Mathematical modeling of the efficiency of a defibrilling biphase rectangular signal of different duration

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Abstract: *According to numerous studies, 76% of sudden cardiac arrest (SCA) are conditionally preventable, because occur due to ventricular fibrillation (VF) [1-3]. Immediate electrical impulse therapy (EIT) by external defibrillation is the main treatment for this type of arrhythmia [3-5]. Earlier, a comparative study of modern forms of impulses made it possible to reveal the concept of the development of this field of science [6]. The analysis of the literature and the results of recent developments made it possible to determine the main parameters of the pulse for the individual selection of the characteristics of the transthoracic defibrillation signal. Representation of the average current (I) and charge (Q) in the form of a certain function I (t) is the optimal way to dose the defibrillation pulse [7].*

Keywords: *TRANSTHORACIC DEFIBRILLATION, BIPHASIC PULSE, CURRENT STABILIZATION, CARDIOMYOCYTES REPOLARIZATION, VENTRICULAR FIBRILLATION*

1. Introduction

The calculation of the main parameters was carried out based on the work of Weiss and Lapicque [8], who proved the existence of the effect of cardiac tissue stimulation and Blair's calculations, who described the existence of the rheobase [9,10]. Irnich's studies describe in detail the effect of the pulse exposure time on cardiomyocytes as the main parameter of the pulse [11,12]. In the future, a large number of studies have proved in practice the high efficiency of a two-phase pulse over a monophasic one. The theoretical substantiation of this fact has not yet been presented, but there is a hypothesis that the second phase prevents the appearance of ectopic foci in the heart tissue, which increases the efficiency of defibrillation [13-17]. A detailed calculation of the ratio of the forward and backward signal of the pulse was carried out by Kroll and showed the possibility of minimizing the energy of the second phase [18], and a number of authors subsequently confirmed the large variability of the current amplitude tolerances [14]. The fact that the phase switching time should not exceed 1 ms and, if possible, should be minimized, otherwise the biphasic signal turns into two monophase signals [19]. In 1978, Bourlands in his article showed the comparative efficiency of pulses with a constant time, regardless of the impedance of the chest [20]. The not rightly forgotten publication by Schuder in 1964 confirms the high efficiency of a rectangular pulse over other pulse variants [13]. Tacker presented a graph from his analysis in 1993 and proved that there is a fine line between effective defibrillation and damage from each pulse [21]. Wilson, in a 1988 study, described the effect of charge storage upon repeated defibrillations [22]. Fishler summed up all the experiments in 2000 by determining the time interval for a rectangular pulse in the range from 3 to 6 ms and the ratio of the amplitude of the current of the first and second phases as 15A to 10A [23].

2. Materials and methods

Taking into account the permissible range of the time interval, obtained from the analysis of the literature and our own calculations, the next stage of optimization of the time interval of the pulse effect is the experimental part [7,23]. With the aim of a humane approach to research at the stage of signal modeling and objectification of the results, the research was carried out by mathematical modeling in the free Cell Electrophysiology Simulation Environment (CESE) [24]. The program includes a mathematical model of biochemical processes occurring on the surface and inside the cardiomyocyte of a guinea pig Luo-Rudy Mammalian Ventricular Model II (dynamic) [25]. Using this model, it is possible to simulate the effect of an electric pulse of a certain duration, shape and intensity in terms of current strength on the cell membrane, and to obtain graphs of the operation of ion channels and changes in the concentration of ions on the surface and inside the cardiomyocyte.

