual electrodes.

The current article investigates changes in postshock electrical activity caused by stretch of cardiac tissue using a two-dimensional electro-mechanical model incorporating heterogeneous fiber structure. The model allowed us to simulate both the recruitment of MSC and the tissue deformation with corresponding changes in conductivities that occur upon stretch.

METHODS

Tissue Geometry

Simulations were performed using a two-dimensional sheet of cardiac tissue (55 × 55 mm). The fiber structure (FIG. 1 A) was identical to the formulation of Beaudoin and Roth,²⁴ with the angle α between x -axis and fiber direction given by:

$$\alpha(x, y) = \frac{\pi}{2} \cos^2 \left(\frac{\pi x}{D} \right) \cos^2 \left(\frac{\pi y}{D} \right), \quad (1)$$

where D is the edge length of the tissue square, with the coordinate system origin located in the center of the sheet.

Mechanics

The tissue mechanics were based on finite element elasticity theory. This approach to modeling cardiac tissue mechanics has been described in detail elsewhere.^{25–27} We considered only the passive mechanical properties of the tissue, as active mechanical properties play a limited role during rapid activation in VF. The central equation of the mechanical problem, solved for the components of the second Piola-Kirchhoff tensor and deformation gradient tensor with respect to the fiber coordinate system (consisting of fiber [f], and cross-fiber [c] directions), is based on the conservation of linear momentum in the absence of body forces.

Stress was formulated as a derivative of the strain energy function. The model incorporated anisotropic mechanical properties using an exponential strain energy function,²⁸ ignoring radial deformations:

$$W = \frac{1}{2} M (e^Q - 1), \quad Q = b_1 E_{ff}^2 + b_2 E_{cc}^2 + 2b_3 E_{fc}^2. \quad (2)$$

Here E_{ff} , E_{cc} , and E_{fc} are components of the Lagrangian strain tensor. This equation has four material parameters: M scales the stress, b_1 and b_2 scale the material stiffness in fiber and cross-fiber directions, respectively, and b_3 scales the material rigidity under shear in the fiber–cross-fiber plane. We used $M = 1.76$ kPa, $b_1 = 18.5$, $b_2 = 3.58$, and $b_3 = 1.63$.

Electrical Behavior

Electrical interaction between cells was based on the bidomain model.²⁹ In bidomain theory, cardiac tissue is considered, at each point, as both an intracellular and an extracellular continuum separated by a membrane. The transmembrane potential, V_m , is governed by the following set of equations:

$$\nabla \sigma_e \nabla \Phi_e = -\beta_m \left(C_m \frac{dV_m}{dt} + I_{ion} \right), \quad \nabla \sigma_i \nabla \Phi_i = \beta_m \left(C_m \frac{dV_m}{dt} + I_{ion} \right), \quad (3)$$

where σ_e and σ_i are extracellular and intracellular conductivity tensors, respectively, Φ_e and Φ_i are the corresponding electrical potentials, C_m is specific membrane capacitance, I_{ion} is transmembrane current density, and β_m is the membrane surface to cell volume ratio. Dirichlet and no-flux Neumann boundary conditions were applied in the extracellular and intracellular spaces, respectively.

We considered three cases: (a) unstretched tissue, (b) stretched tissue with MSC recruitment, and (c) stretched tissue with changes in conductivities and nodal coordinates. In the second case, to simulate the effect of stretch, I_{ion} in Equation (3) included a putative stretch-activated current which depends on the local strain of the tissue; Equation (3) was solved on the unstretched computational grid. In the third case, we altered the spatial coordinates of the nodes in the computational grid according to tissue deformation. We also changed the conductivity tensors in the intracellular space and applied transformations to the conductivity tensors to represent fiber rotation during stretch.³⁰ From this point forward, this collective set of alterations to the nodal coordinates and conductivities upon stretch is referred to as “changes in fiber angle.”

Ionic Model and Electroporation

To describe the membrane kinetics, we used the Luo-Rudy dynamic model.^{31–33} The model includes detailed descriptions of the main sarcolemmal ionic currents such as Na^+ , K^+ , and Ca^{2+} , as well as electrogenic pumps and exchangers, Ca^{2+} induced Ca^{2+} release, and Ca^{2+} buffering. As we are examining the response of the tissue to electric shocks, we also included an electroporation current, as formulated by DeBruin and Krassowska.³⁴

MSC

As a basis for representing MSC, we used the formulation of the nonselective current from Zabel *et al.*³⁵ We modified this formulation by substituting sarcomere length with the stretch

ratio λ that corresponds to the strain in the fiber direction, $\lambda = \sqrt{2E_{ff} + 1}$, to obtain the following expression for the current density:

$$I_{ns,stretch} = -L(\lambda) \times [\gamma \rho (V_m - V_r)], \quad (4)$$

in which the dependence of current magnitude on stretch is as follows:

$$L(\lambda) = \frac{1}{1 + K e^{-\alpha(\lambda-1)}}. \quad (5)$$

In Equations (4) and (5), γ is the single channel conductance, ρ is the channel density, V_r is the reversal potential, K and α are parameters controlling the amount of current at tissue

reference length and the sensitivity to stretch. Values of γ and ρ were taken from the original formulation, and their product being equal to 0.75 mS/cm^2 . The reversal potential V_r was taken as -10 mV . The values of K and α were 110 and 14.7, respectively.

