RESTITUTION OF CONTRACTILITY OF THE ISOTONICALLY AND ISOMETRICALLY CONTRACTING HEART MUSCLE

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UDC 612.171.1-08

KEY WORDS: papillary muscles; regular contraction; isotonic regime; isometric regime.

The contractile function of the myocardium *in situ* is controlled by both inotropic and mechanical factors. Inotropic factors exert their primary influence on the ion transport system, as a result of which changes take place in the concentration of Ca^{++}, which activates myofibrils. Mechanical factors — a change in the return flow of blood or resistance — act mainly on myofibrils, changing their initial length or the degree of development of tension. The question of whether under these circumstances changes arise in the ion transport system is not yet settled. The dynamics of recovery of contractility is an important criterion of work of the ion transport system of the myocardial cells. If the length of the muscle and the load on it remain unchanged, restitution of contractility is determined chiefly by the dynamics of Ca^{++} accumulation in regions from which these ions enter the myoplasm during excitation [13].

In the investigation described below the parameter of restitution of contractility was the maximal velocity of contraction — its peak coincides closely with the peak of free Ca^{++} in the myoplasm [3] and it depends to a lesser degree on activity of the system removing Ca^{++} from the myoplasm than the peak of contraction. Restoration of the velocity of contraction was determined under isotonic and isometric conditions of contraction of the isolated heart muscle over a wide range of Ca^{++} concentrations in the perfusate.

EXPERIMENTAL METHOD

Experiments were carried out on isolated papillary muscles taken from the right ventricle of guinea pigs. The muscles were placed in a chamber containing Krebs' solution saturated with 5% CO_2 + 95% O_2 at 29°C (pH 7.4). The lower end of the muscle was fixed rigidly and the upper end was attached either to an FT 03 Grass transducer to measure the force during isometric contraction or to an isotonic lever, displacement of which was measured by a photoelectric transducer with a linear range of 2 mm. Signals of force or shortening, together with their first derivative obtained with a differentiator, were recorded on a "Gould Brush 2200" two-channel recorder. The rest of the experimental conditions were described previously [1]. To determine restitution of contractility, stimulation by paired pulses was carried out, with a reducing interval between pulses. The total number of pulses per minute remained constant. When the intervals were sufficiently short, extrasystolic contraction merged with regular, and in these cases the velocity and the amount of additional contraction were measured.

EXPERIMENTAL RESULTS

To compare the dynamics of restitution under different conditions of contraction, the maximal velocity of the extrasystolic contractions induced at different time intervals after regular contraction was expressed as a ratio of the corresponding value at a constant frequency of 1 Hz. With a normal Ca^{++} concentration in the solution the restitution curves were very similar in the two regimes (Fig. 1a), but nevertheless significantly faster restitution was found during isotonic contraction within the interval of 0.35-0.50 sec. The difference increased even more with an increase in the Ca^{++} concentration to 7.5 mM, but almost disappeared when it fell to 0.5 mM (Fig. 1b). The time course of strength or amplitude of contraction changed in a similar way.

Laboratory of Physiology of the Myocardium, Institute of Experimental Cardiology, All-Union Cardiologic Scientific Center, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR E. I. Chazov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 95, No. 3, pp. 3-5, March, 1983. Original article submitted August 13, 1982.

0007-4888/83/9503-0255$07.50

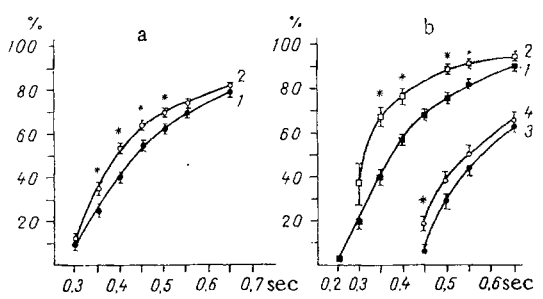

Fig. 1

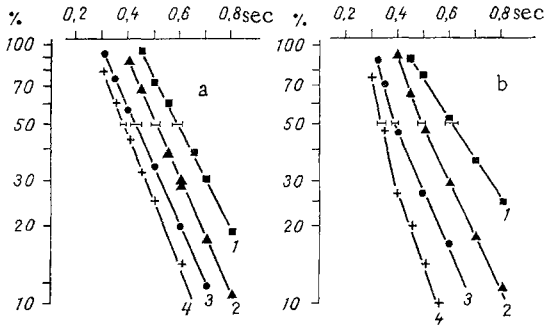

Fig. 2

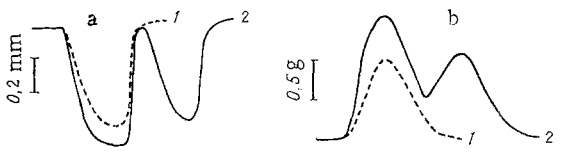

Fig. 3

Fig. 1. Velocity of extrasystolic contraction of papillary muscle under isometric (1, 3) and isotonic (2, 4) conditions as a function of extrasystolic interval with Ca^{++} concentrations of 2.5 mM (a), 7.5 mM (b — 1, 2), and 0.5 mM (b — 3, 4). The velocity of contraction is expressed in percent of its value at the initial frequency of 1 Hz. Asterisks indicate statistically significant differences ($P < 0.01$).

