PACEMAKER SHIFTING IN THE RIGHT ATRIUM DURING VAGUS NERVE STIMULATION IN DOGS

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Under the influence of various factors which alter the heart rate, the location of the pacemaker in the sinus node (SN) changes [6, 10, 11, 14, 15]. Experiments on isolated preparations of the rabbit SN have shown [9, 13] that this is the result of unequal sensitivity of true and latent pacemakers to action of a particular kind. All investigators have confined their attention to determining only the initial and final locations of the pacemaker, and the dynamics of the change in pacemaker location and the associated change in heart rate have so far remained virtually unstudied. Previously the writers developed a method and apparatus for recording the dynamics of pacemaker migration [2] and also carried out investigations on the rabbit SN in hypoxia [3] and hyperkalemia [1].

In the investigation described below this method was used to study the mechanisms of pacemaker migration, together with electrical stimulation of the vagus nerve as a means of inducing pacemaker migration. The preliminary results of this investigation were published previously [4, 5].

EXPERIMENTAL METHOD

Mongrel dogs were anesthetized by intravenous injection of thiopental sodium (40 mg/kg). The chest was opened in the fourth intercostal space and the right strium exposed. The right vagus nerve, dissected in the neck, was stimulated by series (duration 60-90 sec) of square pulses (duration 2 msec) of different frequencies (1-5 Hz). Electrograms were recorded from three points of the epicardium of the right atrium using suction electrodes. Signals were processed by a device of the authors' own design, by means of which the atrial rhythm and two intra-atrial delays (IAD) can be recorded simultaneously [3]. The IAD is the difference between the times of activation of two atrial zones from which the electrograms are recorded. Both the atrial rhythm and IAD were displayed by the apparatus in the form of linearly increasing voltages. By recording these signals on paper of an automatic writer, the time course of changes in the frequency of spontaneous contractions and delays was obtained, and the pacemaker could be located by analysis of their amplitudes. Altogether 33 experiments involving stimulation of the vagus nerve and 11 experiments on a model of the transition process of IAD were carried out.

EXPERIMENTAL RESULTS

It will be clear from Fig. 1a, which gives the generalized results of 33 experiments to study changes in pacemaker location during stimulation of the vagus nerve, that before stimulation the predominant locations were in sector 1, and to a lesser degree, in sector 2. During stimulation locations in sectors 2 and 3 predominated. Stimulation thus causes migration of the pacemaker into the lower part of the SN region, in good agreement with data in the literature [9, 10].

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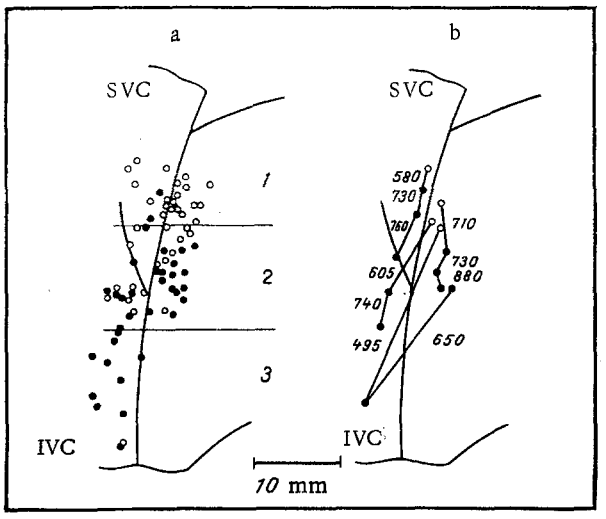

Fig. 1

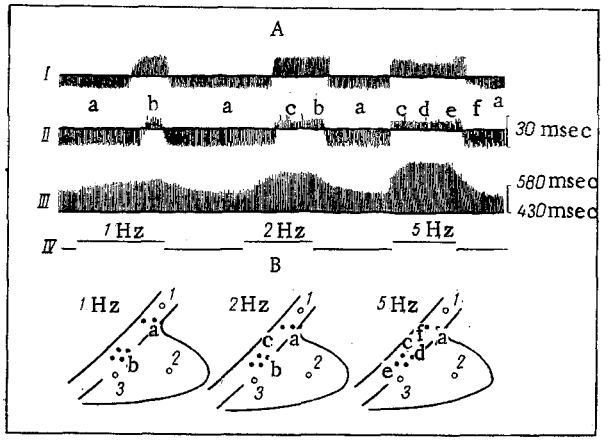

Fig. 2

Fig. 1. Location of pacemaker in right atrium of a dog in initial position (empty circles) and during vagus nerve stimulation (filled circles). a) Results of 33 experiments; b) trajectories of pacemaker migration during vagus nerve stimulation. The results of four experiments. Numbers indicate period of spontaneous excitation (in msec) at which pacemaker shifts from one point to another. Scheme showing part of right atrium in region of sulcus limitans. SVC) Superior vena cava, IVC) inferior vena cava.

