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J. Biomedical Science and Engineering, 2017, Vol. 10, (No. 7), pp: 355-366

Study of the Impact of Rectangular Current Pulses on the Ten Tusscher-Panfilov Model of Human Ventricular Myocyte

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Keywords: Human Ventricular Myocyte Model, Transmembrane Potential, Action Potential, Refractoriness, BeatBox Simulation Environment; Mechanism of Defibrillation

Received: June 21, 2017 **Accepted:** July 18, 2017 **Published:** July 21, 2017

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ABSTRACT

The behavior of the 2006 ten Tusscher-Panfilov model of human ventricular myocytes under the impact of periodic excitation impulses was studied in the BeatBox simulation environment. The cardiomyocyte model has a limited susceptibility to an forced higher frequency excitation rhythm. A high-frequency excitation rhythm can be forced by gradually increasing the frequency of excitation impulses. The mechanism of defibrillation pulse impact consists of presumably prolonging the refractoriness of cardiomyocytes which undermines their susceptibility for a long time to a forced high-frequency rhythm of fibrillation, as a result for which they hinder the propagation of a fibrillation wave. This is the only mechanism of defibrillation that was identified during the simulation. The threshold energy of a depolarizing defibrillation pulse prolonging the refractoriness of the cardiomyocyte varies depending on a delay relative to the excitation impulse (the excitation cycle phase) in a wide range (the maximum value exceeds the minimum by several thousand times). The results show differences in the mechanisms of impact on a cardiomyocyte between an excitation impulse and a monophasic defibrillation pulse.

1. INTRODUCTION

A number of previous theoretical studies have studied the effect on the cardiomyocyte membrane model of a single excitation pulse [1-8]. However, a study of the impact of an electrical defibrillation pulse on cardiomyocytes should consider the fact that during fibrillation a cardiomyocyte is not in a resting state and is subject to the impact of an abnormally frequent parasitic excitation wave while myocardial cardiomyocytes are in different phases of the excitation cycle. To stop fibrillation, it is necessary to change the

state of cardiomyocytes in such a way that they become an obstacle to the propagation of the wave across the myocardium. This study has attempted to explain how to achieve change of its state to prevent the propagation of a fibrillation wave by using the cardiomyocyte model.

2. MATERIALS AND METHODS

The study was conducted in the BeatBox simulation environment [9] using the ten Tusscher-Panfilov 2006 model of human ventricular myocytes [10]. The simulation environment was set up in the Fedora operating system which was installed in the Oracle VM VirtualBox virtualization system on a PC using the Windows 7 operating system. We presented above the rationale for the use of the energy ratio as a parameter indicative of pulse energy efficiency [8]. A rectangular pulse waveform was chosen for the study as it had been described in the BeatBox scripts in elementary terms. Depolarizing excitation impulses with amplitude of 80 mA/cm^2 and duration of 0.5 ms at a predetermined interval were applied to the cardiomyocyte model. These are the standard parameters of the excitation pulses used in the simulation. Such a pulse provides excitation of the cardiomyocyte, and at the same time its duration is small in comparison with the duration of the action potential. At the beginning of the experiment the model parameters were initiated using the values saved upon completing the previous experiment.

In the experiments on the model, the possibility provided by the simulation environment to visualize the change in the transmembrane potential during a given time interval was used. The parameters of the acting pulses changed in the script, after which the appearance of the action potential or prolonging of the refractoriness was visually observed. In addition, simulation results were saved in the files for constructing time diagrams of the change in the transmembrane potential.

All the materials and experimental data in the article are presented in the online resource ResearchGate [11].

3. RESULTS

3.1. Changing the Action Potential Waveform Depending on the Excitation Frequency

Figure 1 shows the action potential waveform in a steady state at different frequencies of excitation impulses.

The action potential waveform was recorded at a hundredth impulse. The model parameters were initiated by finite values obtained for lower frequency of excitation impulses. It was possible to force an excitation rhythm of 240 min^{-1} on the model by increasing the excitation impulse frequency in the following sequence 60 - 180 - 220 - 230 - 240 min^{-1}. It was impossible to force an excitation rhythm of more than 240 min^{-1} on the models. **Table 1** presents the success in forcing a high-frequency rhythm of excitation depending on the source and forced excitation impulse frequency.

The action potential waveform at an excitation impulse frequency of 60 min^{-1} is slightly different from that in a cardiomyocyte in a continuous resting state. As the frequency increases the duration of the action potential decreases, so does the duration of the resting state in relation to the action potential duration. If at a frequency of 60 min^{-1} the resting state duration takes up most of the impulse repetition period, then at a frequency of 240 min^{-1} most of the period is taken up by the action potential.

