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PREDICTION OF THE VULNERABILITY OF THE VENTRICLE TO ARRHYTHMIA WITH LATENCY AND THE DURATION OF THE EXTRASYSTOLIC RESPONSE*

N. I. KUKUSHKIN and M. YE. SAKSON

Institute of Biological Physics, U.S.S.R. Academy of Sciences, Pushchino (Moscow Region)

(*Received* 20 *July* 1970)

For the prophylaxis of fibrillation in acute myocardial infarction a reliable method of predicting it is necessary. The most probable mechanism of fibrillation is thought to be multiple re-entry. In this work we: a) consider the functional model of the myocardium with a two-system conduction of excitation; b) on the basis of it we derive the condition of micro re-entry (the factor of vulnerability VF is determined); c) check in the experiments the validity of predicting the sequelae of extrasystolic stimulation by means of VF. In a strip of the frog myocardium we measure the latent periods (Θ) of extrasystolic response, determine the slope of the function $\Theta(T)$ and the reactivity of the myocardium—the ratio of the duration of the conditioning and extrasystolic responses. Where the test shock elicits extrasystole we recorded the large latencies and high reactivity of the myocardium. Anti-arrhythmics (Inderal, Ethmosin) substantially reduce the latency and the reactivity and thereby eliminate the possibility of extrasystole of the re-entry type. In 88 per cent of the cases the actual reaction of the tissue to the extrasystolic shock coincided with the behaviour predicted by the "vulnerability factor".

SUDDEN death in acute myocardial infarction, the proportion of which is quite high [1] is often not correlated with the severity of the morphological disturbances and is the consequence of fibrillation [2, 3]. In the successful treatment of dangerous arrhythmias particularly topical is their rapid prediction allowing one to make preventive treatment selective and effective. The automatic prognosis of fibrillation of the ventricles [4] is an important trend but is still unacceptable in clinical practice. Little success has attended attempts to correlate the outcome of the acute stage of infarction with the electrolytic imbalance of the blood [5]. Recently, calculations have been made of vulnerability from the character of the first extrasystole. An observation of basic importance was made by Smirk on the connexion between the form of the first extrasystole disrupting

* Biofizika **16**: No. 5, 904–909, 1971.

the T wave and sudden death during infraction [6]. Attempts at prediction have also been made from the latent period of the extrasystolic response [7] although experimental evidence of the importance of this relationship is absent. At the same time, according to investigations of excitable media, the latency (Θ) is an important factor in the genesis of the closed pathways of conduction [8, 9] the multiple character of which is considered by many investigators as the most probable mechanism of fibrillation [10, 11].

In this work, using the concepts of two paths of conduction of excitation [12] the conditions of onset of re-entry in the myocardium of the frog ventricle are derived and checked.

METHODS

In a strip of the frog ventricle we investigated the following characteristics of the myocardium: dependence of the latent period (Θ) of the extrasystolic response on the interval of testing $\Theta(T)$, the reactivity of the myocardium (R) by which is meant the ratio of the durations (D) of the conditioning and extrasystolic responses $D_C/D_E = R$. Cathodic five-threshold stimuli with a duration of 10 msec were applied, the reaction to them was similar to the responses to the spreading pulse [13]. The conditioning shocks followed with a period of 12·5 sec and the test (extrasystolic) stimulation was applied after each ninth conditioning stimulus. The measurements were made in the control (perfusion of the preparation with Ringer) and in conditions of exposure of the myocardium to a definite dose of the anti-arrhythmic agent (Inderal, Ethmosin). The technical details were given in [12].

Condition of micro re-entry. We shall consider a functional model presupposing the existence of two paths of conduction of impulses one of which (P, Fig. 1*a*) is distinguished by a fast speed and refractoriness (analogue of peripheral terminals of the specialized tissue). The protoplasmic link ensures the unimpeded bilateral transition of excitation (from M to P) and back and the spread of the wave with the collective speed. As a result o the asynchronous restoration of the adjacent elements extrasystolic excitation finfds them in different phases of excitability: the system M is repolarized and ready to conduct the next impulse whereas P is still refractory and it is not possible to evoke a spreading response in it. Therefore, in the region AB the wave II runs only along the system M (Fig. 1*b*) and the speed of spread may be considerably less than v_M because of shunting of part of the current by the adjacent refractory region. On emergence from refractoriness the system P is excited (Fig. 1*c*) and here the wave II may move not only in orthograde but also retrograde fashion and given a certain condition, circulation of the pulse appears. Closed conduction appears when the refractoriness at the point A is shorter than the time of conduction in the contour $ABCD$ (Fig. 1*d*). As shown in [12] the time of conduction along the path AB corresponds to the latent period of the spreading response (Θ). The time in the segment $BCDA$ which is made up of the latency in the homogeneous systems P and M and the time of passage of the impulse in the segment CD is approximately 100 msec. With this calculation we started from the following data: the latency in the homogeneous zones of the myocar-

