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Transient Early Afterdepolarization in a Methematical Cardiac Model

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Abstract—In the heart, depolarization may occur early in the repolarization of the action potential, which causes induced activity. This induced activity is called early afterdepolarization (EAD) and considered to be the arrhythmia itself and, may cause sudden death. The study of arrhythmias using cardiac mathematical models is important to reduce the risk of sudden death. In this study, we use a cardiac mathematical model to elucidate the mechanism of EAD generation. By parameterizing the intracellular sodium ion concentration, we could explain the transient EAD generation in the non-parameterized system.

1. Introduction

Heart disease is a dangerous and life-threatening illness and one of the leading causes of death. Among it, sudden cardiac death is mainly caused by arrhythmias such as ventricular tachycardia and ventricular fibrillation. Electrical activity occurs in the cell membranes of cardiac muscle cells, it contracts the heart periodically. Disturbances in this electrical activity can cause depolarization in the early stages of repolarization of the action potential, which lead to early afterdepolarization (EAD).

EAD is associated with lethal arrhythmias such as QT prolongation and Torsade de Pointes (TdP). QT prolongation triggered by EAD may also lead to sudden death through ventricular fibrillation. The occurrence of sustained EAD is associated with either an increase in L-type calcium current or a decrease in rapidly delayed rectifying potassium ion current. Recently, the relationship between the generation of EAD and intracellular sodium concentration $[Na]_i$ has been clarified[1].

The purpose of this paper is to clarify the mechanism of transient EADs generation in the O'Hara model that is the human ventricular model[2]. Studying the $[Na]_i$-parameterized system and its bifurcation, we were able to explain the transient EADs generation in the non-parameterized system.

2. Model Equations

T. O'Hara proposed a detailed mathematical model of the electrophysiology of cardiomyocytes and Ca circulation in the unaffected human ventricle[2]. The O'Hara model shows the time variation of the cell membrane potential in the human ventricular muscle. The cell membrane potential of the O'Hara model is represented by

$$\begin{aligned} C\frac{dV}{dt} = &-(I_{Na} + I_{to} + I_{CaL} + I_{CaNa} + I_{CaK} \\ &+ I_{Kr} + I_{Ks} + I_{K1} + I_{NaCa} + I_{NaK} \\ &+ I_{Nab} + I_{Cab} + I_{Kb} + I_{pCa} + I_{stim}) \end{aligned} \tag{1}$$

where C is the membrane capacitor, t is time, and I_{Na} to I_{pCa} are the respective ion currents. I_{stim} represents the stimulation current with period of 2000(ms), intensity of 60(μA) and duration of 1.0(ms). The O'Hara model consists of 41 ordinary differential equations. 14 currents are shown in Tab. 1. In particular, I_{Kr} are given by the following equations.

$$I_{Kr} = \overline{G_{Kr}} \cdot \sqrt{\frac{[K^+]_o}{5.4}} \cdot x_r \cdot R_{Kr} \cdot (V - E_K) \tag{2}$$

where $\overline{G_{Kr}}$ is the value that determines the ease of passage of I_{Kr}, $[K^+]_o$ is the external concentration of K^+, x_r is activation/deactivation for I_{Kr}, E_K is the reversal potential. R_{Kr} is given by

$$R_{Kr} = \frac{1}{(1 + \exp\frac{V+55}{75}) \cdot (1 + \exp(\frac{V-10}{30}))} \tag{3}$$

The ordinary differential equation for the intracellular sodium concentration is shown below.

$$\begin{aligned} \frac{d[Na^+]_i}{dt} = &-(I_{Na} + I_{NaL} + 3 \cdot I_{NaCa,i} + 3 \cdot I_{NaK} + I_{Nab}) \\ &\cdot \frac{A_{cap}}{F \cdot v_{myo}} + J_{diff,Na} \cdot \frac{v_{ss}}{v_{myo}} \end{aligned} \tag{4}$$

where I_{Na}, I_{NaL} and I_{Nab} are shown in Tab. 1, $I_{NaCa,i}$ is myoplasmic component of Na^+/Ca^{2+} exchange current, A_{cap} is the capacitive area, F is the faraday constant, v_{myo} is the volume of the myoplasmic compartment, $J_{diff,na}$ is diffusion of Na^+ from subspace to myoplasm, v_{ss} is the volume of the subspace compartment. $J_{diff,Na}$ is given by

$$J_{diff,Na} = \frac{[Na^+]_{ss} - [Na^+]_i}{\tau_{diff,Na}} \tag{5}$$

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where $[Na^+]_{ss}$ is concentration of ion Na, in the subcellular subspace compartment, $\tau_{diff,Na}$ = 2.0(ms).

