Increasing the Effective Interstitial Resistivity Promotes the Escape of Premature Beats

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Abstract

Ectopic beats in the heart require a heterogeneous substrate to develop into dangerous, whole-heart arrhythmias. In this study, a 1-D monodomain computer model that incorporated local heterogeneity in both the interstitial and intracellular spaces was used to investigate whether increased interstitial resistivity could modulate the escape of premature beats given at different coupling intervals. Our simulations show that locally increasing the effective interstitial resistivity (ρ_{oeff}) reduces both the conduction delay and the dispersion of repolarization at the boundary between the poorly-coupled and well-coupled regions. Increasing ρ_{oeff} also decreases the dependence of the conduction delay on the coupling beat interval. The interaction between microheterogeneity in the interstitial and intracellular spaces may increase the likelihood that premature ectopic beats will escape and trigger an arrhyhmia.

1. Introduction

Rapidly firing ectopic foci have been identified as a source of abnormal rhythms in both the atria and the ventricles, and a number of research studies suggest that the formation and propagation of focal sources are influenced not only by ionic changes but also by structural changes that occur in the heart[1,2,3]. In particular, intracellular heterogeneity caused by local reductions in coupling has been shown to facilitate the formation of ectopic beats and influence the rate at which an ectopic focus fires[4,5]. While local reductions in coupling facilitate the fomation of focal sources, the loading mismatches between the poorly-coupled and well-coupled areas often increase the likelihood of conduction block, which can make it more difficult for premature beats that originate in a poorly-coupled region to escape and propagate throughout the heart[6]. Experimental and modeling studies in atrial tissue have also shown that the combination of variations in cellular geometry and same-site early premature stimuli can be a source of conduction abnormalities such as microreentry and shifts in propagation[7].

Although the close relationship between cellular geometry, ionic heterogeneity, and abnormal electrical propagation in the heart is widely accepted, very little is known about the impact of microstructural variations in the extracellular space that may be caused by narrow spaces or high concentrations of basement proteins. In this study, our objective was to use 1-D computer models to investigate the effect of increased interstitial resistivity on the propagation of premature beats in structurally heterogeneous tissue. Simulations were performed to test the hypothesis that the effect of increased interstitial resistivity on the conduction delay between well-coupled and poorly-coupled regions is dependent upon the coupling interval(CI) between the first stimulus (S1) and the premature stimulus (S2).

2. Methods

We created a heterogeneous 1-D monodomain model by introducing a 0.4 cm long central zone of poorly-coupled cells into a 1 cm long well-coupled fiber. The fiber was divided into individual cells of length 100 μm, and each cell was further subdivided into elements that were 10 μm each. Gap junctions were modeled as individual resistors (R_g). The well-coupled(WC) region of the fiber was assigned an R_g(WC) of 1.5 Ω-cm^2, while the poorly-coupled (PC) region was uniformly assigned an R_g(PC) of 60 Ω-cm^2 or 70 Ω-cm^2. No-flux boundary conditions were applied at the ends of the fiber. The effective interstitial resistivity was incorporated into the monodomain fiber using an approximation that was based on bidomain simulations. The governing equations for this approximate equivalent monodomain model are

$$\frac{\partial}{\partial x}\left(\frac{1}{\rho_{ieff}(x)+\rho_{oeff}(x)}\frac{\partial V_m}{\partial x}\right)=\beta' I_m \qquad (1)$$