Fig. 2. Time course of disappearance of difference between velocity of regular and extrasystolic contractions at different extrasystolic intervals under isometric (a) and isotonic (b) conditions. Ca^{++} concentration in solution: 1) 0.5 mM, 2) 1.25 mM, 3) 2.5 mM, 4) 7.5 mM. Horizontal lines denote twice the mean error of the time to reach 50% restitution.

Fig. 3. Isotonic (a) and isometric (b) contractions of papillary muscle in a Ca^{++} concentration of 7.5 mM. 1) Regular contractions at a frequency of 1 Hz; 2) contractions during paired stimulation with an extrasystolic interval of 0.4 sec. Calibration for isotonic contraction 0.2 mm, for isometric contraction 0.5 g.

To estimate the steepness of the restitution curve quantitatively the time course of maximal velocity of contraction was expressed in a system of reciprocal coordinates according to the formula 100 — x (in per cent), representing the difference between the maximal velocities of regular and extrasystolic contractions at that given moment. With an increase in the extrasystolic interval this difference, expressed on a logarithmic scale, disappeared as a linear function (Fig. 2). Under isometric conditions a change in the Ca^{++} concentration did not affect the shape of this relationship, which remained linear (Fig. 2a). With an increase in the Ca^{++} concentration only a shift of the straight lines to the left was observed, i.e., restitution began sooner; the constant of the steepness of restitution also increased a little — from 2.1 at a low Ca^{++} concentration (0.5 mM) to 2.5 at a high Ca^{++} concentration (7.5 mM).

Restitution of contractility reflects most closely the dynamics of recovery of the number of Ca^{++} ions entering the myoplasm under the influence of premature excitation [13]. Two pathways of Ca^{++} penetration into the cells are known: the electrogenic Ca^{++} current [12] and Ca^{++}—Na^{+} exchange, which may be electrically neutral [10, 11]. Liberation of Ca^{++} from the third possible source — the sarcoplasmic reticulum — depends on the Ca^{++} concentration in the myoplasm [6] and, consequently, it is determined by the dynamics of restoration of the Ca^{++} inflow into the cell. We know that restitution of the Ca^{++} current is an exponential process [8], which depends primarily on the number of Ca^{++} ions on the inner surface of the sarcolemma [8, 9]. The dynamics of recovery of Ca^{++}—Na^{+} exchange has not yet been established, but it is probably mainly determined by the number of Na^{+} ions bound with the carrier molecule on the inner surface of the sarcolemma. Since removal of Na^{+} from cells in the resting period through the Na^{+}—K^{+} pump takes place exponentially [5, 7], the Ca^{++}—Na^{+} exchange which is dependent on

it ought to decrease exponentially with lengthening of the rest period. This means that both the main pathways of Ca^{++} penetration into the cell are most probably characterized by exponential recovery. It is therefore clear why restitution of contractility under isometric conditions of contraction is exponential in character in the presence of different Ca^{++} concentrations (Fig. 2).

Under isotonic conditions the dynamics of restitution was monoexponential only when the Ca^{++} concentration in the solution was low (0.5 mM, see Fig. 2b). In higher Ca^{++} concentrations the dynamics of restitution became biexponential; the steepness of the first phase, moreover, was much greater than that of the second. An increase in Ca^{++} concentration from 0.5 to 7.5 mM was combined with an increase in the constant of steepness of restitution from 1.6 to 4.5.

The presence of steeper restitution under isotonic conditions in normal and high Ca^{++} concentrations (Fig. 1) was observed within the range from 0.35 to 0.45 sec, when relaxation under isotonic conditions was almost complete, unlike under isometric conditions. This familiar relationship is illustrated in Fig. 3 [4]. In this experiment, when the Ca^{++} concentration was 7.5 mM, extrasystolic contraction, induced after completion of the main contraction, was characterized by almost complete recovery of amplitude (Fig. 3a), whereas under isometric conditions the force of the extrasystolic contraction evoked after the same interval, but before relaxation was complete, was only about half of the force of the regular contraction (Fig. 3b).

These observations suggested a connection between the velocity of relaxation of the muscle and the steepness of restitution of contractility. Since the velocity of relaxation is determined primarily by the amplitude or force of contraction [2], to characterize the relaxation process we used a relaxation index, determined by dividing the maximal velocity of relaxation by the amount of contraction under the given conditions. Over a wide range of Ca^{++} concentrations positive correlation was found ($r = 0.83$) between the relaxation index and the constant of steepness of restitution under isometric conditions. Consequently, acceleration of relaxation was coupled with an increase in steepness of restitution of contractility. Under isometric conditions this relationship was much less clearly expressed.

Accelerated restitution of contractility under isotonic conditions was thus due most probably to more rapid relaxation, as a result of which the outflow of Ca^{++} from the cell was accelerated. The importance of accelerated restitution increases when the frequency of contractions is high and the diastolic pause is greatly reduced.

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