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Models of Stretch-Activated Ventricular Arrhythmias

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Abstract

One of the most important components of mechano-electric coupling is stretch-activated channels, sarcolemmal channels that open upon mechanical stimuli. Uncovering the mechanisms by which stretch-activated channels contribute to ventricular arrhythmogenesis under a variety of pathological conditions is hampered by the lack of experimental methodologies that can record the three-dimensional electromechanical activity simultaneously at high spatiotemporal resolution. Computer modeling provides such an opportunity. This goal of this review is to illustrate the utility of sophisticated, physiologically realistic, whole heart computer simulations in determining the role of mechano-electric coupling in ventricular arrhythmogenesis. We first present the various ways by which stretch-activated channels have been modeled and demonstrate how these channels affect cardiac electrophysiological properties. Next, we employ an electrophysiological model of the rabbit ventricles to understand how so-called commotio cordis, the mechanical impact to the pre-cordial region of the heart, can initiate ventricular tachycardia via the recruitment of stretch-activated channels. Using the same model, we also provide mechanistic insight to the termination of arrhythmias by precordial thump under normal and globally-ischemic conditions. Lastly, we employ a novel anatomically-realistic dynamic 3D coupled electromechanical model of the rabbit ventricles to gain insight into the role of electromechanical dysfunction in arrhythmogenesis during acute regional ischemia.

1. Introduction

The coupling between electrical and mechanical events in the heart is an active area of research. Experimental and clinical research has demonstrated that the mechanical activity of the heart, in health and disease, affects cardiac electrophysiology¹⁻⁴. Disturbances in heart rhythm are often due to mechano-electric coupling mechanisms in combination with dynamical factors or with those associated with remodeling in heart disease.

One of the most important mechanism of mechano-electric coupling is the existence of sarcolemmal channels that are activated by mechanical stimuli. A variety of ionic channels activated by changes in cell volume or cell stretch have been identified in cardiac tissue⁵⁻⁹. Of these, stretch-activated channels (SACs) have long been implicated as important contributors to the pro-arrhythmic substrate in the heart. The nonuniform distribution of positive myofiber strain (stretching) during mechanical contraction under a variety of pathological conditions could produce, via SAC, a pro-arrhythmic dispersion in

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electrophysiological properties^{10, 11}. SACs have been shown to shorten or lengthen APD of a single myocyte or produce ectopic beats depending on the timing of the mechanical stimulus application relative to the phase of the action potential¹². Uncovering, however, the mechanisms by which SACs contribute to ventricular arrhythmogenesis under a variety of pathological conditions is hampered by the lack of experimental methodologies that can record the three-dimensional (3D) electrical and mechanical activity simultaneously and with high spatiotemporal resolution. Thus, computer simulations have emerged as a valuable tool to dissect the mechanisms by which SAC contribute to the ventricular arrhythmogenic substrate. In this review we present physiologically realistic whole heart computer simulations of the role of mechano-electric coupling in ventricular arrhythmogenesis.

2. Modeling the effect of SAC at the myocyte level

Two types of SAC are typically considered to be the most important contributors to the process of cardiac mechano-electric feedback, the cation non-selective SAC (SAC_{NS}) and the K-selective SAC (SAC_K). The current-voltage relationship of both is typically linear, and the activation and inactivation times of these channels are much faster than the time course of a physiologically-relevant mechanical stimulus¹³. Thus, SAC are typically assumed to behave as instantaneously activating linear currents¹⁴⁻²⁰. The reversal potentials of SAC_{NS} and SAC_K are in the range of -10mV and -90mV , respectively^{5, 21}. Thus, the common reversal potential of whole-cell stretch-activated currents varies from -90 to -10mV , depending on the fractional expression of both types of SACs. Values in this range have been widely used in simulation studies^{14-16, 22}, and the effects of SAC on electrophysiology are strongly dependent on this reversal potential. The conductances of the two SAC currents were typically assumed to be dependent on strain rather than stress due to the limited capabilities of current experimental techniques to track changes in stress and were chosen accordingly to match experimental results^{1, 19, 23}. Note that because the behavior of SACs varies significantly across different experimental environments, the choice in SAC conductance values is somewhat arbitrary.

