KINETICS OF ISOMETRIC RELAXATION IN THE MYOCARDIUM OF PATIENTS WITH CONGENITAL AND ACQUIRED HEART DISEASE

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Much evidence has been obtained to show that the parameters of the contraction–relaxation cycle in the myocardium of warm-blooded animals are controlled chiefly by the sarcoplasmic reticulum (SP [3]. Disturbance of the function of SR, discovered in chronic heart failure of varied etiology [4, 5], predicts not only a decrease in the ability of the myocardium to develop tension and shortening, but also a change in the kinetics of relaxation.

In the investigation described below, on the basis of the method of analysis of the kinetics of relaxation suggested previously [2] isometric relaxation was investigated in the myocardium of patients with congenital (septal heart defects – SHD) and acquired (mitral stenosis – MS, and mitral incompetence) heart diseases, and correlation also was studied between the parameters of isometric relaxation and electrical activity, the effects of adrenalin, of the frequency of stimulation and paired stimulation, and of verapamil.

EXPERIMENTAL METHOD

Experiments were carried out on thin strips of myocardium with a cross section of 0.5-1.0 mm^2, excised from the trabeculae of the auricles removed during cardiac surgical operations performed at the Sverdlovsk Interregional Cardiac Surgical Center on patients with MS (25 preparations) and patients with SHD (12 preparations), and also on strips of papillary muscles – PM (10 preparations) obtained during operations for replacement of the mitral valve. Removal of the auricles was an essential part of the operations. The myocardial preparations were placed in a continuous flow (Tyrode solution aerated with a gas mixture consisting of 4% CO_2 and 96% O_2), constant temperature (35 ± 0.5°C, pH 7.4) chamber. The preparations were stimulated by means of massive platinum electrodes with above-threshold pulses 1-5 msec in duration. Mechanical contraction of the muscles was recorded under isometric conditions by the 6MKh1S mechanotron. Electrical activity of the myocardial cells was recorded by means of glass microelectrodes (7-20 MΩ). All experiments were carried out with preparations of a length at which maximal force of isometric contractions was observed.

EXPERIMENTAL RESULTS

Previously, during an analysis of the kinetics of isometric relaxation in the ventricular myocardium of the ventricles of warm- and cold-blooded animals the writers found a linear exponential type of relaxation, when the tension P(t) in the relaxation phase was described by the function $P = P_0 \exp(-Vt)$, a quadratic exponential type of relaxation, when $P = P_0 \exp(-\alpha^2 t^2)$, and a mixed type, in which the beginning of relaxation was described by quadratic and the final part by linear exponents. The parameters of relaxation for a given single contraction are constants of the rate of relaxation K and α. In the preparations studied mainly the mixed type of relaxation was observed, although in some cases the linear type was found.

Mean values of K and α and also their minimal and maximal values for preparations of all groups studied (control), and also values of the increase in the constants K and α, positive (+) and negative (–), in percentages of the control under the influence of adrenalin (10^{-7} M), of verapamil (10^{-5} g/ml), of an increase in the frequency of stimulation from 18 to 60 pulses/min, and of paired stimulation with the optimal interval between the stimuli in the pair (when the maximal inotropic effect occurred), are given in Table 1.

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TABLE 1. Constants of Isometric Relaxation of Myocardium in Patients with Congenital and Acquired Heart Diseases (M ± m)

Material studied	Control		A		V		St		PS	
	K, sec^{-1}	α, sec^{-1}	K	α	K	α	K	α	K	α
Preparations from patients with SHD	11,5±0,6 (7,9—16,7)	6,0±0,6 (3,0—9,5)	+22	+26	—24	—28	+16	+14	—18	—11
Preparations from patients with MS	7,8±0,5 (3,8—11,1)	4,9±0,3 (2,1—7,8)	+89	+141	—36	—20	+32	+15	—14	—12
PM	4,8±0,9 (3,2—7,6)	2,4±0,9 (1,7—3,5)	+35	+52	—28	—22	+34	+31	—16	—29

Legend. A) Adrenalin; V) verapamil; St) stimulation; PS) paired stimulation. Limits of variations shown between parentheses.

