Computer Simulation of Cardiomyocyte Membrane Exposure to First-Phase Bipolar Defibrillation Impulses

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Objective: **to substantiate the efficacy of bipolar impulses of different shapes and duration.** ***Method.*** **The investigation used the dynamic model II of the mammalian ventricular cardiomyocyte membrane in the guinea-pig, proposed by Luo and Rudy (1994—2000). The cardiomyocyte membrane was acted by substituting the current density of the impulse under study. The threshold impulse energy ratio considered as an integral index of the threshold action (a measure of efficiency) of an impulse measured in μA²ms/cm⁴ was then calculated. A comparison was made between a classical quasi-sinusoidal impulse, a stepwise quasi-sinusoidal, rectilinear, classical trapezoidal, trapezoidally modulated (the presence of high-frequency, high-amplitude oscillations of current) impulse and its unmodulated equivalent, and a trapezoidal low-angle front tail impulse of the duration equal to that of the classical quasi-sinusoidal one. The shape of the impulses corresponded to the 100-ohm resistance of the chest.** ***Results.*** **The most effective impulses proved to be a quasi-sinusoidal stepwise impulse (229.6 $\mu A^2 ms/cm^4$), next a classical quasi-sinusoidal impulse (249 $\mu A^2 ms/cm^4$, +9%) and a trapezoidal low-angle front tail one (253.0 $\mu A^2 ms/cm^4$, +10%). The trapezoidally modulated impulse (397 $\mu A^2 ms/cm^4$, +73%) turned out to be lowest effective (in the threshold impulse energy ratio). The other impulses were intermediate between the above impulses in the following order: a modulated trapezoidal impulse equivalent (272.0 $\mu A^2 ms/cm^4$), next a rectilinear impulse (273.5 $\mu A^2 ms/cm^4$), and a classical trapezoidal one (307.0 $\mu A^2 ms/cm^4$).** ***Conclusion.*** **In terms of the excitation threshold of the Luo-Rudy model of the guinea-pig cardiomyocyte membrane, the most effective impulses are quasi-sinusoidal stepwise, next quasi-sinusoidal and trapezoidal low-angle front tail ones.** ***Key words:*** **cardiomyocyte membrane model; bipolar impulse, defibrillation.**

Disturbancies of rythm and conductivity are common complications in critical illness [1—2]. In 1972, the Soviet Union began the production of the world's first defibrillator with biphasic quasi-sinusoidal pulse waveform — DI-03, the maximum energy of which was ~ 1.5—2.1 times less than that of defibrillators generating monophasic pulses [3—5]. Comparison of the efficiency of the above pulses was investigated in experiments on animals (according to the criteria of current and the energy threshold values, stopping short-term ventricular fibrillation), and then in the clinic (criteria — energy dose and success and the ultimate success of defibrillation) [6—8]. Such empirical research methods are necessary, but they require much finance and time (not less than 1 year).

At the beginning of the XXI century 3 more different in shape bipolar pulses (truncated exponential, rectilinear and truncated exponential modulated) were introduced into the world cardiac resuscitation. In this connection, in recent years one of the most urgent tasks has been search for the optimal biphasic pulse, releasing minimum effective energy on the heart. It should be noted that during defibrillation the first phase of the biphasic defibrillation pulse plays the leading role. However, it releases not less than 70—80% of the pulse energy on the heart, and the second — not more than 20—30%. But the comparative effecacy of the first phase of the biphasic pulses of different shapes and duration has not been investigated. At present, thanks to the development of the computer simulation method it is possible to study the threshold effect of pulses of different shape and duration on a model of the cardiomyocyte membrane and thus to compare their efficacy by the criterion of excitation threshold of the membrane (so-called electrophysiological approach). The most well-known model reflecting electrophysiology of myocardial cell membrane, is the Luo-Rudy model [9].

Applying this approach allows conducting quickly exploratory study, the results of which can then be used for advancing scientific hypothesis and its further experimental and clinical test.

PURPOSE: To compare the threshold effect of the first phase of biphasic pulses of different shapes and durations that cause cardiomyocyte membrane excitation using the model Luo-Rudy.

