Effect of Extracellular Calcium Concentration on Controlling Cardiac Alternans

Shiuan-Ni Liang[1], Pik-Yin Lai[2]

[1]Electrical and Computer Systems Engineering, School of Engineering, Monash University, Bandar Sunway, Malaysia
[2]Department of Physics, Graduate Institute of Biophysics, and Center for Complex Systems, National Central University, Chungli District, TaoYuan City, Taiwan R.O.C.

Abstract

Cardiac alternans may lead to life-threatening arrhythmias or sudden cardiac death. Thus, finding an effective method to suppress alternans is crucial. In this paper, we demonstrate that the time needed to control cardiac alternans induced by rapid pacing using the T+T- feedback control can be dramatically shortened if the extracellular calcium concentration is lowered by a very small amount when the control is turned on. Numerical simulations are performed on the Hund-Rudy dynamic (HRd) model for single cell. Since controlling alternans is important as it can be a precursor of sudden cardiac death, the results of our research may have important clinical implications and will lead to the development of a better control scheme for alternans or a smart defibrillator.

1. Introduction

Cardiac arrhythmia is a condition where heartbeats are abnormal. Every year, millions of people worldwide experience arrhythmias and many of them can return to their normal lives if the arrhythmias are treated at early stages and properly. However, many arrhythmias are dangerous and may lead to sudden cardiac death.

Cardiac alternans [1,2], which can be induced by fast pacing, is the condition of having alternate-beat oscillation in the electrical activity (the action potential durations, APDs, oscillate in a long-short-long-short pattern) or alternating strong and weak beats in a heart under a constant pacing. It may lead to life-threatening cardiac arrhythmias [3,4], such as ventricular tachycardia and ventricular fibrillation, or sudden cardiac death [4,5] if it is left without any further medical treatment or intervention. Therefore, searching for an effective alternans control method is crucial.

Besides the earlier proposed methods for alternans suppression: the proportional feedback control [6,7] and adaptive scheme [8-10], a new control scheme, the *T*+*T*- feedback control [11-14] was proposed recently. The basic pacing period T in this method is designed to change between two values, $T + \varepsilon$ and $T - \varepsilon$ (where ε is a pre-determined control parameter and is much less than T), repeatedly until the alternans is suppressed. Experiments [11,13] and theoretical [11-14] studies have been carried out and the results showed that the *T*+*T*- control method can suppress alternans effectively. However, when the pacing rate continues to increase, the amplitude of the alternans also increases and becomes more difficult to be controlled. Thus, it is necessary to look into how the *T*+*T*- control method can be improved to suppress alternans induced by rapid pacing.

During cardiac alternans, the intracellular calcium concentration ($[Ca]_i$) can also alternate between high and low levels [15]. Experimental [16] and theoretical [2] studies have shown that suppression of $[Ca]_i$ alternans can eliminate APD alternans. Since $[Ca]_i$ can be regulated by extracellular calcium concentration ($[Ca]_o$) [17] and there are experimental studies [18,19] showing that lowering extracellular calcium concentration ($[Ca]_o$) can suppress alternans, it is interesting to examine the combination of *T*+*T*- control method and low $[Ca]_o$ as a possible more effective alternans control method. In this study, we investigated the time needed to suppress cardiac alternans using the *T*+*T*- control method with lower $[Ca]_o$ during the control. The details of the control scheme and numerical calculation are given in the next section, followed by the results. In the last section, we discuss our significant findings and the clinical implications.