Fig. 2. Changes in IAD and cardiac rhythm during vagal stimulation at different frequencies. A: I and II) Intra-atrial delays between recording points 3-2 and 2-1, respectively; III) cardiac rhythm from point 1; IV) duration of stimulation. Letters alongside delays indicate different combinations of delays, corresponding to different locations of pacemaker indicated in b; B) graphic interpretation of experimental data given in *a*. Dots indicate position of pacemaker. Letters indicate pacemakers found from corresponding combinations of delays. Circles with numbers indicate position of recording electrodes.

Investigation of the time course of pacemaker migration during stimulation showed that in most cases one or more intermediate locations existed between the initial and final locations (Fig. 1b). These staggered migrations of the pacemaker were described by the writers previously in a study of effects of hyperkalemia [2]. Other workers have not observed this phenomenon, evidently because there is no convenient method of tracking the course of pacemaker migration. Another distinguishing feature of pacemaker migration during stimulation of the vagus nerve was that a shift from one location to another took place when the period of the cardiac contractions had a particular value (Fig. 1b).

Experimental curves obtained by recording two IAD and the cardiac rhythm during vagal stimulation by pulses with frequencies of 1, 2, and 5 Hz are given in Fig. 2 and a graphic interpretation of the results of this experiment also is shown. Stimulation of the nerve evoked a gradual increase in the period of pacemaker activity followed by a change in IAD. An increase in the frequency of stimulation always led to an increase in the rate of rise of the period of the cardiac contractions, shortening of the interval between the beginning of stimulation and the beginning of the change in IAD, and also to a decrease in the duration of the transition process of the change in IAD. For instance in the experiment whose results are given in Fig. 2, with a frequency of stimulation of 1 Hz the switch of IAD from one steady-state value to another took about 20 cycles, whereas at 5 Hz it took only a few cycles. As was pointed out above, IAD began to change when the period of cardiac contractions had reached a certain value regardless of the frequency of stimulation; the switch from location *a* to location c in the experiment described took place strictly at 560 msec. Pacemaker locations found from the IAD data before, during, and after stimulation are shown in Fig. 2b. Before and after stimulation the pacemaker was located at the junction of the superior vena cava with the right atrium, whereas during stimulation it shifted through 10-15 mm toward the inferior vena cava. Characteristically, with an increase in the intensity of stimulation the number of successively shifting pacemakers in each of these zones increased.

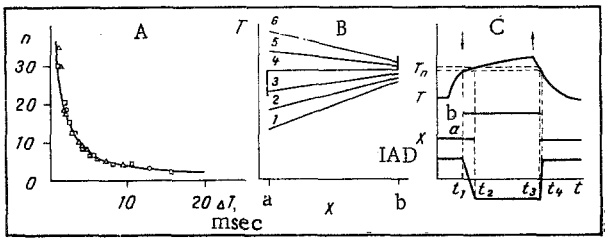

Fig. 3. Experimental (A) and theoretical (B, C) models of discrete pacemaker migration. A) Dependence of number of cycles (n) of transition process of change in IAD on difference between periods of stimulation (ΔT) of two sites of dog right atrium. Results of one experiment with three values of period of stimulation: circles T = 620 cm, squares T = 510 cm, triangles T = 340 msec. Curve drawn in accordance with Eq. (1); B) chronotropic response of unidimensional model of SN to agency slowing rhythm. Thin lines denote dependence of period of automaticity (T) of indidual cells and their position in SN (X). Cell *a* represents original pacemaker located in central part of SN; cell b located at periphery of SN and, is initially a latent pacemaker. Lines 1-6 show change in periods of different pacemakers with time under the influence of factor with negative chronotropic action. Cells between *a* and b differ in sensitivity to this factor. Bold lines denote change with time in period of excitation of whole system of cells: on left — with pacemaker in position *a*; on right — with pacemaker in position b; C) relationship between dynamics of experimentally measured values — period of automaticity (T) and IAD — on change in location of pacemaker (X) with time (t). Arrows indicate beginning and end of action of factor slowing rhythm. Letters *a* and b denote initial and final positions of pacemaker, respectively. T_p) Critical value of period at which change in IAD begins; t_1 and t_3 indicates beginning, t_2 and t_4 end of transition process.