In addition, the change in the inwardly rectifying K^+ current (I_{K1}) and the outwardly rectifying K^+ current (I_{Ko}) due to their mechanosensitivity were also incorporated in the model. Assuming the same stretch ratio dependence $L(\lambda)$, it was formulated as:

$$\Delta I_{K^+} = 5.25 \times L(\lambda) \times [I_{K1(\text{stretched})} + I_{Ko(\text{stretched})} - I_{K1(\text{unstretched})} - I_{Ko(\text{unstretched})}]. \quad (6)$$

In Equation (6), $I_{K1(\text{stretched})}$ is the inwardly rectifying K^+ current and $I_{Ko(\text{stretched})}$ is the outwardly rectifying K^+ whole cell current measured at 22% local stretch of the cell.¹⁶ The term in brackets in Equation (6) is modeled via a piecewise linear function, which depends on membrane potential (FIG. 2 A). The scaling factor 5.25 ensures that the product $5.25 \times L(\lambda)$ equals 1 at $\lambda = 1.22$ (22% stretch). This formulation reproduces experimental results,¹⁶ such as action potential duration shortening at early plateau levels, after depolarization at 22% stretch, delayed repolarization, and depolarization of the resting potential by approximately 10 mV (FIG. 2 B). A large degree of stretch (close to 30%) depolarizes the membrane to approximately -16 mV and prevents the repolarization of the action potential.¹⁶

Computation

Numerical solutions for the bidomain model employed the explicit finite-element method with a spatial discretization of $100 \text{ }\mu\text{m}$. Dynamic time stepping was used for ionic model solution. The finite element method was used to solve the mechanical formulation. We used bilinear interpolation with square finite elements of edge length 0.37 mm .

Simulation Protocol

In a series of simulations, we compared the postshock behavior of unstretched tissue with tissue stretched in the horizontal direction at 0, 10, 15, or 20% of its reference length. The stretched tissue included introduction of either MSC or changes in the fiber angle distribution.

We used an S1–S2 protocol consisting of a train of 10 S1 transmembrane stimuli applied from the left edge of the sheet at a basic cycle length of 300 ms and S2 monophasic shocks of 8 ms duration and of strengths 10–50 V/cm delivered at various coupling intervals (100–240 ms) via line electrodes at the top and bottom sides of the sheet (FIG. 1 B).

Analysis

As part of the analysis of the simulation results, we constructed vulnerability areas. A vulnerability area encompasses episodes of reentry induction for various coupling intervals and shock strengths.³⁶ Vulnerability areas were constructed for unstretched tissue, tissue with activated MSC, and tissue with changes in the fiber angles. In addition, we examined the locations of phase singularities of the reentrant circuits using the algorithm employed by Eason and Trayanova.³⁷

For visualization purposes, data from stretched tissue, such as transmembrane potential and strain, were mapped from the deformed computational grid onto the undeformed grid.

RESULTS

Tissue Stretch

FIGURE 3 A shows the stretch ratio (corresponding to strain in the fiber direction) for 20% stretch. The smallest strain was observed in the middle of the sheet, because fibers in this region are oriented close to the vertical direction, and horizontal stretch of the sheet increases strain mostly in the cross-fiber direction. In the middle of the left and right edges of the sheet strain was also small, despite the horizontal orientation of the fibers. This is due to the fact that tissue compliance is larger in the cross-fiber direction as compared to the fiber direction, and stretch in the middle of the sheet prevented stretch of the tissue close to the edges.

Typically, fibers in the sheet rotated in a clockwise direction upon stretch, aligning themselves in the horizontal direction as shown in FIGURE 3 B. In the middle of the left and right edges, fibers rotated in a counterclockwise direction. The largest magnitude of rotation was approximately 17° .

Virtual Electrodes and Vulnerability of the Tissue to Electric Shocks

FIGURE 4 shows the transmembrane potential during and after the shock in unstretched tissue (FIG. 4 A), tissue with recruited MSC due to a stretch of 20% (FIG. 4 B), and tissue with changes in the fiber angle directions as the result of 20% stretch (FIG. 4 C). Stretch changes the amplitude (FIG. 4, top panels) of the virtual electrodes. The greatest effect is observed for tissue with changes in the fiber angle, where a significant decrease in shock-induced positive and negative polarization takes place.

