

The Roles of Stretch-Activated Channels on Antiarrhythmic Therapies: Computer Simulations

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Abstract

The recognition of abnormal ventricular stretch as a potent arrhythmogenic factor that can be modulated by chemical agents has opened new avenues for anti-arrhythmia therapy. Experimental evidences showed the depolarized currents induced by stretch-activated channels (SACs) could lead to arrhythmias. The major objective of this study is to explore the interactions between SACs and gap junctions on modulating the action potential. A pair of rat ventricular cells model is developed based on the dynamical equations described by Beeler and Reuter. Two cells are connected together by gap junctions, which are modeled as T-network of resistances. While an external current stimulus is applied on the first cell, the action potential is measured at the second cell in the stretch status based on Poisson ratio of 0.7. Results indicate that (1) under the status of cell uncoupling, the measured maximum amplitude of action potential is reduced from 25 mV to -10 mV, the action potential duration is shortened largely from 300 ms to 150 ms, and the membrane potential is elevated from -82 mV to -60 mV; (2) under the condition of cell coupling, the measured overshoot amplitude of action potential is reduced slightly from 25 mV to 22mV, the action potential duration is lengthened slightly from 300 ms to 320 ms with the crossover near -40 mV, and the membrane potential is elevated to -70 mV. In conclusions, the presences of SACs in cellular uncoupling can be arrhythmogenic. The targets for therapies are likely to be the interactions between SACs and gap junctions.

1. Introduction

1.1. Stretch-activated channels

Action potential duration (APD) is recognized as one of important vulnerable factors to induce arrhythmias. Recent clinical reports indicated that the use of traditional class I or class III drugs on anti-arrhythmic interventions could lead to proarrhythmic effects [1,2]. Evidences of

mechanical changes which can initiate electrophysiological changes via mechano-electrical feedback (MEF) were recognized as a potential cause arrhythmias [3]. The major pathway of mechano-electrical transduction may be through SACs found abundantly in ventricular and atrial myocytes [4]. Sacs are highly conductive approximately 100 ps, with reversal potential at -30 mv. Since it conducted both sodium and potassium in a permeable ratio, 4:3, it was moderately depolarising. SACs can also trigger the action potential directly. The action currents were triggered by direct suction of SACs from the cellular patch by using patch clamping in cell-attached model. This has been simulated in a single channel model [5]. However, the exact pathway to MEF remains unclear. A variety of experiments from single myocytes to intact heart indicated that continuous diastolic stretch of heart muscle shortened the APD [6]. Reiter et al (1994) found the double-wave reentry can be initiated when the experimental cardiac ring was inflated by a balloon, but that the double-wave reentry was prevented when the balloon was deflated [7]. Double-wave reentry was typically observed in the dilated ring and The congestive heart in experiments and the MEF was thought to be influential on double-wave reentry. MEF can increase the excitable gap in dilated ring path, and it can shorten APD by passive stretch. At present, the mechanisms of double-wave reentry cause by MEF are not elucidated. Experimentally, the double wave reentry was usually observed in dilated ventricle; thus, MEF could be a potential cause of ventricular tachycardia acceleration [7].

1.2. Gap junctions

Evidences showed APD can also be influenced by gap junction. The inhomogeneous distribution of cellular coupling could initiate reentry [8]. According to Rudy's ring model, cells were coupled by resistive gap junctions. The conduction velocity was reduced and vulnerable window was lengthened due to the uniform increasing of uncoupling. In Rudy's simulations, the size of vulnerable window was approximately 0.5 ms in normal coupling;

however, the vulnerable window was extended to 30 ms in a high degree of uncoupling.

Because that both of SACs and gap junctions could be affected in cellular stretched status. The major objective of this paper is to explore the interactions between SACs and gap junctions on modulating APD.

2. Methods

2.1. The tissue model

A one-dimensional ring model was developed to simulate action potential propagation on a ring tissue. The ring was composed 1600 cells, modeled as the modified Beeler-Reuter ionic behaviors [9] and SACs were included based on experimental data [10]. Each cell was coupled by gap junctions, model as simple resistance. Based on the Beeler-Reuter cellular dynamic formulations involving space clamp conditions, the membrane is treated as a circuit node, where the Kirchoff's current law is applied. Accordingly, the stimulus current entering the node is equal to the sum of the membrane currents leaving the node. The traditional cable equation can be applied to represent action potential propagation on a ring as the following:

$$\frac{\partial^2 V}{\partial X^2} = \left(\frac{2}{a}\right)(r_m + r_d)(C \frac{\partial V}{\partial t} + I_{ion} + I_{sti}) \quad (1)$$