$$I_m = I_{ion} + C_m\frac{\partial V_m}{\partial t} - I_{stim} \qquad (2)$$

where Φ_i and Φ_e are the intracellular and extracellular potentials, $V_m=\Phi_i - \Phi_e$ is the transmembrane potential, I_m is the transmembrane current, ρ_{ieff} and ρ_{oeff} are the effective intracellular and interstitial resistivities, β' is the modified surface to volume ratio, I_{ion} is the ionic current as calculated using the LRd membrane model of guinea pig ventricular myocytes, C_m is the membrane capacitance equal to 1 $\mu F/cm^2$, and I_{stim} is the intracellular stimulus current[8]. Premature beats were generated in the central zone using an S1-S2 stimulus protocol. The first stimulus (S1) was generated by stimulating cell 51 with a stimulus that was 1.5 times threshold. The second stimulus (S2) was given at the same site and the same amplitude as the S1, and the S1-S2 coupling interval was varied from 200 ms to 3500 ms. Conduction delays between the poorly-coupled central zone and the well-coupled region were measured by subtracting the difference in activation times (taken at V_m=-50mV) measured at the last node of the 69th cell and the first node of the 70th cell. The action potential duration was measured at 90% repolarization. All simulations were run using the in-house Cardiowave software package [9].

3. Results

In order to create a baseline for comparison, we first investigated the effect of the S1-S2 coupling interval on the conduction delay in a heterogeneous fiber with normal effective interstitial resistivity of ρ_{oeff} = 0.5 kΩ-cm. As expected, we observed a conduction delay at the transition between the poorly-coupled and well-coupled region that became more pronounced as the gap junction resistivity of the poorly-coupled region was increased. Conduction block occurred when R_g=64 Ω-cm^2. The mechanism for this conduction delay and block has been studied in detail by Wang and Rudy[6]. We also observed that there was a local dispersion of repolarization at the boundary between the poorly-coupled and well-coupled region. The APD profile for the case of R_g=63 Ω-cm^2 is shown in Figure 1. The smaller peak at cell 51 is a response to the stimulus given within the cell. Steinhaus et. al have previously reported a similar effect of heterogeneous coupling on action potential duration[10]. At the onset of block, the dispersion of repolarization at the boundary increased even further because the additional load from the well-coupled region drained current from the border cells during the plateau phase thus causing them to repolarize faster.

The combination of increased conduction delay and dispersion of repolarization (both of which were caused by structural heterogeneity alone) led to interesting results as the coupling interval between the S1 and S2 was decreased. Even for normal values of effective interstitial resistivity, intermediate decreases in the coupling interval led to a decrease in the conduction delay measured between the poorly-coupled and well-coupled regions of the fiber (Figure 2, solid lines). In the case of the fiber with R_g=70 Ω-cm^2, intermediate reductions in the coupling interval restored conduction along the fiber.

At very short coupling intervals (<250 ms), the conduction delay measured at the transition zone increased sharply from the minimum value. The

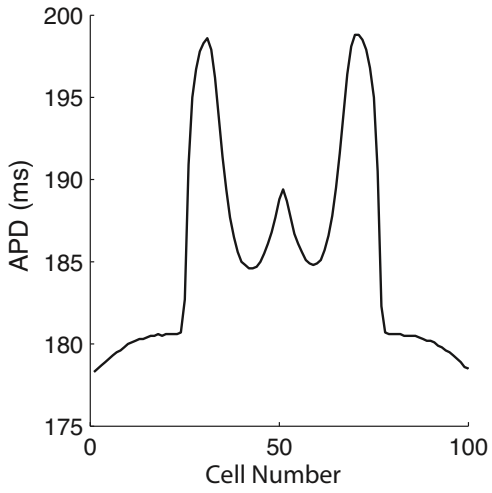

Figure 1. Action potential duration (APD) profile for heterogeneous cable with normal interstitial properties (ρ_{oeff}) and R_g (PC)= 63 Ω-cm^2