During sustained stretch, the SAC current can have a significant impact on cardiac electrophysiological properties. The effects of a constant, time independent current via SAC on general electrophysiological properties has been studied by our team previously²⁴. We found that SAC opening progressively depolarized resting cells, caused reduction in the magnitude of the transmembrane potential during early repolarization, and prolonged action potential duration (APD) when the SAC reversal potential was above -20mV . Studies^{15, 19} have also investigated the effects of SAC recruitment during different phases of the action potential. Different responses were found, determined by the timing of the stretch and its magnitude. If stretch was applied during the plateau phase, it changed the time course of repolarization, resulting in either shortening or lengthening of APD. If SAC were activated when the cell is already repolarized, it resulted in a new activation if the magnitude of the SAC current was above threshold.

3. Modeling mechanically-induced arrhythmias in *Commotio Cordis*

A body of research has demonstrated that moderate mechanical impact to the pre-cordial region of the chest (*Commotio cordis*) can lead to cardiac arrhythmias without concomitant damage to the heart or other organs of the chest²⁵⁻²⁸. A computational study by Li et al.¹⁵ from our team examined the mechanisms by which mechanical stimulation via the recruitment of SAC can result in the initiation of ventricular tachycardia (VT) in the rabbit heart. The study used a purely electrophysiological model, in which mechanical impact was assumed to open SACs. The mechanical impact was delivered to the anterior epicardium of the rabbit model during ventricular repolarization. The area in which SAC were activated by the mechanical

intervention was assumed circular on the cardiac surface and of 16 mm diameter, a dimension of impact scaled from baseball-impacts in man or pig models²⁹ to that of rabbit.

In the study by Li et al.¹⁵ the vulnerable window^{30, 31} was of duration 10 to 20 ms, consistent with experimental data^{26, 27}. Figure 1 presents two examples of mechanical impact, each corresponding to a coupling interval outside or inside the vulnerable window. Figure 1A portrays the events associated with a mechanical impact that did not induce reentry. The coupling interval is after the vulnerable window. Since the tissue was largely recovered at the time of mechanical impact, an ectopic excitation was elicited in a large proportion of the impact region, forming a figure-of-eight reentry pattern, but not giving rise to sustained reentry. Figure 1B presents a case of mechanically-induced sustained reentry within the vulnerable window. The 50 ms panel depicts the ventricles at the end of the first reentrant cycle, when the ectopic wavefront was entering the region of impact. The activation still managed to propagate through the original zone of impact. The second cycle of the reentry started in the epicardial layers of the LV, and then continued mostly as a figure-of-eight reentrant circuit, later deteriorating into ventricular fibrillation (VF).