Examples of the results of forced rhythms are presented in **Figure 2**. The arrows in the figures show the action time of excitation impulses, the dashed line shows changes in the transmembrane potential after a rhythm was successfully forced.

In **Figure 2(c)**, every second excitation impulse hits the refractoriness, and therefore no excitation of the cardiomyocyte model occurs. In fact, the model is excited at a frequency that is 2 times lower than the frequency of the excitation impulses.

The aim of a defibrillating pulse is to hinder fibrillation wave propagation in the myocardium. Fibrillation results in a high frequency of cardiomyocyte excitation in which, as is shown in **Figure 1**, the duration of the refractoriness is reduced. If the defibrillating pulse manages to prolong the refractoriness in

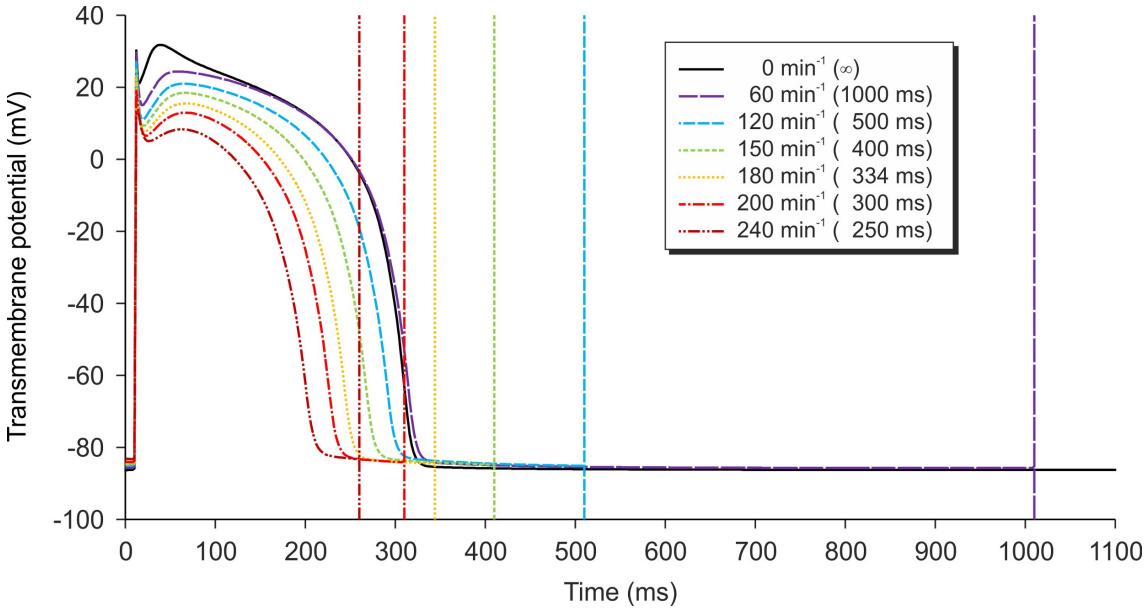


Figure 1. The action potential waveform at different frequencies (repetition periods) of excitation impulses. The vertical lines show the action time of the next excitation impulse.

Table 1. Success in forced excitation rhythm.

Initial excitation impulse frequency, min^{-1}	Forced excitation impulse frequency, min^{-1}							
	120	150	180	200	210	220	230	240
60	yes	yes	yes	no	no	no	no	no
120		yes	yes	no	no	no	no	no
150			yes	yes	yes	no	no	no
180				yes	yes	yes	*	no
200					yes	yes	*	*
210						yes	*	*
220							yes	*
230								yes

*Greatly varying forms of related action potentials (alternation).

cardiomyocytes, it will block fibrillation wave propagation across the myocardium, and this wave will be destroyed. An assumption was made in [12] about the role of prolonging the refractoriness at the expense of recovering the cardiomyocyte excitation channel by a defibrillating pulse. The effect of prolonging the refractoriness was also obtained in experiments [13].