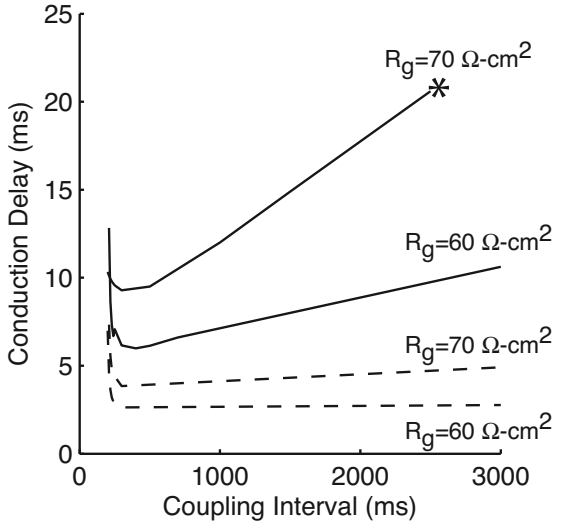

Figure 2. The conduction delay measured at the boundary between the poorly-coupled and well-coupled region as a function of the coupling interval. *Solid lines:* p_{oeff}=0.5 kΩ-cm. *Dashed lines:* p_{oeff} = 2.5 kΩ-cm. * indicates conduction block.

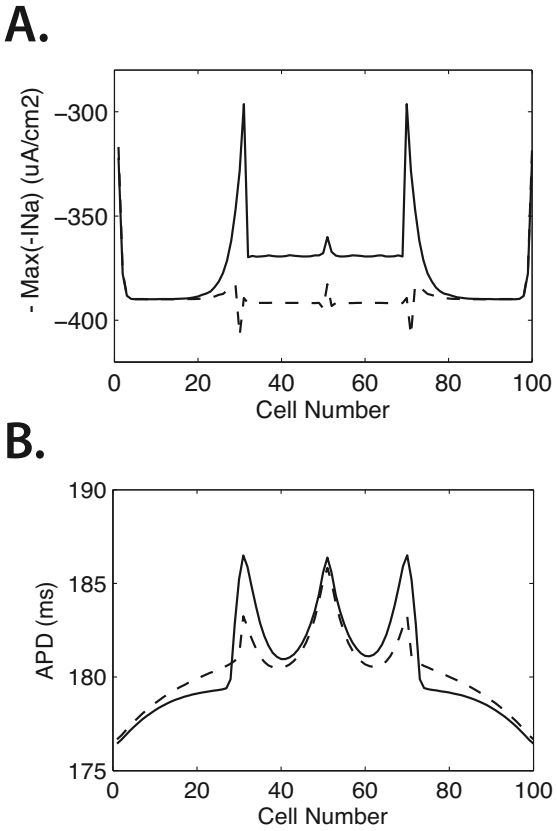

Figure 3. (A) The maximum sodium current and (B) the APD profile in response to the first stimulus (S1) along the fiber with R_g (PC)= 60 Ω-cm^2. *Solid lines:* p_{oeff}=0.5 kΩ-cm. *Dashed lines:* p_{oeff} = 2.5 kΩ-cm.

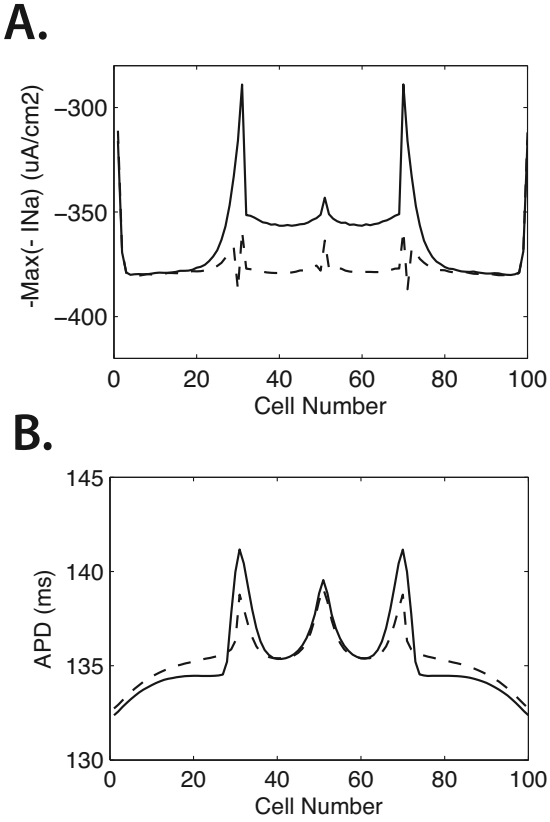

Figure 4. (A) The maximum sodium current and (B) the APD profile in response to the second stimulus (S2 with CI=230 ms) along the fiber with R_g (PC)= 60 Ω-cm^2. *Solid lines:* p_{oeff} =0.5 kΩ-cm. *Dashed lines:* p_{oeff} = 2.5 kΩ-cm.

