EFFECTS OF SYNCHRONIZATION IN THE PACEMAKER DURING HIGH-FREQUENCY ATRIAL STIMULATION

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A tendency toward synchronization is one of the fundamental properties of the cardiac pacemaker, as of other living systems. The question of synchronization of the pacemaker with an external rhythmic source is closely bound up with the temporal organization of activity in the pacemaker itself and the nature of automatism. It has been shown [3, 5, 6] that the single rhythm of the pacemaker is the result of synchronizing bioelectrical interaction between cells and also aggregates of cells with a higher and lower rhythm of excitation. Udel'nov's views on the nature of automatism have been confirmed by the use of mathematical models [1, 8].

It was decided to examine, from the standpoint of synchronizing interaction, the results of experiments also conducted on the frog heart, but under simpler conditions, when one of the interacting biological objects was replaced by a rhythmic source with stable and controllable frequency. Dependence of pacemaker activity on the frequency of stimulation in experiments of this kind has been proved [2, 10], and this has encouraged the expectation that additional information would be forthcoming about the methods and forms of synchronization.

EXPERIMENTAL METHOD

Experiments were carried out on the frog (*Rana temporaria*) heart. The sinus venosus (SV) was isolated together with the atria (AT), unfolded into a flat slab of tissue by a modified Gramenitskii's method [7], and transferred into Ringer's solution, pH 7.2. Recording suction electrodes with a tip not more than 100 μ in diameter were made from silver wire, introduced into a thin polyethylene tube filled with Ringer's solution, and connected to a syringe. The electrode tip was applied firmly to the myocardial surface; on the withdrawal of a small, measured quantity of fluid from the tube the electrode became securely held in a constant position. Electrodes of this type have been shown to have little effect on tissue [9]. AT were stimulated with square pulses 5 msec in duration from a "Physiovar" stimulator and applied in series for 30-40 sec, after which the preparation was stimulated for 20-30 sec in its intrinsic rhythm. The frequencies of stimulation were 37.5, 43, 50, 63, and 77 ± 4 stimuli/min and these series were repeated twice or three times with a change of order. The pulses were of above threshold strength, with an amplitude of 2-3 V. The change in the frequency of excitation of SV was brought about not by the direct action of impulses of a given amplitude, but by excitation of AT, on which the rhythm of the stimulator was completely imposed [2].

EXPERIMENTAL RESULTS

There were 20 experiments altogether. Fragments of one of them are illustrated in Figs 1-3. During excitation of the preparation with its intrinsic rhythm, i.e., with a frequency of 32 min^{-1} (f_{orig} = 32 min^{-1}), stimulation orig was begun at a frequency of 38 min^{-1} (f_{st} = 38 min^{-1}). The period of stimulation (T_{st} = 1560 msec) was 82% of its initial value (T_{orig}^{sv} = 1900 msec). This rhythm was imposed completely on SV ($T_{st}^{sv} = T_{st}$), and complete synchronization took place

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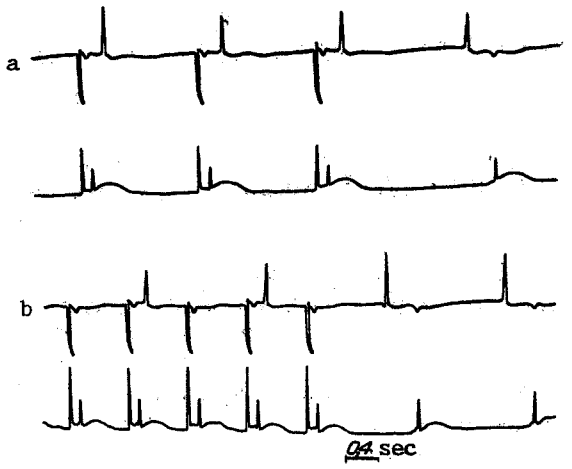

Fig. 1. Synchronization in frog SV. a) With frequency of stimulation, b) with frequency division. Top trace shows electrical potential in sinus venosus, bottom trace — in atria. Signals of stimuli precede electrical potential. a: $T_{st}^{sv} = T_{st} = 1560$ msec. Last complex appeared in SV after discontinuation of stimulation with period of $T_{pst}^{sv} = 1640$ msec ($T_{orig}^{sv} = 1900$ msec); b) $T_{st}^{sv} = 2T_{st} = 1600$ msec; $T_{pst}^{sv} = 1620$ msec ($T_{orig}^{sv} = 1900$ msec).