Figure 1C is a schematic representation of the transmembrane potential distribution in and around the impact zone at the time of mechanical stimulation. The propagating wavefront has traveled from bottom to top, and the wave tail is near the middle of the tissue. The circle represents a projection of the impact profile on the epicardial surface. Three different types of responses can be induced within the region of impact. Where the circle overlaps with zone #1, the APD in mechanically stimulated tissue is shortened. Where circle and zone #2 overlap, APD is prolonged. In the mechanically stimulated tissue of zone #3, a new action potential is elicited. Both the size of the impact region and its location relative to the trailing repolarization wave determine which responses will be induced by a mechanical stimulus. If mechanical stimulation occurs at a coupling interval prior to the onset of the vulnerable window, the trailing end of the repolarization wave would, at that point in time, be located closer to the bottom of the scheme in Figure 1C, so that only zone #1, or zones #1 and #2, would appear inside the circle depicting the impact area. For a coupling interval past the vulnerable window (Figure 1A), the trailing wave would have moved further up towards the top and only zones #2 and #3, or zone #3 alone, would appear in the circle representing the impact site. While in this case an action potential was elicited by the mechanical stimulus, the ectopic excitation propagated towards the region of lengthened APD (zone #2) where propagation was blocked. In the case presented in Figure 1B, all three zones were inside the impact area. A new wavefront was initiated at the lower portion of the impact region. The wavefront propagated more slowly than the one elicited by the impact in Figure 1A since mechanical stimulation took place earlier and the ventricles had not completely recovered from the preceding paced beat. On the return pathway, upon reaching the original region of impact, the propagating wavefront encountered first a fully recovered tissue (zone #1; APD was shortened there). The next zone on the way of the reentering wavefront was zone #2 where APD was extended. However, in contrast to Figure 1A, the tissue had already recovered from the impact by the time the ectopic wavefront arrived at zone #2; the activation successfully traversed the original region of impact and arrhythmia was established.

Despite the simplified representation of the mechanical impact, the study of Li et al.¹⁵ uncovered important mechanisms by which mechanical impact in *commotio cordis* leads to the establishment of ventricular arrhythmias in a narrow time interval during the T-wave.

4. Modeling the termination of VT by precordial thump

Ventricular arrhythmia can be initiated by a mechanical impact, and it can also be terminated by it. An early study by Bierfeld et al.³² suggested that the mechanism of mechanical

conversion of VT or VF into sinus rhythm might be that the mechanical stimulus interrupted reentrant pathways or depressed ectopic foci. The goal of another simulation study by our team, the one by Li et al.¹⁶ was to elucidate the mechanisms for termination of arrhythmia by precordial thump (PT) under normal and globally-ischemic conditions and to determine the reasons for the decreased efficacy of PT in global ischemia. The study hypothesized that one manifestation of SAC_K could be the ATP-sensitive K^+ channels (K -ATP); reduction in ATP content under ischemic conditions sensitizes this channel to mechanical stimulation^{6, 33}. Using the same purely electrophysiological model of the whole heart as in the previous section, the study delivered PT to different cases of VT to examine how SAC activation interacts with the 3D pre-thump scroll wavefronts in the normal and ischemic ventricles and to identify the determinants of PT success rate. PT was assumed to cause activation of SAC current in the right ventricular (RV) free wall and the septum only, the reason being that since PT is administered directly to the chest, it causes an increase mostly in RV pressure³⁴. The timing of PT delivery was chosen randomly within the reentrant cycle of a given VT.

The simulation results demonstrated that the increased mechano-sensitivity of the K -ATP channels in ischemia lowers PT efficacy: in the normal heart, PT succeeds in terminating VT in 60% of the cases, while success decreased to 30% in ischemia. As shown in Figure 2A, PT succeeded in terminating VT in the normal heart following an extra beat. PT caused excited tissue in the RV to repolarize, while RV tissue at rest became depolarized. Therefore, propagation of the pre-thump wavefronts was blocked in the RV; propagation proceeded through the LV, resulting in VT termination. Figures 2B and C display post-PT activity under ischemic conditions. Both PTs failed to terminate VT, however, the post-PT reentries were different from each other and from the pre-PT case. As illustrated in Figure 2B, PT under mild ischemic conditions, which recruited a mechano-sensitive outward current of reversal potential -45mV , depolarized resting tissue. Repolarization of excited cells was much greater than in the normal heart (5ms panel). The immediate post-thump activity (35ms panel) gave rise to a new reentrant circuit (see schematic, red arrow). Figure 2C presents post-PT activity in the case of increased ischemia severity, where PT caused a mechano-sensitive current of -65mV reversal potential. The increased contribution of I_{KATP} greatly repolarized excited tissue in the RV (5ms panel). Post-PT activity originated from undisturbed excitation in the LV (10 and 35ms panels), which invaded the repolarized RV. A new reentrant circuit was established that encompassed the entire ventricles.