dium does not exceed 40 msec [13], the speed in the frog ventricle at 18°C is 10 cm/sec, the jump of excitation from M to P occurs over a distance of 1–3 mm from the stimulating electrode [12]. Then the condition of micro re-entry may be formulated by the inequality:

$$\Theta_{\max} + 100 \text{ msec} > R_{0\,\min} \tag{1}$$

where $\Theta_{\max}$ and $R_{0\min}$, latency and refractoriness of the extrasystolic response respectively and may be measured in the experiment. The expression $\Theta_{\max} + 100$ msec $- R_{0\min}$ is

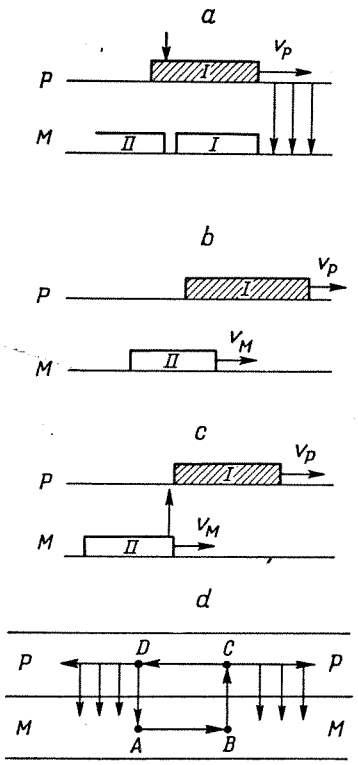

FIG. 1. Diagrammatic representation of two-system spread of excitation in myocardium and micro re-entry on their basis; *a*: P—rapidly conducting fibre (analogue of Purkinje fibre); v_P—speed of conduction of pulse in it; M—slowly conducting fibre; v_M—speed of spread in it; $v_P > v_M$. Arrow shows arrival of extrasystolic excitation; *b*: only system M responds to extrasystolic excitation (wave *II*); P is refractory; *c*—emergency of P from refractoriness and "jump" of wave *II* to P; *d*: appearance of closed conduction.

called the vulnerability factor (VF) and characterizes the degree of predisposition of the myocardium to a disordered reaction to an extrasystolic shock. A similar analytical model of the excitable medium was independently considered and the possibility of the appearance in it of reverberators was demonstrated [14].

RESULTS

In subsequent experiments we analysed the after-action of the test (extrasystolic) stimulation in the myocardium of the frog ventricle.

Of 49 control experiments in 18 per cent of the cases in response to the test shock extrasystoles appeared both multiple (4 cases) and single (5 cases). Analysis of the

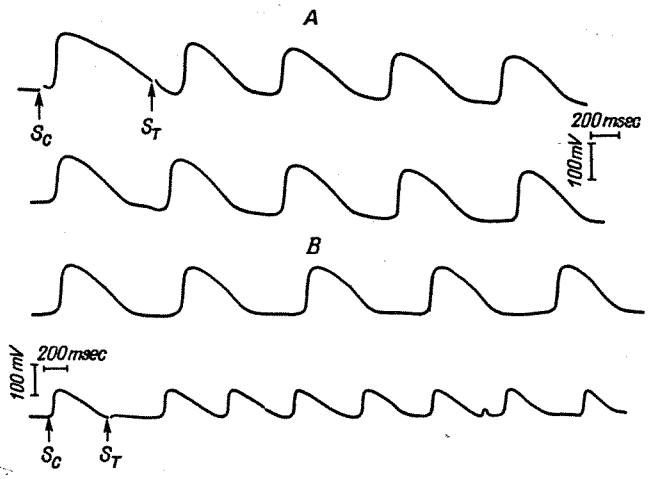

FIG. 2. Multiple extrasystole after action of cathodic test stimulus: *A*—shows long latent delay of first extrasystolic response; *B*—high reactivity (shortening of duration of first extrasystolic response). Conditioning stimulus—S_C, test stimulus—S_T.

