EFFECT OF CERTAIN BIVALENT CATIONS ON DURATION OF THE VENTRICULAR PREAUTOMATIC PAUSE

S. K. Saidkarimov

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Addition of Ni^{++}, Ba^{++}, and Cd^{++} cations to Tyrode perfusion solution or exclusion of Ca^{++} ions from it shortens the period of asystole after cessation of rapid electrical stimulation of the ventricles and, hence, reduces the depression of automatic activity of the ventricular pacemakers evoked by frequent stimulation. Co^{++} ions and an increase in the concentration of Ca^{++} and Mg^{++} ions in the Tyrode solution lengthen the period of asystole after cessation of electrical stimulation and, consequently, increase the depression of automatic activity of the ventricular pacemakers by high-frequency stimulation.

It can now be taken as established that high-frequency electrical stimulation depresses automatic activity of the potential ventricular pacemakers [1, 2]. If such stimulation is applied during a period of complete atrioventricular block, its cessation will be followed by temporary asystole. This asystole is analogous to the preautomatic pause arising after application of a ligature to the excitation-conducting system of the heart.

The writer concluded from an analysis of the mechanism of onset of this asystole that the depression of automatic activity of the potential ventricular pacemakers by high-frequency excitation is a disturbance of the balance between passive and active ion transport [3, 5].

The effect of some monovalent ions on the duration of the preautomatic pause was examined in a previous publication [4].

In this investigation the action of some bivalent cations was studied on the preautomatic pause, the duration of which is an indicator of the depression of automatic activity of the cardiac pacemakers by high-frequency stimulation.

EXPERIMENTAL METHOD

Experiments were carried out on rabbits' hearts, isolated by Langedorf's method and perfused with Tyrode solution of the following compositions (in mmoles/liter): NaCl 137, KCl 2.6, $CaCl_2$ 1.8, $NaHCO_3$ 12, $MgCl_2$ 1, Na_2HPO_4 0.4, glucose 5.5. The solution was saturated with oxygen and supplied to the heart under a constant pressure and at 37°C; the pH of the solution was 7.3-7.4. To investigate the action of Mg^{++} and Ca^{++} cations, these cations were excluded from the perfusion fluid or their concentration was increased to 4 times that in normal Tyrode solution. The action of the remaining bivalent cations on the isolated heart was investigated in the following concentrations (in mmoles/liter): $NiCl_2 \cdot 6H_2O$ 2; $CdCl_2 \cdot H_2O$ 0.05; $BaCl_2 \cdot 6H_2O$ 0.25; $CoCl_2 \cdot H_2O$ 1.

At the beginning of each experiment complete atrioventricular block was created by application of a ligature to the upper part of the bundle of His. Electrical activity of the ventricles was recorded by needle electrodes applied to the surface of the ventricles. The dc amplifier of a VÉKS-01 vector-electrocardioscope and an ink-writing recorder designed by the "Biofizpribor" Design Bureau were used.

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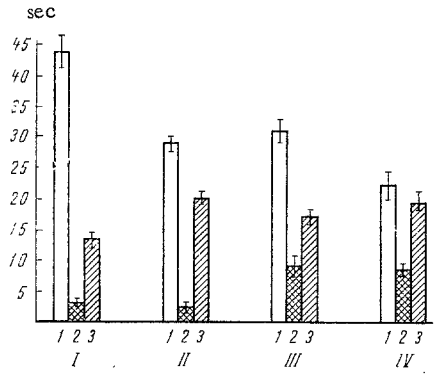

Fig. 1. Effect of Ni^{++} (I), Ba^{++} (II), and Cd^{++} ions (III) and of Tyrode solution not containing Ca^{++} ions (IV) on duration of ventricular asystole after cessation of rapid electrical stimulation. 1) Duration of asystole during perfusion of heart with Tyrode solution; 2) during action of above-mentioned ions; 3) during subsequent perfusion with Tyrode solution. Vertical lines show standard error (m).

