31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Influence of Channel Blockers on Cardiac Alternans

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Abstract—**Sudden cardiac arrest (SCA) due to fatal cardiac arrhythmias such as ventricular fibrillation is the leading cause of death in the United States, killing 350,000 Americans each year. Thus, it is of great importance to investigate the mechanisms that can suppress abnormal heart rhythms. In this work, we study the effects of drugs such as channel blockers through mathematical modeling of cardiac electrophysiological phenomena. In particular, we carry out multi-level simulations to study how channel blockers affect arrhythmias at cellular, fiber, and tissue levels. Numerical simulations show that the drugs have different effects at different scales (cellular versus fiber or tissue). Moreover, the drugs may appear to be arrhythmic in one model but antiarrhythmic in another. These observations indicate that analysis and simulation based on multiple scales and multiple models are crucial to fully understand the properties of drugs in treating arrhythmias.**

I. Introduction

SUDDEN cardiac arrest (SCA) results from fatal arrhythmias such as ventricular fibrillation [1]-[4], which is characterized by rapid, erratic, disorganized electrical pulses in the heart. When SCA occurs in a patient, the heart stops pumping blood to the brain and the body. As a result, the patient dies within 4 to 5 minutes if left untreated. In the industrialized world, SCA is a leading cause of death. For example, SCA kills 350,000 people in the US each year [5]. Ventricular fibrillation (VF) is frequently initiated by ventricular tachycardia (VT) because of rapid repeated stimulation of the ventricular muscle caused by mechanisms such as intramural reentry [6]. In patients, a premature ventricular contraction of the heart (PVC), instead of radial propagation, may spread in a circular pathway and maintain a rotating pattern, leading to tachycardia [7]-[9]. This phenomenon may even happen in a small area of cardiac muscle without anatomical obstacles [7]. PVCs can result from factors such as cigarettes, coffee, lack of sleep and even emotional irritability [6]. Although most PVCs are benign, those occurring during the vulnerable period (VP) may lead to dreadful arrhythmias. Vulnerable period refers to the time intervals when the heart is not fully recovered from a previous cycle such that areas of refractoriesness and nonrefractoriness exist simultaneously in the heart muscle. Thus, during VP, the heart muscle has heterogeneous properties. As a result, PVCs occurring in VP will spread successfully in some directions while fail to spread in other directions, and thus can lead to spiral waves.

Drugs that prolong the refractory period of cardiac cells had been thought to be antiarrhythmic. For example, encainide and flecainide were used to suppress PVCs in patients of post-myocardial infarction [10]-[11]. However, the effects of these drugs were disappointing – patients treated with drugs had a higher rate of death from arrhythmias (4.5%) than those assigned to placebo (1.2%). Using computer simulations, Starmer and associates investigated how sodium channel blockers, although presumably antiarrhythmic, increase the rate of sudden cardiac death [12]-[14]. Using computer simulations, Starmer et al. studied excitability of cardiac cells as well vulnerable period in a cardiac fiber. These simulations show that although sodium channel antagonists reduce the cardiac excitability by increasing the refractory period, they prolong the duration of VP by both slowing conduction velocity and reducing the gradient of excitability. As such, although drugs suppress premature ventricular contractions were suppressed, the proarrhythmic vulnerability to unsuppressed premature ventricular contractions was actually increased.

Much research has demonstrated that the induction and maintenance of fatal arrhythmias is connected to electrophysiological dynamics of heart tissue [15]-[21]. When stimulated by an electrical signal, cardiac cells generate an action potential [22], which consists of a rapid depolarization of the transmembrane voltage followed by a much slower repolarization process before returning to the resting value (see the schematics in Figure 1). The time interval during which the voltage is elevated is called the action potential duration (APD). The time between the end of an action potential to the beginning of the next one is called the diastolic interval (DI). The time interval between two consecutive stimuli is called the basic cycle length (BCL). Under periodic stimuli, the steady-state response gives rise to 1:1 pattern when the pacing rate is slow (see Figure 1 (a)). When the pacing rate becomes sufficiently fast, the 1:1 pattern may be replaced by a 2:2 pattern, so-called electrical alternans, where the APD alternates between short and long values (see Figure 1 (b)). A causal link between alternans and ventricular fibrillation has been established by various authors in theory and experiments. Therefore, studying the mechanism of alternans is a crucial step in understanding fatal arrhythmias. The goal of this article is to investigate how alternans is affected by sodium channel blockers.

Manuscript received April 7, 2009. This work was supported in part by the National Science Foundation under Grant CMMI 0845753.

