

Investigation of the Electrophysiological Remodelling in Acute and Chronic Post-Myocardial Infarction

Xin Zhou¹, Jakub Tomek², Blanca Rodriguez¹

¹Department of Computer Science, University of Oxford, Oxford, UK

² Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK

Abstract

Sudden cardiac death was reported in both the acute stage and the chronic heart failure (HF) stage after myocardial infarction (MI). The goal of this study is to investigate the pro-arrhythmic cellular effects of post-MI electrophysiological remodelling for both the acute stage and the chronic stage, using human-based computer modelling and simulation.

The ToR-ORd human ventricular cellular model was used as baseline, and a new formulation of the calcium activated potassium current was also included in order to reflect its enhanced expression in the HF stage. We constructed and calibrated populations of human ventricular cell models to represent electrophysiological variability of normal zone (NZ) myocytes. For the acute post-MI stage, three types of border zone (BZ) ionic remodelling were considered based on canine experimental data. For the chronic phase with the development of HF, ionic remodelling in BZ and the remote zone (RZ) were introduced based on minipig and human experiments.

For both the acute stage and the chronic stage post-MI, simulations showed that both large and small pro-arrhythmic dispersion in action potential duration can be present between BZ and non-infarcted NZ or RZ, and the post-MI ionic remodelling led to weak calcium transient in the BZ.

crucial to understand the effects of post-MI ionic remodelling for both the acute and the chronic stages.

For the acute stage post-MI, experimental data from 4 to 5 days post-MI dogs showed reduced sodium current (I_{Na})[2], L-type calcium current (I_{CaL})[3], potassium currents (I_{Kr} and I_{Ks})[4], and enhanced CaMKII phosphorylation [5] in the BZ. However, these aspects of ionic remodelling may recover in the healing process [6], and it is essential to consider different healing stages in the proarrhythmic risk investigations.

For the healed stage, one recent study conducted in minipigs investigated the electrophysiological remodelling of individual currents after 5 months post-MI with the progression towards heart failure (HF)[7]. In the HF remote zone (RZ) myocytes, decreased I_{Kr} , increased late sodium current (I_{NaL}), calcium activated potassium and chloride currents (I_{KCa} and I_{ClCa}) were observed [7]. Similar remodelling also occurred in the BZ myocytes, and with additional decrease of I_{CaL} and inward rectifier potassium current (I_{K1}).

Due to the lack of ionic remodelling data from human post-MI myocytes, these experimental data obtained from infarcted animals provide valuable insights to mimic human electrophysiological changes. The goal of this study is to explore the proarrhythmic effects of post-MI ionic remodelling in human ventricular myocyte models of electrophysiology based on experimental observations from both the acute and the chronic stages.

1. Introduction

The incidence of sudden cardiac death (SCD) was reported to be highest within the first month after a myocardial infarction (MI), followed by a progressive decline to a plateau after a few months. Ventricular tachyarrhythmia accounts for about 50% of these SCD [1]. The electrophysiological heterogeneity in post-MI human cardiac tissue, such as the dispersion of action potential duration (APD) between normal zone (NZ) and border zone (BZ), provides substrates for the generation and maintenance of lethal reentrant waves. Therefore, it is

2. Methods

2.1. The baseline model

The ToR-ORd human ventricular cellular model [8] was used as the baseline model in this study. In order to introduce the enhanced activity of I_{KCa} in HF, a new formulation of the I_{KCa} was added into the ToR-ORd model based on the data by [9], and the ratio of the current in the subspace (ss) was set to be the same as I_{CaL} . The conductance of the background potassium current was

rescaled to 90% to adapt to the implementation of I_{KCa} . The formulation of the I_{KCa} is the following:

$$gkca = 0.003; ikcan = 3.5; kdikca = 6.05e-04; \\ \text{Fraction}I_{KCa}ss = 0.8; \text{Fraction}I_{KCa}i = 1 - \text{Fraction}I_{KCa}ss;$$

$$I_{KCa}ss = gkca \times \text{Fraction}I_{KCa}ss \times \frac{Ca_{ss}^{ikcan}}{Ca_{ss}^{ikcan} + kdikca^{ikcan}} \times (Vm - EK)$$

$$I_{KCa}i = gkca \times \text{Fraction}I_{KCa}i \times \frac{Ca_i^{ikcan}}{Ca_i^{ikcan} + kdikca^{ikcan}} \times (Vm - EK)$$

$$I_{KCa} = I_{KCa}ss + I_{KCa}i;$$

2.2. Cell model population

In order to simulate the effect of electrophysiological variability in human cardiomyocytes, an initial population of 500 human endocardial ventricular cell models was constructed based on the baseline model by varying 11 key ionic currents by up to $\pm 50\%$ as in previous studies [10]. After pacing at 1Hz by 500 beats, the models were calibrated with human experimental data [11], [12]. 253 models were accepted and used as NZ population of models (POMs).