3.2. Changing the Threshold Energy Ratio and the Duration of the Energetically Optimal Cardiomyocyte Excitation Impulse According to the Excitation Impulse Frequency

The parameters for energy-optimal rectangular excitation impulses were determined for a cardiomyocyte both in the continuous resting state (0 min^{-1}) and at excitation rhythms of 200 and 240 min^{-1}. Figure 3 presents graphs showing the dependence of threshold energy ratios on excitation impulse

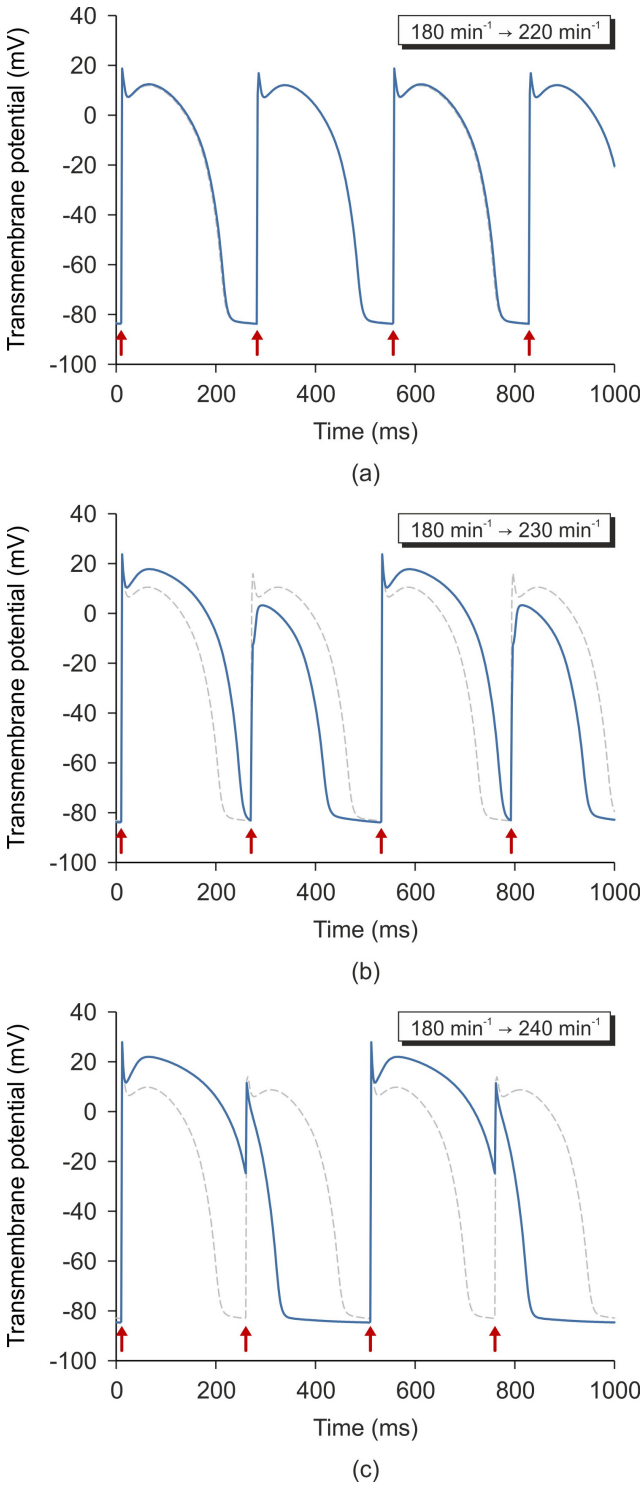


Figure 2. Examples of the results of forced rhythms. (a) A successfully forced rhythm when switching the excitation impulse frequency from 180 to 220 min^{-1}; (b) Significantly different forms of the related action potential when switching the excitation impulse frequency from 180 to 230 min^{-1} (alternation); (c) The failure to force an excitation rhythm when switching the excitation impulse frequency from 180 to 240 min^{-1}.

