MECHANISMS OF ELECTRICAL DEFIBRILLATION OF THE HEART

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SUMMARY

This paper discusses the development of theoretical models of heart defibrillation by a bipolar impulse. These are based on theoretical mechanisms as well as our results obtained in a series of fibrillation/defibrillation experiments carried out in anesthetized mongrel dogs. The procedures for fibrillation and defibrillation have been previously described. During the experiments, blood pressure, ECG, and ventricular wall contraction strength are continuously recorded. The methods of recording have been previously described.

Electrical defibrillation of the heart is an efficient method used to terminate ventricular fibrillation (VF). Although it is widely used in present-day clinical practice, the mechanism of defibrillation still remains obscure. This can be accounted for by the methodical difficulties involved in recording physiological and biophysical parameters against high-voltage impulses. Until today the parameters of electric shock needed to provide effective defibrillation remain disputable: is the impulse amplitude to be significantly or slightly higher than the defibrillation threshold [1,2] and what form of the impulse is to be used [3,4]; another parameter to be thoroughly investigated is the contractile response of the myocardium to a defibrillator shock.

In this paper we will discuss the development of theoretical models of heart defibrillation by a bipolar impulse. These are based on theoretical mechanisms as well as our results obtained in a series of fibrillation/defibrillation experiments carried out in anesthetized mongrel dogs. The procedures for fibrillation and defibrillation have been previously described [5]. During the experiments, blood pressure, ECG, and ventricular wall contraction strength are continuously recorded. The methods of recording have been previously described [6].

In all our experimental trials, the contractile response of the myocardium to
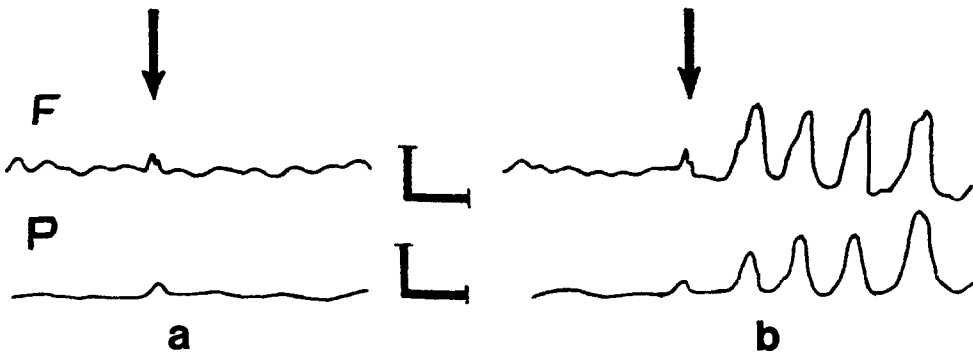
Fig. 1. Contractile response of the myocardium to a defibrillator impulse during ventricular fibrillation. (a) subthreshold impulse; b, suprathreshold impulse; F, mechanical tension in the myocadium. Calibration: ordinate — 1 g/mm², abscissa — 0.5 s. P, hydraulic pressure in the left ventricle. Calibration: ordinate — 100 mmHg, abscissa — 0.5 s. Arrows indicate the time of impulse application.

a defibrillating impulse was monitored. At the time of high-voltage impulse applied to the heart in VF the contractile response of the myocardium was always incomplete. The myocardial contraction was only 10—20% of the normal contraction in response to electric shocks, the voltage of which was either above or below the threshold of defibrillation. During exposure to subthreshold impulses of 200—300 V the myocardial mechanical response was incomplete irrespective of the shock level (Fig. 1a). The threshold and suprathreshold impulses of the defibrillator terminated VF; however, in all the tests there was cardiac arrest of 300—500 ms duration between the shock delivered and the first coordinated contraction of the myocardium (Fig. 1b). At the moment of shock application the F and P curves showed a transient peak, the amplitude of which was 10—20% of the normal [7].

In our experiments the defibrillation effect was provided by bipolar impulses of about 300 V peak-to-peak. Taking into consideration the electrical properties of cardiac compartments [8], heart size and geometry, and electrode localization, it can be estimated that the field intensity generated in the myocardium was E_0 = 70—80 V/cm. Similar values of E_0 equal to 90 V/cm calculated for rectangular and exponential impulses were reported by Jones et al. [9].