2.3. Three types of BZ remodelling for the acute post-MI stage

Three types of BZ remodelling for the acute post-MI stage were applied to the NZ based on previous publications [13]–[16].

Table 1. BZ ionic remodelling of individual currents in the acute stage post-MI.

Scaling factors	Acute BZ1	Acute BZ2	Acute BZ3
I_{Na}	0.4	0.38	0.4
I_{to}	0.1		0
I_{CaL}	0.64	0.31	0.64
I_{Kr}	0.7	0.3	
I_{Ks}	0.2	0.2	
I_{K1}	0.3		0.6
I_{Cab}			1.33
aCaMK			1.5
Tau relp			6 ‡

‡ Slower calcium release was introduced to reproduce effects of CaMKII activation in experiments.

2.4. BZ and RZ remodelling for the chronic post-MI HF stage

The chronic post-MI BZ and one type of RZ remodelling were introduced based on [7] [17] [18]. Another type of RZ remodelling was established based on multiple experimental references[9], [17], [19]–[22].

Table 2. BZ and RZ ionic remodelling of individual currents in the chronic HF stage post-MI

Scaling factors	Chronic BZ	Chronic RZ1	Chronic RZ2
I_{Na}	0.43	0.43	0.43
I_{NaL}	1.275	1.413	2
I_{to}			0.6
I_{CaL}	0.7		
I_{Kr}	0.89	0.87	0.6
I_{Ks}			0.4
I_{K1}	0.76		0.6
I_{NaK}			0.6
J_{up}	0.4	0.4	0.3
I_{KCa}	2	2	3.75*
I_{ClCa}	1.25	1.25	1.25
aCaMK	1.5	1.5	1.5
Tau relp	6	6	6

* $kdikca = 3.45e-04$ for Chronic RZ2

3. Results

3.1. Variable APD dispersions in both the acute and the chronic post-MI stages

For the acute stage, the three types of BZ remodelling led to different extent of APD prolongation in the baseline model (Figure 1, left). The Acute BZ1 and Acute BZ2 remodelling caused significant APD prolongation in both the endocardial and epicardial BZs. The Acute BZ2 remodelling also resulted in a significant reduction in the action potential (AP) plateau level. On the other hand, the Acute BZ3 remodelling caused the mildest change in both endocardial and epicardial models. In the population of 253 models, the Acute BZ2 remodelling group tended to show the longest APDs, while the Acute BZ3 remodelling group displayed similar APDs with the NZ group in both the epicardial and endocardial POMs (Figure 1, right).

For the chronic post-MI stage with HF, BZ and two types of RZs all led to longer APD than NZ, and the prolongation was more significant in the endocardial model (Figure 2, left). Chronic BZ and Chronic RZ1 had similar extent of APD prolongation, especially in the epicardium, corresponding to very small APD dispersions. However, the APD dispersion between the Chronic RZ2 and the Chronic BZ was much bigger due to a more significant APD prolongation in this type of RZ (Figure 2, left). The population of models showed similar trend as the baseline model, with APD prolongation most significant in the Chronic RZ2 (Figure 2, right).

Therefore, for both the acute stage and the chronic stage post-MI, variable APD dispersions can exist depending on the types of ionic remodelling present.

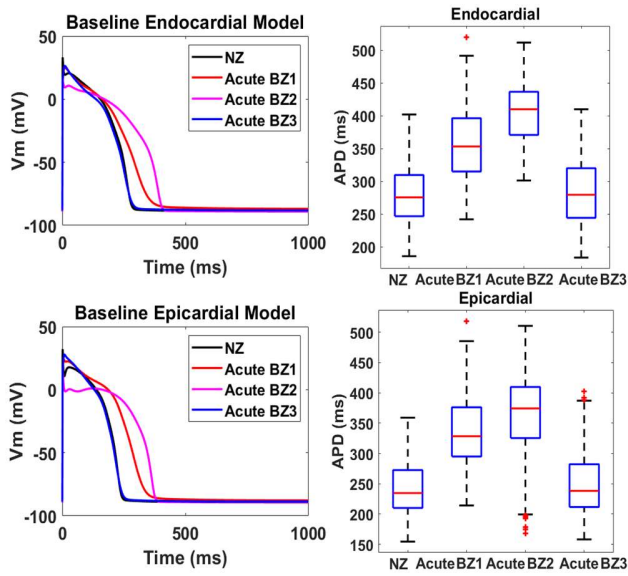


Figure 1. Effects of the three types of acute stage post-MI BZ remodelling on AP. Left: the baseline models; Right: the 253 POMs.