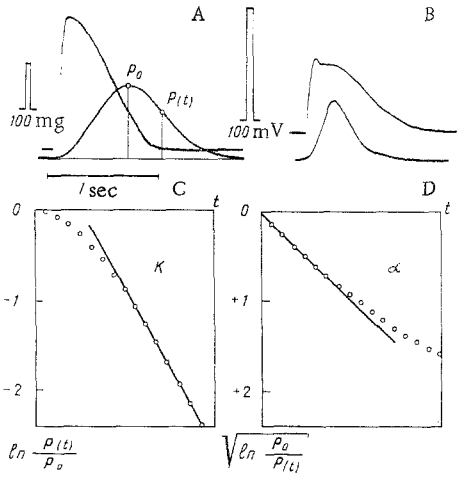

Fig. 1. Correlation between AP and isometric contraction of the pathological myocardium (determination of relaxation constants). A, B) AP and isometric contraction in PM and material from patient with MS respectively; P_0, P(t) — amplitudes of isometric contraction at time 0 and t from beginning of relaxation; C, D) determination of constants K and α for mixed type of relaxation (curves of isometric relaxation in the above-mentioned coordinates).

It will be clear from Table 1 that the constants K and α had their highest value for preparations obtained from patients with SHD and the lowest value in PM. This is in agreement with other observations which show that relaxation takes place significantly more slowly in the myocardium of the ventricles than in the atria [1, 2]. Meanwhile, in the myocardium of the left ventricle of warm-blooded animals, such as the rabbit, the constant K is much greater, namely 14 sec^{-1}. Such a large difference between the constants can hardly be attributed to species differences, but a more likely suggestion is that relaxation in PM was significantly retarded because of pathological changes. This suggestion is also confirmed by the fact that the constants K and α were appreciably higher in the myocardium of the atria of patients with SHD than in the myocardium of patients with MS. Disturbance of relaxation is evidently closely connected with rheumatic processes.

The data in Table 1 also show that adrenalin and an increase in the frequency of stimulation led to an increase in the relaxation constants, whereas verapamil and paired stimulation reduced them. The high sensitivity of the relaxation constants of preparations from patients with MS deserves particular attention. This fact suggests that a high proportion of the SR in most myocytes of patients with MS is in the inactivated form, and is activated by the action of adrenalin.

The mechanism of the effect of stimulation on relaxation is not clear. It is worth noting that in preparations obtained from patients with MS and SHD, and also in PM, with an increase in the frequency of stimulation the force of contractions could either increase, decrease, or remain unchanged. In all cases, however, the constants K and α increased. This means that the kinetics of relaxation probably is independent of the inotropic state of the myocardium. The decrease in the relaxation constants during paired stimulation cannot thus be connected with an increase in the amplitude of contractions. It may be that the increase in the total duration of membrane depolarization during paired stimulation (doubling of the action potential – AP) reduces the relaxation constants.

It is likewise not clear why verapamil reduced the relaxation constants, and although we know [6] that it depresses the calcium-sequestering function of the SR, there are no data on the ability of verapamil to penetrate into the sarcoplasm.

It was postulated that the temporal course of relaxation in the myocardium is under the control of the duration of AP because of the influence of the transmembrane potential on the sequestering ability of the reticulum. To test this hypothesis coefficients of linear correlation (r) were calculated between the duration of AP at the level of 80% repolarization (T) and the relaxation constants. The results showed strong correlation between the duration of AP and the relaxation constants in PM – the value of r between T and K was –0.93 and between T and –0.87. Weaker correlation was found in preparations from patients with MS: this coefficient for the constants K and α was –0.71 and –0.67 respectively. Correlation was virtually absent in patients with SHD: –0.57 and –0.35. Consequently, AP in PM and preparations taken from patients with MS probably controls the temporal course of relaxation, whereas in preparations from patients with SHD this type of control is absent. It can be tentatively suggested that under normal conditions correlation between the duration of AP and the relaxation constants in the atria is very weak (preparations from patients with SHD were closer to normal). In MS, however, when the duration of the repolarization phase is long and it often exceeds the duration of contraction (Fig. 1B), the temporal course of repolarization can affect the kinetics of relaxation.

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