The simulation studies presented above employed purely electrophysiological models, representing mechanical stimuli via their effect on SAC. In the section below, a coupled electromechanical model was used, for the first time, to examine the mechanisms of cardiac mechanics-mediated induction of ventricular arrhythmias in acute regional ischemia.

5. Modeling mechanically-induced spontaneous arrhythmias in acute regional ischemia

In the normal heart, tissue stretch can result in spontaneous firing of the myocytes and ventricular premature beats (VPBs).⁸⁻¹¹ The inducibility of VPBs has been found to depend on the magnitude, velocity, and time of application of stretch.^{9,10,12} In the acutely ischemic heart, occurrence of VPBs has been also associated with rapid regional distension. During acute ischemia, the probability of occurrence of spontaneous arrhythmias is much lower in the isolated unloaded heart than in the working heart.¹⁶ Furthermore, several studies have shown that most VPBs arise from regions around the electrophysiological ischemic border.^{3,18,19} The mechanisms by which ischemia-induced mechanical dysfunction can induce VPBs is the subject of recent study by Jie et al.³⁵ The study used a novel anatomically-realistic dynamic 3D electromechanical model of the rabbit ventricles to gain insight into the role of electromechanical dysfunction in arrhythmogenesis during acute regional ischemia.

The 3D electromechanical model of the beating rabbit ventricles was developed. This model contained a central ischemic zone (CIZ) and a border zone (BZ) and represented the electrophysiological and mechanical milieu in the heart at 4 min post-occlusion. Dynamic mechano-electrical feedback was represented via spatially and temporally non-uniform membrane currents through SACs, the conductances of which depended on local fiber strain rate, dE_{ff}/dt_f .

Figure 3A depicts traces of transmembrane potential (V_m) and of E_{ff} following the last pacing stimulus from three representative epicardial sites located in NZ, BZ and CIZ. The figure shows that during the last pacing beat, CIZ was associated with the largest ischemia-induced elevation in resting potential, smallest action potential amplitude, and shortest action potential duration. In both BZ and CIZ, after the pacing beat, the strain and its rate started to rise gradually while in NZ they remained unchanged. In both BZ and CIZ, cell membranes underwent associated mechanically-induced sub-threshold depolarizations, i.e. delayed after-depolarization (DAD)-like events in BZ and CIZ, while such depolarizations were absent in NZ.

Figure 3B depicts the events following the last pacing beat in the acutely ischemic heart, where a VPB was induced. Cross-sectional views show that the VPB originated from two locations around the endocardial BZ in the LV (arrows in 191-ms inset), propagated fully intramurally in the apical region (193 and 195 ms) until part of the wavefront (enclosed by the ellipse in the bottom 195-ms inset) made a breakthrough onto the epicardium at the location enclosed by the ellipse in the 198-ms inset. Another part of the wavefront made a later epicardial breakthrough, shown enclosed by rectangle in the 200-ms inset, since it propagated across a thicker part of the wall. Both epicardial breakthrough sites were located close to the anterior ischemic border. The wavefront that these activations coalesced into initially encountered conduction block within CIZ and propagated around it (240 ms), then entered CIZ (300 ms) and terminated there.

Figure 3C presents action potentials recorded at sites 1 (in BZ) and 2 (in CIZ) marked in the bottom 191-ms inset. At both sites, cells underwent mechanically-induced DAD-like events following the pacing beat. At site 1, the depolarization (solid arrow) evoked spontaneous firing. At site 2, despite the fact that the peak magnitude of sub-threshold depolarization (encircled by dashed circle) was 8.5 mV larger, no action potential was triggered. Rather, following the end of the DAD-like event, the site was subsequently activated (dashed arrow) in the course of the propagating wave.