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Materials and methods

For the investigation we used the model of the cardiomyocyte membrane of guinea pig Luo-Rudy Mammalian Ventricular Model II (dynamic), 1994—2000, part of the Cell Electrophysiology Simulation Environment (CESE) OSS 1.4.7 — which is part of the modeling environment [10]. The effect of the electrical pulses on the cardiomyocyte membrane model was performed by clamping parameter «stimulus amplitude» (st) — current density of the acting pulse is expressed in $\mu A/cm^2$. This study determined the threshold value of the current density amplitude (I_{thr}), which formed the action potential of the cardiomyocyte membrane (excitation of cardiomyocyte). Then the threshold energy ratio was calculated: $K_E = I^2_{thr} \cdot t_{pulse} \cdot K_{shape}$ $[\mu A^2 \cdot ms/cm^4]$, where t_{pulse} — pulse duration, K_{shape} — pulse shape ratio (ratio of the pulse energy to the energy of a rectangular pulse of the same amplitude and duration). Along with this, relative threshold energy (the ratio of the threshold energy coefficient of the pulse to the threshold energy coefficient with its minimum values was calculated. As an integral index, reflecting the effectiveness of the pulse, the threshold energy ratio was considered. It should be noted that the duration of a rectangular pulse with a minimum threshold energy of the excitation of the Luo-Rudy cardiomyocyte membrane model is 11 ms [11], and about 4 ms (for) of the membrane of the cardiomyocyte of a human being [12]. In this regard, the studied pulse duration in relation to the actual pulses was increased 2.75 times (Fig. 1*a* and 1*b*). Along with the threshold, subthreshold pulses were administered (0.1% less than the current threshold), which caused local excitation of the membrane. Subthreshold pulses were used for detailed study of the reaction of the membrane for the time approximate to the pulse duration (Fig. 2 and 3). A comparison was drawn between pulses: classic quasi-sinusoidal, stepped quasi-sinusoidal, rectilinear, classic truncated exponential, truncated exponential modulated (high-frequency, high-amplitude oscillations) and its unmodulated equivalent, trapezoidal with sloped rising and falling with duration equal to the duration of the classic quasi-sinusoidal (Fig. 1*a* and 1*b*). Pulse shape corresponds to thoracic impedance of approximately 100 Ω [13].

Results and discussion

Fig. 1*a* and 1*b* show the shape of the investigated pulses with threshold current density amplitude, and Table — the values of the investigated parameters of these pulses.

Fig. 2 shows the response of the cardiomyocyte membrane model to the effect of two pulses (truncated exponential modulated and its unmodulated equivalent) at the subthreshold[1] current density amplitudes. As it can be seen from the Fig. the effects of the above pulses on cardiomyocyte membrane are virtually indistinguishable, except for minor reactions of membrane to high-frequency component of the modulated pulse. It should be noted that the presence the high-frequency component in truncated exponential modulated pulse (in comparison with its unmodulated equivalent) leads to a substantial increase in the threshold energy necessary for excitation of the cardiomyocyte membrane (Fig. 1*b*, Table).

Fig. 3 shows the response of the model of cardiomyocyte membrane to pulses with step controlled waveform (stepwise quasi-sinusoidal and rectilinear, Figure 1*a* and *b*. As it is seen from the Fig. the response of membrane to the indicated pulses has practically a smooth form.

According to these results, the stepped quasi-sinusoidal pulse (229.6 $\mu A^2 ms/cm^4$) had the minimum threshold energy ratio. This (by membrane excitation threshold) indicates its highest efficacy. In classic quasi-sinusoidal and trapezoidal with sloped rising and falling pulse the threshold energy ratio and relative threshold energy were almost equal and close enough to the values of stepwise quasi-sinusoidal pulse (Table). These results indicate that in case of trapezoidal pulse smooth rise and fall of current leads to a decrease in the threshold energy ratio, i. e. an increase in the efficacy of the pulse. It should be noted that with external defibrillation during smooth increase of pulse current the chest resistance decreases, which can also increase the efficacy of the pulse [14][2]. In rectilinear pulse the threshold values of studied parameters were bigger in comparison with stepwise quasi-sinusoidal pulse by 19%, with a classic quasi-sinusoidal — 9% and trapezoidal with sloped rising and falling — 10%. In classic truncated exponential pulse the similar parameters were by 34% and 12% more than stepwise quasi-sinusoidal and rectilinear, respectively.