Table 1: Ionic currents in O'Hara model

Abbreviation	name of ionic current
I_{Na}	Na current
I_{to}	transient outward current
I_{Kr}	rapidly activated K current
I_{Ks}	slowly activated K current
I_{K1}	inward rectifying K current
I_{NaCa}	Na-Ca exchange current
I_{NaK}	Na-K pump current
I_{CaK}	Ca-K pump current
I_{CaNa}	Ca-Na pump current
I_{CaL}	L-type Ca current
I_{Nab}	background Na current
I_{Cab}	background Ca current
I_{Kb}	background K current
I_{pCa}	Ca pump current in muscle cell membrane

3. Result

Figure 1 shows a two-parameter bifurcation diagram with the average number (n=50) of peaks of the membrane potential in one period of the external current in the $[Na]_i$-parameterized system. The horizontal axis is the G_{Kr} multiple denoted by Z_{Kr}. The orange and gray curves indicate period-doubling and Neimark-Sacker bifurcation sets, respectively. To obtain bifurcation sets in two-parameter plane, we used the algorithm proposed by Kawakami[3]. These two bifurcations were subcritical, so we observed neither stable higher-periodic solutions nor stable quasi-periodic solutions. The purple squares and black circles mean the maximum and minimum values of the intracellular sodium concentration at the steady state in the non-$[Na]_i$-parameterized system (original O'Hara model).

First, we show the waveforms of the membrane potential in the $[Na]_i$-parameterized system. We observed a normal state as shown in Fig. 2 in the deep blue region in Fig. 1. In the light blue region alternate EADs occur as shown in Fig. 3. It became sustained EADs (Fig. 4) in the green region, and the number of peaks was increased in the orange and brown areas. We observed 2:1 EADs (Fig. 5) and sustained 4 EADs (Fig. 6) in these areas.

Second, we show the waveforms of the membrane potential in the original system. Figure 7 shows the waveforms when Z_{Kr} = 0.44 and the initial state of $[Na]_i$ is 2.0. We can see that the state is sustained EADs at these two values in Fig. 1. Therefore, we observed the sustained EADs at the beginning of time in Fig. 7(a). Then, $[Na]_i$ was gradually increased and when it entered the light blue area, we observed alternate EADs as shown in Fig. 7(b). The convergence point of $[Na]_i$ in the original system was in the deep blue area in Fig. 1, so finally we observed the normal waveforms (Fig. 7(c)) as a steady state in the original system. The change in $[Na]_i$ in the same interval is shown in Fig. 8. Figure 9 shows the waveforms when Z_{Kr} = 0.36 and the initial state of $[Na]_i$ is 2.0. In this case we observed 4 EADs (Fig. 9(a)) and after the transition the final state was alternate EADs (Fig. 9(c)). The change in $[Na]_i$ in the same interval is shown in Fig. 10.

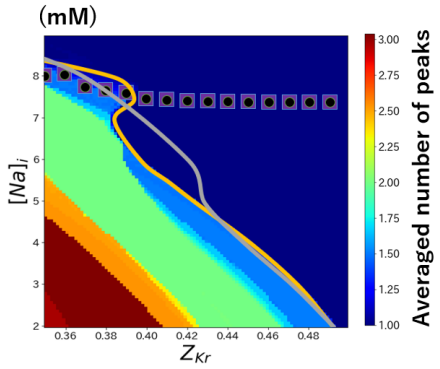

Figure 1: Bifurcation diagram in $[Na]_i$-parameterized system

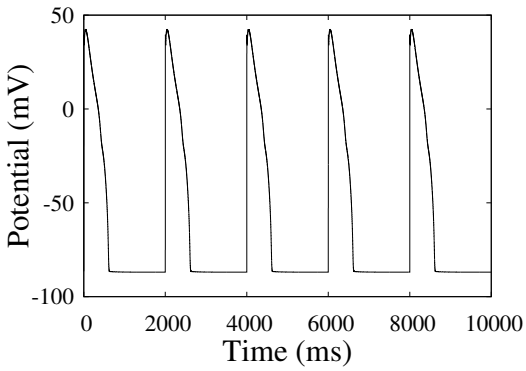

Figure 2: Normal waveform in blue area in Fig. 1

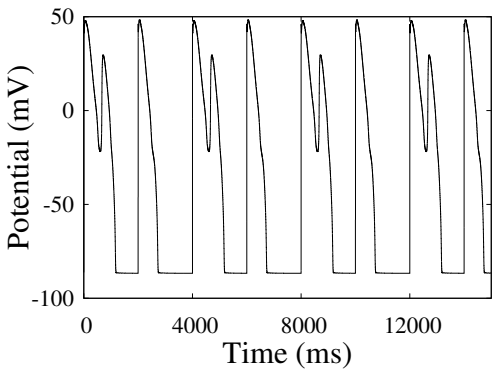

Figure 3: Alternate EAD in light blue area in Fig. 1 ($[Na]_i$=2.0, Z_{Kr}=0.48)

