RELATIONS BETWEEN OSCILLATIONS OF CONTRACTIONS AND TONE IN THE MYOCARDIUM OF PATIENTS WITH HEART DEFECTS

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The writers showed previously that during repetitive stimulation of myocardial preparations from patients with rheumatic heart diseases, the evoked contractions were accompanied by after-oscillations of tension ("postcontractions") [1]. During repetitive stimulation of myocardial preparations from patients, tone is also known to increase [1, 3].

The object of this investigation was to study correlation between oscillations and tone in the pathologically changed human myocardium and also to study the action of catecholamines (noradrenalin, isoproterenol, dopamine) and strophanthin on oscillations of contractions.

EXPERIMENTAL METHOD

The auricles of the right atria of patients with acquired and congenital heart defects were used as the test objects. The auricles were removed during operation. Altogether 97 preparations were investigated (73 from patients with acquired and 24 from patients with congenital defects). Auricles removed before connection to the artificial circulation apparatus were immersed in Tyrode's solution at room temperature and sent to the laboratory for investigation in a container. The transportation time was 15 min. Trabeculae 3-5 mm long and not more than 1 mm thick were isolated from the auricles. The trabeculae were placed in a working chamber through which Tyrode's solution saturated with carbogen (95% O_2 + 5% CO_2) was passed, at a temperature of 32-34°C. During 1-1.5 h before the experiment began the myocardial preparations were stimulated by above-threshold stimuli with a duration of 10-20 msec and a frequency of 0.5 Hz. The stimulation was applied through laminated silver electrodes located in the chamber along the preparation. Contractions were recorded under isometric conditions by a 6MKh1S mechanotron. Contractions were recorded on photographic film from the screen of an S1-18 oscilloscope. The duration of repetitive stimulation was 3 min. Tyrode's solution of the following composition (in mM) was used: NaCl 131, KCl 4.5, $NaHCO_3$ 11, NaH_2PO_4 0.6, $MgCl_2$ 0.25, $CaCl_2$ 2.16, glucose 11; pH 7.3.

Noradrenalin (1×10^{-6} g/ml), isoproterenol (1×10^{-7} g/ml), dopamine (1×10^{-6} g/ml), and strophanthin (1×10^{-6} g/ml) were used. The amplitude of contractions and oscillations which followed them were measured under steady-state conditions. The effect of catecholamines and strophanthin on contractions and oscillations was assessed during stimulation of myocardial preparations with the same frequency. Contractions and oscillations in Tyrode's solution served as the control.

EXPERIMENTAL RESULTS

A trace of evoked contractions, oscillations, and tone during repetitive stimulation (0.5 Hz) of a myocardial preparation from a patient with rheumatic heart disease is shown in Fig. 1A. The amplitude of contractions during repetitive stimulation remained unchanged, i.e., the classical "Bowditch's staircase" was absent. Oscillations appeared to stimulation with a frequency of 0.1 Hz (Fig. 1B), but at this frequency of stimulation the amplitude of

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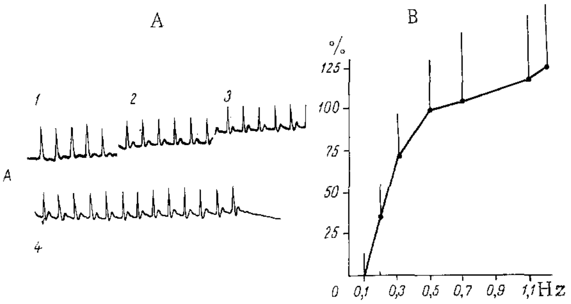

Fig. 1

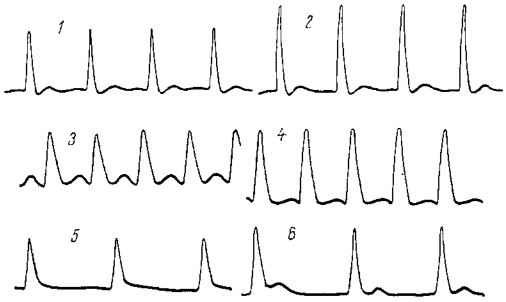

Fig. 2

Fig. 1. Development of tone and oscillations during repetitive stimulation of myocardial preparation from patient with rheumatic heart disease. A: 1-4) Successive recording of contractions, oscillations, and tone during repetitive stimulation: B) changes in tone (continuous curve) and amplitude of oscillations (vertical lines) depending on frequency of stimulation. Abscissa, frequency of stimulation (in Hz); ordinate, amplitude of oscillations and tone (in %, amplitude of first contraction at all frequencies of stimulation taken as 100%).

