COMPUTERIZED STUDY OF THE TIME COURSE OF ADAPTIVE RESERVES OF THE HEART IN ALCOHOLICS TREATED WITH NONACHLAZINE

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The use of computer techniques in cardiology has enabled mathematical methods to be used successfully to analyze the cardiac rhythm [1, 5]. For instance, production of histograms of the cardiac rhythm by computer before, during, and after measured physical exertion can reveal disturbances of adaptation of the cardiovascular system to loads in alcoholics [4].

One of the clinical manifestations of alcoholic cardiomyopathy is pain of anginal character, accompanied by a reduction in myocardial contractility. Accordingly it was decided to investigate the effectiveness of treatment of such patients with the original Soviet drug nonachlazine, which combines antianginal properties with a potentiating effect on the contractile function of the heart [3]. Despite numerous investigations into the mechanism of action of nonachlazine, its effect on the adaptive reserves of the heart has not hitherto been studied.

The aim of this investigation was to study changes in parameters of the cardiac rhythm and adaption of the heart to exertion during treatment of alcoholics with nonachlazine.

EXPERIMENTAL METHOD

The patients, in whom stage II alcoholism was diagnosed, consisted of 24 men aged from 17 to 46 years, complaining of frequent (8-10 times a day) and strong retrosternal pains. The duration of the illness was between 3 and 24 years. Besides evaluation of the clinical picture of the disease, a large-scale (1 mV = 30 mm) recording of the ECG was obtained on paper tape with a polygraph (RM-86, from Nihon Kohden, Japan), with a transmission band of between 0.01 and 100 Hz. Parallel recordings were obtained on magnetic tape by an SDR-41 tape recorder (Japan) for subsequent processing by computer (Mediac-401, Japan). The computer constructed histograms of distribution of R-R intervals (accuracy 5 msec), and the sample consisted of 100 consecutive R-R intervals on the ECG.

The program for analysis of the cardiac rhythm included determination of the following parameters: M_0 — the mode, the most frequently encountered value of the duration of the R-R interval of the cardiac cycle, Δx — the range of variation (regularity of the heart beat), AM_0 — the amplitude of the mode of the R-R intervals, representing the mode as a percentage of the total number of intervals in the sample (the number of times the most frequently encountered value of the duration of the cardiac cycle occurred, expressed as a percentage, Fig. 1).

After the background ECG had been recorded, in order to assess the adaptive power of the heart, a physical exertion test was used (isometric contraction of the upper limb muscles by supporting a weight of 0.5 kg on the outstretched hand for 5 min). The performance of work under these conditions enabled histograms of distribution of the R-R intervals to be plotted at the 1st, 3rd, and 5th minutes of physical exertion and 3 min after removal of the weight.

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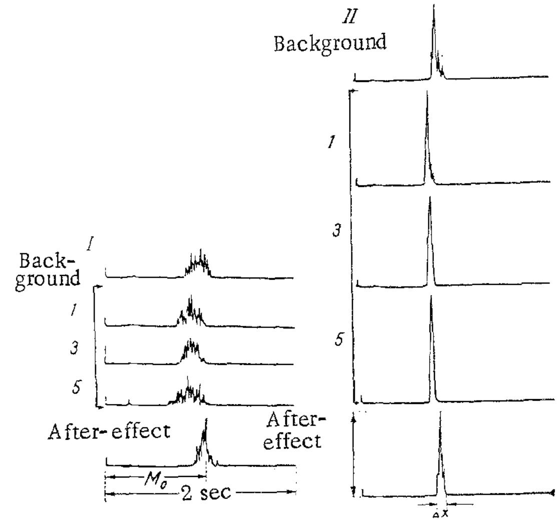

Fig. 1. Families of histograms of distribution of R-R intervals in the ECG at rest, during physical exertion, and after its end, for a clinically healthy subject (I) and an alcoholic (II). Sample of 100 consecutive R-R intervals (durations of the cardiac cycle) on ECG, exposure 2 sec. M_0) Most frequently encountered duration of cardiac cycle, AM_0) number of times M_0 occurred as a percentage of total number of cardiac cycle (100 R-R intervals), Δx) range of variation, reflecting variability of cardiac rhythm from beat to beat. 1, 3, 5) 1st, 3rd, and 5th minutes of exertion, respectively. Age of subject 29 years.

The parameters were studied 3 times in each patient: on the 2nd-3rd day of development of withdrawal symptoms, before treatment had commenced, after 7-14 days of treatment when the clinical manifestations of withdrawal had completely disappeared, and 2 months later, after the complete course of treatment. Nonachlazine was given in doses of 120 mg daily for 14 days after the primary investigation and recording of the ECG before treatment to 12 patients (group 1); 12 other patients did not receive nonachlazine but instead were given a placebo for the same time (group 2).

