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BIOPHYSICS OF COMPLEX SYSTEMS. MATHEMATICAL MODELS

RETROGRADE EXCITATION IN THE MYOCARDIUM AND ITS ROLE IN THE GENESIS OF ARRHYTHMIAS OF THE VULNERABLE PERIOD*

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A spatial analysis of extrasystolic excitation in the myocardium of the cat is made. The reverse waves have been recorded and their properties investigated. The conditions of formation of a reverberator (micro reentry) have been demonstrated. The findings point to a link between the repeat responses in the vulnerable period and circulation of excitation.

THE existence of a vulnerable phase in the cardiac cycle is well known. Dangerous arrhythmias appearing in this period are directly related to a fatal outcome in a number of cardiac pathologies [1, 2]. However, the ability of the tissue to generate multiple discharges in response to early extrasystolic excitation has still not received a satis-

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factory explanation. It is known that vulnerability is sharpened by all factors promoting the temporary dispersion of excitability in the myocardium [3, 4]. This circumstance is considered by many authors to favour the hypothesis of the origin of closed pathways of conduction in the presence of vulnerability.

Earlier we demonstrated the role of the parameters of latency, refractoriness and reactivity in the genesis of vulnerability [5]. The present paper presents a spatial analysis of early extrasystolic excitation. The findings on a link between the repeat responses in the presence of vulnerability and circulation of excitation have been obtained.

METHODS

The experiments were carried out on strips of the right ventricle of the cat. The preparation was perfused with oxygenated Ringer at $t=37\pm0{\cdot}5°C$.

To the strip were applied conditioning (leading) and test stimuli (each test after ten conditioning stimuli). The time interval T between the stimuli was gradually reduced.

Analysis of the spread of the test wave of excitation was made by means of two-channel microelectrode recording. The membrane potentials and the latent delay (θ) were studied as a function of T. The latent delay was defined as the difference in in the times of conduction of the test and conditioning pulses. The measurements were made in controls and after pharmacological treatment of the myocardium.

RESULTS

In more than half the preparations investigated the maximum latent delay θ_{max} of the test wave exceeded 30 msec. In all the preparations of this group it was possible to record a reverse wave of excitation. The conclusion that a reverse wave forms was drawn from recording after the test stimulation of two responses at the near electrode and one at the far one (Fig. 1*I*, *A*). The responses appeared in the following order: first response at the near electrode ($\theta_{max}\approx10$ msec), then a single response at the far electrode ($\theta_{max}\approx40$ msec) and the last to appear was the second response at the near electrode ($\theta_{max}\approx80$ msec). The second response appearing at the near electrode with a considerable delay was interpreted by us as a reverse wave. The first response in the near electrode and the single response in the far electrode will be called the forward wave.

I. Propagation of reverse wave. The reverse wave (noted by the numeral *2*) is characterized by a number of features which are demonstrated in Fig. 1.

A. The reverse wave may be recorded only in the direct proximity of the site of stimulation not more than 1–2 mm from it (all the upper records in Fig. 1*I*, *A*).

B. The reverse excitation wave appeared with considerable delay after the test pulse. Figure 1*I*, *B* presents the case in which the maximum delay of the back wave $\theta_{max}\approx70$ msec (crosses in the graph $\theta(T)$) whereas the forward wave recorded 10 mm away was delayed by only 40 msec (points in the graph $\theta(T)$). However, in a number of cases the values of the delays of the forward and reverse waves were similar.

C. The amplitude and delay of the reverse wave depend on the time interval T. With reduction in T both parameters increase so that for small T the back wave con-

stitutes a pulse normal in amplitude and duration (Fig. 1*I*, *A*). The forward wave (close to the site of stimulation) in these conditions, on the other hand, falls in amplitude and duration (Fig. 1*I*, *A*; noted by the numeral *1*). For certain T both reverse and forward waves of excitation are fused ($T=170$ msec, Fig. 1*I*, *A*; $T=190$–210 msec, Fig. 2*II*, *B*). The duration of such a fused response often exceeded the duration of the pulse at the leading frequency. The associated increase in refractoriness R may be the cause of transformation in the zone of the extrasystolic focus.