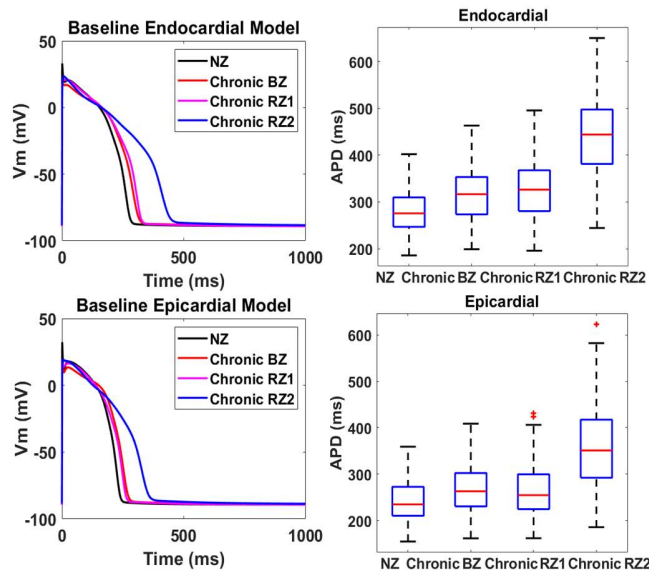


Figure 2. Effects of the chronic stage post-MI BZ and RZ remodelling on AP. Left: the baseline models; Right: the 253 POMs.

3.2. BZ had weaker calcium transient at both the acute and the chronic post-MI stages

All three types of acute stage BZ remodelling inhibited calcium transient (CaT) magnitude (CaTmax), with the effect strongest in the Acute BZ2 (Figure 3). The three types of chronic post-MI remodelling also caused weaker CaTmax than NZ, and the CaT was weaker in the Chronic

BZ than the two Chronic RZs (Figure 4). Therefore, at both the acute and chronic post-MI stages, BZ always tended to have the weaker CaT than the corresponding NZ and RZ.

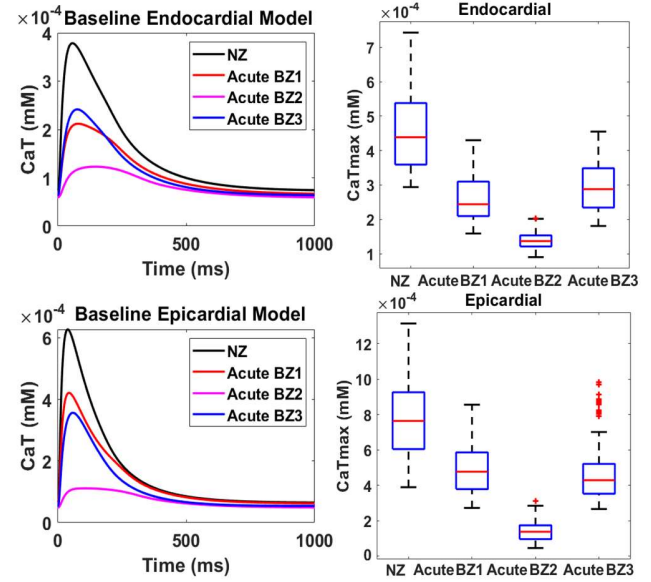


Figure 3. Effects of the three types of acute stage post-MI BZ remodelling on CaT. Left: the baseline models; Right: the 253 POMs.

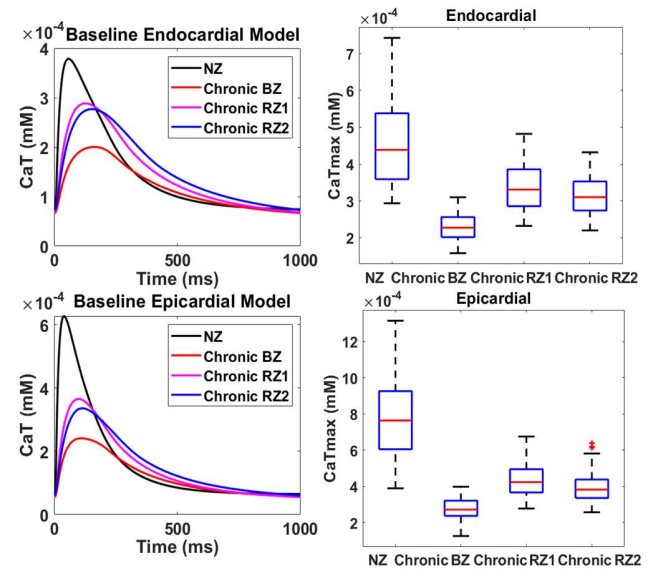


Figure 4. Effects of the chronic stage post-MI BZ and RZ remodelling on CaT. Left: the baseline models; Right: the 253 POMs.

4. Conclusions

In this study, we showed for both the acute and chronic post-MI stages, large and small APD prolongations can be present depending on the ionic remodelling implemented. Weak CaT was always observed in the BZ for both stages, which could contribute to stretch induced alterations.

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Address for correspondence:

Xin Zhou.
Department of Computer Science, University of Oxford
Wolfson Building, Parks Road, Oxford OX1 3QD, UK.
xin.zhou@cs.ox.ac.uk