We have written in the Java programming language and implemented into the CESE environment a rectangular signal of sufficient intensity to overcome the excitability threshold of the cardiomyocyte. Taking into account the analyzed literature and our own calculations [6, 7], several rectangular signals with a duration of 3 to 6 ms with a step of 1 ms were selected for analysis to determine the optimal pulse duration. Experiments have previously established a difference in the duration of the threshold impulses for the Luo-Rudy Mammalian Ventricular Model II (dynamic) cardiomyocyte model and the results on the human cardiomyocyte model. The 11 ms pulse for the Luo-Rudy model turned out to be identical in its effects for the 4 ms signal in the human cardiomyocyte model [26, 27]; the ratio of the pulse duration in the used model to the human cardiomyocyte model is 1: 2.75. In this regard, it was decided to introduce a correction factor for the pulse duration: Kt = 2.75.

As the main investigated parameter, we define the voltage on the membrane surface Membrane voltage (mV). On the surface of the membrane, the resting membrane potential (RMP) is constantly present, which is formed mainly due to the diffusion of Na + and K + ions. The BMP of the cardiomyocyte is approximately - 86 mV [28]. When an electrical impulse is applied to the cell membrane, depolarization occurs and an action potential (AP) is formed on its surface. PD of the cardiomyocyte occurs at a voltage of 56 mV. In this case, the protein channels of the cell membrane are activated and Na + ions rush into the cell. The flow of Na + ions into the cell occurs according to the “all or nothing” principle; therefore, the formation of AP can be clearly traced by the change in the rate of movement of Na + ions through the membrane [29]. The used mathematical model allows us to plot the Na + ion flow (Total Na ion flow (mM / ms)) and we use it as a criterion for the efficiency of the signals under study.

In the repolarization phase, active cellular channels are actively involved, the work of which is aimed at restoring the MPP. Calcium ions play an important role at the stage of repolarization. Their function is to maintain the MPP at a certain level (86mV) and, with a decrease in their concentration, the excitability of the cell decreases. The maintenance of Ca2 + concentration is regulated by the Na + / Ca2 + pump and, as a rule, its work is aimed at pumping Ca2 + out of the cell using a Na + / Ca2 + pump [30]. The peculiarity of the Na + / Ca2 + pump is the exchange of one Ca2 + ion for three Na +. It follows from this that the overload in the work of this mechanism, associated with the excessive intake of Na + ions, can lead to a decrease in the excitability of the cardiomyocyte [31]. To assess the effectiveness of defibrillation pulses, a graph showing the activity of the Na + / Ca2 + pump - Na-Ca exchanger current (uA / uF) was included in the study model. A comprehensive analysis of the above parameters allows you to assess the effectiveness of pulses and assess their safety..

3. Discussion Results

Modeling was carried out in the CESE environment on the Luo-Rudy Mammalian Ventricular Model II (dynamic) model, using its own rectangular signal of sufficient intensity to form the AP. Changing the duration of a rectangular pulse in CESE occurs by manually adjusting the parameter - this function is called clamp, the parameter is stimulus duration. As described above, from earlier studies, in order to obtain results applicable to human cardiomyocytes, it is necessary to introduce a correction factor Kt. After correction, the pulse duration was 8.25 ms (4 ms), 11 ms (4 ms), 13.75 (5 ms) and 16.5 (6 ms).

In the simulation environment, summary plots were plotted showing changes in membrane surface voltage (Membrane voltage (mV)), Na + ion flow (Total Na ion flow (mM / ms)), and Na + / Ca2 + pump activity (Na-Ca exchanger current (uA / uF)) for each pulse separately.

When considering the graph obtained by simulating a signal with a duration equivalent to a pulse of 3 ms (8.25 ms), shown in Figure 1, the following data were obtained: the action potential (AP = -56 mV) develops at 0.35 ms, Na + channels open at 0.4 ms ... In this case, the reverse current of Na + ions begins immediately after closing and reaches its peak at 4.2 ms, followed by a smooth ramp-like decline. The operation of the Na + / Ca2 + pump on the graph duplicates the dynamics of restoring the Na + balance. In general, the effect of a rectangular pulse with a duration of 3 ms can be characterized as sufficient to create a general repolarization. The impulse creates conditions for a standard contraction in terms of its duration and activity of ion channels [32].