Potential mechanisms of defibrillation can be clarified if the potential evoked at the myocyte membrane in response to a defibrillating shock can be calculated. A cardiac cell is normally described as a sphere or as an ellipsoid of revolution, which is closer to reality. The amplitude of voltage evoked at the membrane φ_e for a dielectric ellipsoid located in the external electric field E_0 can be calculated according to the equation:

$$\varphi_e = \frac{a\, E_e E_0 \cos\theta}{[E_e + N(E_i - E_e)]\sqrt{1 + (\omega\tau)^2}}, \tag{1}$$

where E_e and E_i are dielectric permeabilities of the environment and the membrane, respectively, N is an integrated depolarizing factor, a is the half of the major axis of the ellipsoid, ω is the circular frequency of the alternating field, τ is the time of relaxation, and θ is the angle between the normal to the membrane plane and the relaxation of the vector of the field intensity.

If the membrane permeability can be neglected, then in the absence of a breakdown

$$\tau = a\, C_m\, (\varrho_i + 0.5\, \varrho_e), \tag{2}$$

where C_m is the specific capacity of the membrane $\cong 1\ \mu F\ cm^{-2}$, ϱ_i and ϱ_e are the internal and the external specific resistances equal to 300 and 30 Ω/cm, respectively [10].

For a cardiac cell shaped as an ellipsoid of revolution with the major axis running parallel to the field intensity vector $N = 0.2$. In a general case, N depends on the position of the major axis relative to field applied. However, if the ratio a/c is within 0.3 to 3, this dependence is weak. In the case under examination, if the myocyte is normal to the field intensity vector, then N is equal to 0.6 and variation of φ_e is less than 3%. Thus, the potential evoked at the cell membrane is essentially independent of the site of electrode placement on the surface of an intact heart, which has been observed in clinical practice and experimental tests.

The process of polarization of the membrane of a resting cardiac cell exposed to a bipolar impulse is shown in Fig. 2. Figure 2A presents the values of evoked potential φ_e, resting potential φ_r and transmembrane difference of the potentials $\Delta\varphi_m$ at the cell at the moment when the positive half-wave has reached a maximum. Figure 2B shows these values at the moment when the negative half-wave has reached a maximum. Figure 2C illustrates the shape of a bipolar impulse. When the heart is under the action of a positive half-wave (Fig. 2A), the left side of the cell becomes hyperpolarized (AL) and the right side, depolarized (AR). Under the influence of a negative half wave (Fig. 2B) reverse polarization occurs, i.e. the left side becomes depolarized (BL) and the right side, hyperpolarized (BR). In this situation the peak of the transmembrane potential difference $\Delta\varphi_m$ for a resting myocyte can be described by the equation:

$$\Delta\varphi_m = \varphi_r - \varphi_e. \tag{3}$$

Since one side of the cell is always depolarized, this voltage will act upon the membrane only when fast Na channels are opened, i.e. within the time period when the front t_f of the action potential of a myocyte increases, amounting to $0.1 - 0.5$ ms. Then for the values indicated $\omega\tau \cong 0.6$ and at $E_0 = 80$ V/cm, as follows from Eqn. 1 $\varphi_e = 210$ mV and $\varphi_e^+ = 140$ and $\varphi_e^- = 70$ if the half-wave ratio is taken into account. Thus, if φ_r is assumed to be -90 mV, the left side is at first hyperpolarized to -230 mV (Fig. 2 AL) and then depolarized to -20 mV (Fig. 2 BL) whereas the right side is at first depolarized to $+50$ mV (Fig. 2 AR)
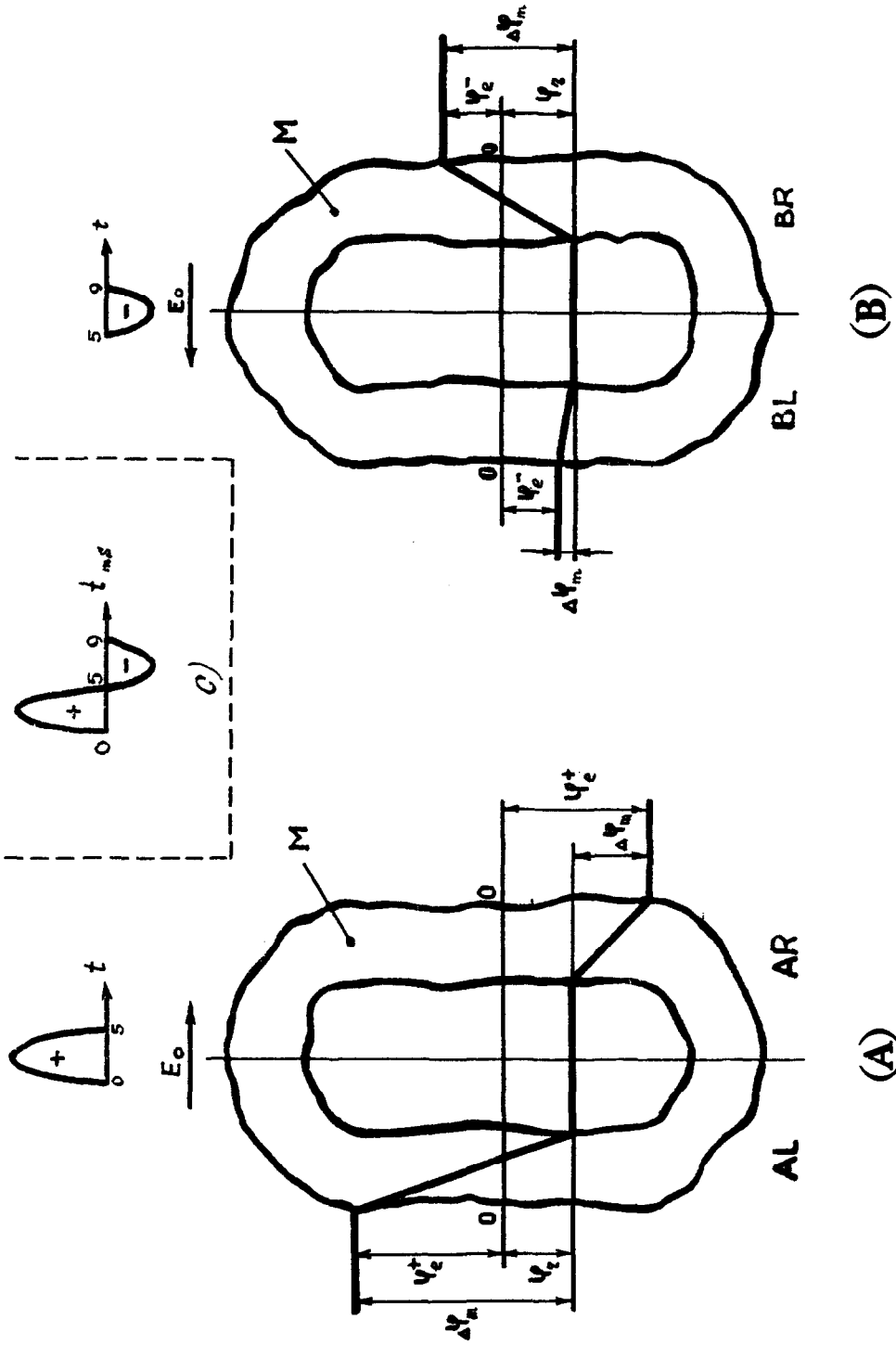
Fig. 2. Polarization of the membrane of a myocyte at rest during exposure of the heart to a bipolar impulse. (A) upon the action of a positive half-wave, (B) upon the action of a negative half-wave, (C) shape of the bipolar impulse of the defibrillator. M, myocyte membrane; AL and AR, left and right sides of the myocyte upon the action of a positive half-wave, respectively; BL and BR, left and right sides of the myocyte upon the action of a negative half-wave, respectively. E_0 is indicated by an arrow. φ_r, resting potential; $\Delta\varphi_m$, transmembrane potential, φ_e^+ and φ_e^-, evoked voltage at the membrane upon the action of the positive and the negative half-wave, respectively; t, time.

and then hyperpolarized to -160 mV (Fig. 2 BR). The quantities φ_e and $\Delta\varphi_m$ have been calculated for the amplitude value of the external field. However, the positive half-wave E_0 reaches its maximum within 2.5 ms and during $t_f \cong 0.5$ ms E_0 increases to no more than 0.3 of its peak value. According to Eqn. 3, by this moment $\Delta\varphi_m$ on the left side will be only -130 mV and the right side will be depolarized to -50 mV. This voltage is already sufficient to excite a cardiac cell but too low to break down the left hyperpolarized side.