The criteria of the normal state were the results of investigation of the ECG of 30 clinically healthy subjects aged from 17 to 45 years.

EXPERIMENTAL RESULTS

In patients complaining of pain in the heart during the period of severe withdrawal symptoms, which were abolished by nitroglycerine, pathological changes were found on the ECG in 75% of cases. The most frequent findings on the ECG were sinus tachycardia (16 patients, 66.6% of the total number), shortening of PQ (six patients, 25%), a negative, flattened, biphasic, or isoelectric T wave (14 patients, 58.8%). In six patients superventricular, and in four patients ventricular extrasystoles were recorded. In two patients, with a past history of myocardial infarction, intraventricular conduction was disturbed with a right bundle branch block. During physical exertion at the first examination, before the beginning of treatment, retrosternal pain occurred in 15 patients (62.5%); in only nine of these patients was the appearance of pain in the heart during physical exertion accompanied by changes in the ST segment. In seven patients the ST segment showed a horizontal shift in the downward direction, in two patients this segment was raised above the isoelectric line.

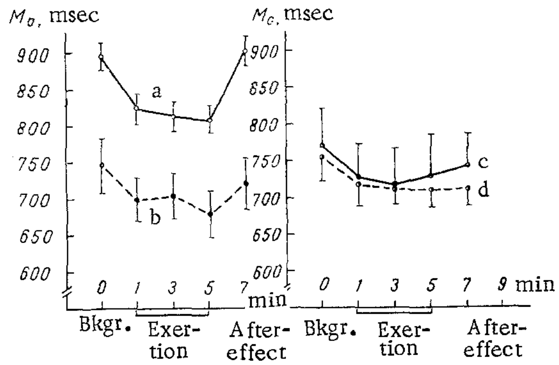

Fig. 2. Time course of changes in mode of distribution of R-R intervals (M_0) during physical exertion and after its end in clinically healthy subjects (a), alcoholics before treatment (b), and alcoholics after treatment for 14 days with nonachlazine (c), and after receiving a placebo during the same period (d).

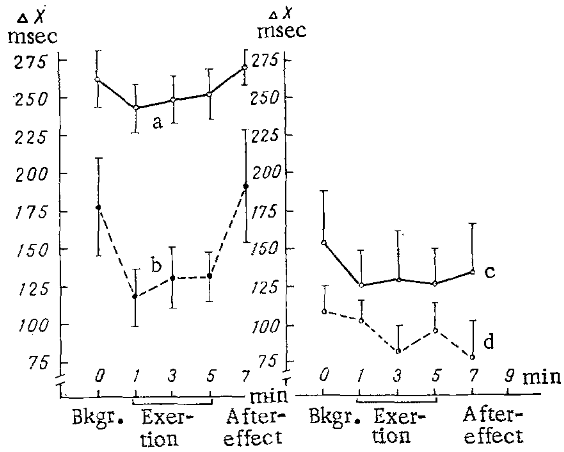

Fig. 3. Time course of changes in range of variation of R-R intervals (Δx) during physical exertion and after its end, in clinically healthy subjects (a), alcoholics before treatment (b), and alcoholics after treatment for 14 days with nonachlazine (c) or after receiving a placebo during the same period (d).

Investigation of clinically healthy subjects showed slight changes in the ECG of some of them (seven patients, 23.3%). These changes consisted mainly of changes in the amplitude and configuration of the T wave in individual ECG derivations. None of the 30 healthy subjects developed pain in the heart during physical exertion, although in four of them (13.3%) physical exertion caused a horizontal downward shift of the ST segment.

The results of routine electrocardiography thus revealed no "absolute" differences between the ECG of the healthy subjects and that of the alcoholics, and this therefore could not serve as a reliable criterion of the objective state of the patients during treatment. A search for more reliable criteria of the objective state of the cardiovascular system, reflecting in particular its adaptive powers, was necessary.

