Length-dependent changes in myocardial contractile state

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Parmley, William W., and Leonard Chuck Length-dependent changes in myocardial contractile state. Am. J. Physiol. 224(5): 1195-1199. 1973.—The present study describes an alteration of myocardial contractile state which is intimately associated with changes in muscle length. Seventy-one right ventricular cat papillary muscles were studied isometrically or isotonically in vitro. When muscle length was increased from 10% less than Lmax up to Lmax, there was an immediate rise in isometric force due to the Starling mechanism. This was followed by a gradual secondary increase in force (average 25%), which occurred over the subsequent 10 min. This effect was reversible, since a reduction in muscle length to 10% less than Lmax produced a fall in force due to the Starling mechanism, followed by a gradual secondary reduction in force over the next 10 min to the original base line. This slow secondary change in contractile state was unrelated to the cross-sectional area of the muscles or catecholamine depletion by reserpine and persisted during hypoxia. The same effect was seen during isotonic contractions with a preload only, suggesting that it was primarily a length-dependent, rather than force-dependent, phenomenon. This study indicates that one cannot simply relate muscle performance to length without knowledge of the previous history.

preload; afterload; calcium; hypoxia; homeometric autoregulation; stress relaxation

The two basic mechanisms available to cardiac muscle to alter its performance are 1) a change in end-diastolic fiber length (preload) and 2) a change in contractile state. These two mechanisms have been assumed to be different from each other since the former appears to be related to the degree of overlap of actin and myosin filaments, whereas the latter effect presumably relates to the rate at which cross bridges between the myofilaments are formed and broken (2, 10). Although changes in afterloading are known to alter contractile state (1), there have been no previous studies to suggest that changes in preload or fiber length also alter contractile state.

The present study describes alterations in contractile state which are intimately associated with changes in preload and muscle length, thus suggesting that there may be a closer interrelationship between muscle length and contractile state than has previously been assumed.

Methods

Seventy-one right ventricular cat papillary muscles were studied in vitro utilizing previously described myographic techniques (6). Following intraperitoneal anesthesia (pentobarbital, 25 mg/kg), the chest was rapidly opened, the heart was removed, and suitable right ventricular papillary muscles were placed in a muscle bath in vitro. In the isometric studies, one end was fixed while the other end was attached to a force transducer by a short length of wetted 4-0 silk. Each muscle was bathed with Krebs-Ringer bicarbonate solution at specified temperatures between 24 and 37 °C and was stimulated at 12/min (American Electronic Laboratories stimulator 104A) utilizing mass electrodes placed parallel to the muscle in the bath with a voltage 10% above threshold. Each bath was bubbled with 95% oxygen and 5% CO2 except when the effects of hypoxia were examined (six muscles), whereupon the mixture was changed to 95% nitrogen and 5% CO2. In the isotonic muscle studies, a previously described lever system (equivalent mass 100 mg) was utilized (5). One end of the muscle was fixed by a spring clip extension of a force transducer, and the other end was attached to the tip of the lever system. Appropriate weights were placed on the other end of the lever system to establish a given preload. Eight muscles were removed from cats that had been previously reserpinized, 3 mg/kg, 48 and 24 hr prior to sacrifice to produce catecholamine depletion (9). The relative changes in muscle length were quantitated by a micrometer dial, which allowed for precise changes in length. At the end of each experiment, absolute muscle length was measured at Lmax, and the muscle was weighed to the nearest 0.01 mg for calculation of cross-sectional area. The average control stress developed by all muscles was 5.2 ± 0.2 (SE) g/mm2.