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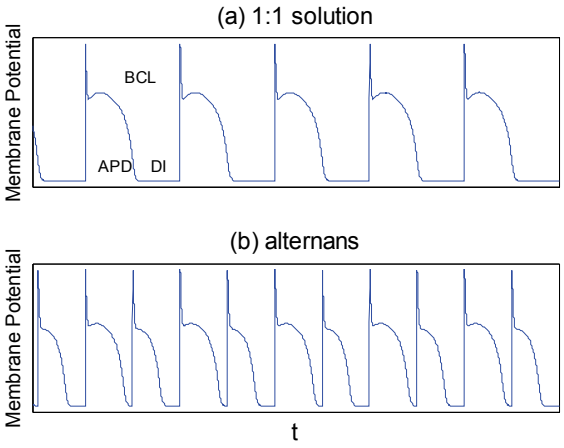

Figure 1. Schematic response of cardiac tissue: 1:1 solution (a) and alternans (b).

II. Problem Formulation

A. Cardiac Dynamics

Cardiac dynamics in extended tissue can be modeled using a reaction-diffusion equation:

$$\frac{\partial \boldsymbol{v}}{\partial \boldsymbol{t}} = \boldsymbol{D}\nabla^2 \boldsymbol{v} - \frac{1}{\boldsymbol{C_m}}(\boldsymbol{I_{ion}} + \boldsymbol{I_{ext}}), \tag{1}$$

where v represents transmembrane voltage, t is time, D represents the effective diffusion coefficient of v in the tissue, the Laplace operator ∇^2 represents spatial differential, C_m represents the transmembrane capacitance, I_{ion} is the total ionic current, and I_{ext} represents the external stimulus. In case of single-cell dynamics, the partial differential equation (1) reduces to an ordinary differential equation by dropping the diffusion term. The total current I_{ion} consists of currents from various ions including sodium, potassium, and so on. The number of currents and the form of each current depend on the specific model. Usually, the sodium current takes the following form:

$$\boldsymbol{I_{Na}} = \boldsymbol{g_{Na}}\boldsymbol{m}^3\boldsymbol{hj}(\boldsymbol{V} - \boldsymbol{E_{Na}}), \tag{2}$$

where g_{Na} is the maximum Na conductance, m is the fraction of open activation gates, and h is the fraction of open fast gates, j is the fraction of slow inactivation gates, and E_{Na} represents the Nernst potential [22]. A gate variable typically has two states: open and close. Dynamics of a gate can be written according to the mass-action law [23]. Equation (1) is complemented by a number of ODEs that describe the dynamics of various gate variables as well as the variation of certain ion concentrations.

B. Channel Blockade

Sodium blockers will block the sodium channels by reducing the conductance. In addition to the original open and close states, channels bounded to blockers will have a "blocked" state. Following Starmer et al. [12]-[14], we describe the states of channel blockade as

$$\text{Closed} \underset{\beta}{\overset{\alpha}{\rightleftarrows}} \text{Open} \underset{l}{\overset{k[D]}{\rightleftarrows}} \text{Blocked}. \tag{3}$$

Let us denote the fraction of blocked channels by b. We adopt the arguments in Starmer et al. and write the kinetics of b as

$$\frac{\boldsymbol{db}}{\boldsymbol{dt}} = \boldsymbol{k}[\boldsymbol{D}]\boldsymbol{m}^3\boldsymbol{hj}(1-\boldsymbol{b}) - \boldsymbol{lb}. \tag{4}$$

As a result of blockade, the current of sodium channel is changed to

$$\boldsymbol{I_{Na}} = \boldsymbol{g_{Na}}\boldsymbol{m}^3\boldsymbol{hj}(1-\boldsymbol{b})(\boldsymbol{V} - \boldsymbol{E_{Na}}). \tag{5}$$

III. Results

Over the years, many models have been developed based on different experimental measurements. In this work, we use the Beeler-Reuter (BR) model [24] and the Fox-McHarg-Gilmour (FMG) model [25] to investigate how sodium channel blockers affect alternans at cellular and tissue levels.

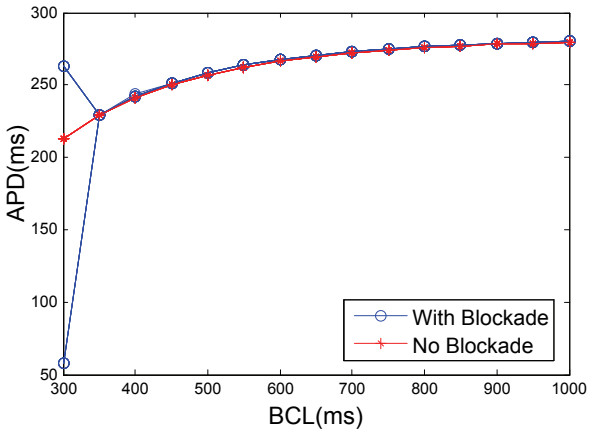

Figure 2. Bifurcation to alternans in an isolated cardiac cell using BR model with (blue) and without blockade (red).