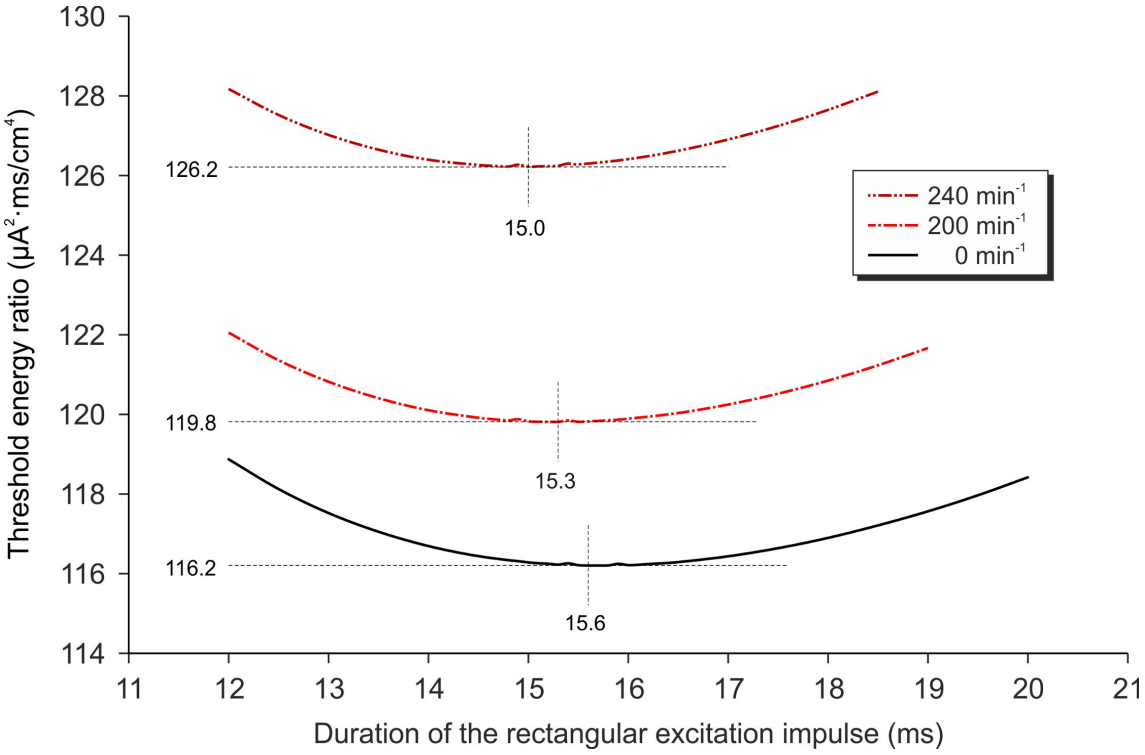


Figure 3. Dependence of the threshold excitation energy ratio on the rectangular impulse duration for the cardiomyocyte model in continuous resting state (0 min^{-1}) and at excitation rhythms of 200 and 240 min^{-1}.

duration at optimal values for these cases. The parameters of the energy-optimal excitation impulse at a rhythm of 240 min^{-1} differ insignificantly from those in a continuous resting state: optimal impulse duration is reduced by 5% and the threshold energy value is increased by 9%.

3.3. Threshold Impact

Proceeding from the assumption that a defibrillating pulse prolongs refractoriness of cardiomyocytes, dependences of threshold values of the energy ratios of depolarizing rectangular pulses prolonging the refractoriness of the cardiomyocyte model, were built, depending on the delay relative to excitation impulse when defibrillating pulse duration was 15, 30 and 45 ms at an excitation impulse frequency of 240 min^{-1} (**Figure 4(a)**).

Depending on the delay relative to the excitation impulse the depolarizing pulses had a different impact on the cardiomyocyte model. Four types of impacts were identified (**Table 2**). **Table 3** gives ranges of delay values of the depolarizing pulse relative to the excitation impulse for different types of impact.

The parameters of the maximum and minimum values of threshold impacts are presented in **Table 4**.

Examples of the types of impact of depolarization pulse with 15 ms duration at an excitation impulse frequency of 240 min^{-1} are presented in **Figure 5**. The arrows in the figure show the action time of excitation impulses; the dashed line shows transmembrane potential changes at an excitation rhythm of 240 min^{-1}.

Figure 6 shows the diagrams of the change in the threshold energy ratio as a function of the duration of the depolarization pulse at delays in relation to the excitation impulse 70 ms (impact type B) and 160 ms (impact type D).

When the delay relative to the excitation impulse was 70 ms (impact type B) the minimum threshold energy ratio was obtained when depolarizing pulse duration was 31 ms, when the delay was 160 ms