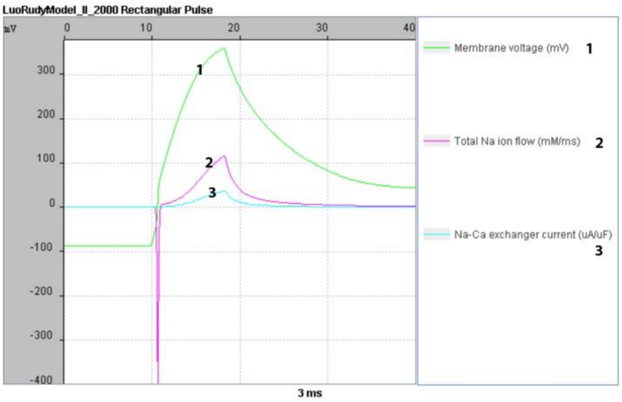

Fig. 1 *Mathematical modeling of changes in voltage indicators on the surface of the cardiomyocyte membrane, Na^+ transmembrane current and Na^+-Ca^{2+} pump activity, when exposed to an equivalent pulse of 3 ms duration*

In Figure 2, obtained by simulating a 4 ms pulse (11 ms under the simulation conditions on the presented model), the AP is also formed at 0.35 ms, and the Na + channels are opened at 0.4 ms. The graph shows the key difference between pulses of 3 and 4 ms: a plateau appears on the cell membrane from 0.9 ms to 10.1 ms with an average amplitude of 64 mV. Due to this plateau, the reverse flow of Na + ions and their active transport from the cardiomyocyte cell are blocked. The operation of the Na + / Ca2 + pump has a smooth start and decline and is a direct reflection of the dynamics of the Na + ion current. The formation of a "blocking" plateau on the surface of the cardiomyocyte membrane reflects the very essence of defibrillation, which consists in creating a general repolarization for all heart cells.

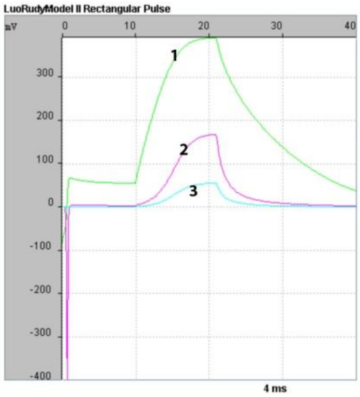

Fig. 2 *Mathematical modeling of changes in voltage indicators on the surface of the cardiomyocyte membrane, Na^+ transmembrane current and Na^+-Ca^{2+} pump activity, when exposed to an equivalent pulse of 4 ms duration*

When examining a 5 ms pulse (13.25 ms for the model under study), shown in Figure 3, the formation of AP and the opening of Na + channels are similar to the previous results of 0.35 and 0.4 ms, respectively. Noteworthy is the absence of a plateau as at a 4 ms pulse, and the formation of the first peak on the membrane surface at 3.7 ms with an amplitude of 238 mV. At the same time, the first peak in the reverse flow rate of Na + ions is also noted. A detailed examination of the data from the performed modeling revealed a regularity: the active current of Na + ions from the cell begins at a voltage on the membrane surface of more than +80 mV. A further decrease and repeated rise in the membrane voltage is accompanied by the synchronous activity of the current of Na + ions and the operation of the Na + / Ca2 + pump. In this case, the total operating time of the Na + / Ca2 + pump is 19 ms (from 1.35 ms to 30.35 ms). And if we turn to the fact that the duration of Na + -channel opening is 0.6 ms at any pulse duration, and the maximum speed does not differ significantly (395 - 398 mM / ms), we can conclude that there is excessive Na + transport from the cytoplasm of the cardiomyocyte. Do not forget that this is the transport of Ca2 + ions into the cell and, as a consequence, a decrease in the excitability of the cardiomyocyte [31]. From the results of modeling a rectangular pulse with an equivalent duration of 5 ms, it can be concluded that prolonged exposure to a high-density current on the cardiomyocyte leads to excessive transport of Ca2 + and Na + ions into the cell and onto its surface, respectively.