The results of this study clearly demonstrate that stretch of ischemic tissue, which loses its ability to contract, by the surrounding normal tissue during contraction leads to increased strain rates, causing mechanically-induced depolarizations via SAC in the ischemic region, the magnitude of which increases from BZ to CIZ. Mechanically-induced VPBs originated from the ischemic border in the LV endocardium, then traveled fully intramurally until emerging from the ischemic border on the epicardium, initiating reentry. The study by Jie et al.³⁵ thus provided the first direct evidence that mechanically-induced membrane depolarizations and their spatial distribution within the ischemic region are a possible mechanism by which mechanical activity contributes to the origin of spontaneous arrhythmias.

6. Concluding Remarks

This review article illustrates the use of advanced computer simulations to uncover the mechanisms by which mechano-electric coupling may contribute to ventricular arrhythmogenesis. The studies presented here demonstrate the power of computer models and simulations to probe mechanisms where experimentation, due to the current limitations in experimental techniques, fails to do so. From the chronological exposition of the studies in this chapter it is clear that models of mechano-electric coupling have undergone major development. They have moved from the realm of the purely electrophysiological models,

which represent mechano-electric coupling via the opening of SAC at pre-assigned locations, to sophisticated models of coupled electromechanics, where mechanical deformation can exert a multitude of stretch-related effects.

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Figure 1.

(**A**) Evolution of the spatial distribution of transmembrane potential in a rabbit ventricular model following a mechanical impact delivered at coupling intervals (CI) of 155 ms. The CI is outside the vulnerable window; the impact does not result in reentry. (**B**). Evolution of the spatial distribution of transmembrane potential in the rabbit ventricular model at a CI of 145 ms. Mechanical stimulation results in reentry. Time is counted since the onset of the impact and is denoted by the numbers above each image with “impact” referring to the transmembrane potential distribution at the end of impact. The smaller images are semi-transparent renditions of the transmembrane potential distribution in the ventricular volume, and represent anterior, basal, or side views of the ventricles; they refer to the couplings shown in the images to their left. In the semi-transparent images, the propagating wavefront is shown as a white surface. White arrows in 20, 80 and 150 ms panels indicate direction of propagation. (**C**). Schematic representation of transmembrane potential distribution in and around the impact zone prior to mechanical stimulation. Based on figures from the paper by Li et al.¹⁵ and reproduced here with permission from Springer.

Figure 2.

Evolution of post-impact transmembrane potential distribution on the epicardial surface (anterior view) in a simulation of rabbit ventricles under normal (**A**) and ischemic (**B, C**) conditions. In all cases, the pre-impact ventricles were in VT. Time, counted from impact onset, is shown above each column. Color scale as in Figure 1. Based on a figure from the paper by Li et al.¹⁶; reproduced with permission from Elsevier Limited.

Figure 3.

(A) Traces of V_m (solid lines) and E_{eff} (dashed lines), from sites in NZ, BZ and CIZ in the rabbit model of acute regional ischemia. Time zero is the onset of the last pacing stimulus. (B) Evolution of mechanically-induced VPB. 191 to 195-ms insets present short and long axis views of the apical region. 198 to 300-ms insets present a titled anterior view of the ventricles. Arrows in 191-ms inset indicate locations of earliest spontaneous firing. The ellipse and rectangle in the bottom 195-ms inset indicate parts of the wavefront that make the earliest epicardial breakthrough at the locations enclosed with the ellipse in 198-ms inset and the rectangle in 200-ms inset, respectively. (C) Traces of V_m (black) at sites 1 (solid lines, BZ) and 2 (dashed lines, CIZ) marked in the bottom 191-ms inset in panel B. Solid arrow and dashed circle denote mechanically-induced depolarizations at sites 1 and 2, respectively. Dashed arrow indicates activation at site 2 by propagation of the mechanically-induced VPB. Based on figures from the paper by Jie et al.³⁵ and reproduced here with permission from Wolters Kluwer Health.