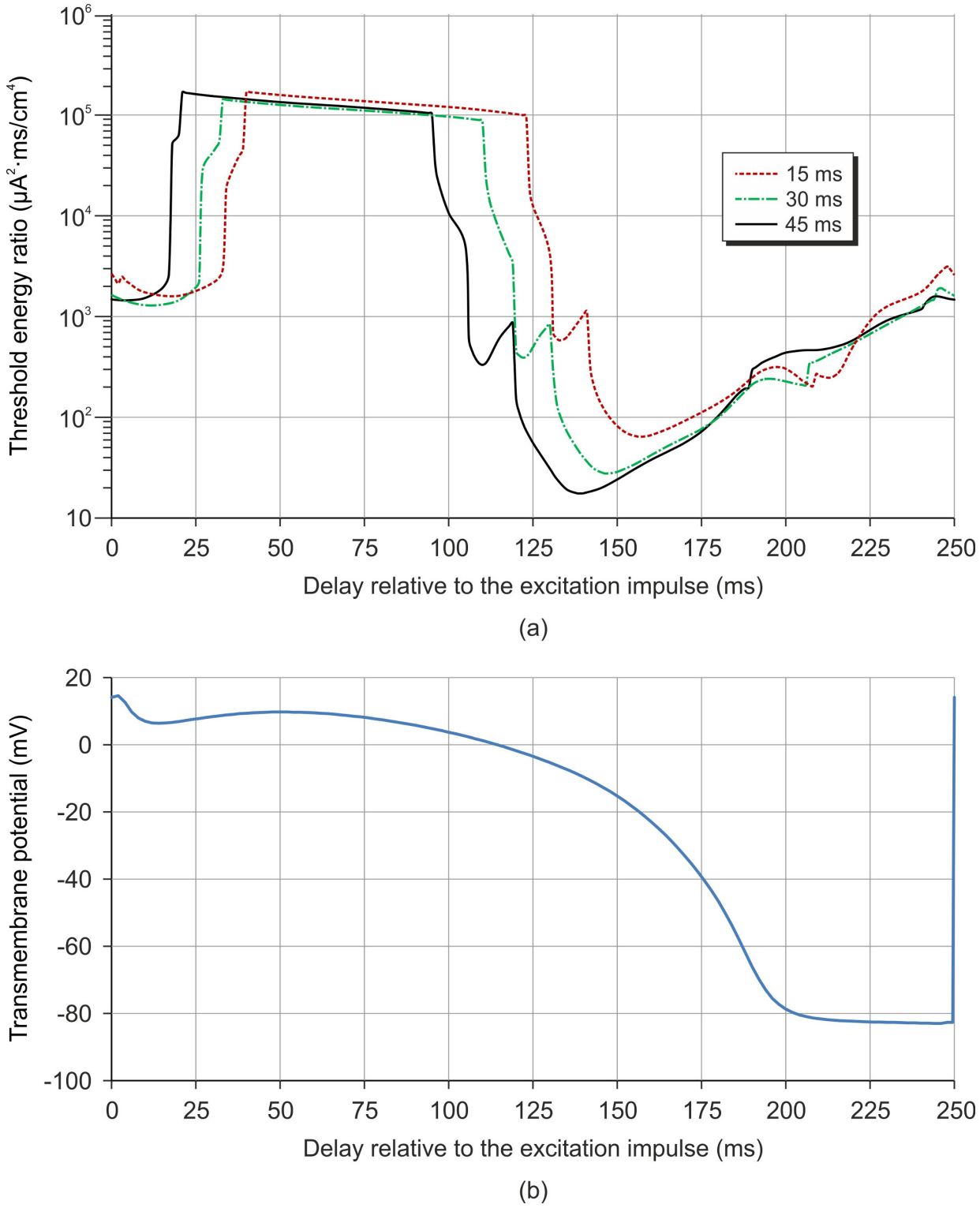


Figure 4. Dependences of threshold values of the energy ratios of depolarizing rectangular pulses prolonging the refractoriness of the cardiomyocyte model depending on the delay relative to excitation impulse when pulse duration is 15, 30 and 45 ms at an excitation impulse frequency of 240 min^{-1}; (b) The cycle of changes in the transmembrane potential of the cardiomyocyte model at excitation impulse frequency of 240 min^{-1}.

Table 2. **Types of depolarizing pulse impact on the cardiomyocyte model.**

Designation of impact type	Impact description
A	Shortening of the current refractoriness causes the next one to be longer
B	High-energy suppression of the next refractoriness causes a longer third refractoriness
C	Shortening of the next refractoriness causes a longer third refractoriness
D	Low-energy suppression of the next refractoriness causes a longer third refractoriness

Table 3. **Types of depolarizing pulse impact on the cardiomyocyte model.**

Depolarizing pulse duration, ms	Value ranges of delay of the depolarizing pulse relative to the excitation impulse, ms, for different types of impacts			
	A	B	C	D
15	0 - 39	40 - 123	124 - 141, 209 - 250	142 - 208
30	0 - 32	33 - 110	111 - 130, 207 - 250	131 - 206
45	0 - 20	21 - 95	96 - 119, 190 - 250	120 - 189

Table 4. **Parameters of maximum and minimum values of threshold impacts.**

Parameter	Depolarizing pulse duration, ms		
	15	30	45
	Maximum threshold value		
Delay relative to excitation impulse, ms	40	33	21
Current amplitude, μA/cm^2	106	69	61
Energy ratio, μA^2·ms/cm^4	170000	143000	168000
	Minimal threshold value		
Delay relative to excitation impulse, ms	157	147	139
Current amplitude, μA/cm^2	2.07	0.96	0.63
Energy ratio, μA^2·ms/cm^4	64	28	18