Fig. 2. Action of noradrenalin, isoproterenol, and strophanthin on contractions and oscillations in patients' myocardium. 1, 3, 5) Normal; 2) noradrenalin (1×10^{-6} g/ml, 0.7 Hz); 4) isoproterenol (1×10^{-7} g/ml, 1.0 Hz); 6) strophanthin (1×10^{-6} g/ml, 0.5 Hz).

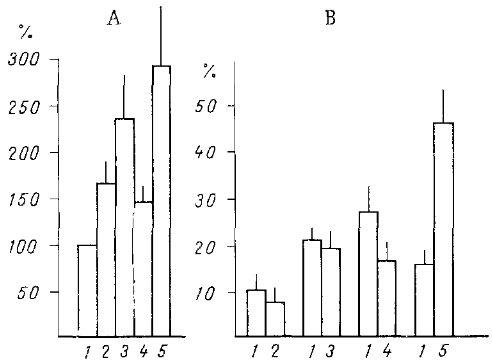

Fig. 3. Effect of noradrenalin, isoproterenol, dopamine, and strophanthin on amplitude of contractions and oscillations in myocardial preparations from patients. A) Amplitude of contractions, B) amplitude of oscillations; 1) control, 2) noradrenalin (1×10^{-6} g/ml), isoproterenol (1×10^{-7} g/ml), 4) dopamine (1×10^{-6} g/ml), 5) strophanthin (1×10^{-6} g/ml). $^{*}P < 0.05$.

the oscillations remained unchanged. An increase in the amplitude of oscillations in a regular series was observed starting with 0.2 Hz, and the higher the frequency of stimulation, the more marked was this increase. With an increase in the amplitudes of oscillations, the steepness of their leading edge was increased, and additional oscillations appeared on their trailing edge (Fig. 1A). Dependence of amplitude of oscillations measured 2 min after the beginning of stimulation on the frequency of stimulation within the range from 0.1 to 1.2 Hz is illustrated in Fig. 1B. At a frequency of 1.1-1.2 Hz the amplitude of oscillations reached 50% of the amplitude of the first contraction, taken as 100%. The tone of the preparation gradually increased in the course of repetitive stimulation (Fig. 1A), and reached the amplitude of the first contraction after 2 min. After the end of repetitive stimulation the last oscillation appeared spontaneously, and the tone began to fall slowly. About 1 min was needed for restoration of the original level of tone. The relationship between tone and frequency of stimulation of this particular preparation is shown in Fig. 1B.

Altogether 73 myocardial preparations from patients with acquired heart disease were studied. In half of the cases (37) there was a parallel increase in tone and oscillations, similar to that illustrated in Fig. 1. Oscillations in 19 preparations were not accompanied by the development of tone. In 17 preparations there were neither tone nor oscillations. In 10 of these, distinct signs of myocardial pathology were found: the absence of a positive Bowditch's "staircase" and a monophasic, falling character of the frequency-strength curve [1, 3]. In seven other preparations the rhythm-inotropic relations were close to normal.

The same scheme was used to study 24 myocardial preparations from patients with congenital heart defects. In 15 of them tone and oscillations were absent and the rhythm-inotropic relations (Bowditch's "staircase," frequency-strength curve) were normal in character. Low-amplitude oscillations (10-12% of the amplitude of contractions) were present in seven preparations, but they appeared only in response to a high frequency of stimulation (1-2 Hz). Tone was not increased at these frequencies. Only in two preparations were high-amplitude oscillations (20-40% of the amplitude of contractions), accompanied by tone, recorded.

The writers showed previously that in some cases the myocardium of patients with heart disease has reduced sensitivity to catecholamines and to strophanthin [2]. In the present investigation the effects of catecholamine and strophanthin on the myocardium of patients with acquired and congenital heart disease were compared in cases when the positive ionotropic reaction to these cardiotropic drugs still remained. As Fig. 2 shows, noradrenalin in a dose of 1×10^{-6} g/ml and isoproterenol in a dose of 1×10^{-7} g/ml considerably increased the amplitude of the rhythmic contractions and, at the same time, did not change or actually reduce the amplitude of the oscillations. By contrast strophanthin, in a dose of 1×10^{-6} g/ml, increased the amplitude of contractions and caused the development of high-amplitude oscillations even in those preparations in which, under the original conditions, there had been no oscillations. The results of statistical analysis of the data are given in Fig. 3. Noradrenalin (eight preparations), isoproterenol (17 preparations), dopamine (11 preparations), and stophanthin (10 preparations) caused an increase ($P < 0.05$) in the amplitude of contractions (Fig. 3). The amplitude of oscillations was unchanged under the influence of catecholamines, but it was increased by strophanthin ($P < 0.01$). These effects of catecholamines and strophanthin were exhibited at all frequencies of stimulation investigated and they were independent of the type of rhythm-inotropic relations in the patients' myocardium and also of the character of the heart disease (acquired or congenital).

