EFFECT OF MYOCARDIAL HYPERTROPHY ON THE DYNAMICS OF RESTORATION OF DIASTOLIC CONTRACTILITY

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The amplitude of extrasystolic contraction of the papillary muscle of rats is always smaller than the amplitude of the regular contraction. In hypertrophy of the heart this rule is disturbed and extrasystolic contraction exceeds regular throughout most of diastole. A similar pattern is found in the normal frog heart muscle. In experiments on the papillary muscles from hypertrophied hearts automatic activity was frequently observed. The amplitude of the contractions was much smaller than the amplitude of the regular contractions evoked by electrical stimulation. This phenomenon was not observed in experiments on papillary muscles from the hearts of control rats. The results evidently reflect disturbances of the process of calcium binding by the sarcoplasmic reticulum in hypertrophy.

KEY WORDS: myocardial hypertrophy; extrasystole.

The restoration of myocardial contractility in the diastolic phase is characterized by a certain dynamics that differs in frogs and mammals [6, 10, 13, 14, 15]. A very probable basis for this process is the difference in the accumulation of calcium in places where it is released to the myofibrils [6, 14, 15], where it activates the contraction process.

In the hypertrophied heart muscle the process of coupling of excitation with contraction is evidently disturbed. Accordingly, in the present investigation changes in the process of restoration of contractility during hypertrophy were studied.

EXPERIMENTAL METHOD

Hypertrophy of the heart was produced in rats by constricting the abdominal aorta [3, 5]. After 1.5 years the relative weight of the left ventricle in the experimental rats was 95% higher than in intact controls. The papillary muscles were removed from the left ventricle of the rats. The thickness of these muscles determines the maximal strength of contraction and the inotropic response to an increase in the frequency of contraction [1, 10]. For this reason experiments were carried out on strips of equal thickness isolated from the muscles [3, 5]. The strips contracted in Krebs' solution at 29°C, saturated with 95% O_2 + 5% CO_2, raising a weight of 0.5 g. Their shortening during electrical stimulation at a frequency of 20/min was recorded after amplification (Disa Electronic) on a Cardiovar apparatus. In this isotonic regime, where the measure of mechanical energy of contraction was the amplitude of contraction, the dynamics of restoration of contractility was determined by comparing the amplitude of contraction evoked by electrical stimulation at various times after a regular contraction and the amplitude of the regular contraction. The inotropic reaction of the myocardium to a successive increase in the frequency of contractions from 20 to 40, 60, 100, 150, and 200/min was then determined. In another series of experiments carried out on strips of ventricle from the frog Rana temporaria, the strength of contraction under isometric conditions was

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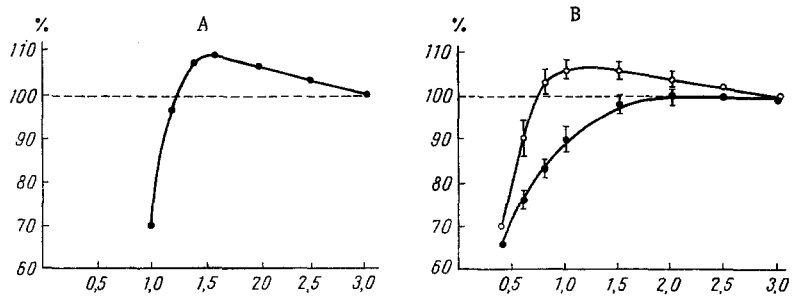

Fig. 1. Dynamics of strength of extrasystolic contractions of a strip of ventricle from the frog's heart (A) in the period of diastole when contracting at 20/min (isometric regime) and amplitudes of contractions of strips of papillary muscles from control (filled circles, eight experiments) and hypertrophied (empty circles, six experiments) rat hearts (B) (isotonic regime). Abscissa, time after beginning of preceding regular contraction (in sec); ordinate, strength (A) or amplitude (B) of contractions (in percentage of amplitude of regular contraction). Vertical lines indicate twice the error of the mean.

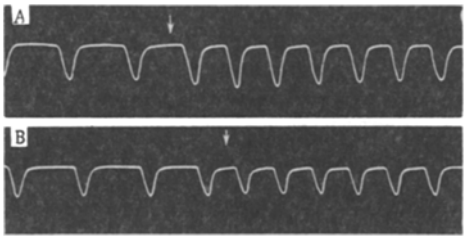

Fig. 2. Effect of increase in frequency of contractions on amplitude of contractions of myocardial strips from hypertrophied (A) and control (B) rat hearts. Downward deflection corresponds to shortening. Frequency of contractions increased from 100 to 150 (A) and 165 (B) min. Times of increase of frequency indicated by arrows.

recorded by means of a strain gauge, TU-4M amplifier, and OSM-4-01 oscilloscope. The strips were contracted by electrical stimulation at a frequency of 20/min in Krebs' solution at 18-20°C.

EXPERIMENTAL RESULTS AND DISCUSSION

With an increase in the interval between the regular and extrasystolic contraction of the frog heart muscle the strength of the latter increased rapidly (Fig. 1A), and throughout most of diastole it exceeded the strength of the regular contraction. The amplitude of the extrasystolic contraction of the heart muscle of the control rats usually never exceeded the amplitude of the regular contraction. The initial level was reached about 2 sec after the regular contraction (Fig. 1B). The hypertrophied heart muscle of the rats regained its initial level of contraction after as little as 0.8 sec (Fig. 1B), and it showed a small but definite increase in the amplitude of the extrasystolic contraction compared with that of the regular contraction, just as is observed in experiments on the frog myocardium.