The main reason for the lower efficiency of the classic truncated exponential pulse (by membrane excitation threshold), was its long duration, which differ significantly from the optimum (Fig. 1*a* and 1*b*). At the same time with unmodulated equivalent of truncated exponential modulated pulse (having duration close to the optimal) the threshold energy ratio was by 11% less. The highest threshold energy ratio was obtained with truncated exponential modulated pulse (396.8 $\mu A^2 ms/cm^4$). This is 46% more than that of its unmodulated equivalent, 57 and 59% — than in classic quasi-sinusoidal and trapezoidal with sloped rising and falling pulse, respectively (Table).

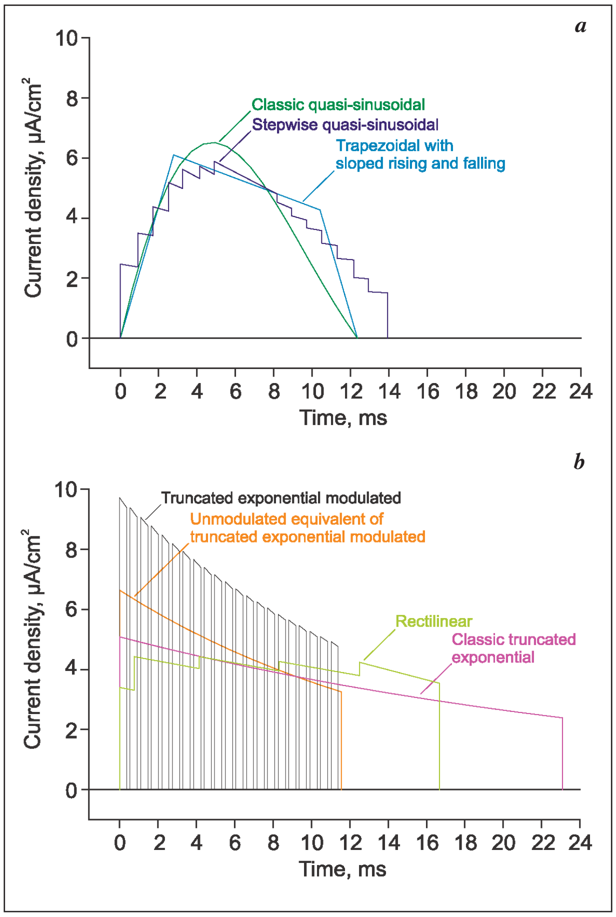

Fig. 1. The shape of the investigated pulse at the threshold current density amplitude, with causes excitation of the membrane. *A* — classic quasi-sinusoidal, stepwise quasi-sinusoidal and trapezoidal with sloped rising and falling; *B* — truncated exponential modulated and its unmodulated equivalent, rectilinear and classic truncated exponential.

[1] At the subthreshold current density amplitude an action potential is not formed. Action potential has a large duration and amplitude, so the micromorphology of the change of transmembrane potentials shown in Fig. 2 and 3 was distinguishable.

[2] With external defibrillation during the first two milliseconds exposure to quasi-sinusoidal pulse the chest resistance of experimental animals is reduced by 10...20% [14].

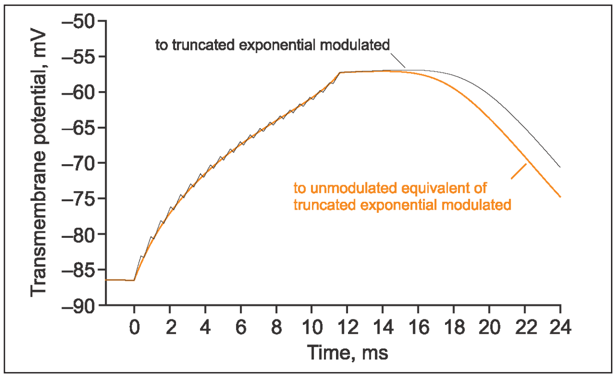

Fig. 2. Response of model of cardiomyocyte membrane to truncated exponential modulated pulse and its unmodulated equivalent with subthreshold amplitude of the current density.