It is known that the strength of contraction of the myocardium is a function of the Ca^{2+} concentration in the sarcoplasm and is determined by the potential-dependent transport of Ca ions through the cell membranes [11,12]. It implies that the lack of a complete mechanical response to a defibrillator impulse may be associated either with the dysfunction of internal contractile systems of myocytes or with the damage of the structure of the lipid matrix of their membranes.

At least two mechanisms of these lesions seem plausible: (1) electrical breakdown of the membranes and (2) depolarization of the membrane of the cardiac cell and action of the electrical field directly upon its inner structures. In our case only reversible breakdown can be considered due to two factors: first, during electrical defibrillation by moderate voltage no serious lesions of the myocardial ultrastructure, necrotic foci, irreversible asystole or other changes typical of impulses that are several times higher than the defibrillation threshold develop; second, irreversible breakdown of a large number of myocytes would have completely arrested their contractility and no defibrillation would have been achieved.

In the event of a breakdown the Ca^{2+} concentration in the cell increases by 3 -4 orders of magnitude (the concentration is 10^{-7} M in the cell and 3×10^{-3} M in the extracellular fluid). As a result, at first the cell contracts only in part and then loses its ability to contract and remains in the state of mechanical relaxation until the recovery of the transport function of the membrane. This process was recorded by Jones et al. [13] and in our experiments is was observed at $E_0 > 200$ V/cm in the form of a delay of the first contraction by 300 -500 ms after the application of a defibrillator impulse. Within this time period all cardiac cells had time to reach the state of mechanical rest and the first impulse of the pacemaker restored the coordinated contraction of the heart. According to Jones et al. [9], defibrillation can be regarded as a result of acute depolarization occurring due to electric breakdown upon exposure to an electric field of 200 V/cm. In this situation depolarization developed in response to an external field E_0 applied at first to the one half (Fig. 2A) and then to the other half (Fig. 2B) of the cardiac cell and therefore its emergence was not necessarily associated with a breakdown. The most important consequence of a possible breakdown is termination of the contractile function of the myocardial for a time period which is longer than the action potential; this allows all the cells to reach a resting state and generate a coordinated contractile response of the myocardium to the first pacemaker impulse. Thus, the phenomenon of a direct reversible electric breakdown may cause cardiac arrest after shock and also heart defibrillation.

However, in our experiments the highest transmembrane voltage originating during hyperpolarization in response to a positive half-wave (Fig. 2A) was -230 mV and during time t_f it was only -130 mV. This voltage may prove insufficient to break down the membrane because the breakdown voltage is equal to 1000 mV for an impulse of 5 ms [10,14]. The voltage can be evoked on the membrane only when the amplitude of the defibrillator impulse increases more than 2-fold as compared to the threshold voltage, i.e. at external fields over 200 V/cm.

Moreover, as has been shown above, one of the sides of the myocyte exposed to an external electric field is always depolarized. In this event, the conductivity of the depolarized part of the membrane increases several orders of magnitude within 0.5 ms. As a consequence, φ_e on the membrane of the order side of the cell decreases by more than three orders of magnitude because the quantity a in Eqn. 1 is determined by the membrane thickness rather than by the cell size and amount only to 25−50 nm. This makes impossible electric breakdown of the membrane after depolarization of one of the sides of the cell. In other words, if electric breakdown of the membrane is possible, it would be realized within the time period shorter than the depolarization time; therefore the threshold voltage of the breakdown grows to 1.2−1.5 V.