The experimental procedure was as follows. The initial pattern of cardiac electrical activity was recorded for a few minutes against the background of complete atrioventricular block. For the next 3 min electrical stimuli were applied to the ventricles at a frequency 2-3 times higher than the intrinsic frequency of excitation of the cardiac ventricles. Each stimulus was 2-4 msec in duration and 0.5-4 V in amplitude. When electrical stimulation was stopped, a preautomatic pause of varied length occurred, and its duration was measured in seconds. Often the determination was made twice at the beginning of the experiment; this acted as the control.

After the duration of the preautomatic pause had been determined and the character of recovery of cardiac activity ascertained, the perfusion fluid of the above composition was replaced by a solution containing an excess or deficiency of Mg^{++} and Ca^{++} ions, or containing the cations Ni^{++}, Cd^{++}, Ba^{++}, or Co^{++}. After a few minutes the ventricles were stimulated electrically (duration and parameters of the stimuli remained unchanged throughout each separate experiment). The duration of the preautomatic pause and the course of recovery of cardiac activity were recorded during perfusion of the heart with these solutions, after which it was again perfused with normal Tyrode solution and electrical stimulation repeated in order to determine whether the original duration of the preautomatic pause had been restored.

EXPERIMENTAL RESULTS AND DISCUSSION

Altogether 50 experiments were performed. The action of Ni^{++} cations was tested in 5 experiments. During perfusion of the heart with $NiCl_2$ solution, the rate of spontaneous excitation of the ventricles was slowed on the average by 52.4% ($P < 0.01$). The preautomatic pause was shortened by many times after discontinuation of frequent electrical stimulation (Fig. 1: I, 2), and in some experiments it disappeared completely so that the ventricles began to work in their independent idioventricular rhythm immediately after the end of electrical stimulation (Fig. 2). During subsequent perfusion of the heart with Tyrode solution, the period of asystole was somewhat lengthened but did not attain its original level.

The effect of Ba^{++} cations was investigated in 6 experiments. During perfusion of the isolated heart with a solution of this substance, the frequency of spontaneous excitation of the ventricles was increased

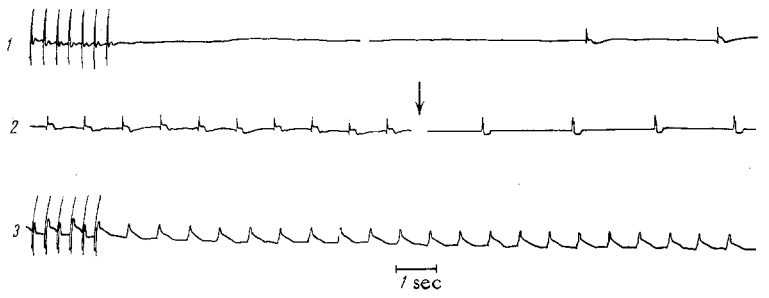

Fig. 2. Disappearance of preautomatic pause during perfusion of heart with solution containing $NiCl_2$ in concentration of 2 mmoles/liter. 1) Asystole after stopping electrical stimulation of ventricles and during perfusion of heart with ordinary Tyrode solution; 2) slowing of ventricular rhythm during perfusion of heart with solution containing $NiCl_2$ (arrow indicates change of solution); 3) absence of preautomatic pause after cessation of frequent electrical stimulation of ventricles and during perfusion of heart with solution containing $NiCl_2$.

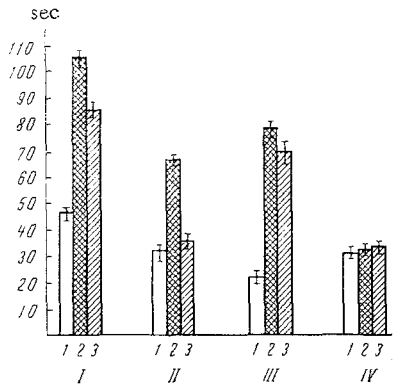

Fig. 3. Effect of Co^{++} ions (1) and of an increase in concentration of Ca^{++} (II) and Mg^{++} (III) ions and of exclusion of Mg^{++} ions (IV) in Tyrode solution on duration of preautomatic pause of ventricles on cessation of frequent electrical stimulation. 1) Duration of asystole during perfusion of heart with Tyrode solution; 2) during action of Co^{++} ions or of an increased concentration of Ca^{++} or Mg^{++} ions; 3) during perfusion subsequent with Tyrode solution.

on the average by 96.5% ($P < 0.001$) and the preautomatic pause was considerably shortened (Fig. 1: II, 2). The effect of Ba^{++} was reduced during subsequent perfusion of the heart with ordinary Tyrode solution, but the original duration of asystole was not regained.