One such criteria is evidently the change in some parameters of the cardiac rhythm in response to physical exertion. For instance, histograms of distribution of R-R intervals in the alcoholics differed sharply from those of the healthy subjects both at rest and during

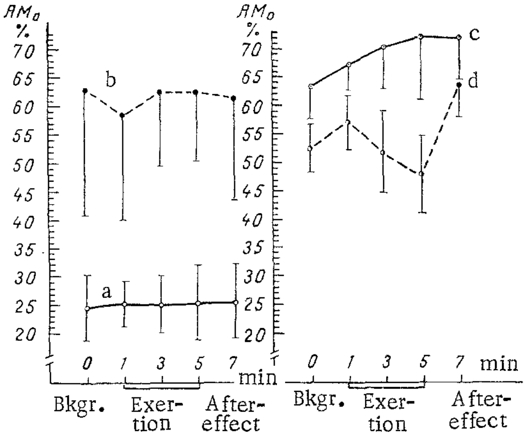

Fig. 4. Time course of changes in amplitude of mode of R-R intervals (AM_o) during physical exertion and after its end, in clinically healthy subjects (a), in alcoholics before treatment (b), and in alcoholics after treatment with nonachlazine for 14 days (c) and after receiving a placebo during the same period (d).

physical exertion (Fig. 1). Meanwhile, even at rest, the typical histogram of distribution of R-R intervals on the ECG of an alcoholic differed from the normal pattern in the following features: The mode M_o was shifted toward the region of shorter intervals, the range of variation Δx was much narrower than normally, and the amplitude of the mode AM_o was higher (Fig. 1). Whereas normally M_o = 892 ± 17.3 msec, Δx = 261 ± 16 msec, and AM_o = 24.4 ± 1.6%, in alcoholics during development of a withdrawal syndrome M_o = 742 ± 37 msec, Δx = 178 ± 34 msec, and AM_o = 63.0 ± 7.1% (n = 10).

Under the influence of physical exertion the mode of the R-R intervals on the ECG of the healthy subjects was considerably reduced, and a tendency remained for a further decrease throughout the period of exertion (1st minute of exertion: M_o = 819 ± 20.2 msec, 3rd minute: M_o = 810 ± 20.6 msec, 5th minute: M_o = 809 ± 19 msec). After the end of exertion M_o was restored or actually rose to a higher level than in the background (Fig. 2a), on average to 900 ± 20.6 msec (n = 20).

In the alcoholics, against the background of a much lower initial value of M_o (Fig. 2b), a further decrease also was observed under the influence of exertion, but it was smaller and did not recover during the first 3 min after the end of exertion.

During exertion by the healthy subjects the range of variation Δx was narrowed (Fig. 3a), whereas in the background it was 261 ± 16 msec, and decreased during exertion (1st minute 241 ± 16.7 msec, 3rd minute 247 ± 15 msec, 5th minute 250 ± 18 msec), in the after-period the initial value was restored: 269 ± 12 msec (n = 20).

Investigation of this parameter of distribution of the R-R intervals of the cardiac cycle also revealed marked abnormalities. In patients with alcoholism, against the background of a much lower initial value of Δx (178 ± 34 msec), under the influence of physical exertion there was a much sharper fall in its value to 117 ± 18 msec at the 1st, to 129 ± 20 msec at the 3rd, and to 130 ± 16 msec at the 5th minute of exertion (Fig. 3b).

Analysis of the amplitudes of distribution of R-R intervals also revealed marked differences between the clinically healthy subjects and alcoholics. AM_o of the healthy subjects was much lower than that of the alcoholics (Fig. 4). Under the influence of exertion the changes in this parameter were small — within the limits of error in both groups ($P > 0.05$).

Comparative analysis of the parameters of distribution of the R-R intervals on the ECG of the healthy subjects and alcoholics thus revealed two different types of adaptation of the cardiac rhythm to exertion. In healthy subjects a wide range of variation of the cardiac intervals enables the heart to switch easily to a new rhythm of contraction, whereas in the alcoholics the narrow range of variations of the cardiac cycle within the zone of higher frequencies makes the system less flexible, less adaptable to different conditions, namely physical exertion and the state of rest following the end of work. In other words, the cardiovascular system in alcoholics has sharply reduced powers of adaptation to different conditions.

It can be postulated on the basis of research [1, 2, 5] revealing correlation between the parameters of distribution of the R-R intervals with neurohumoral regulation of the cardiovascular system that changes in the power of adaptation of the cardiovascular system in alcoholics reflect disturbances of one or another stage of regulation. For instance, the value of AM_0, which can be regarded as an indicator of activation of sympathetic influences, was sharply increased in the alcoholics during the withdrawal period, but Δx — an indicator of the tone of parasympathetic influences on the myocardium — was sharply reduced. The mode M_0, an indicator of the humoral channel of control of the cardiac rhythm according to the workers cited above, was considerably lower in the alcoholics than in the healthy subjects.