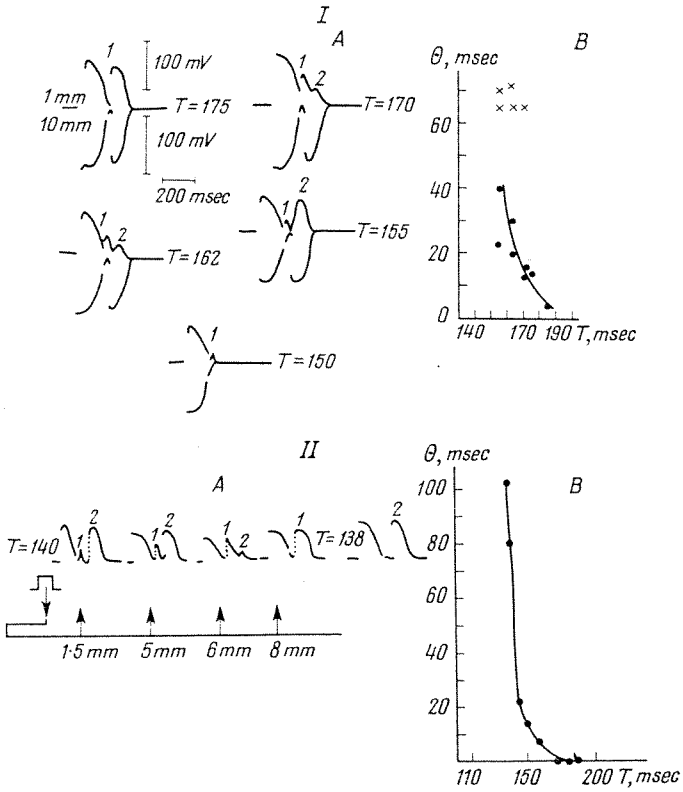

FIG. 1. Reverse waves in the cat myocardium. *I*: *A*—Curves of membrane potentials at different distances from site of stimulation; upper curves close (1 mm); lower curves at a distance of 10 mm; the numeral *2* denotes the back wave; dynamics of its amplitude and duration is shown as a function of time interval T; *B*—graph of latent delay of forward (points) and reverse (crosses) waves as a function of T. *II*: *A*—Spatial analysis of extrasystolic excitation: membrane potentials recorded at four points from site of stimulation at a distance of 1·5 to 8 mm; *B*—broken form of graph $\theta(T)$ recorded at a distance of more than 8 mm from site of stimulation; upper points of graph ($\theta \geqslant 80$ msce) reflect delay of reverse wave.

D. Well marked reverse waves were recorded only in those preparations where θ_{max} of the forward wave was high (θ_{max} 40–50 msec). The reverse waves were weakly marked or not recorded at all if $\theta_{max} \leqslant 30$ msec. These facts suggest the common nature of the genesis of the reverse wave and the long delays of excitation in the myocardium.

II. Propagation of forward wave. We investigated the spatial organization of the latent delay in the myocardium. For this purpose the delay of the forward wave was determined at different distances X from the site of stimulation. It is shown that with fixed X the value θ increases as T falls. The maximum delay θ_{max} T depended on the distance as follws. For most of the preparations at small distances ($X<1$ mm)

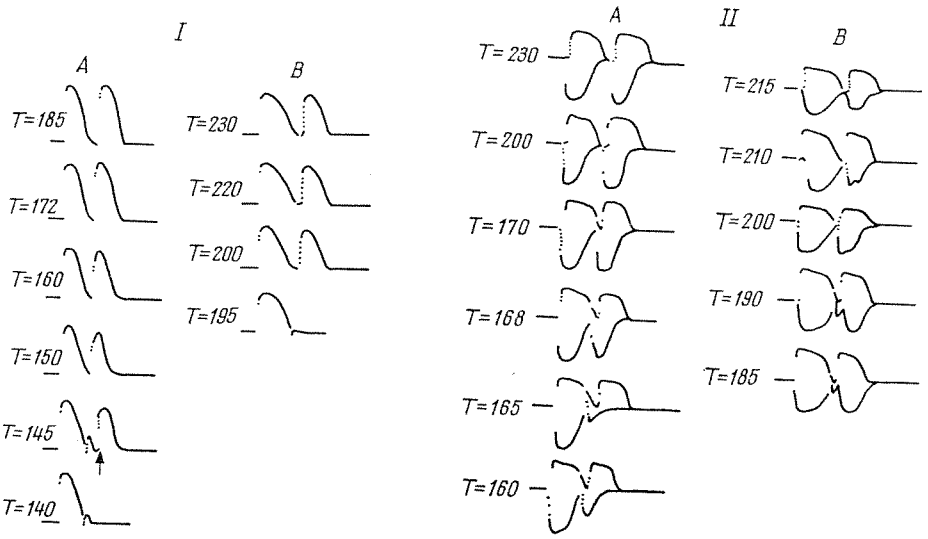

FIG. 2. Reverse waves on pharmacological treatment. *I*—Reverse waves (denoted by arrow) are recorded in control (*A*) and disappear (*B*) after anti-arrhythmic action of the preparation RS-118, 1 mg/l. *II*—Reverse waves absent in control (*A*) and appear (*B*) after action of adrenaline, 0·1 mg/l.