It should also be taken into consideration that during electric breakdown of the membrane there is a correlation between the time of exposure and the voltage of breakdown: an increase in the transmembrane voltage by 100 mV leads to a 10-fold decrease of the life-time of the membrane [14]. In the course of defibrillation such kind of correlation may be absent: an increase in the impulse time from 5 to 30 ms does not reduce the defibrillation threshold and its further increase over 30 ms induces refibrillation [15,16]; the correlation may be reverse: an increase in the impulse time lowers its efficacy [17].

In the experiments illustrated in Fig. 1 the contractile response to electric impulse is lacking; there is only a short peak whose amplitude makes 10−20% of the normal contraction which coincides in time with the moment of impulse application. This could be induced by the displacement of inner Ca^{2+} ions in response to the fast component of the action potential [18] during impulse application. Since it has been previously demonstrated [19] that microscopically cardiac lesions are characterized by Ca^{2+} penetration into the myocytes and by myofibrillar contraction, then the absence of such contraction at the moment of impulse application in our experiments may also indicate that a moderate suprathreshold impulse did not elicit membrane breakdown.

It is not easy to attribute the effect of summation of subthreshold impulses during defibrillation to the mechanism of electric breakdown [20,21]. This requires that two 10-ms impulses, each of which cannot produce a breakdown when applied separately, break the membrane down when applied at an interval of 100−300 ms. This appears possible on the assumption that the first impulse transforms the membrane into an unsteady stressed state [14]. However, this probability is very low because the stressed state of the membrane occurs within a narrow range of voltages and the effect of summation of subthreshold impulses during defibrillation is stable.

It has also been demonstrated that breakdown of the myocyte membrane is followed by discontinuation of contractions for 30 s to several min [9]; however, in our studies contractions were arrested for no longer than 0.6 s.

The above findings suggest that when the membrane is exposed to external fields of 70−100 V/cm, its direct electrical breakdown may not yet be realized and the effects of these fields may be different. They are determined by complex processes that occur on the membrane in response to defibrillator impulses. First, this is a consecutive hyperpolarization of one side (Fig. 2A) and then of the other side (Fig. 2B) of the membrane. Second, this is a simultaneous opposite polarization on the two different sides of the cell (Fig. 2A, B): hyperpolarization of one side and depolarization on the other. In this situation a very distinct topographical and potential (Fig. 2) non-homogeneity of the distribution of the transmembrane potential develops on the surface of the cell membrane. The external electric field, depolarizing the membrane on one side of the myocyte, acts directly upon internal cell structures, sarcoplasmic reticulum and myofibers, and disturbs their contractility. It was experimentally shown [9] that, when an electric field of 120 V/cm was applied to the cell culture, the membrane became depolarized at the moment of impulse application but the single mechanical response was incomplete, which later led to electromechanical uncoupling and termination of myocyte contractions. The ineffectiveness of mechanical contractions of the ventricles and their increased refractoriness after electric shock were also reported by Müller [22] and Prystowsky et al. [23]. This result is in agreement with our data (Fig. 1). In order to estimate the action of an external electric field on myocardial contractility, let us introduce a critical potential, φ_{cr}, which is the smallest value of the hyperpolarizing transmembrane potential the emergence of which results in the loss of cardiac contractility. Obviously, φ_{cr} per se cannot terminate cardiac contractions but its value is a convenient quantitative parameter since it is independent of cell excitation and the intensity of an external electric field E_0. The zone that lies below φ_{cr} will be henceforth termed the zone of silence. By definition, there is no contractile response of the myocardium to the pacemaker in this zone. The time within which $\Delta\varphi_m$ remains in the zone of silence is determined by the period of recovery (T_r) of myocardial contractility. It was measured as a delay of the first coordinated contraction of the heart after the defibrillator impulse. The duration of T_r in different experiments was proportional to E_0 and varied from 300 to 600 ms. φ_{cr} calculated from Eqns. 1 and 2 for the defibrillation threshold $(E_0 = 70 \text{ V/cm})$ was $\cong 200$ mV.