During a stepwise increase in the frequency of contraction of the normal and hypertrophied rat myocardium from 20 to 200/min, the negative inotropic effect well known for this species was observed [1, 7, 12]. However, with each new frequency the amplitude of the first contractions of strips from the hypertrophied hearts was greater than the amplitude of the stable contractions at the previous frequency (Fig. 2A). This transient excess, analogous to that observed in Fig. 1B, occurred in all experiments and it varied in magnitude from 15 to 25%. Strips from the control hearts were characterized by an initial decrease in the amplitude of contractions by 10-15% with each new increase in frequency (Fig. 2B). This response is characteristic of the mammalian myocardium [13]. The unique response of the hypertrophied myocardium was similar to that of the frog myocardium [13].

When this similarity is analyzed it must be noted that the relatively rapid restoration of contractility of the frog myocardium was combined with the relatively weak development of the sarcoplasmic reticulum [16], the function of which is to extract calcium from the myofibrils and to bind it. The rat myocardium, with its more highly developed sarcoplasmic reticulum, is characterized by the relatively slow restoration of contractility, just like the myocardium of other mammals [13, 15]. However, overloading the rat myocardium with calcium sharply accelerates the restoration of its contractility [15], and the curve acquires the characteristic form for the frog myocardium.

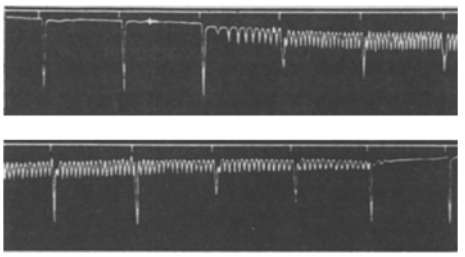

Fig. 3. Continuous recording of contractions of strip from hypertrophied rat heart. Above: marker of stimulation, below: record of contraction of muscle directed downward. After three regular contractions, spontaneous contractions can be seen to arise against the background of the regular.

These results suggest that the curve of amplitude of extrasystolic contractions (Fig. 1B) characteristic of the hypertrophied rat heart muscle may be attributable to at least two factors: an increase in the intracellular calcium concentration or disturbance of calcium binding in the structures of the sarcoplasmic reticulum. The calcium concentration in the hypertrophied myocardium is known to be increased [18], whereas the ability of isolated fragments of the sarcoplasmic reticulum to bind calcium is reduced [17].

The following observation supports this view. In the period of stabilization in three of the six experiments on papillary muscles from hypertrophied rat hearts spontaneous automatic activity was observed. It appeared about 1 h after the muscles had been placed in the chamber, and it lasted for between 10 and 30 min in periods each of 30-40 sec (Fig. 3). A characteristic feature of this phenomenon was the low amplitude of the contractions; however, this was not due to their high frequency because regular pulses of excitation evoked a much stronger response. Its magnitude varied depending on the phase of spontaneous contraction at which the electric pulse arrived (Fig. 3). The impression was thus gained that only a certain part of the muscle contracted without the development of a spreading action potential. No spontaneous contractions occurred in any of the control experiments. The development of spontaneous automatic activity in fibers of the rat myocardium with injured sarcolemma under special conditions is regarded as the result of the regenerative liberation of calcium from the structures of the sarcoplasmic reticulum [8] because its ability to retain calcium is exceeded.

The results of these investigations thus evidently point to a disturbance of the process of calcium binding during considerable myocardial hypertrophy. The compensatory value of this change may lie in the increase of the calcium ion concentration acting on the myofibrils. Such a change is probably necessary because of the increase in the number of myofilaments in each cell.

LITERATURE CITED

1. V. I. Kapel'ko, Byull. Éksperim. Biol. i Med., No. 12, 6 (1970).
2. F. Z. Meerson, V. I. Kapel'ko, and A. A. Nurmatov, Kardiologiya, No. 5, 41 (1970).
3. F. Z. Meerson and V. I. Kapel'ko, Vestn. Akad. Med. Nauk SSSR, No. 11, 14 (1970).
4. F. Z. Meerson, V. I. Kapel'ko, and A. A. Nurmatov, Acta Cardiol. (Brussels), 26, 547 (1971).
5. F. Z. Meerson and V. I. Kapel'ko, Cardiology, 57, 183 (1972).
6. R. S. Orlov, V. Ya. Izakov, and V. M. Shevelev, Fiziol. Zh. SSSR, 57, 223 (1971).
7. A. Fabiato and F. Fabiato, Circulat. Res., 31, 293 (1972).
8. J. M. Benforado and L. L. Wiggins, J. Pharmacol. Exp. Ther., 147, 70 (1965).
9. H. Gelband and A. L. Bassett, Circulat. Res., 32, 625 (1973).
10. A. H. Henderson, D. L. Brutsaert, W. W. Parmley, et al., Am. J. Physiol., 217, 1273 (1969).
11. R. L. Kaufmann, H. Homburger, and H. Wirth, Circulat. Res., 28, 346 (1971).
12. J. Koch-Weser, Am. J. Physiol., 204, 451 (1963).
13. J. Koch-Weser and I. R. Blinks, Pharmacol. Rev., 15, 601 (1963).
14. P. K. Orkand, J. Physiol. (London), 196, 311 (1968).
15. C. J. Posner and D. A. Berman, Circulat. Res., 25, 725 (1969).
16. J. R. Sommer and E. A. Johnson, Am. J. Cardiol., 25, 184 (1970).
17. P. V. Sulakhe and N. S. Dhalla, J. Clin. Invest., 50, 1019 (1971).
18. L. Tobian and M. Duke, Am. J. Physiol., 217, 522 (1969).