We start with the BR model. Simulations of an isolated cell shows that the drug intends to induce alternans at a slightly larger value of BCL; see Figure 2. However, the responses before alternans are almost identical for both blockade and no blockade cases. The effect of the drug is more dominant in extended tissue. For example, simulations of a fiber of 200 cells show that alternans are induced by the drug at a much larger value of BCL (~750ms); see Figure 3. Moreover, the magnitude of alternans is also significantly increased by the drug.

The drug also influences the spatial distribution of APD along the fiber. For example, we plot the APD values along the fiber at BCL=700 ms; see Figure 4. The figure shows that the drug increases spatial gradient of APD, making the tissue more dynamically heterogeneous. The increased dynamic heterogeneity indicates higher risks for reentrant arrhythmias [18]-[19]. Indeed, our simulations of a square tissue of 200 by 200 cells show conduction block at BCL=700 ms when treated with the drug whereas the tissue without block continues to show proper conduction properties until BCL=300 ms.

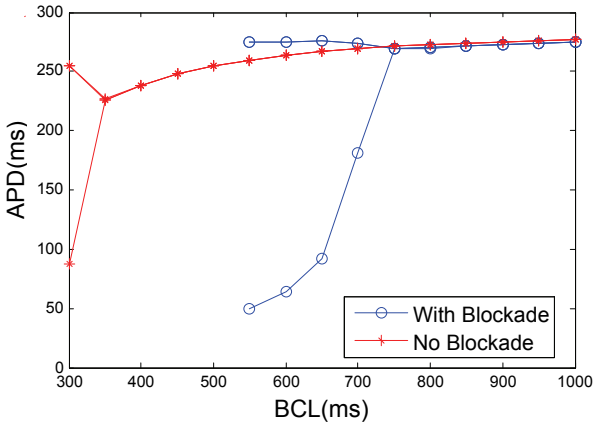

Figure 3. Bifurcation to alternans in a fiber of 200 cells: with (blue) and without (red) blockade. The middle cell is plotted.

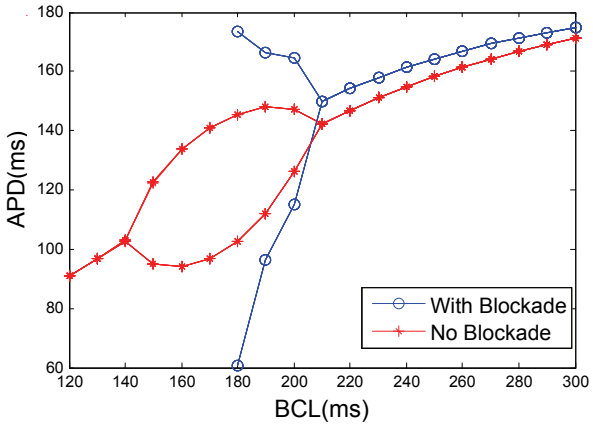

Figure 5. Transition to alternans in an isolated cell using FMG model: with (blue) and without (red) blockade.

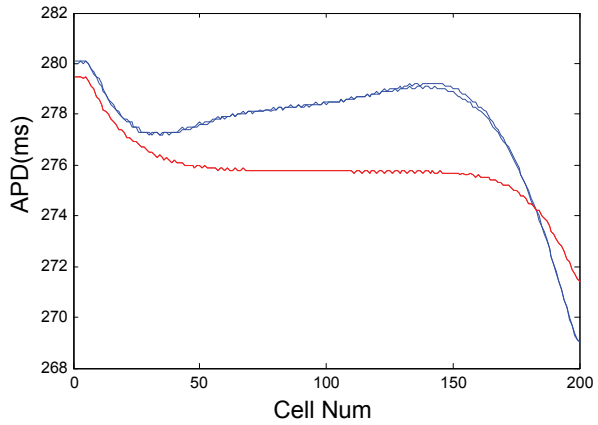

Figure 4. APD distribution along a fiber of 200 cells using BR model when BCL=700 ms: with (blue) and without (red) blockade.