dispersion of repolarization at the boundary also had a stronger effect on the available sodium current which caused small variations in the onset of conduction block for CI<210 ms. Conduction block at the transition zone eventually occurred for CI=200 ms in the fiber with Rg=60 Ω-cm^2 and for CI=199 ms in the fiber with Rg=70 Ω-cm^2.

Increasing ρ_{oeff} also reduced conduction delay and facilitated the escape of premature beats. In the fiber with R_g=60 Ω-cm^2, increasing the ρ_{oeff} of the central zone from 0.5 to 2.5 kΩ-cm reduced the delay at the transition between the well-coupled and poorly-coupled region in a coupling-dependent manner. As shown in Figure 2, the greatest decreases in delay occurred at very long (3500 ms) and very short (210 ms) coupling intervals, which showed decreases of 74% and 65% respectively. At intermediate coupling intervals (300-500 ms), the delay decreased by 57%. As shown in Figure 3B, increasing interstitial resistivity also reduced the APD dispersion at the boundary between the well-coupled and poorly-coupled region from 6.5 mV to 2 mV.

In the fiber with R_g set to 70 Ω-cm^2, increasing the effective interstitial resistivity to 2.5 kΩ-cm enabled action potentials generated at long intervals to escape from the poorly-coupled region. Increasing ρ_{oeff} also reduced the conduction delay for action potentials generated at intermediate and short coupling intervals by 58% and 28% respectively. Conduction block occurred at the transition zone when the coupling interval was reduced to 200 ms.

4. Discussion and conclusions

The results suggest the presence of two different mechanisms that restore conduction at the transition between the poorly-coupled and well-coupled region. In the first mechanism, the interaction between the

premature stimulus and the dispersion of repolarization reduces the difference in sodium current at the boundary between the well-coupled and poorly-coupled region and causes a curvature of $-|I_{Na}max|$ in the poorly-coupled region that can be observed in Figure 4A. This method of reducing loading is most effective at intermediate coupling intervals as evidenced by the gradual drop in the conduction delay for the fibers with p_{oeff}=0.5 kΩ-cm (Figure 2). In the second mechanism, the increase in effective interstitial resistivity increases the available sodium current and reduces the resistive loading effects along the fiber. As shown in Figures 2, 3, and 4, this reduces both the conduction delay and the dispersion of repolarization at the boundary between the well-coupled and poorly-coupled region. Increased interstitial resistivity has the greatest effect at long and short coupling intervals where the APD dispersion at the boundary is less effective at reducing loading. Although these two mechanisms have competing modes of action (one mechanism decreases the total amount of available INa while the other increases the total amount of available INa), they both reduce loading at intermediate coupling levels which in turn increases the likelihood that a premature beat will escape from a poorly-coupled region into surrounding well-coupled regions.

The results of this study are in agreement with other studies that have looked at the effect of heterogeneous coupling on conduction delay and APD dispersion; however, this study adds a new component in that it shows how heterogeneities in both the intracellular and interstitial space influence conduction delay and APD dispersion at the microstructural level even in the absence of ionic heterogeneity[10,11]. Similar to microstructural studies of conduction disturbances in atria done by Spach et. al, this study suggests that variations in sodium current caused by both ionic and structural microheterogeneity may play a major role in the development of conduction abnormalities in cardiac tissue [7].

The delicate interplay between low intercellular coupling, dispersion of repolarization, and increased interstitial resistance at the microscale level may enable complex activation patterns to develop from a small rapidly firing focal source. Future studies will use both 1-D and 2-D computer models to systematically investigate the effect of increased interstitial resistivity on the formation and propagation of multiple ectopic beats.

Acknowledgements

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