Results

The basic phenomenon under consideration is illustrated in a representative muscle in Fig. 1. The muscle was standardized for 2 hr at a preload of 0.6 g, which corresponds to a muscle length of 99% of Lmax. When muscle length was shortened 10%, resting force fell to zero and developed force was reduced from 9.5 to 4.6 g. Following a transient rise for a few beats to 5.3 g (point A), there was a slow further fall in force at the same muscle length to 4.1 g (point B). After force had again stabilized at this new level, muscle length was returned to the original length, with an increase in force due to the Starling mechanism. In addition, however, following a transient decrease to point C, a gradual increase in force occurred over the next few min-

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tractions C to D of Fig. 1) as muscle length was increased from 89% \(L_0\) to 99% of \(L_{\text{max}}\). If the muscles with the larger cross-sectional area had a central hypoxic core, they might be expected to benefit more from an increase in length and reduction in cross-sectional area and thus show the greatest secondary increase in force. There does not appear, however, to be any dependence of the increase in force on cross-sectional area. The lower panel of Fig 3 shows the secondary reduction in force produced by shortening muscle length from \(L_{\text{max}}\) to \(L_0\) (contractions A to B of Fig. 1). Again, there is no obvious dependence of the magnitude of this change on cross-sectional area. Although there was a considerable variability in the response of different muscles, no muscle either failed to respond or went in the opposite direction. Furthermore, the magnitude of the changes in a given muscle was quite reproducible on repetitive (up to five) experiments. The magnitude of the response was also proportionally reduced by smaller changes in muscle length. The time constant of the decrease in force (A to B of Fig. 1) was similar to the time constant of the increase in force (C to D of Fig. 1). However, the muscles showing the lesser responses did so in slightly less time.

FIG. 1. Slow-speed recordings of isometric contractions from a representative cat papillary muscle. Cross-sectional area equals 1.4 mm\(^2\). Following a decrease in muscle length, secondary fall in force occurs from contractions A to B. Following an increase in muscle length, secondary increase in force occurs from contractions C to D. See text for details.

FIG. 2. Contractions A, B, C, and D of Fig. 1 are superimposed on a memory oscilloscope for comparative evaluation.

utes (point D) without a further change in muscle length. Care was taken in all experiments not to stretch the muscle to a resting force or length beyond the apex of the length-tension curve. In particular, the muscle was always increased to a length just short of the apex of the length-tension curve. Although the magnitude of the phenomenon was variable, no muscle either failed to show the above alterations or showed changes opposite to those illustrated above.

Figure 2 illustrates superimposed tracings on a Polaroid photograph of contractions at the A, B, C, and D points of the same muscle. The slight increase in time-to-peak force at the longer muscle length (C and D) is a usual finding (5). Note, however, that there was little change in time-to-peak force with a change in contractile state from A to B or from C to D. Since there was no change in time-to-peak force at a given muscle length, the maximum rate of force development changed to a similar extent as developed force and is indicative of a change in contractile state.

One explanation for this phenomenon might be related to a decrease in cross-sectional area as the muscle was stretched and subsequent improvement in oxygenation of a central core. Therefore, an analysis of the results relative to the cross-sectional area of each muscle was made. Figure 3 illustrates the results in all muscles studied at 30 C. The top panel represents the secondary increase in force (contractions C to D of Fig. 1) as muscle length was increased from 89% \(L_0\) to 99% of \(L_{\text{max}}\). If the muscles with the larger cross-sectional area had a central hypoxic core, they might be expected to benefit more from an increase in length and reduction in cross-sectional area and thus show the greatest secondary increase in force. There does not appear, however, to be any dependence of the increase in force on cross-sectional area. The lower panel of Fig 3 shows the secondary reduction in force produced by shortening muscle length from \(L_{\text{max}}\) to \(L_0\) (contractions A to B of Fig. 1). Again, there is no obvious dependence of the magnitude of this change on cross-sectional area. Although there was a considerable variability in the response of different muscles, no muscle either failed to respond or went in the opposite direction. Furthermore, the magnitude of the changes in a given muscle was quite reproducible on repetitive (up to five) experiments. The magnitude of the response was also proportionally reduced by smaller changes in muscle length. The time constant of the decrease in force (A to B of Fig. 1) was similar to the time constant of the increase in force (C to D of Fig. 1). However, the muscles showing the lesser responses did so in slightly less time.