Taking into consideration the above findings, the mechanism of electrical defibrillation can be viewed as follows (Fig. 3). In VF myocardial cells are either in the refractory (absolute or relative) state or in the resting state. The defibrillating impulse shifts $\Delta\varphi_m$ of the contractile myocardial cells to the zone of silence by $T_r \cong 300−500$ ms, as shown in Fig. 3a (curve 1). Within this time period the cells that were in the state of excitation have enough time to reach the resting state and those that were in the resting state remain such. After leaving the zone of silence all the cells find themselves in the resting state in time T_r. The first pacemaker impulse causes a coordinated contraction of the
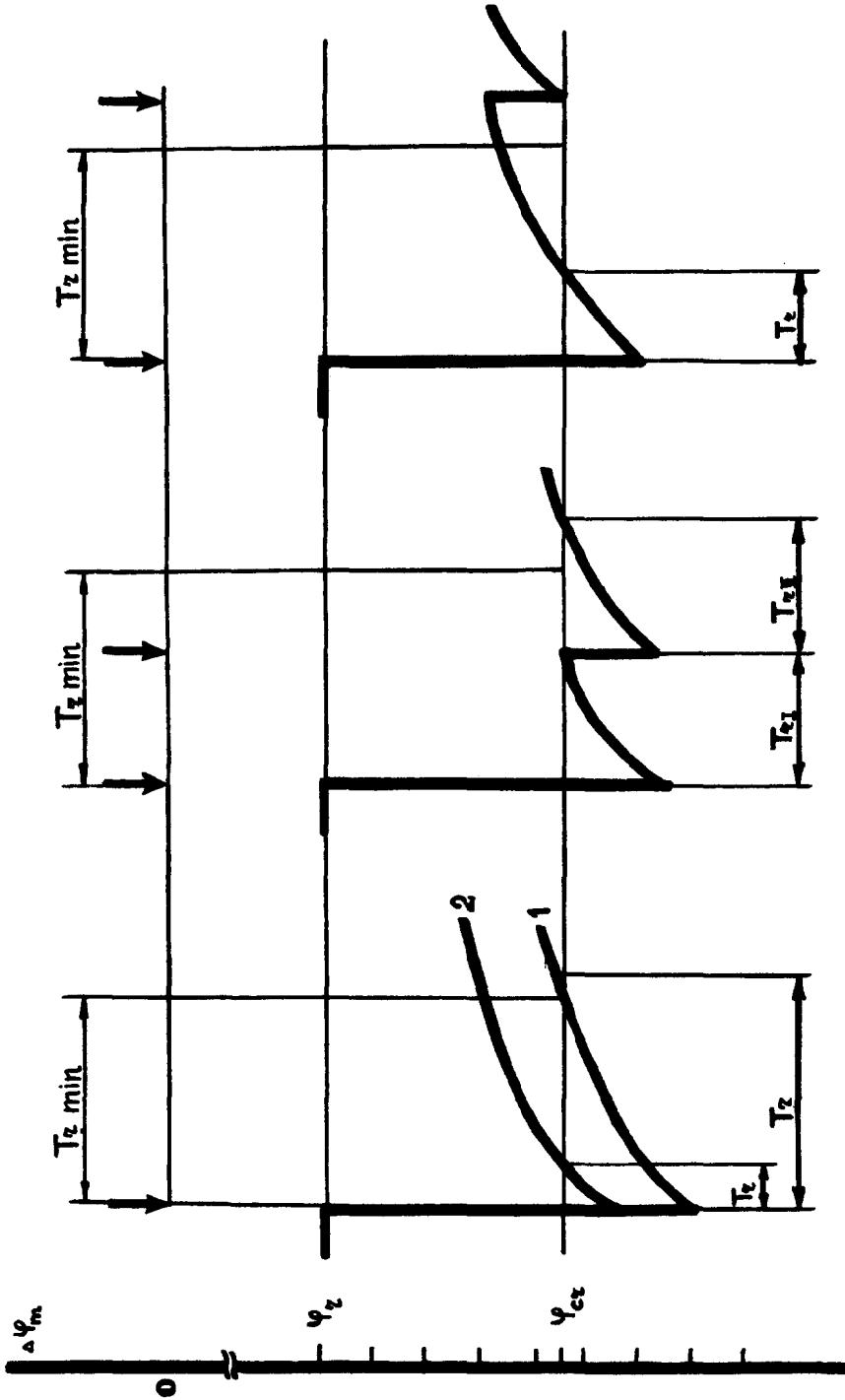
Fig. 3. Variation of the transmembrane potential $\Delta\varphi_m$ upon heart defibrillation. (a) upon the action of suprathreshold (curve 1) and subthreshold (curve 2) impulses. (b) upon the action of two subthreshold impulses at an interval of $< T_{r, min}$; (c) upon the action of two subthreshold impulses at an interval of $> T_r$; φ_z critical potential of hyperpolarization; T_r, time of recovery; $T_{r, min}$, minimal time of recovery. Arrows indicate the time of application of defibrillator impulses.