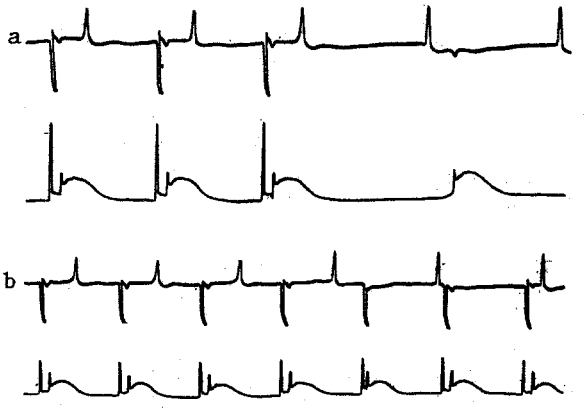

Fig. 2. Retrograde excitation of SV. a) Regular ectopic rhythm, b) formation of Wenckebach periods. a: $T_{st} = 1340$ msec, $T_{pst}^{sv} = 1600$ msec ($T_{orig}^{sv} = 1800$ msec). During stimulation impulses are conducted retrogradely with a time constant of $\tau_{at\text{-}sv} = 420$ msec; $T_{st} = 1280$ msec ($T_{orig}^{sv} = 1860$ msec). The first three impulses also were conducted retrogradely, but with increasing delay.

(Fig. 1a). After the end of stimulation the preparation was excited in its intrinsic rhythm, which initially was quickened, but returned to the original value in the course of 20-30 sec. Impulses in SV preceded the atrial impulses with a delay interval of ($\tau_{sv\text{-}at} = 400$ msec).

With a high frequency of stimulation ($f_{st} = 75$ min^{-1}) synchronization was reached not only by acceleration of the pacemaker, but also by frequency division (Fig. 1b).

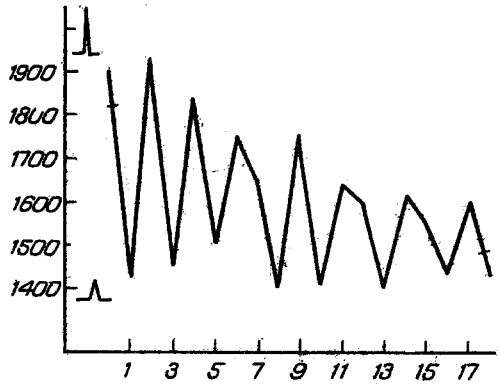

Fig. 3. Fragment of intervalogram during cyclic synchronization. Abscissa, serial number of intervals during stimulation; ordinate, intervals between impulses in SV (in msec). Symbols Λ and λ denote impulses arising in SV or conducted in the retrograde direction from the atria. Explanation in text.

The methods of synchronization illustrated in Figs. 1a and b are characterized by an identical shape of their electrical potentials before, during, and after stimulation, evidence of absence of any retrograde conduction. When T_{st} amounted to 74% of the initial value (f_{st} = 45 min^{-1}), retrograde conduction of impulses of a lower amplitude and longer duration appeared, alternating with ordinary complexes after termination of stimulation (Fig. 2a). The shortened (compared with initially) poststimulation interval (T_{pst}^{sv}) revealed a latent process of synchronization in SV, accompanied by acceleration of the pacemaker T_{pst}^{sv} = 1600 msec (T_{orig}^{sv} = 1800 msec).

A small increase in f_{st} to 47 min^{-1} (T_{st} = 1280 msec) significantly changed the pattern of activity in SV (Fig. 2b): the first three impulses also were conducted in the retrograde direction but the delay increased successively (τ_1 = 450 msec, τ_2 = 480 msec, τ_3 = 500 msec), whereas the last three impulses were of the usual form for activity of SV and appeared after intervals of 1600-1620 msec (T_{orig}^{sv} = 1860 msec).

With an increase in f_{st} to 54 min^{-1} (T_{st} = 1120 msec) arrhythmia developed in SV, and a fragment of it is shown in Fig. 3 in the form of an intervalogram. Periods or cycles including two or three intervals are clearly distinguishable: short — long or short — long — long. Short intervals are formed by premature retrograde conduction of impulses from AT, as shown schematically in Fig. 3, whereas long intervals conclude with ordinary impulses from SV. The first long interval can be regarded conventionally as postextrasystolic, whereas the second long interval reflects the rhythmic intrinsic activity of SV at that particular moment of stimulation.