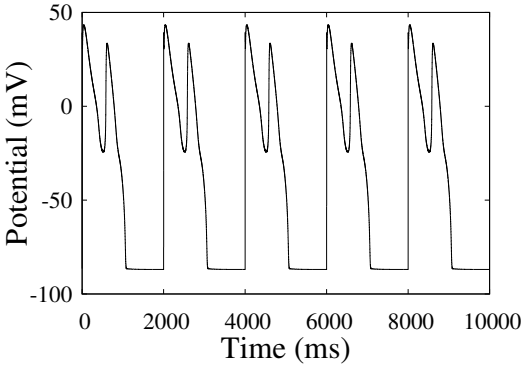

Figure 4: Sustained EAD in green area in Fig. 1 ($[Na]_i$=7.0, Z_{Kr}=0.37)

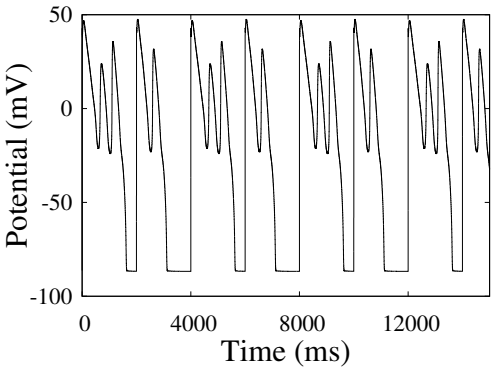

Figure 5: 2:1 EADs in orenge area in Fig. 1 ($[Na]_i$=4.0, Z_{Kr}=0.38)

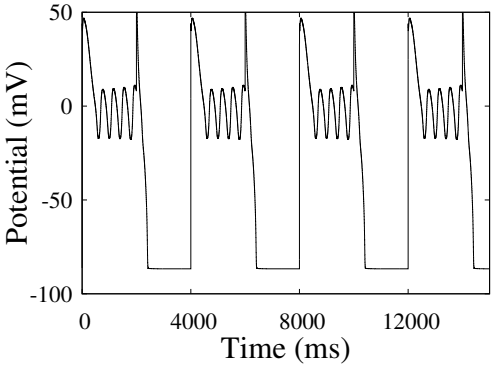

Figure 6: Sustained 4 EADs in brown area in Fig. 1 ($[Na]_i$=2.0, Z_{Kr}=0.38)

4. Conclusion

Transient EAD development was investigated using the O'Hara model, a human ventricular myocyte model. To begin with, we considered the $[Na]_i$-parameterized system. We calculated bifurcation sets, and made a two-parameter diagram in which what kinds of EADs were observed. Next, using this diagram, we clarified the transient EAD appearance and disappearance. Usually, analysis of transient states was very difficult. However, in this study, considering the $[Na]_i$-parameterized system we achieved the transient EADs analysis. To study the detailed bifurcation structure is one of our future problems.

Acknowledgments

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References

[1] K. Tsumoto et al., Hysteretic Dynamics of Multi-Stable Early Afterdepolarisations with Repolarisation Reserve Attenuation: A Potential Dynamical Mechanism for Cardiac Arrhythmias, Scientific Reports, 7(1), 10771, 2017.

[2] T. O'Hara, L. Virag, A. Varro, Y. Ruddy, Simulation of the Undiseased Human Cardiac Ventricular Action Potential: Model Formulation and Experimental Validation, PLOS Computational Biology, pp.6-16, May 26, 2011.

[3] H. Kawakami, Bifurcation of periodic responses in forced dynamic nonlinear circuits: Computation of bifurcation values of the system parameters, IEEE Transactions on Circuits and Systems, 31(3), 248-260, 1984.