heart. It is obvious that the shortest time in the zone of silence $T_{r\ min}$ (Fig. 3) should be longer than the duration of the action potential of the defibrillating myocardial cells. This condition at $T_r \geqslant 250$ ms is nearly always met because the duration of the action potential in VF is shorter when compared with the norm and may amount to 100 ms [24]. In this situation the threshold impulse of the defibrillator is the impulse that shifts $\Delta \varphi_m$ to the zone of silence for the time period as long as at least $T_{r\ min}$. If $\Delta \varphi_m$ lies in the zone of silence for less than $T_{r\ min}$, then this impulse is subthreshold. The defibrillation threshold is determined by the upper limit of the potential of the zone of silence calculated as φ_{cr} (Fig. 3). The lower limit of this zone depends on the breakdown voltage of the membrane for impulses of 0.1 ms in duration. Then the depth of the zone of silence varies from 200 mV to 1.5 V.

The subthreshold impulse of the defibrillator may cause either a negligible or no shift of $\Delta \varphi_m$ to the zone of silence (Fig. 3, curve 2); due to this the shift leaves the zone of silence rapidly, the condition $T_{rII} < T_{r\ min}$ being satisfied. In this case the myocardial region that has left the zone of silence may be excited again by the adjacent region which was unable within time T_{rII} to transform into the resting state and therefore VF continues.

The concept of the zone of silence may explain the effect of summation of subthreshold impulses. This effect is impossible if the impulses are applied at an interval no more than $T_{r\ min}$ (Fig. 3b). Then the shift potentials are summed up $T_{rI} + T_{rII} \geqslant T_{r\ min}$ and $\Delta \varphi_m$ becomes lower than φ_{cr}, which causes the effect of defibrillation. The value of the membrane potential in this case will depend on the interval between two impulses. If this interval exceeds $T_{r\ min}$ (Fig. 3b), then the effect of summation is impossible, which has been demonstrated in experiment [21].

Thus, in the course of electric defibrillation of the heart the following processes occur. At the first stage, within the time interval less than 0.1 ms after the shock, the external electric field is applied to the membrane of the myocyte hyperpolarizing it on the side of $+E_0$ and depolarizing it on the side $-E_0$. In this situation defibrillation of the electric breakdown type is possible. Since the time during which the electric field acts upon the cell is short, the breakdown voltage should be sufficiently high (not less than 1 V). Voltages of this level are evoked on the membrane when impulses $3-4$ times greater than the defibrillation threshold are applied. At the second stage, i.e. after depolarization, the external electric field is applied to internal cell structures disturbing their contractility. The time of recovery of the mechanical response to an electric stimulus is proportional to the external field intensity. If it exceeds the time required by the myocardial cells to reach the state of adequate homogeneous repolarization, then after a $300-500$-ms delay the heart resumes its normal function, i.e., the effect of defibrillation takes place.

The mechanisms described are consistent with the general theory of defibrillation advanced by Gurvich [17]. The probability of a specific mechanism of defibrillation to occur is determined by the value of the impulse applied.

It has been shown that strong impulses ($E_s > 200$ V/cm) destroy the myocardial ultrastructure and their action is in all likelihood associated with

the direct electric breakdown of membranes [13]. A moderate impulse is also effective but causes no important injuries in the myocardium [2]. It is probable that in this case the mechanism of depolarization of the myocyte membrane and the shift of the transmembrane potential to the zone of silence works, this type of defibrillation being optimal.

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