Estimating the average interval of SV activity roughly as half the sum of the short and long intervals, we obtain a series of values (1680, 1645, 1625, 1575, 1520, 1515, and 1540 msec), i.e., gradual acceleration takes place, followed by some retardation of discharge of the pacemaker. Successive shortening of the intervals also can be observed by comparing the first (postextrasystolic) and second long intervals, corresponding to the firing time of SV. Taking these estimates into account, the increase in frequency of SV found after discontinuing stimulation may be considered to begin as soon as stimulation began: the firing interval in SV shortened, abruptly at first but later more smoothly, and may have undergone minor wavelike fluctuations near to a certain constant value, close to the period of stimulation. We may call this effect asymptotic synchronization.

Each cycle or sum of two neighboring cycles contains an approximately whole number of periods of stimulation, equal to 1120 msec: 3360:1120 = 3.0; 3290:1120 = 2.9; (4900 + 3150):1120 = 7.1; 4640:1120 = 4.1; 4610:1120 = 4.1:3080:1120 = 2.8, and the whole fragment, with a total duration of 27 sec, contains 24.1 periods of stimulation.

On the other hand each cycle contains two or three periods of activity of SV, whose frequency increases during stimulation: 3360:2 = 1680; 3290:2 = 1645; 4900:3 = 1633; 3150:2 = 1575, 4640:3 = 1546; 4610:3 = 1537; 3080:2 = 1540.

Simple calculations show that the duration of the cycles thus formed contains an approximately whole number of intervals between impulses arising from both sources. This synchronization effect can be conventionally called cyclic synchronization.

Analysis of the other experiments revealed intermediate links and enabled a consecutive series of synchronization effects, replacing each other in response to a stepwise increase in the frequency of stimulation, to be constructed.

When the frequency of stimulation was close to its initial value, SV exhibited rhythmic activity of its own: first a switch to the frequency of stimulation (complete synchronization), followed by a switch to a close frequency (asymptotic synchronization); separate impulses, conducted in the retrograde direction, appear and, with an increase in frequency, they become increasingly regular, and periods (or cycles) are formed, when interaction between the sources acquires the form of cyclic synchronization. Later the pacemaker becomes increasingly under the influence of the external source, and an ectopic rhythm with the frequency of stimulation arises. The latent tendency toward synchronization under these conditions is found only when the stimulation is discontinued: the rhythm of SV is quickened. Next, with an increase in f_{st}, signs of intrinsic activity of SV reappear: retrograde conduction is delayed (stable lengthening of delay or the onset of Wenckebach periods), impulses of sinus origin appear and cycles are formed, which are multiples of periods of activity of the two sources. When the frequency of stimulation exceeds the initial frequency of the pacemaker by a factor of 2 or more, division of the frequency takes place (as is shown in Fig. 1b), and the effects of synchronization are repeated. Frequency division also is a method of synchronization: periods of activity of SV formed are equal or (in the case of asymptotic synchronization) approximately equal to twice the period of stimulation. The effects described above can be classed as unilateral synchronization, for the frequency of one rhythmic source was stable and was controlled externally.

During interaction between two biological objects, forms of synchronization have been found such as the onset of a common rhythm through approximation of frequencies, or acceleration of automatic sources to a common frequency value, with the establishment of multiple frequencies [2, 5, 6]. In the present investigation, because of simplification of the experimental conditions and allowance for the shape of the complexes formed, other effects could also be observed: asymptotic synchronization, latent synchronization during retrograde conduction of impulses, ectopic rhythms with lengthening of delay and the formation of periods of the Wenckebach type, arrhythmias with the formation of cycles that are multiples both of periods of stimulation and of the momentary interval of SV activity. Thus the range of manifestations of synchronization is widened for further study.

The diversity of forms of synchronization is linked, on the one hand, with the fact that a tendency toward synchronization is a characteristic property of the pacemaker and, on the other hand, that the range of its deviations from the basic value is limited. Changes in the forms of synchronization take place as the frequency of stimulation moves away from the original frequency of SV.

The fundamental differences discovered in the temporal organization of the pacemaker, obtained on a relatively simple object, require generalization at a higher level, unconnected with any concrete type of activity [4].

On the basis of these results new approaches can be suggested for the interpretation of certain arrhythmias observed in clinical practice and, in particular, atrial flutter.

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