In FIGURE 5, the transmembrane potential at shock end along the length of the white arrow depicted in FIGURE 4 A, top panel, is shown. The horizontal axis shows the distance along the arrow starting at the lower left corner of the sheet. The transmembrane potentials for unstretched tissue and tissue with inclusion of MSC were similar. However, the virtual cathode in the tissue incorporating changes in fiber angle revealed different behavior: the transmembrane potential decreased by more than 30 mV, and the spatial transition between the virtual anode and the virtual cathode shifted toward the top edge of the sheet.

Shocks created virtual electrodes with an interlocking spiral morphology. Virtual electrode polarization prolonged repolarization in regions where tissue had not recovered before the shock (FIG. 4). For coupling intervals in the range 100–160 ms, no reentrant circuits were formed. For coupling intervals in the range 160–180 ms, cathode-break excitation was observed, which led to reentry. When the coupling interval was increased to 180–220 ms, the virtual cathodes excited recovered regions, resulting in immediate propagation and reentry. In FIGURE 4, behavior of the tissue is shown at 10 and 40 ms postshock. In unstretched tissue and stretched tissue with changes in fiber angles, shocks produced a figure-of-eight reentry, as depicted with black arrows. In tissue incorporating MSC, a prolonged refractory period in the top right corner of the sheet prevented activation near that edge, and the shock produced a single spiral wave. As the coupling interval increased beyond 240 ms, the virtual cathode closest to the right edge of the sheet increased in magnitude, resulting in an activation which led to collision of propagation fronts and failure to induce reentry.

We did not find a difference in the vulnerability areas between unstretched tissue and tissue with involvement of MSC. However, change in the fiber angles due to stretch decreased vulnerability significantly (FIG. 6, gray area); for instance, the shock strength required to induce reentry increased from 20 V/cm to 28 V/cm at a coupling interval of 180 ms. At a coupling interval of 160 ms, we did not succeed in inducing reentry in the deformed tissue

even for a shock strength of 100 V/cm, while in unstretched tissue the 28 V/cm shock was sufficient to produce reentry.

Postshock Spiral Wave Breakup Due to Stretch

In unstretched tissue, reentrant circuits were characterized by figure-of-eight morphology with a rotation period of approximately 100 ms. In stretched tissue incorporating changes in fiber angle, postshock behavior was qualitatively the same. However, in stretched tissue with MSC recruitment, spiral wave breakup and onset of VF were observed. An example is shown in FIGURE 7 A; reentrant circuit phase singularities, as shown in FIGURE 7 B, occur at locations of a large strain gradient. FIGURE 8 depicts action potentials at the location of spiral wave breakup (FIG. 8 A) and in regions with large and small strains (FIG. 8 B). Wave breakup occurred on the fifth rotation of the spiral wave for any shock strength (FIG. 8 A). In the area with large strain, the effective refractory period (ERP) was increased, and was approximately 130 ms long, as compared to 100 ms in the region of small strain. Also evident is an increase of about 5 mV in the transmembrane potential at the end of the ERP in areas with a large strain magnitude.

Spiral wave breakup did not depend on shock strength or coupling interval. Breakup also occurred at smaller degrees of stretch (10% and 15% of reference length), but at the sixth or seventh rotation of the spiral wave, and phase singularities shifted closer to the top and bottom borders of the sheet.

DISCUSSION

The current study used a two-dimensional electro-mechanical model of cardiac tissue to investigate how stretch applied to a substrate with heterogeneous fiber structure influences postshock activity. A previous theoretical study has shown that a possible mechanism of decreased efficacy of defibrillation shocks is activation of MSC.³⁸ However, it involved homogeneous recruitment of MSC throughout the tissue, ignoring heterogeneous loading conditions in the ventricular wall. This limitation constituted the basis of the current study, in which a highly heterogeneous fiber structure determined a strain gradient and resulting dispersion in electrophysiological properties due to incorporation of MSC in the tissue. In addition to the effects of MSC recruitment, the current study examined the influence of tissue deformation and corresponding changes in tissue conductivities on postshock behavior.