single extrasystoles shows that they appear in the presence of a long latent delay ($\bar{\theta}_{max}$ =271 msec), considerable slope ($\bar{K}$=11·6) of the function $\Theta(T)$ and considerable reactivity of the myocardium ($\bar{R}$=1·53). The main prognostic indicator—the vulnerability factor was positive ($\overline{VF}$=+32) which indicates the possibility of the appearance of arrhythmia. The main difference in multiple extrasystole was the smoother slope ($\bar{K}$=4·09) of the graph $\Theta(T)$. The values of latency ($\bar{\theta}_{max}$=205 msec) and reactivity ($\bar{R}$=1·45) remain just as considerable as in the cases of single extrasystole. Figure 2 presents two examples of multiple discharges and *A* demonstrates the long latent delay of the extrasystolic response and *B* the substantial reduction in duration. In the other 40 control experiments no extrasystoles were recorded. In these preparations we noted somewhat greater refractoriness, weaker reactivity $\bar{R}$=1·29 chiefly through the inconsiderable shortening of the duration of the extrasystolic response. All this ensured a negative vulnerability factor ($\overline{VF}$=−219).

Action of anti-arrhythmics. Inderal. At low concentrations (9 experiments: 0·25–0·75 mg/l.) Inderal changed only one characteristic—raised the slope of the graph $\Theta(T)$: $\bar{K}$ =15·0 (in the control $\bar{K}$=5·38). In the preparations where with the test shock we were able to induce extrasystoles they were single and the vulnerability factor predicted their appearance ($\overline{VF}$=+20·3). At higher concentrations of the anti-arrhythmic (1–2 mg/l.)

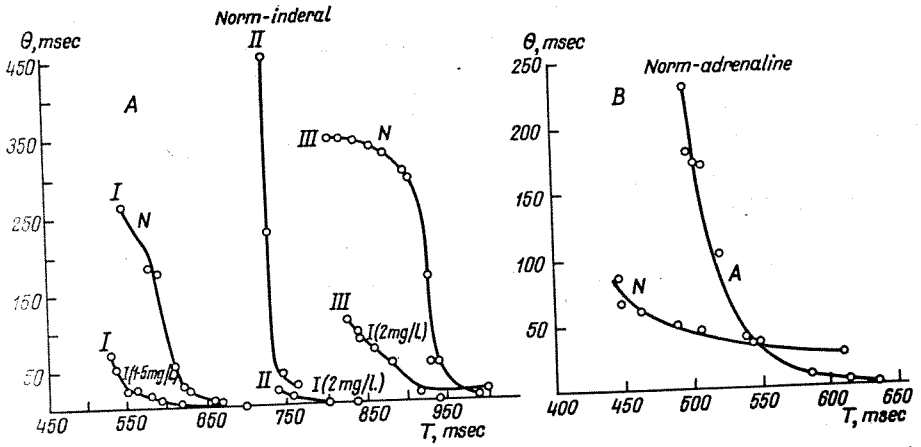

FIG. 3. Graphs of latent period (Θ) as a function of the interval of testing T. A—In normal conditions (N) and on exposure to Inderal (I) (1·5–2 mg/l.). Fall in Θ_{max} is shown. Graphs presented for cells *I*, *II* and *III* with different degrees of refractoriness. B—In normal conditions (N) and on exposure to adrenaline (A) (0·1–0·3 mg/l.). Increase in Θ_{max} and slope of $\Theta(T)$ is shown.

the maximum latency fell (≈3 times, Fig. 3*a*), the reactivity fell, the vulnerability factor become negative ($\overline{VF} = -304$) and extrasystoles to the test stimulus did not appear.

Ethmosin (0·125–0·5 mg/l) (19 experiments) like Inderal reduced the activity of the myocardium and Θ_{max} (≈4 times) which in toto increased the negative vulnerability

Type of experiment	Number of experiments	$\bar{\Theta}_{max}$, msec	Refractoriness, msec	K, slope	Vulnerability factor, msec	Reactivity, R
Control	49	221·0 ± 17·3	650 ± 22·2	−538 ± 0·9	−181 ± 27·7	1·32 ± 0·027
Inderal	9	226 ± 49·7	503 ± 22·4	−15·8 ± 3·76	−44·4 ± 44·7	1·38 ± 0·049
0·25–0·75 mg/l. Inderal	18	83 ± 16·8	589 ± 24	—	−304 ± 28·4	1·28 ± 0·072
1·0–2·0 mg/l. Ethmosin		60 ± 14	704 ± 37	—	−412 ± 31·8	1·15 ± 0·023
0·125–0·5 mg/l.	19	(218 ± 27·5)	(673 ± 36·9)	(−5·75 ± 1·06)	(−206 ± 52·2)	(1·35 ± 0·062)
Adrenaline	8	275 ± 41	637 ± 48	−4·5 ± 2·25	−76 ± 52	1·54 ± 0·051
0·1 0–0·3 mg/l.		(171 ± 41·4)	(593 ± 52·3)	(−2 ± 0·36)	(−224 ± 63)	(1·23 ± 0·06)