In the existing view, relaxation of myocardial cells in warm-blooded animals and man is due to the active ATP-dependent accumulation of Ca^{++} by the sarcoplasmic reticulum (SR) and exchange of parts of the myoplasmic Ca^{++} for external Na^{+} (Na-Ca^{++} exchange diffusion) [6]. In the normal, repetitively stimulated myocardium, these transport systems are efficient enough to prevent accumulation of Ca^{++} in the myocardium at physiological frequencies of stimulation (1-2 Hz) and so to avoid poststimulation tone in the preparations. In the myocardial preparations from patients with congenital heart defects tone was absent in the overwhelming majority of cases at a frequency of 1.5-2 Hz. In patients with acquired heart defects, an increase of tone was absent in only 7 of the 73 preparations. In 50% of myocardial preparations of this group of patients an appreciable increase of tone took place in response to stimulation with a frequency as low as 0.2 Hz. Any further rise in frequency led to an even greater increase of tone. The increase of myocardial tone during repetitive stimulation must probably be regarded as disturbance of the function of transport systems removing Ca^{++} from the myoplasm.

Contraction oscillations which increased during repetitive stimulation were evidently processes due also to a disturbance of Ca^{++} sequestration in the patients' myocardium. This is shown by the fact that catecholamines, which potentiate Ca^{++} sequestration (as a result of activation of the adenylate cyclase — cyclic AMP system) [4] of SR, reduced the oscillations despite an increase in amplitude of contractions connected with strengthening of the inward Ca^{++} current [5].

Unlike catecholamines, strophanthin increased the amplitude of the oscillations. The reason was probably that inhibition of Na^{+}-K^{+} exchange in the cell membrane due to strophanthin led to accumulation of Na^{+} in the myoplasm, and the Na^{+} was exchanged for external Ca^{++} [6]. As a result of exchange the Ca^{++} concentration in the myoplasm and, correspondingly, in SR increased, and the ability of SR to perform effective sequestration of Ca^{++} from the myoplasm was reduced.

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EFFECT OF ADAPTATION TO HIGH ALTITUDE HYPOXIA ON CATECHOLAMINE METABOLISM IN SPONTANEOUSLY HYPERTENSIVE RATS

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Adaptation to periodic hypoxia under pressure chamber conditions is known to inhibit the development of spontaneous hereditary hypertension (SH) in spontaneously hypertensive rats (SHR) [5], the nearest model we have to essential hypertension in man [6]. An important pathogenetic mechanism of SH in its early stages is increased activity of the sympathetic nervous system, leading to increased vascular tone followed by structural changes in the vessel walls [10]. It has been suggested that one factor in this antihypertensive effect mentioned above is inhibition of activity of the sympathetic nervous system arising during adaptation to altitude hypoxia.

To test this hypothesis, parameters of function of the sympathico-adrenal system were studied in SHR during the development of hypertension and the effect of adaptation to hypoxia on these parameters was studied.

EXPERIMENTAL METHOD

Rats of both sexes 5 weeks old were divided into three groups. Group 1 contained 12 Wistar rats, group 2 contained 13 SHR rats; the animals of this group were not exposed to any outside influences. Group 3 consisted of 13 SHR rats which were placed for 6 h a day 6 times a week in a pressure chamber in which the pressure was reduced on the first day of the experiment to correspond to an altitude of 1100 m above sea level, on the 2nd day 2200 m, on the 3rd day 3300 m, and on the 4th and subsequent days 5000 m. The systolic pressure (BP) was measured once a week in the tail by a sphygmographic method on a "Narcobiosystem" physiograph. The concentrations of noradrenalin (NA) and adrenalin in the adrenals and of NA in the ventricles of the heart and the vas deferens were determined on the 40th and 70th days of the experiment by a fluorometric method after adsorption on columns with Dowex-50 ion-exchange resin [3]. The sensitivity of a segment of small intestine to NA and acetylcholine (ACh) was determined at the same times by determining the dissociation constant of the mediator-receptor complex [4]. On the 40th day the rate of synthesis of ^{3}H-NA and ^{3}H-dopamine from ^{3}H-tyrosine was estimated in the isolated atria [1]. The results were subjected to sta-

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