Where V represents the membrane potential, I_{sti} represents the external pacing stimulus, I_{ion} represents the ionic current density, C represents the membrane capacity, a represents the radius of the cell, X represents the cell length, and r_m and r_d represent the internal resistivity and resistive gap junctions, respectively. The ring model of cardiac tissue was composed 1600 cells, each 150 μm in length and 8 μm in radius, with internal resistivity (r_m) of 200 $\text{ohm}\cdot\text{cm}$. Resistive gap junction (r_d) of either 4 or 50 $\text{ohm}\cdot\text{cm}^2$ connected the adjacent cells.

2.2. The SACs model

Based on experimental observation, the SACs were usually modeled as time-independent currents as the shown in the equation (2):

$$I_{SACs} = \frac{-(V - V_{rev})\gamma\rho A}{[1 + K \exp(-\alpha(L - L_0))]} \quad (2)$$

Where V_{rev} represents the reversal potential of SACs, γ represents the single channel conductance of SACs, A represents the surface area of a single cell, K represents the

equilibrium constant for controlling current at L_0 , L_0 represents the resting sarcomere length.

3. Results

3.1. Action potential duration influenced by stretch-activated channels and gap junctions

Figure 3-1 indicated the interactions between SACs and gap junctions on the modulating the APD. SACs were modelled as a length-dependant and time-independent function as described in equation (2). The cellular shape was assumed to be a cylinder with length 150 μm and radius 8 μm . In Figure 3-1, the shorting of APD from 200ms to 60 ms in the presence of activated SACs in a stripe with cellular uncoupling ($r_d=50$).

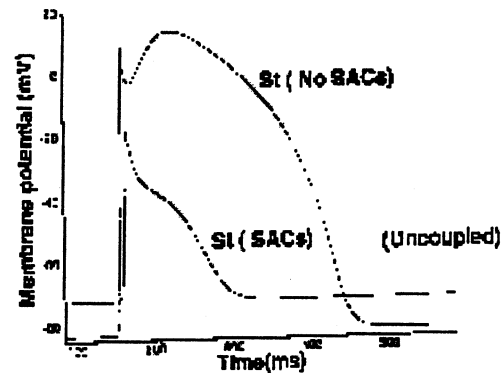


Figure 3-1: APD was shortened at the presence of SACs under cellular uncoupling.

Figure 3-2 showed that APD was prolonged to 370 ms with the crossover near -35 mV in cellular coupling ($r_d=4$) despite of the presence of SACs. The results shown in Figure 3-2 was similar to those simulations of SACs in a single myocyte with the steady-state stretch [10].

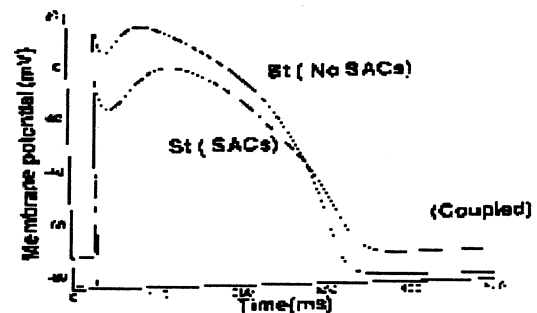


Figure 3-2: APD was lengthened at the presence of SACs under cellular coupling.

3.2. Induction of reentry

To advanced explore the role of gap junctions on the induction of reentry. The 1600 cells were connected together to form a ring tissue. To initiate the reentry, a S1-S4 protocol described as our previous models [11] was used to test the vulnerability of the ring tissue. With normal gap junctions ($rd=4$) and inactivated SACs, the excitable gaps were too small for any S3 to propagate, thereby preventing a second wave, as illustrated in Figure 3-3A. Figure 3-3A indicated the iso-potential contours during single wave reentry. In the panel B of Figure 3-3, the APDs and cycle length varied irregularly from beat-to-beat. Panel C also indicated the irregular variability in the peak of sodium currents. DWR can be induced within 1600 cells normally coupled cells, only when SACs were activated.

