ABSTRACT

A beat-to-beat variation in cardiac action potential durations (APD) is a phenomenon known as electrical alternans. Alternans desynchronizes depolarization, increases dispersion of refractoriness, and creates a substrate for ventricular fibrillation. In the heart, APD alternans can be accompanied by alternans in intracellular calcium ([Ca^{2+}]). Recently, we demonstrated experimentally that the onset of APD alternans in the heart is a local phenomenon that undergoes complex spatiotemporal dynamics as pacing rate increases. Moreover, the local onset of APD alternans can be predicted by measuring the restitution properties of periodically paced cardiac tissue. The purpose of this research is to investigate the interplay between local onsets of APD and [Ca^{2+}], alternans using 2D simulation of action potential model of cardiac myocytes.

NOMENCLATURE

APD  Action potential duration.
B      Basic cycle length.
DI     Diastolic interval.
2D     Two-dimensional.
[Ca^{2+}]  Intracellular calcium transients.

INTRODUCTION

A beat-to-beat variation in cardiac action potential durations (APD) is a phenomenon known as electrical alternans. Alternans desynchronizes depolarization, increases dispersion of refractoriness, and creates a substrate for ventricular fibrillation. Electrical alternans in single cells is associated with T-wave alternans in the heart that is recognized as a precursor of ventricular arrhythmias [1]-[3]. Electrical alternans in single cells is associated with T-wave alternans in the heart that is recognized as a precursor of ventricular arrhythmias [4]-[6].

It has been proposed that the onset of alternans in cardiac myocytes can be predicted by analyzing the responses of myocytes to periodic pacing at different frequencies and by constructing a restitution curve – the non-linear relationship between the APD and the preceding diastolic interval (DI). It was predicted that the slope of the restitution curve being equal to 1 predicts the onset of alternans in cardiac myocytes [7]. However, the actual dynamics of periodically paced cardiac myocytes cannot be described by a single restitution curve since the APD depends on the entire pacing history, the phenomenon known as short term memory [8]-[10]. Several pacing protocols, including the restitution portrait, have been developed to predict the onset of alternans in the presence of short term memory.

In addition, the dynamics of periodically paced whole hearts are more complex, mainly due to the presence of a propagation effects, and therefore the onset of alternans in the whole heart occurs both spatially and temporally. Recently, we demonstrated experimentally that the onset of APD alternans in the heart is a local phenomenon that undergoes complex spatiotemporal dynamics as pacing rate increases [11]. Moreover, we
demonstrated that the local onset of APD alternans can be predicted by measuring the restitution properties of periodically paced cardiac tissue.

It is known that in the heart, APD alternans can be accompanied by alternans in intracellular calcium ([Ca^{2+}]_i) transients [12], [13], however the direct link between voltage and calcium alternans is missing. The purpose of this research is to investigate the interplay between local onsets of APD and [Ca^{2+}]_i, alternans using 2D simulation of action potential model of cardiac myocytes.

METHODS

We modeled two-dimensional (2D) tissue of 150x150 cells using the reaction-diffusion equation

\[
\frac{\partial V}{\partial t} = -\frac{I_{ion}}{C_m} + D \left( \frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V}{\partial y^2} \right)
\]

where V is a transmembrane voltage, C_m = 1 μF/cm² is the membrane capacitance, D = 5x10^{-4} cm²/ms is the effective diffusion coefficient, and I_{ion} is the total ionic current density. The reaction-diffusion equation was integrated with an operator splitting method and fixed time step method. The space step was 0.015 cm and the time step was 0.1 ms. The ionic current was split using the splitting method and fixed time step method. The space step was 0.015 cm and the time step was 0.1 ms. The ionic current was modeled by integrating a rabbit ventricular action potential model with fully formulated [Ca^{2+}]_i, cycling [14].

The 2D tissue was stimulated at the left bottom corner (10x10 area) at progressively reduced basic cycle length (B) starting from 300 ms, and 5 stimuli were applied at each B. The APDs were measured at 80% repolarization, and DI was calculated as DI = B - APD. At each pixel, a dynamic restitution curve consisting (APD, DI) responses measured at different values of B was constructed, and the slope S_{dyn} was measured by fitting these responses with an exponential function. The maximum slope \( S_{max} \) was calculated at the smallest DI in which the entire tissue exhibited a 1:1 response. Alternans was calculated at each pixel as a difference in APDs and peak of [Ca^{2+}]_i between odd and even beats: \( \Delta APD = |APD_{even} - APD_{odd}| \) ≥ 6ms, and \( \Delta Ca = |Ca_{even} - Ca_{odd}| \) ≥ 6μM, respectively.

The local spatial onset of alternans, B_{onset}, was defined as the value of B at which at least 10% of the 2D tissue exhibited alternans. Two spatial regions of the heart were defined at the B_{onset}: the ‘1:1_%alt’ region, where alternans was present and the ‘1:1’ region exhibiting 1:1 behavior. These two regions were virtually projected to all previous Bs, and the mean values for all parameters were calculated and averaged separately for these two regions.