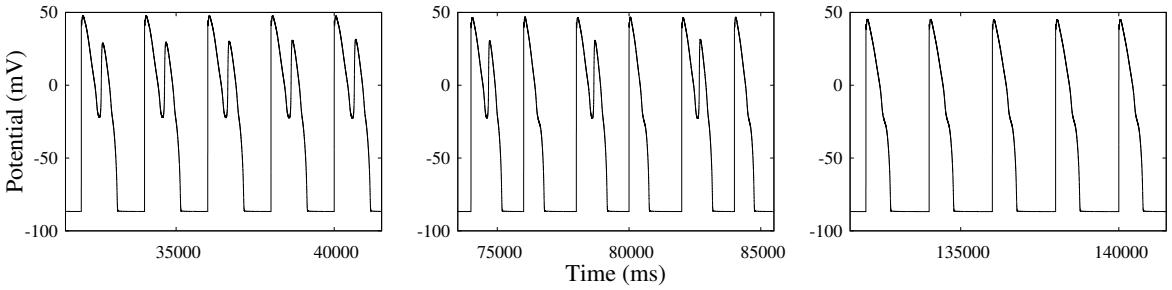

Figure 7: Membrane potential in original system at $Z_{Kr} = 0.44$

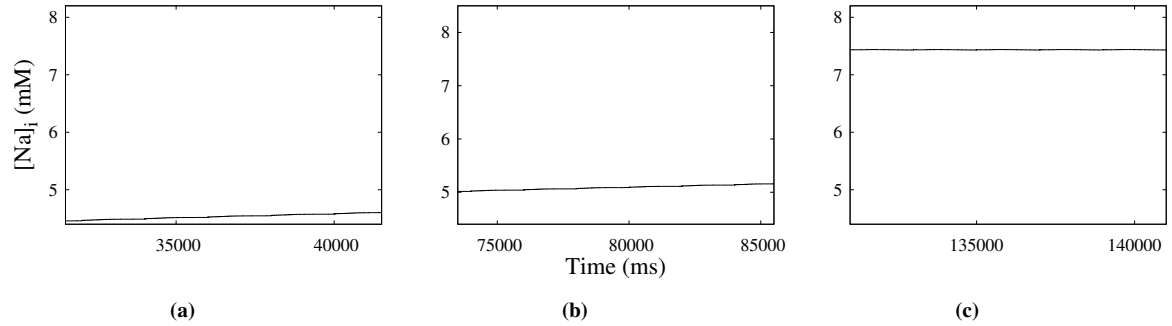

Figure 8: $[Na]_i$ in original system at $Z_{Kr} = 0.44$

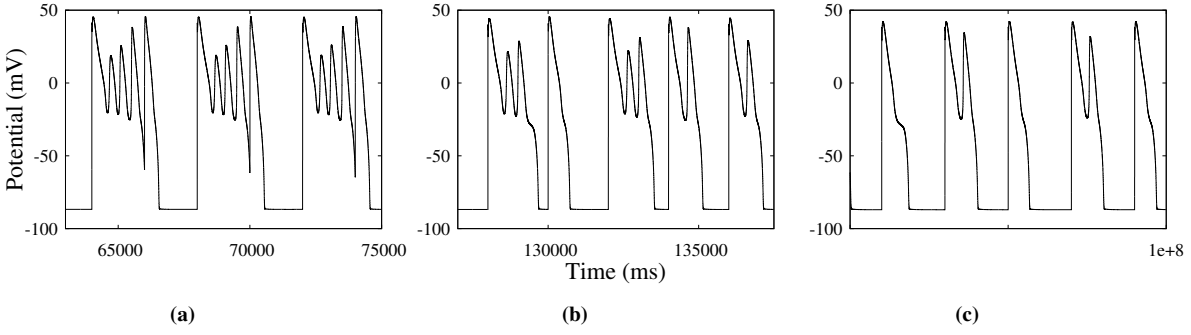

Figure 9: Membrane potential in original system at $Z_{Kr} = 0.36$

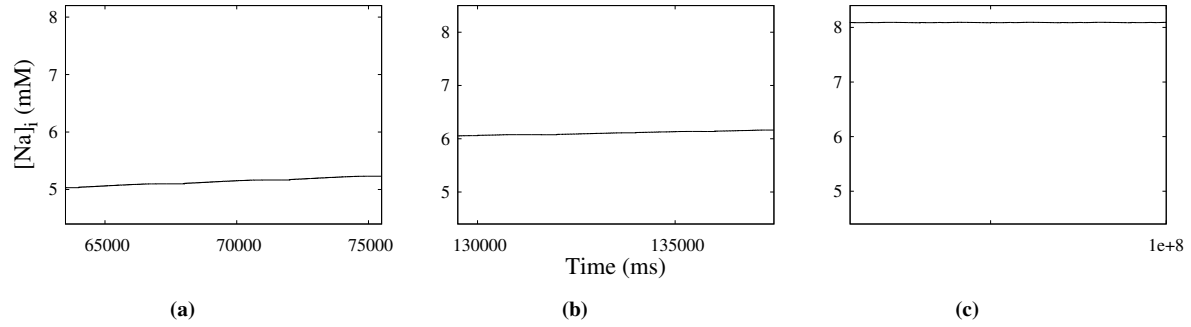

Figure 10: $[Na]_i$ in original system at $Z_{Kr} = 0.36$