2. Methods

The Hund-Rudy dynamic (HRd) model of canine ventricular action potential [2,20], which is one of the typical mathematical models used to study cardiac alternans, was used in this study to simulate the alternans of a single cell. The HRd model includes the ionic-currents, pumps, exchangers, dynamic concentration change of ions, and calcium cycling. The rate of change of the membrane potential (V) is described by the following equation:

 ISSN: 2325-887X DOI:10.22489/CinC.2017.199-418

$$dV/dt = -(I_{ion} + I_{stim})/C_m \quad (1)$$

where t is the time, C_m is the cell membrane capacitance, I_{ion} is the total membrane current density and I_{stim} is the stimulus current. During the simulations, the cell was paced with a current stimulus of -80 μA/μF for 1 ms. The numerical integration of the differential equations was performed using the MATLAB subroutine ode15s [21,22], which is a variable-step and variable-order solver, with error tolerance of 10^{-6}.

In the T+T- control method [11-14] that was employed in our study to suppress the alternans, the basic cycle length at the n-th beat (T_n) depends on two successive peak-$[Ca]_i$ as follows

$$\begin{aligned} T_n &= T + \varepsilon \quad \text{if } [Ca]_{i,n} > [Ca]_{i,n-1} \\ &= T - \varepsilon \quad \text{if } [Ca]_{i,n} < [Ca]_{i,n-1} \end{aligned} \quad (2)$$

where T is the basic cycle length, ε is a pre-determined parameter and $[Ca]_{i,n}$ is the peak-$[Ca]_i$ at the n-th beat.

In the simulations, first, the alternans is generated using $[Ca]_o$ = 1.8 mM (the original value used in the HRd model) for a particular basic cycle length T. The alternans has reached a steady state when the peak-$[Ca]_i$ alternans showed < 0.1% variability over 100 alternans (i.e. 200 beats). Then, the control is turned on and, at the same time, the $[Ca]_o$ is changed to a lower or higher (than 1.8 mM) value until the alternans is successfully suppressed at beat number n, that is, when the criteria

$$APD_n - APD_{n+1} < \varepsilon \quad (3)$$

where APD_n is the APD at the n-th beat, is satisfied. The APD is measured from the time at the maximum value of dV/dt during depolarization to the time at 90% repolarization from the maximum value of V. Finally, the time needed to suppress the peak-$[Ca]_i$ alternans (τ) is calculated from the beat number when the control is turned on until the first beat number n when the criteria (3) is satisfied.

3. Results

To illustrate the general results of our findings, we will use an example based on T = 240 ms for this purpose. Since the results for APD alternans suppression are similar to that of peak-$[Ca]_i$ alternans suppression, we will only present the results for controlling peak-$[Ca]_i$ alternans. Figure 1 shows that when $[Ca]_o$ = 1.8 mM (as in the original HRd model), the peak-$[Ca]_i$ alternans exists and the amplitude is about 0.00065 mM. When the $[Ca]_o$ is decreased (increased), the amplitude of the alternans also decreases (increases). If $[Ca]_o$ is reduced to 1.5 mM or even lower, then there is no alternans. This implies that lowering $[Ca]_o$ can suppress alternans and elevating $[Ca]_o$ will enhance alternans.

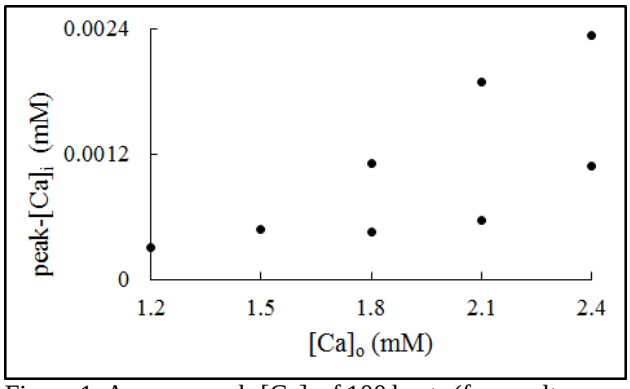

Figure 1. Average peak-$[Ca]_i$ of 100 beats (for no alternans cases) or alternans (for alternans cases, that is, over 200 beats) for different $[Ca]_o$ when T = 240 ms. $[Ca]_o$ = 1.8 mM is the value used in the original HRd model.