The action of Cd^{++} cations was studied in 5 experiments. Under the influence of this ion, the frequency of spontaneous ventricular excitation was increased on the average by 33.3% ($P < 0.02$). The preautomatic pause of the ventricles was considerably shortened, on the average by 3.5 times ($P < 0.002$), but to a lesser degree than by Ni^{++} and Ba^{++} ions (Fig. 1: III, 2). After replacement of the $CdCl_2$ solution by ordinary Tyrode solution, the period of asystole was slightly lengthened.

The effect of Mg^{++} cations was tested in 11 experiments. During perfusion of the heart with a solution containing a fourfold concentration of Mg^{++} cations, the frequency of spontaneous excitation of the ventricles was reduced on the average by 46.4% ($P < 0.01$). The period of ventricular asystole was lengthened on the average by 3.4 times ($P < 0.001$; Fig. 3: III, 2). Subsequent perfusion of the heart with ordinary Tyrode solution led nearly to a slight decrease in duration of the preautomatic pause.

Tyrode solution not containing Mg^{++} ions did not affect the frequency of spontaneous ventricular excitation or the duration of the preautomatic pause. The action of Co^{++} cations was tested in 6 experiments. Perfusion of the isolated heart with a solution containing Co^{++} cations caused a decrease in the frequency of ventricular excitation on the average by 35.3% ($P < 0.05$), and the preautomatic pause was lengthened on the average by 2.29 times ($P < 0.001$) after the cessation of electrical stimulation. During subsequent perfusion of the heart with ordinary Tyrode solution, the period of asystole was slightly shortened.

The effect of Ca^{++} cations was tested in 17 experiments. During perfusion with a solution containing a 4 times higher concentration of Ca^{++} cations, the frequency of spontaneous ventricular excitation was increased only slightly, by 16.2% ($P > 0.05$). Ventricular asystole was on the average doubled in duration after discontinuation of the electrical stimulation ($P < 0.001$; Fig. 3: II, 2). Perfusion of the heart with ordinary Tyrode solution shortened the preautomatic pause almost to its initial level.

During the action of a solution not containing Ca^{++} cations, the frequency of spontaneous ventricular excitation was reduced on the average by 30% ($P < 0.01$). The preautomatic pause was shortened on the average by 2.88 times ($P < 0.001$; Fig. 1: IV, 2), while in some experiments it disappeared completely. During subsequent perfusion with normal Tyrode solution the duration of the preautomatic pause was considerably increased.

It was shown previously that shortening of the period of asystole after cessation of electrical stimulation produced by increasing the concentration of K^+ ions or reducing the concentration of Na^+ ions in the perfusion fluid is due to activation of membrane Na–K ATPase and, conversely, lengthening of the period of asystole produced by reducing the concentration of K^+ ions or increasing the concentration of Na^+ ions in the solution is associated with a decrease in the activity of this ATPase.

Changes in the duration of the preautomatic pause on the cessation of electrical stimulation may also be dependent on other factors: activity of other enzyme systems participating in energy metabolism and connected with active ion transport, and also on changes in passive ion transport.

It is impossible at present to define the mechanism of action of the bivalent cations tested on the preautomatic pause. It is a noteworthy fact that barium, nickel, and cadmium ions, which evoke spontaneous activity of the heart muscle fibers, which under normal conditions do not possess spontaneous activity, shorten the preautomatic pause on the cessation of electrical stimulation. The action of these ions, like the effect of a reduced concentration of Ca^{++} ions in the solution, is very possibly connected with disturbances of permeability of the cell membrane and changes in passive ion transport. The possible role of

the action of bivalent cations on active ion transport in the changes observed in the preautomatic pause likewise cannot be ruled out. Further investigation is necessary to shed light on this problem.

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