The study mentioned above³⁸ found that stretch leading to homogeneous recruitment of MSC resulted in a small increase in vulnerability to monophasic shocks. The current study did not find such an increase in the case of heterogeneous recruitment of MSC. While heterogeneous MSC recruitment following stretch did not alter the vulnerability of cardiac tissue to electric shocks, it increased dispersion of refractoriness, thus altering the complexity of induced arrhythmias. In contrast, we found that the vulnerability of the tissue incorporating stretch-induced changes in the fiber angle was decreased. This decrease in vulnerability can be explained by the alignment of the fibers in the horizontal direction with stretch, which decreases the fiber curvature. Large fiber curvature results in the development of high magnitude shock-induced virtual electrodes³⁹ that may result in the establishment of postshock reentry.

The difference in the compliance of the tissue in the fiber and cross-fiber directions results in anisotropic strain of the tissue upon stretch. Differences in strain between the fiber and cross-fiber directions result in a change in the intracellular anisotropy ratio.³⁰ Changes in the anisotropy ratio in the intracellular versus extracellular space affect virtual electrode polarization⁴⁰ and can influence tissue vulnerability to electrical shocks.

Chorro *et al.* have shown an increased complexity of VF due to ventricular dilatation,¹¹ which occurred due to the modulation of electrophysiological properties, such as ERP, by stretch. In our study, sustained stretch resulted in an increase in ERP. Other studies have shown that ventricular dilatation may cause either a decrease or an increase in ERP. Most experiments with porcine or rabbit ventricles show a consistent decrease of ERP.^{19,20,41} However, data on canine ventricles show contrary results,^{42,43} which suggests that the effect of stretch on ERP is species-dependent. Despite these contradictory findings, all studies have shown an increased dispersion of ERP with applied stretch.^{19–21} One cause of increased dispersion of repolarization may be regional differences in strain, as demonstrated in this study. Indeed, as shown here, dispersion of refractoriness resulted in postshock conduction block and induction of VF at the location of a high strain gradient. To our knowledge, this is the first theoretical study which investigates the relationship between heterogeneous fiber structure and stretch-induced arrhythmias in cardiac tissue.

Chattipakorn *et al.*⁴⁴ have shown that biphasic defibrillation shocks near the DFT produce focal activity near the apex. In failed defibrillation episodes, the onset of VF was observed after five postshock cycles of the focal activity. Attempts to explain this phenomenon focus on the origin of the postshock activations near the apex,⁴⁵ with little investigation into the transition to fibrillation following these activations. In the porcine heart, the effect of stretch is larger at the apex than at the base of the left ventricle,²¹ creating a dispersion of repolarization. Based on our findings, we suggest that rapid activation of the left ventricle apical region leads to reentry at the locations of high strain gradient. Interestingly, we observed the same number of postshock reentrant cycles (5) preceding wave breakup as was observed in the experiments of Chattipakorn *et al.*

Limitations

This study assumed that activation of MSC was a function of strain in the fiber direction only. However, it is possible that MSC recruitment could depend on cross-fiber strain. This might be related to the fact that ventricular dilatation has a larger effect on refractoriness at the endocardial as compared to the epicardial surface,⁴¹ while the transmural distribution of diastolic and systolic strain is more uniform in the fiber as compared to the cross-fiber direction during normal conditions.

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FIGURE 1.
Geometry of the model (A) and shock protocol (B).

FIGURE 2.
Current-voltage relationship of the differential potassium current ΔI_{k+} (see text for detail) (A) and action potentials of a single cell at different degrees of stretch (B).

FIGURE 3.

Stretch ratio for a horizontal stretch of 20% of the reference length (A). Rotation angle between the pre- and poststretch fiber direction (B). Clockwise angles of rotation are positive.

FIGURE 4.

Virtual electrode polarization in unstretched tissue (A), tissue with recruitment of MSC due to 20% stretch (B), and tissue with changes, Δ , in the fiber angle (C). The top panel shows the transmembrane potential distribution at shock end. The middle and bottom panels show transmembrane potential maps at 10 ms and 40 ms postshock, respectively. Coupling interval is 200 ms and shock strength is 50 V/cm.

FIGURE 5.
Transmembrane potential along the length of the arrow shown in FIGURE 4.

FIGURE 6.

Vulnerability areas for unstretched tissue and tissue including MSC recruitment (white area bordered by black line; vulnerability areas are identical). Vulnerability area for tissue with change in the fiber angles is shown in gray. Dots correspond to episodes of stable reentry.

FIGURE 7. Postshock reentry for tissue incorporating MSC (**A**) and locations of the phase singularities from 10 to 1600 ms postshock (**B**). Coupling interval is 200 ms and shock strength is 10 V/cm.

FIGURE 8.

(A) Action potentials at the location of spiral wave breakup in the tissue with involvement of MSC shown in FIGURE 7. The location of the spiral wave breakup corresponds to a location of high strain gradient (point 1 in panel C). (B) Action potentials in an area of large strain (thick line, point 2 in panel C) and in an area of small strain (thin line, point 3 in panel C).