Complaints of attacks of retrosternal pain were reduced 14 days after the beginning of treatment in the alcoholics of both groups, but by a different degree. Three patients (25%) of group 1 and five patients (41.7%) of group 2 still had pain in the heart. The frequency of the attacks was reduced to 1-2/day in both groups of patients. Treatment for 2 weeks led to favorable changes in the ECG parameters of all patients. Initially ECG changes were observed in nine patients in each group, but after treatment a favorable course was observed in six patients of group 1 and five patients on group 2. The shift to the ST segment from the isoelectric line under the influence of physical exertion was less marked or was absent altogether; normalization of the T wave also was observed. The number of ventricular extrasystoles in one patient receiving nonachlazine fell from 3-4/min to 1/min in the course of 20-30 min. The remaining ECG changes continued. The mean heart rate in the patients during the withdrawl period was 91 ± 13.4 beats/min, but 14 days after the beginning of treatment it was reduced to 80.4 ± 12.3 beats/min.

Comparative analysis of histograms of distribution of R-R intervals in the two groups of patients showed that M_0 in the patients of group 1 had a strong tendency toward the distribution observed in healthy subjects (Fig. 2c). This picture was still far from normal, but the principal phases of the change in this parameter were similar to the structure of its changes in normal subjects. This was not observed in the patients receiving the placebo. M_0 in the background period remained lower in value, the alteration of the rhythm in response to exertion was marked, but the parameters did not return to their initial levels after the end of exertion. During the 3 min rest period the cardiac rhythm remained virtually the same as during exertion, evidence of disturbances of the adaptive properties of the cardiovascular system (Fig. 2d).

The time course of changes in the range of variation Δx during physical exertion also indicated an improvement in the power of adaptation of the cardiovascular system in alcoholics during treatment with nonachlazine. In patients receiving the placebo, against the background of very low initial values of Δx, there was a further decline in the range of variation which, in the after-period, not only was not restored to its initial level, but continued to fall even more (Fig. 3d). In the patients receiving nonachlazine the changes in Δx followed a different time course: The initial value of the range of variation was higher than in patients of the previous group, and in the after-period there was a tendency toward restoration of the initial value of Δx (Fig. 3c).

Analysis of AM_0, reflecting the state of the sympathetic system, showed that in patients treated with nonachlazine activation of the sympathico-adrenal system was more intensive in response to physical exertion than in the patients before treatment or in patients receiving the placebo during the same period (Fig. 4). In the patients of group 2, moreover, a paradoxical reaction to physical exertion was observed: The value of AM_0 fell until the 5th minute of exertion, but rose sharply after its end.

Consequently, nonachlazine substantially improves the adaptive powers of the heart. This effect can be linked with the ability of nonachlazine to increase myocardial contractility, while at the same time improving the blood supply to damaged areas of the myocardium [6, 7]. The mechanisms lying at the basis of improvement of the adaptive powers of the heart under the influence of nonachlazine are in process of being investigated.

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LOWERING THE CONCENTRATION OF HIGH-AFFINITY BINDING SITES FOR CALCIUM IONS IN RAT HEART SARCOLEMMAL MEMBRANES BY THE BETA-BLOCKER PROPRANOLOL

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Injection of large doses of natural catecholamines or of the synthetic analog isoproterenol into rats causes a marked increase in accumulation of calcium ions by the heart muscle [1, 5]. This is one of the main causes of the cardiotoxic action of catecholamines [5]. Most effects of catecholamines are known to be mediated through their interaction with β-receptors on the cytoplasmic membrane and activation of the adenylate cyclase system. The β-blocker propranolol, when administed *in vivo*, partially inhibits the increase in calcium ion accumulation induced by catecholamines. However, it not only inhibits the binding of catecholamines by β-receptors by a competitive mechanism, but also evidently has side effects, the mechanism of which has not yet been adequately studied [4, 7].

The aim of the present investigation was to study the effect of propranolol *in vivo* on the accumulation of ^{45}Ca by heart tissue after injection of isoproterenol into intact rats or animals receiving repeated doses of hydrocortisone. Binding of calcium ions by preparations of sarcolemma from the hearts of intact rats also was investigated *in vitro* after addition of glucocorticoids and isoproterenol.

EXPERIMENTAL METHOD

Male Wistar rats weighing 200-250 g were kept on the standard laboratory diet. The rate of assimilation of calcium by myocardial tissue was determined by the method in [1]. The protein concentration was determined as in [6]. To obtain preparations of the sarcolemma the rats were killed, the heart tissue homogenized, and the homogenates fractionated by the method in [2]. The fraction of isolated sarcolemmal membranes was used on the same day to estimate ^{45}Ca binding [3]. The suspension of membranes with a protein concentration of 20-40 μg/ml was incubated with $^{45}CaCl_2$ in a concentration of about 1 μCi/mmole in the presence of nonradioactive $CaCl_2$ within the concentration range from 30 to 3000 μM at room temperature for 5 min.

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