RESULTS

Our recently published experimental data (see Fig. 1, adapted from [11]) demonstrated that in isolated rabbit heart alternans first appeared locally at B = B_{onset} and then evolved spatially throughout the heart as the B decreased. The color bar represents the amplitude of alternans ΔAPD. Note the presence of 1:1 behavior

![FIGURE 1. (ADAPTED FROM [11]) EXPERIMENTAL DATA: REPRESENTATIVE EXAMPLE OF THE 2D ΔAPD MAPS IN RABBIT LEFT VENTRICLE AT DIFFERENT VALUES OF B. THE COLOR BAR REPRESENTS THE AMPLITUDE OF ALTERNANS (RED) AND 1:1 RESPONSES (WHITE). THE LOCAL SPATIAL ONSET OF ALTERNANS OCCURS AT B_{ONSET} AT WHICH THE TWO REGIONS (1:1 Alt AND 1:1) ARE INTRODUCED AND PROJECTED TO ALL PRECEDING B VALUES (BLACK OUTLINES).](image)

We investigated the interplay between APD and [Ca^{2+}]_i alternans. Figure 3 illustrates the appearance of alternans in peak of [Ca^{2+}]_i as the B was progressively reduced. Note that the onset of APD and [Ca^{2+}]_i alternans occurs at the same value of B_{onset}=194 ms. However, also note the presence of small region of [Ca^{2+}]_i

![FIGURE 2. NUMERICAL SIMULATIONS: ΔAPD MAPS IN 2D CARDIAC TISSUE. LOCAL ONSET OF APD ALTERNANS OCCURS AT BONSET AT WHICH THE TWO REGIONS (1:1 Alt AND 1:1) ARE INTRODUCED AND PROJECTED TO ALL PRECEDING B VALUES (BLACK OUTLINES). THE STIMULATION SITE IS SHOWN BY THE ASTERISK.](image)
alternans at \( B^{\text{onset}} \) at the pacing site indicating difference in voltage and calcium dynamics. The 1:1 and 1:1\(_{\text{alt}}\) regions for APD and \([Ca^{2+}]_i\) alternans correspond well in shape and location, although there is slight difference between them.

**FIGURE 3. NUMERICAL SIMULATIONS: \( \Delta \text{CA MAPS IN 2D CARDIAC TISSUE. LOCAL ONSET OF CA ALTERNANS OCCURS AT BONSET AT WHICH THE TWO REGIONS (1:1}_{\text{ALT}} \) AND 1:1) ARE INTRODUCTED AND PROJECTED TO ALL PRECEDING BCL VALUES (BLACK OUTLINES). THE STIMULATION SITE IS SHOWN BY THE ASTERISK.**

Figure 4A,B illustrates representative examples of APD restitution curves and peak \([Ca^{2+}]_i\) at different \( B \), respectively, taken from 1:1 and 1:1\(_{\text{alt}}\) regions. A mean values of \( S_{\text{dyn}} \) and peak \([Ca^{2+}]_i\) are shown in Fig. 4C,D respectively. Note a minimal difference in these parameters between 1:1 and 1:1\(_{\text{alt}}\) regions. The voltage data (Fig. 4A,C) are in qualitative agreement with experimental results that are shown by Cram et al [11]. Indeed, the data demonstrate that there is no statistical differences between \( S_{\text{dyn}} \) measured in 1:1 and 1:1\(_{\text{alt}}\) regions. However, the quantitative agreement is absent: the maximum values of slope \( S_{\text{dyn}}^{\text{max}} \) from the numerical simulations (\( S_{\text{dyn}}^{\text{max}} =0.52 \) for 1:1 and \( S_{\text{dyn}}^{\text{max}} = 0.41 \) for 1:1\(_{\text{alt}}\)) are much smaller than experimentally measured ones (\( S_{\text{dyn}}^{\text{max}} =0.86\pm0.08 \) and \( S_{\text{dyn}}^{\text{max}} =0.96\pm0.03 \), respectively). In addition, while the experimental data demonstrate that \( S_{\text{dyn}}^{\text{max}} \) measured in 1:1\(_{\text{alt}}\) region is larger that the one measured in 1:1 region, the numerical simulation data show the opposite trend.

**FIGURE 4. REPRESENTATIVE EXAMPLES OF (A) APD RESTITUTION CURVES AND (B) PEAK [CA\(^{2+}\)]\(_i\) AT DIFFERENT \( B \) TAKEN FROM SINGLE PIXELS OF 1:1 (OPEN CIRCLE) AND 1:1\(_{\text{ALT}}\) (FILLED CIRCLE) REGIONS. (C) MEAN VALUES OF \( S_{\text{dyn}} \) AND (D) PEAK [CA\(^{2+}\)]\(_i\) AT DIFFERENT \( B \) FOR THE TWO REGIONS.**

Figure 5 A,B illustrates spatial distribution of \( S_{\text{dyn}}^{\text{max}} \) and peak \([Ca^{2+}]_i\) respectively, calculated at \( B^{\text{onset}} \). Note a progressive decrease of \( S_{\text{dyn}}^{\text{max}} \) and a progressive increase of peak \([Ca^{2+}]_i\) as one moves far away from the pacing site.

**DISCUSSION**

In this paper, we confirmed our recent experimental finding that the onset of alternans is a local spatio-temporal phenomenon in a cardiac tissue. Specifically, we performed 2D simulation of action potential model of cardiac myocytes and demonstrated that APD alternans appeared locally at certain pacing rate in a completely homogeneous tissue. This fact indicates a dynamic reason for the development of local alternans rather than tissue heterogeneity in the heart. We also demonstrated a qualitative agreement between experimental and numerical data while measuring maximum slope of dynamic restitution curve. Nevertheless, a quantitative agreement is absent. Other pacing protocols were used to determine whether slopes of different restitution curves, specifically the ones measured in the restitution portrait, would have a better quantitative agreement with the model. When perturbations were added to the protocol, alternans was seen to develop globally without any local onset. Further investigation is needed to understand why adding perturbations causes alternans not to appear locally first.

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**REFERENCES**