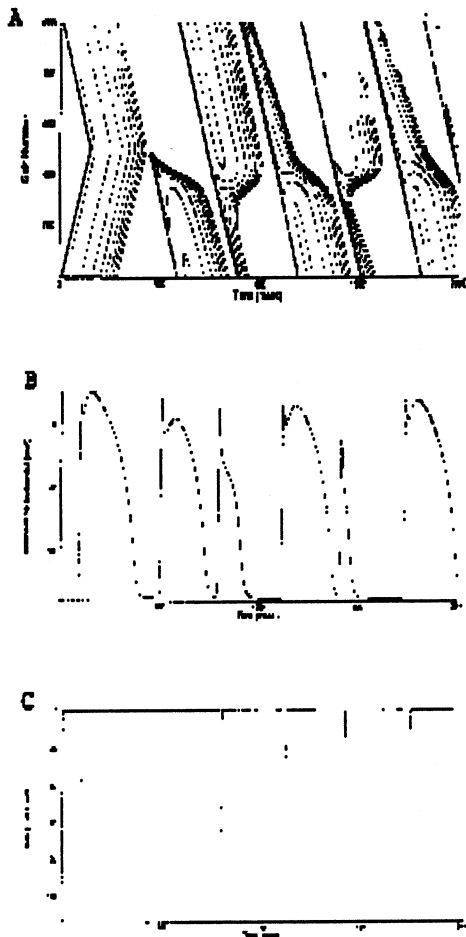


Figure 3-3: Alternating APD is shown by spatio-temporal map in Panel A and electrogram in Panel B with corresponding sodium current in Panel C.

With cellular uncoupling ($rd=50$), excitable gap became large enough for the insertion of new propagating waves, and DWR was readily inducible, as shown in the panel D of Figure 3-4. APD and cycle and sodium currents varied under these conditions, as shown in panel E and F of Figure 3-4. Note that the peak of sodium currents was reduced by 15 % in uncoupling. By activating the SACs, the excitable gap was widened by shortening refractory period.

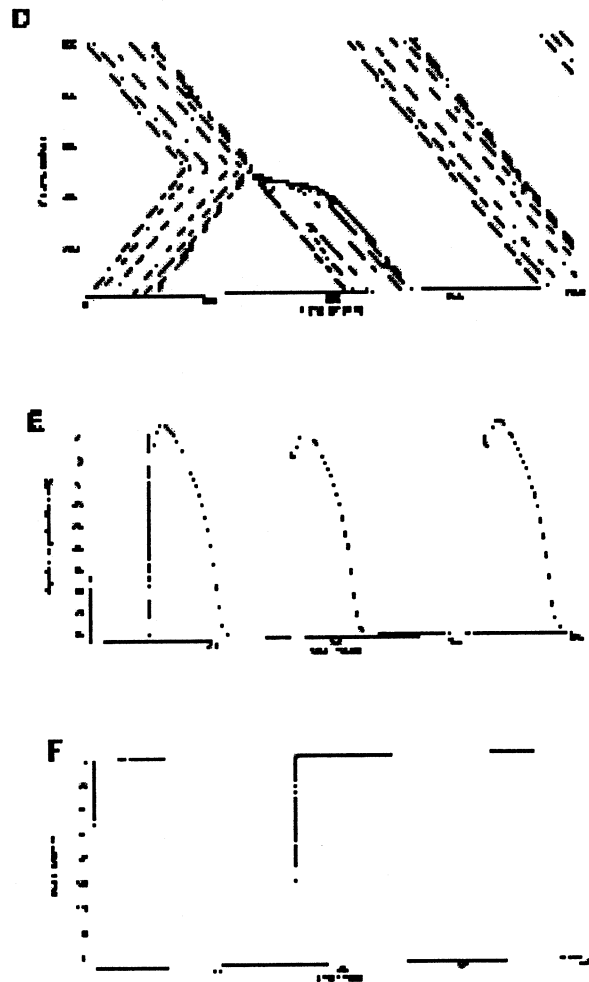


Figure 3-4: Excitable gap is enlarged shown in Panel D by increasing cellular uncoupling. Alternating APD with corresponding sodium currents disappear shown in Panel E and Panel F due to reduced conduction velocity during uncoupling condition.

4. Conclusions

The interactions between gap junctions and SACs were explored to determine their roles on APD. Based on model simulations, APD was shortened due to the presence of SACs under stretch in uncoupling cell connection shown in Figure 3-2. In such a conduction, acceleration of tachycardia could be facilitated by low ratio of APD to excitable gap shown in Figure 3-4. The lengthening of APD was shown under stretch due to the presence of SACs in coupling condition (shown in Figure 3-1).

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