FIG. 3. Secondary increase in isometric force (contractions C to D of Fig. 1) is shown in upper panel for each muscle studied isometrically. Percent increase in force is plotted as a function of cross-sectional area (and calculated radius) of muscle. Percent decrease in force (contractions A to B of Fig. 1) is plotted in lower panel for each muscle. Muscles from reserpinized cats and muscles studied during hypoxia are indicated by appropriate symbols.
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FIG. 4. Normal muscles studied at 24 C (n = 17), 30 C (n = 24), and 37 C (n = 10) are grouped accordingly. Data are expressed as means ± se and arc in same format as in Fig. 3. Not all of muscles of Fig. 3 are included in the 30 C group in Fig. 4, in order to compare only muscles of similar cross sectional.

Those muscles from cats that had been reserpinized and depleted of catecholamines showed a similar change in force (Fig. 3), suggesting that this change was unrelated to intrinsic stores of catecholamines. In the six muscles made hypoxic, developed force fell 68% to a new plateau after 30 min (11). The percentage changes in force following a change in muscle length, however, were similar to the oxygenated state (Fig. 3). Figure 4 illustrates the temperature dependence of this phenomenon in a group of muscles that were studied at 24, 30, and 37 C. The data of Fig. 4 are expressed as the mean ± se for all muscles studied in each group. The format of the data presentation is similar to that of Fig. 3. It is apparent that the magnitude of the percentage response at 37 C was less than the magnitude of response at 24 or 30 C (P < 0.05). Furthermore, the time course of the change in force was more rapid at 37 C as compared to the lower temperatures.

In order to determine whether this phenomenon was dependent on the increase in force produced at the longer muscle length or the increase in muscle length per se, 17 muscles were studied isotonically with only a preload. The change in velocity of shortening of the preloaded contraction was utilized as an index of the change in contractile state. Figure 5 shows the overall results in muscles studied at different temperature. Although there was some variability of the response, there does not appear to be any obvious dependence of the magnitude of the change on either cross-sectional area or temperature. The magnitude of the increase in velocity of the isotonic contraction following an increase in muscle length (top panel of Fig. 5) was less than the corresponding changes during isometric contraction (top panel of Fig. 3). The percentage decrease in isotonic velocity following a decrease in muscle length (lower panel of Fig. 5), however, was similar to the corresponding isometric changes (lower panel of Fig. 3).

DISCUSSION

The results of the present study indicate that not only is length history an important factor in determining muscle performance, but also that it brings about time-dependent changes in contractility. Thus, one cannot simply relate muscle performance to length without a clear knowledge of the previous history of the muscle. This fact is further illustrated by load-dependent alterations in contractile state (4), which also have a definite time course.

In a few muscles studied isometrically, following changes in calcium concentration, the percentage change in force was reduced (see Fig. 6). For each muscle in Fig. 6, the secondary increase in force (isotonic equivalent of contractions C to D of Fig. 1) following a change in muscle length from L0 to Lmax (●) is plotted in the upper right-hand quadrant, with each axis representing a different calcium concentration. The percentage change following 5.0 mM calcium was less than that found in 2.5 mM calcium, presumably because the muscle had already been potentiated by the higher calcium and was closer to its ceiling of contractility. Any point on the dashed line would represent an equal percentage response in each calcium concentration. Similarly, the percentage fall in force (A to B of Fig. 1), following a decrease in muscle length (A), was also less in three of six muscles in the higher calcium concentration.