the delay was small ($\theta(X)\approx\frac{1}{4}\theta_{max}$). At distances of 1–2 mm the delay became equal to θ_{max} and then for all X stayed at this level. Figure 3*I* presents the dimensions of $\theta(X)$ for three preparations. It will be seen that at small distances ($X<1$ mm) the delay was insignificant. Then $\theta(X)$ rapidly rises in a small portion of tissue so that for $X\geqslant 2$ mm the delay is equal to θ_{max}.

III. Reverse waves and the form of the function $\theta(T)$. In a number of experiments in the frog ventricle very steep relations of $\theta(T)$ close to T_{min} were obtained [6]. Such a case for the preparation of the cat ventricle is demonstrated in Fig. 1*II, B*. The graph $\theta(T)$ was recorded at a distance of 8 mm from the site of stimulation. It will be seen that the experimental points are grouped in two portions of the graph: below 30 and above 80 msec. Spatial analysis of the extrasystolic excitation showed that the upper points of the graph (greater than θ) reflect the delay of the reverse wave formed outside the zone of recording and in certain conditions spreading over considerable distances in the direction of recording. Figure 1*II, A* shows the curves of the membrane potentials at four points at distances of 1·5, 5, 6 and 8 mm from the site of stimulation. It will be seen that for $T=140$ msec the reverse wave (it appeared in the zone of recording) dies away and does not spread further than 6 mm. At a distance of 8 mm a response

is recorded with a delay $\theta_{max}=25$ msec. With fall in T to 138 msec the return wave spreads over a distance of more than 8 mm (whereas the forward wave of excitation denoted by the numeral *1* is no longer recorded) and its delay sharply rises to $\theta_{max}\sim 80$ msec.

IV. Reverse waves during pharmacological treatment. Previously it was shown that inderal, ethmosin and RS-118 reduce θ_{max} [7]. It was assumed that these substances may block the formation of the reverse waves. In fact, on perfusion of these preparations

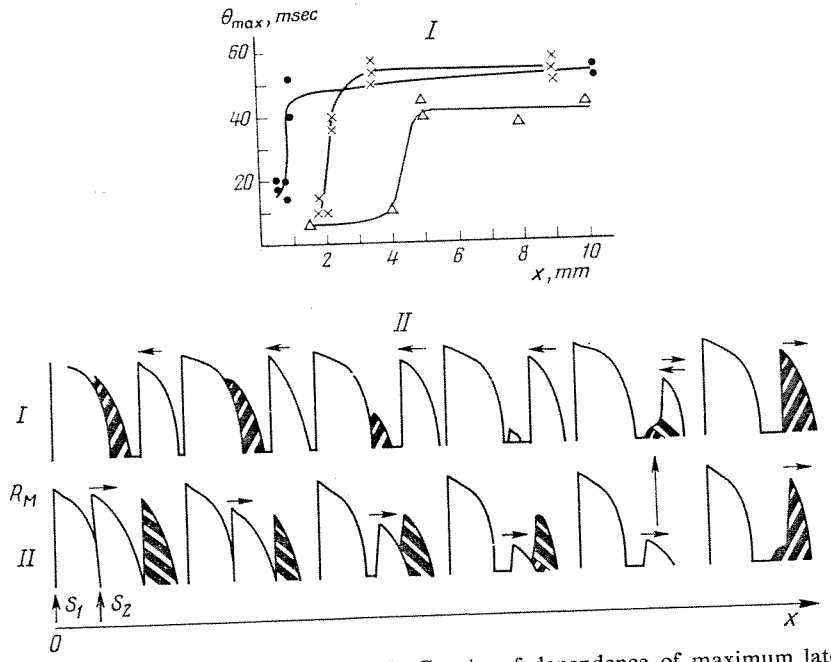

FIG. 3. Spatial organization of latent delay. *I*—Graphs of dependence of maximum latent delay of forward wave on distance to site of stimulation in myocardium of cat for three preparations. *II*—Scheme of formation of reverberator in two fibres with refractoriness $R_B > R_M$: S_1—conditioning, S_2—test pulses; active waves not shaded, electronic shaded; direction of spread of excitation is indicated by horizontal arrows, site of "jump" of excitation by vertical arrow.

the return waves are either not recorded or are weakly marked. Thus, Fig. 2*I*, shows the curves of the membrane potentials at distances of 1 mm from the site of stimulation in the controls and after treatment with RS-118 (1 mg/l.). The reverse waves (denoted by an arrow) are recorded in the control ($T=145$ msec) and disappear after treatment with RS-118.