factor ($\overline{VF} = -412$) i.e. this forecasted the impossibility of obtaining extrasystoles. In fact, the extrasystoles on perfusion with Ethmosin in the test did not appear whereas in the corresponding controls in some cases they were possible and the VF was less ($\overline{VF} = -56$).

Action of adrenaline. Administration of a fibrillating agent, adrenaline, is accompanied by rise in the maximum latency and reactivity which promoted the onset of extrasystoles to the test stimulus which appeared in 5 of 8 experiments. An unexpected observation was the rise in the slope of the graph $\Theta(T)$ (Fig. 3*b*). Probably therefore adrenaline with the test shock in the main elicited single extrasystoles absent in the controls.

The Table presents the values of the test parameters in the controls and their change with use of anti-arrhythmics (Inderal, Ethmosin) and a fibrillator (adrenaline). The parentheses show the preceding control measurements.

DISCUSSION

Thus, in only 18 per cent of the cases did repeat responses to cathodic five-threshold stimulus appear. From the work of Brooks on the vulnerability we know not only of the considerable variability of the width of the vulnerable zone and the threshold of fibrillation but also the impossibility of eliciting extrasystoles and fibrillation even to a supra-threshold stimulus [15]. Our experiments allow us to relate vulnerability directly to the length of latency and the reactivity of the myocardium: extrasystoles appeared in the preparations where a long latency and high reactivity were noted. The significance of this relation can be traced in pathology. Thus, in a focus of experimental ischaemia the development of extrasystoles and fibrillation correspond to lengthening ($\approx$2·5 times) of the latent delays, shortening of the refractoriness [16] and fall in the threshold to fibrillation [17]. In our experiments we noted rise in vulnerability, the maximum latency and reactivity with use of adrenaline. As is known sympathetic stimulation increases the asynchrony of restoration of the elements of the myocardium and the probability of multiple responses [18]. From this angle vulnerability may be defined as a state of maximum inhomogeneity of the ventricle. The action of anti-arrhythmic agents (Inderal, Ethmosin) probably makes the myocardium more homogeneous with a resulting fall in latency (3–4 times) and reactivity and also in vulnerability to the test shock. In this connexion it is understandable why fibrillation cannot be elicited in homogeneous sections of the heart, for example, in the papillary muscles not containing specialized tissue [3].

The vulnerability of the myocardium is expressed in the form of multiple responses as a result of the extrasystolic shock. The most probable mechanism of disorganization of the activity is multiple re-entry. A significant role in their genesis is assigned to local blocks and the retarded conduction of ecxitation in individual zones of the myocardium [19–22]. A further possibility of closed conduction may be ensured by the electrophysiological inhomogeneity of the adjacent fibres. A particular variant of inhomogeneity may be the differences in refractoriness and speed of conduction in the adjacent usual and specialized fibres so that circulation of an impulse is possible. In terms of the spread of excitation in two systems [12] the conditions of micro re-entry are facilitated by factors deepening the temporal dispersion of the processes in the muscular and specialized branches (K^+ in low concentrations [23], adrenaline). At the same time their different sensitivity to pharmacological treatments makes possible

pharmacological regulation of the return extrasystole. Anti-arrhythmics (Inderal) selectively accelerate repolarization in Purkinje fibres [24] which makes possible the simultaneous repolarization of different types of fibres and eliminates the conditions for the formation of micro re-entry.

Such a condition (vulnerability factor) in simplified form is the difference between the maximum latency and refractoriness of the extrasystolic response. A check in the experiment on condition (1) showed the legitimacy of using the vulnerability factor as a prognostic index of arrhythmia. In 88 per cent of the cases the actual reaction of the tissue to the extrasystolic shock coincided with that predicted. For a positive factor (i.e. the tissue is vulnerable) we recorded extrasystoles; when it was negative (in 87 per cent of the cases out of 95) extrasystoles did not appear.

If the corresponding indicators are found in the electrocardiogram the vulnerability factor may prove to be an effective agent in predicting dangerous arrhythmias.

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