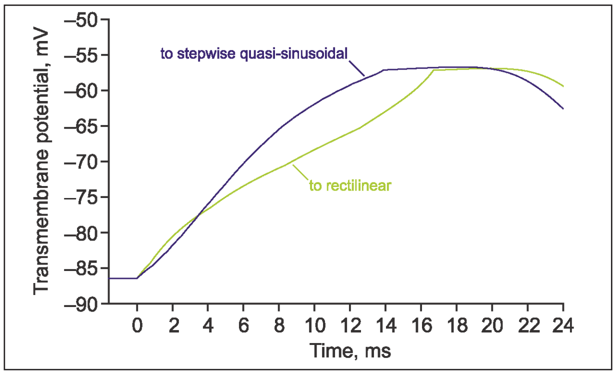

Fig. 3. Response of model of cardiomyocyte membrane to pulses with stepped controlled waveform (stepwise quasi-sinusoidal and rectilinear) with subthreshold amplitude of the current density.

Parameters of investigated pulses and their value

Pulse name	Shape ratio	Duration, ms	Threshold current density amplitude, $\mu A/cm^2$	Threshold energy ratio, $\mu A^2 \cdot ms/cm^4$	Relative threshold energy
Stepwise quasi-sinusoidal	0.4772	13.9	5.884	229.6	1.00
Classic quasi-sinusoidal	0.4757	12.3	6.515	249.2	1.09
Trapezoidal with sloped rising and falling	0.5512	12.3	6.098	253.0	1.10
Rectilinear	0.8375	16.7	4.425	273.5	1.19
Classic truncated exponential	0.5164	23.1	5.082	307.7	1.34
Truncated exponential modulated	0.3683	11.4	9.722	396.8	1.73
Unmodulated equivalent of truncated exponential modulated	0.5330	11.6	6.639	271.7	1.18

Thus, the modulation of defibrillation pulse results in a significant decrease in its effectiveness. Similar results were obtained with the Blair RC-model of cardiomyocyte membrane [15] and in animal experiments [16].

Conclusion

According to the criterion of the cardiomyocyte membrane excitation (model Luo-Rudy) most effective pulses are stepwise quasi-sinusoidal followed by classic quasi-sinusoidal and trapezoidal with sloped rising and falling. The lowest efficiency was found with truncated exponential modulated pulse. The rest of pulses are in between the above indicated pulses and they go in the following order: the unmodulated equivalent of truncated exponential modulated, then rectilinear and classic truncated exponential pulses.

The results obtained on a computer model of the cardiomyocyte membrane, as well as in experimental (animal) and clinical studies [7, 8, 13] allow us to make the following scientific conclusion: quasi-sinusoidal pulse of bipolar shape is the «gold standard» of cardiac ventricular defibrillation. Wide use of this pulse in clinical practice, by means of increasing low energy discharges efficacy, will allow to reduce their number and correspondingly the duration of resuscitation, and as a consequence — minimize the direct and indirect damage/dysfunction of myocardium and tissue damage beneath the electrodes.

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Диссертации на соискание ученой степени доктора наук без опубликования основных научных результатов в ведущих журналах и изданиях, перечень которых утвержден Высшей аттестационной комиссией, будут отклонены в связи с нарушением п. 10 Положения о порядке присуждения ученых степеней.

Перечень журналов ВАК, издаваемых в Российской Федерации по специальности 14.01.20 «Анестезиология и реаниматология», в которых рекомендуется публикация основных результатов диссертаций на соискание ученой степени доктора и кандидата медицинских наук:

- *Анестезиология и реаниматология;*
- *Общая реаниматология.*