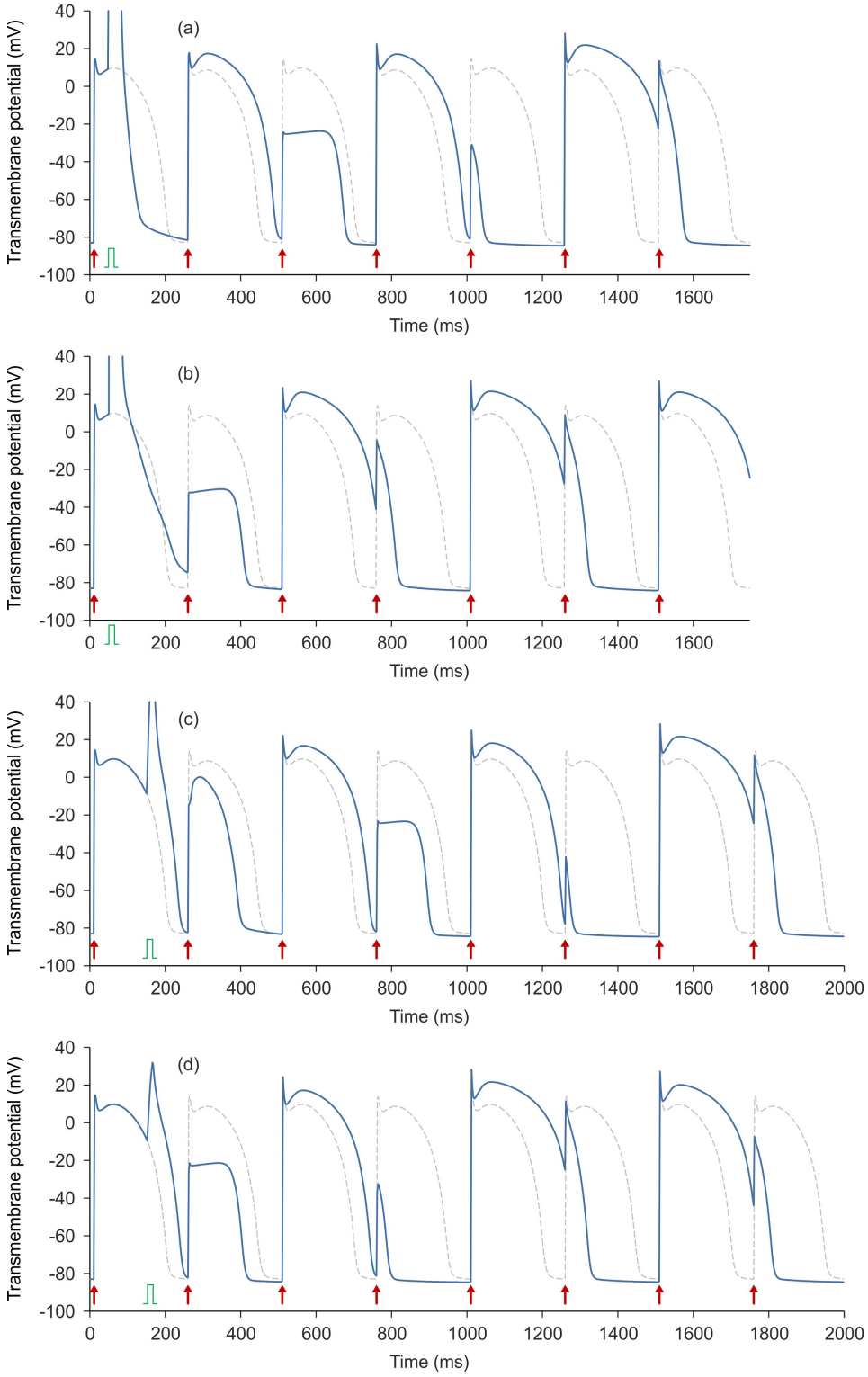
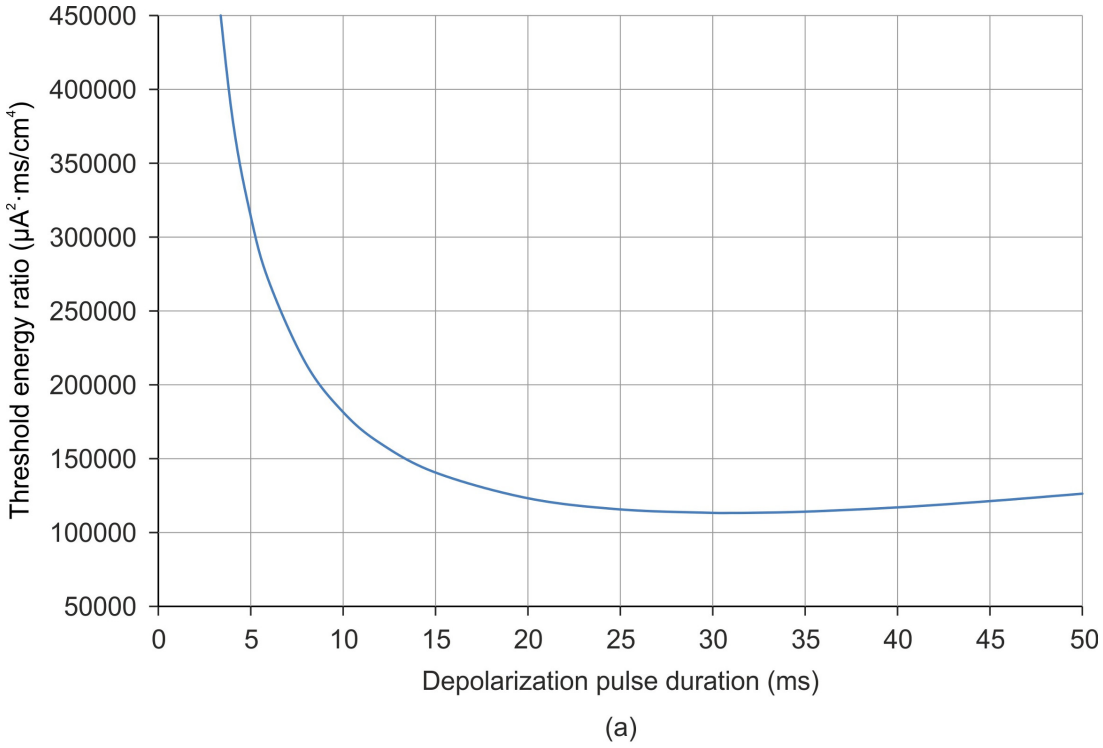