The question arises how does a pacemaker shift from one loaction to another. IAD, from which pacemaker migration was judged, changed either with a well-defined transition process (during weak vagal stimulation) or almost stepwise (strong stimulation). It can thus be assumed that the pacemaker migrates either smoothly, with a certain change in frequency of its automatism, or stepwise, discretely. We showed experimentally that the transition process of the change in IAD can in any case be interpreted as the result of appearance of a second focus of excitation with a frequency of automaticity a little higher than that of the original pacemaker. A model of the transition process reflecting such a discrete pacemaker shift was created by electrical stimulation of two sites of the atrium with close and constant frequencies. The results of the 11 experiments showed unequivocally that, other conditions being the same the number of cycles of the transition process depends only on the difference between the periods of stimulation. The results of one of these experiments are shown in Fig. 3A. They show that the duration of the transition process is independent of the period of stimulation, and on the whole the data are described sufficiently well by the following empirical equation:

$$n = \frac{2s}{v} \cdot \frac{1}{\Delta T}, \qquad (1)$$

where n is the number of cycles of the transition process, s the distance between foci of excitation, v the velocity of spread of the excitation wave, and ΔT the difference between the periods of stimulation. The value of the coefficient 2 s/v was determined experimentally in this case and was found to be 38 msec.

A discrete pacemaker shift can be explained qualitatively by the following unidimensional model of SN. It is based on data in the literature showing that during a shift from the center to the periphery of SN the automaticity of its cells decreases regularly [7], but the pacemaker of a system consisting of several interconnected pacemakers is the cell which has the

highest frequency of automaticity [12]. Let us imagine that SN consists of a chain of electrically connected cells a–b, whose periods of automaticity increase in the direction $a \rightarrow b$ (curve 1 in Fig. 3B). The system as a whole will work with intermediate period T (the bold curve in Fig. 3B and the top curve in Fig. 3C), but excitation arises first of all in cell a (the middle curve in Fig. 3C). The delay a–b under these circumstances will be positive (the bottom curve in Fig. 3C). Let us assume that the degree of decrease of the frequency of excitation of the cells in response to a certain action, stimulation of the vagus nerve for example, falls steadily as the distance increases from the initial pacemaker. With the beginning of stimulation, the rhythm of individual cells (curves 2 and 3 in Fig. 3B) and of the system as a whole becomes slower, and under these circumstances cell a remains the pace maker. This will continue until time t_1 (Fig. 3C), when the periods of all the cells become equal to T_p (curve 4 in Fig. 3B). The next very small decrease in the frequency of the rhythm gives rise to a transition process of delay a–b. Its duration will depend on the velocity of spread of excitation and on the rate of rise of the difference between the periods of cells a and b. At time t_2, when the excitation wave spreading from cell b reaches cell a the delay is set at a new steady-state level with negative value, and cell be comes the pacemaker (Fig. 3C). From this same moment the rate of increase of the period of automaticity of the whole system becomes less, for the sensitivity of cell b to vagus nerve stimulation according to this model is less than that of the cell a. At the end of stimulation the opposite order of events will take place. By means of this model the interconnected dynamics of the change in cardiac rhythm and in IAD observed experimentally can be explained sufficiently well. For example, in the experiments whose results are given in Fig. 2, from the beginning of stimulation with frequency 2 Hz the period of automaticity of pacemaker a increases, and when it reaches 560 msec, the pacemaker shifts to position c, and the period virtually ceases to rise. In the same way pacemaker c responds to stimulation of the nerve with a freuqnecy of 5 Hz by slowing of the rhythm, but after pacemaker migration into position d the frequency of spontaneous contractions stabilizes. Thus there is a shift toward a pacemaker less sensitive to vagus nerve stimulation, in agreement with the model of SN described above, and confirmed by data of other workers [9]. The presence of special points where the character of dynamics of the cardiac rhythm changes, which coincide in time with changes in pacemaker location, is evidence in support of the view that pacemaker shifts are discrete.

The method of mapping the spread of the excitation wave could be most informative as regards the study of the dynamics of pacemaker migrations. Technically this method is much more difficult than that we have developed and for that reason it may perhaps not have been used so far for these purposes. Nevertheless, a group of American investigators has shown that several foci of exciation may exist simultaneously in the region of SN of the dog's heart [8]. Although it is impossible to represent the dynamics of interaction between these foci on the basis of the published data, the possibility cannot be ruled out that it reflects the location of the pacemaker at the separate moments of the transition process of IAD which we have described. Consequently, pacemaker migrations can be regarded as the result of competition between two foci of automaticity with closely similar exciation frequencies.

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