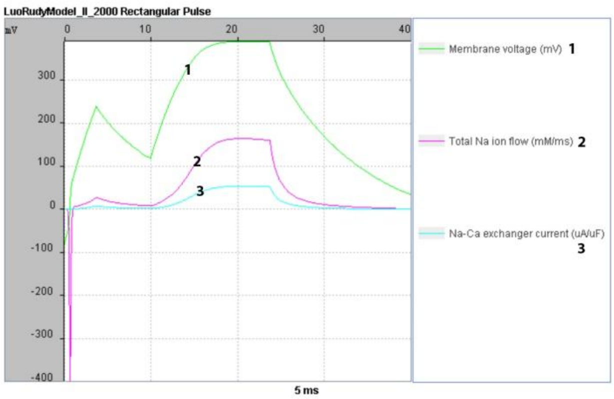

Fig. 3 *Mathematical modeling of changes in voltage indicators on the surface of the cardiomyocyte membrane, Na^+ transmembrane current and Na^+-Ca^{2+} pump activity, when exposed to an equivalent pulse of 5 ms duration*

A further increase in the pulse duration to 6 ms (16.5 ms in the model under study) confirms the conclusions drawn from the previous simulation. High voltage on the membrane surface leads to active substitutional transport of ions, which as a result leads to a decrease in the concentration of Ca + ions on the surface of the cardiomyocyte membrane and, as a consequence, to a decrease in cell excitability, including for subsequent defibrillating impulses. Figure 4, showing a graph of a pulse with an equivalent duration of 6 ms, characterizes it as excessive in all the parameters under study.

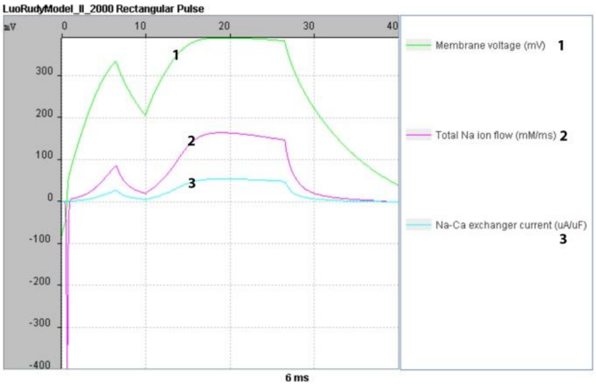

Fig. 4 *Mathematical modeling of changes in voltage indicators on the surface of the cardiomyocyte membrane, Na^+ transmembrane current and Na^+-Ca^{2+} pump activity, when exposed to an equivalent pulse of 6 ms duration*

As a result of modeling, we obtained graphs characterizing the reaction of the cardiomyocyte to rectangular pulses of various duration. With the help of this study, it is possible to assess the main processes of cell excitability: the formation of AP upon short-term exposure to a defibrillating pulse, membrane repolarization and restoration of the MPP..

4. Conclusion

The aim of our study was to study the effectiveness of a biphasic rectangular signal of various durations using a cardiomyocyte model in the CESE mathematical modeling environment. By analyzing the results obtained, we have determined the optimal defibrillation pulse time from the range obtained by analyzing the data of previous studies and calculations [7]. The most effective was a pulse with a duration of 4 ms. Since the study was carried out directly on the mathematical model of the cardiomyocyte, the errors that could arise during the experiment on animals were leveled. The differences in the geometry of the thorax of animals create a number of difficulties in the application of the results obtained in humans, and mathematical modeling in order to study the time interval can be called a preferable option. The next step in biphasic pulse design is to calculate the optimal current amplitude for the most effective defibrillation, taking into account the changing chest impedance of the patient.

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