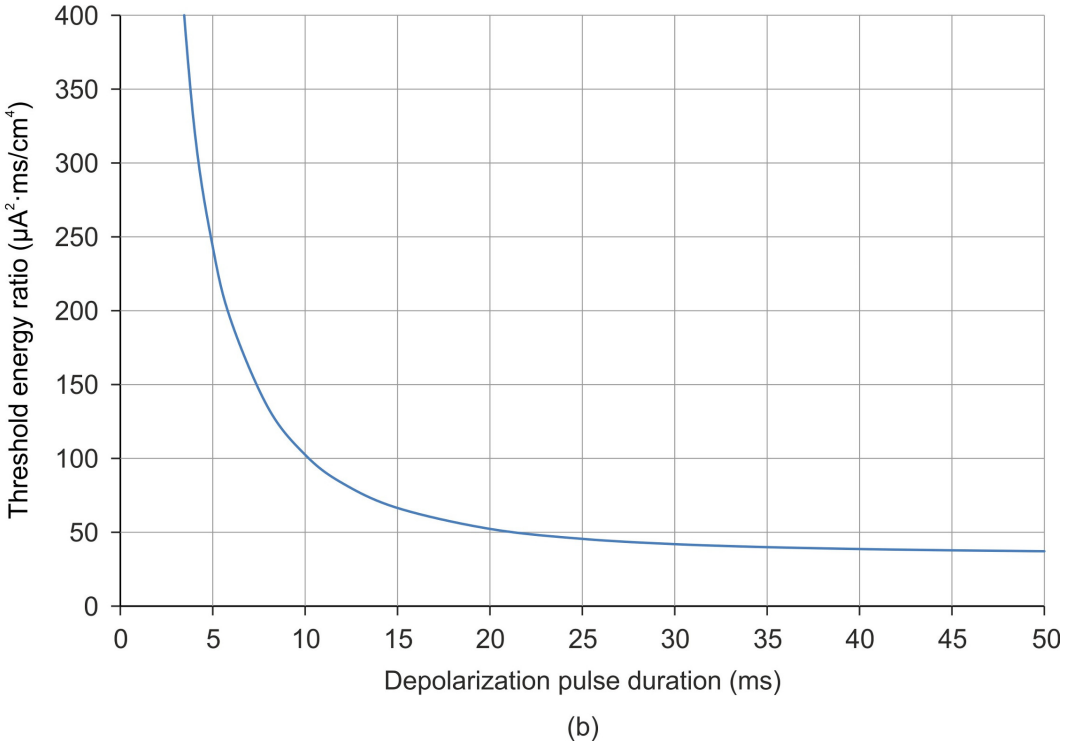