Figures 2 and 3 show the control of alternans using the T+T- control scheme with ε = 5.7 ms, which is very near the critical value of 5.68 ms, when T = 240 ms (there is a

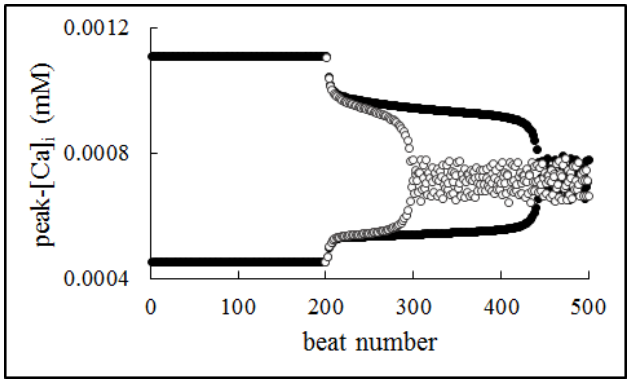

Figure 2. The time sequences of peak-$[Ca]_i$ when the control is turned on at beat number 201 with ε = 5.7 ms and T = 240 ms: (filled circles) $[Ca]_o$ = 1.8 mM and (unfilled circles) $[Ca]_o$ = 1.79 mM when the control is turned on.

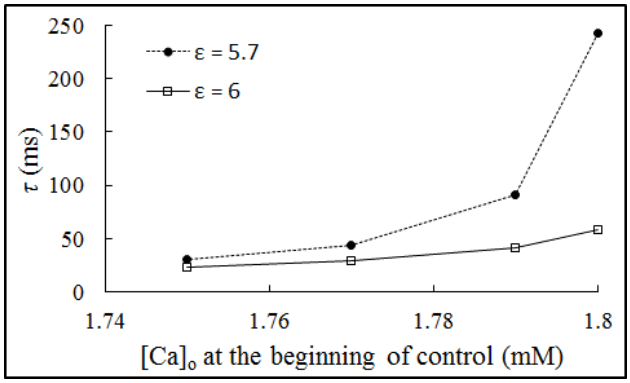

Figure 3. The time needed to suppress the alternans (τ) for different $[Ca]_o$ at the beginning of the control with ε = 5.7 and 6 ms , and T = 240 ms.

high possibility that the alternans cannot be suppressed if ε is lower than its critical value [11-13]). If $[Ca]_o$ is remained at 1.8 mM when the control is turned on, we get τ = 243 beats. However, if $[Ca]_o$ is decreased by 0.01 mM (0.6%) to 1.79 mM when the control is turned on, we have τ = 91 beats, which is decreased by 62.5%. If the $[Ca]_o$ is further decreased to 1.75 mM (decreased by 2.8% from 1.8 mM) at the beginning of the control, it is found that τ can be further reduced to just 30 beats (decreased by 87.7% compared to τ = 243). This implies that the control time needed to suppress the alternans can be dramatically reduced by lowering a small percentage of $[Ca]_o$ when the T+T- control is turned on with ε near its critical value.

4. Conclusion

In summary, we have shown that the effectiveness of alternans suppression by using the T+T- control scheme can be improved by changing the $[Ca]_o$ during control. In particular, the time needed to suppress the peak-$[Ca]_i$ alternans, and thus, the APD alternans, can be dramatically shortened if a very small amount of $[Ca]_o$ is reduced at the beginning of the control. Since controlling alternans is important as it can be a precursor of sudden cardiac death, the results of our research may have important clinical implications and lead to the development of a better control scheme for alternans or a smart defibrillator.

Acknowledgements

Part of this work is supported by the Ministry of Science and Technology research grant of Taiwan R.O.C..

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Address for correspondence.

Shiuan-Ni Liang
Electrical and Computer Systems Engineering, School of Engineering, Monash University, 47500 Bandar Sunway, Malaysia.
liang.shiuan-ni@monash.edu