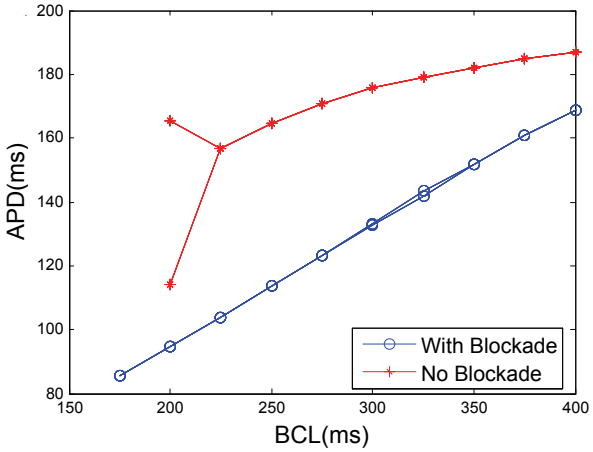

Figure 6. Transition to alternans in a fiber of 200 cells using FMG model: with (blue) and without (red) blockade.

The transition to alternans using FMG model shows different trends. First, simulations of an isolated cell show that alternans occurs almost at the same value of BCL for both blockade and no blockade cells; see Figure 5. Interestingly, when the BCL value is further decreased, the cell without blockade returns to 1:1 response when BCL is about 140 ms. On the other hand, the alternans response in the cell with blockade gives way to 2:1 response when BCL is approximately 180 ms.

Then, we look at the transition to alternans in fibers using the FMG model; see Figure 6. Here, the fiber without blockade first experiences alternans at BCL approximately 220 ms. Alternans in the fiber with blockade appears approximately at BCL=350 ms, but the magnitude of alternans is only several ms large. Moreover, the bifurcation diagram demonstrates a bubble structure so that for BCL values below 300 ms, the responses become 1:1 again. Since the magnitude of the alternans in blockade fibers is extremely small, it is not arrhythmic. In contrast, the fiber without block shows signficant magnitudes of alternans when BCL value is less than 220 ms.

We first investigate the APD distribution along the fiber using FMG model; see Figure 7. It is clear that the drug reduces the APD along the fiber. However, the spatial gradients of APD in fibers with and without blockade do not show significant difference. Summarizing the observations in Figures 5-7, one can see that the drug shows some antiarrhythmic effects in the FMG model by reducing the magnitude of alternans. Moreover, the drugs are also able to suppress alternans when applied to tissues.

IV. Conclusion and Discussion

We have used two different models to study the effects of sodium channel blockers on cardiac alternans. Numerical simulations demonstrate that sodium channel blockers applied to an isolated cardiac cell are able to prong the refractory period at regular pacing periods. While the blockers do not significantly modify the cell's dynamic restitution property, they slightly increase the critical pacing period for the onset of unstable electrical behaviors. Based on conventional theories of cardiac dynamics, these observations indicate that a prolonged refractory period reduces the chance for the occurrence of arrhythmias. However, simulations for fibers and tissues of the BR model

show opposite results – the channel blockers induce alternans in fibers and tissues at much larger values of BCL, making the fibers and tissues more vulnerable to arrhythmic activities. Therefore, although channel blockers appear to be antiarrhythmic at cellular level, they may significantly promote the onset of arrhythmias when applied to fibers and tissues. Nevertheless, simulations of the FMG model show that the drugs significantly reduce the magnitude of alternans, demonstrating antiarrhythmic properties. These observations indicate that analysis and simulation based on multiple scales and multiple models are crucial to fully understand the properties of drugs in treating arrhythmias. A complete understanding on why the drugs have different effects on different levels and in different models requires more detailed simulation and analysis.

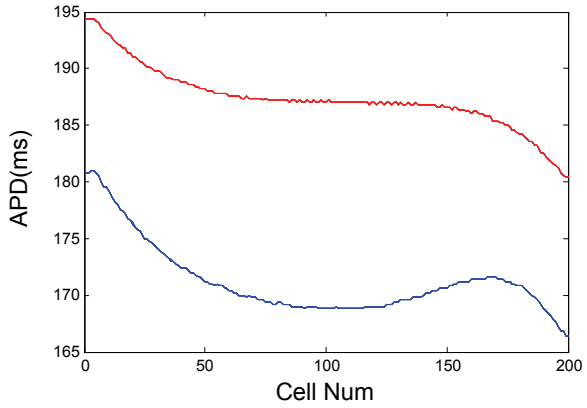

Figure 7. APD distribution along a fiber of 200 cells using FMG model when BCL=400 ms: with (blue) and without (red) blockade.

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