Quinidine and procainamide (1–2 mg/l.) do not block the reverse waves. Adrenaline promotes appearance (Fig. 2*II*). As shown in [8] these preparations increase θ_{max}. These findings confirm the previously noted pattern of the link between long latent periods and formation of reverse waves in the myocardium.

DISCUSSION

Thus, reverse waves may appear in the myocardium of the ventricle of the cat. The appearance of reverse waves clearly correlates with the latent delay of the forward test wave. Return excitation may be considered to be the initial stage of a reverberator. Earlier [5] we considered the scheme of formation of a reverberator in two fibres differing in refractoriness R and the speeds of conduction V. We shall consider the situation in which the fibres have equal V but different R ($R_B > R_M$). At the moment of delivery of the extrasystolic stimulus $R_M < T < R_B$ only the fibre R_M is excited. The fibre R_B is refractory and shunts part of the current of the active fibre R_M. (The speed of conduction of excitation along the fibre R_M falls to the value KV, where K—mean value of slowing down of extrasystolic wave). This leads to a fall in the safety factor and excitation in R_M is a less effective stimulus of the repolarized portion of the fibre R_B. Therefore, more prolonged action of a current just above threshold is necessary for the transmission of excitation from R_M to R_B ("jump" of excitation from R_M to R_B is shown by the arrow in Fig. 3*II*), i.e. at the point of the jump a situation may occur similar to measurement of the "useful time" on exposure to a threshold strength of current when prolonged exposure is necessary for eliciting excitation. The useful time for the heart muscle may reach hundreds of milliseconds. The latent delay in the path of the wave of excitation may be the consequence both of the retarded spread and to a greater extent the time necessary for transmission of excitation ("arrest" of wave) in the system of asynchronously activated fibres. This concept is in good agreement with the experimental relation $\theta(X)$ where the main part of the delay appears in a small portion of tissue (Fig. 3*I*).

An essential contribution to the value of the delay may also be made by the accommodation properties of the myocardial fibres.

Evaluation of inhomogeneity (ΔR). From schematic analysis it follows that the "jump" of excitation must occur at a certain distance L from the site of extrasystolic excitation. This distance is determined by a number of parameters: the ratio of the speeds in the fibres, the value of the coefficient of slowing down K, time interval T, the difference in refractoriness $\Delta R = R_B - R_M$. If the speeds of conduction along the fibres $V_B = V_M = V$, then the following expression is valid:

$$R_B - T = L/KV - L/V = \alpha L/V,$$

where $\alpha = (1 - K)/K$.

On the assumption that the "jump" of excitation occurs in the portion of sharp rise in the latent delay, L is put at a value of about 1–2 mm. The value of the coefficient of slowing down K of the speed of conduction according to [9, 10] may be of the order 0·3–0·4. Then, for $T = R_M$ and $V \sim 1$ m/sec, we find that $\Delta R \sim 2$–5 msec. ΔR of the order of 10 msec was found for the myocardium of homiothermic animals in a radius of 1–2 mm from the site of stimulation [11]. According to Ham this inhomogeneity varies both from preparation to preparation and within the individual zones of the myocardium which is connected with fluctuation in the ionic gradients, gas balance and temperature [11].

The reverberator and the vulnerability of the myocardium. After the "jump" the wave may spread not only in the forward direction but also in the reverse direction along the repolarized fibre R_B. We would recall that at the moment of application of the extrasystolic stimulus R_B was refractory. Reverse excitation may pass into closed excitation, that is, a reverberator forms. Previously we found the condition for the appearance of a reverberator—vulnerability factor (v.f.) [5]. The time of the reverse spread in [5] was evaluated approximately. In the present experiment it was possible to define it more accurately: the maximum delay of the reverse wave on average is equal to two maximum delays of the forward wave. Then the condition of appearance of the reverberator assumes the following form:

$$\text{v.f.} = 2\theta_{max} - R_{min} \geqslant 0, \qquad (I)$$

where θ_{max}—maximum delay of forward wave and R_{min}—minimum refractoriness of tissue in the test zone.

If v.f. < 0, the repeat responses (reverberator) do not appear. Experimental verification showed that in 90 per cent of the cases (*I*) correctly describes the appearance of the extrasystoles (vulnerability of the preparation) and in 87 per cent of the cases correctly predicts its non-vulnerability. The findings suggest that the vulnerability of the myocardium is associated with the functioning of the source of waves of a reverberator type.

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