Figure 5. Examples of the types of impact of depolarization pulse with a duration of 15 ms at a excitation impulse frequency of 240 min^{-1}. (a) Impact type A, the delay relative to the excitation impulse is 39 ms; (b) Impact type B, the delay relative to the excitation impulse is 40 ms; (c) Impact type C, the delay relative to the excitation impulse is 141 ms; (d) Impact type D, the delay relative to the excitation impulse is 142 ms.



(a)



(b)

Figure 6. Examples of the types of impact of depolarization pulse with a duration of 15 ms at a excitation impulse frequency of 240 min^{-1}. (a) Impact type A, the delay relative to the excitation impulse is 39 ms; (b) Impact type B, the delay relative to the excitation impulse is 40 ms; (c) Impact type C, the delay relative to the excitation impulse is 141 ms; (d) Impact type D, the delay relative to the excitation impulse is 142 ms.

(impact type D) the threshold energy ratio decreased as the pulse duration increased in the entire range of the values studied.

4. DISCUSSION

The study found only one mechanism that explains the impact of defibrillating pulses on the cardiomyocyte—that of prolonging its refractoriness.

The study revealed differences in the mechanisms of action on cardiomyocytes between excitation and defibrillation impulses. If the threshold energy ratio of the excitation impulse is ~120 $\mu A^2 \cdot ms/cm^4$ at the optimal duration of ~15 ms, then threshold energy ratio is ~140,000 $\mu A^2 \cdot ms/cm^4$ in the phase of the high-energy defibrillation at an optimal pulse duration of ~30 ms. In the phase of low-energy defibrillation the threshold energy ratio decreases as pulse duration increases and is ~20 $мкА^2 \cdot мс/см^4$ at a pulse duration of 45 ms.

The duration of energetically optimal excitation impulse (15 ms) is higher than that obtained for the Luo-Rudy model (11 ms) [14].

Impact types A and B are presumably associated with classical defibrillation in which the energy of a monophasic pulse can be as high as 360 J. However, the duration value of an energetically optimal defibrillating pulse (~30 ms) on the model significantly differs from the energetically optimal duration of the human defibrillating pulse obtained experimentally (approx. 4 ms [15]). Impact types C and D explain the efficacy of low-energy defibrillation [16].

Low-energy defibrillation is extremely attractive for use in clinical practice. With external cardioversion, it can solve the problem of exceeding the pain threshold, since current of the pulse of cardioversion becomes many times smaller and lower than the pain threshold. As a result, the use of medication for pain relief before cardioversion will not be required. Also, the reducing of energy necessary for defibrillation arrives to reduce the size and weight of the power module of the defibrillator and its cost has been reduced. However, the possibility of low-energy defibrillation requires further theoretical studies and experiments on animals.

5. CONCLUSIONS

The cardiomyocyte model has a limited susceptibility to a forced rhythm of high frequency excitation. It is possible to force a high frequency excitation rate by increasing the excitation impulses frequency gradually.

Presumably, the mechanism of defibrillation pulse impact is the prolongation of the refractoriness of cardiomyocytes which undermines their susceptibility to a forced high-frequency fibrillation rhythm for a long time, as a result for which they hinder the propagation of a fibrillation wave. This is the only defibrillation mechanism that has been identified during the simulation.

The threshold energy of a defibrillation depolarizing pulse that causes a longer cardiomyocyte refractoriness varies depending on a delay relative to the excitation impulse (the excitation phase) on a wide range, with the maximum value exceeding the minimum one as much as several thousand times).

The results show that the excitation impulse and the monophasic defibrillation pulse have different mechanisms of impact on cardiomyocyte.

Myocardial cardiomyocytes are in different phases of the excitation cycle in the process of fibrillation wave propagation. The study suggests that applying a series of low-energy defibrillating pulses during a repetition period of excitation impulses will violate susceptibility of the myocardium myocytes to the forced high-frequency fibrillation rhythm in amounts large enough to destroy the fibrillation wave. The effectiveness of this defibrillation method has been confirmed by experimental studies [16].

ACKNOWLEDGEMENTS

The author is grateful to I. V. Biktasheva (University of Liverpool, UK) and V. N. Biktashev (Univer-

sity of Exeter, UK) for their advice on the use of the BeatBox simulation environment. This work was funded by Ministry of Education and Science of the Russian Federation according to the government research project № 12.2418.2014/K.

CONFLICTS OF INTEREST

The author declares that there is no conflict of interest regarding the publication of this article.

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