FIG. 5. Percent change in preloaded velocity of shortening for all muscles studied isotonically is plotted as a function of muscle cross-sectional area and radius. Percent secondary increase in velocity is plotted in upper panel as muscle length is increased (isotonic equivalent of contractions C to D of Fig. 1). Percent secondary decrease in velocity is shown in lower panel as muscle length was decreased (isotonic equivalent of contractions A to B of Fig. 1). Muscles studied at 24, 30, and 37 C are appropriately designated.
muscle. Recent studies demonstrated in isolated heart muscle that a change from the isotonic to isometric mode of contraction at a constant muscle length resulted in a decrease in contractile state over several beats with little change in time-to-peak force (4). The magnitude of this previously reported change was similar to the present study, but differed as follows: a) there was no change in muscle length; b) the increase in developed force was associated with a fall in contractile state; and c) the effect was complete in a few beats rather than the several minutes required for the length-dependent effect observed in the present study.

Two other force-dependent effects on contraction are important relative to the present study. The first, homeometric autoregulation, is characterized by an apparent increase in contractile state and pump performance of the intact heart following an increase in afterload (7). This phenomenon is similar to the present study only in that an increase in contractility occurs subsequent to an increase in developed force. The present effect, however, does not require an increase in developed force, since it was also observed in the nonafterloaded isotonic experiments. Thus, the present phenomenon does not appear to be the same as homeometric autoregulation.

The second force-related effect is the alteration of diastolic compliance that has been attributed to a force-dependent series viscous element (VE) (1, 8). Relative to the present study, for example, if muscle length were increased beyond Lmax and held there, there would ensue a slow fall in resting force (stress relaxation), presumably associated with the slow lengthening of a series viscous element. The consequent reduction in contractile element length as the viscous element elongated might produce an increase in force as the contractile element shortened to its optimum length (1). To avoid this as a potential factor in the present study, however, muscle length was never increased to Lmax or beyond. Thus, any stress relaxation observed on the ascending limb of the length-tension curve would tend to shorten the contractile element and reduce force rather than increase it. Thus, stress relaxation is inadequate to explain the slow time-dependent increase in contractile state observed in the present study.

However, a series viscous element might be responsible for the transient phenomena (first few beats) observed after each change in length (Fig. 1). This is illustrated conceptually in Fig. 7. Assuming a simplified model of muscle consisting of a contractile portion (C) and a series viscous element, the interaction of the two following a

![Graph showing comparison of secondary change in force at calcium concentrations of 2.5 and 5.0 mM. For each of 6 muscles, circles in upper right-hand quadrant plot relationship between secondary increase in force (contractions C to D of Fig. 1) at 2 different calcium concentrations following an increase in muscle length. Triangles in lower left-hand quadrant plot relationship between secondary decrease in force (contractions A to B of Fig. 1) following a decrease in muscle length. Dashed line represents a line of identity (all points falling on this line would represent an equal percentage change in force at 2 different calcium concentrations). Most points did not fall on dashed line, indicating a lesser alteration in contractile state with higher calcium concentration.](image)

![Diagram showing mechanical model representation of changes in length of contractile element (C) and series viscous element (VE) following a decrease in muscle length (a, b, c) and following an increase in muscle length (d, e, f). See text for details.](image)
change in muscle length is diagrammatically represented. At the longer muscle length and higher preload (Fig. 7A), the viscous element is stretched out. Following a reduction in muscle length and preload (Fig. 7B), the viscous element does not immediately change length, but after a few beats shortens to Fig. 7C. The slight increase in length of the contractile portion (B-C) would produce an increase in force, followed by a gradual decline in force as the length-dependent reduction in contractility took effect. The opposite effect would occur as length was increased (Fig. 6, D, E, and F). Thus, although a series viscous element either in the muscle itself or in the connections with the myograph might explain the transient alterations in force occurring immediately after a change in length (Fig. 1), it cannot explain the subsequent effects that are directionally opposite.

The mechanism responsible for the length-dependent change in contractile state observed in the present study is unknown. However, it is reasonable to speculate that it may be due to an increase in available calcium to the myofilaments. In a previous study, for example, alterations in the duration of the action potential were observed during the transition from isotonic to isometric contraction (3). It was suggested that the fall in contractility observed in that situation was produced by an abbreviation of phase 3 of the action potential and a subsequent reduction in calcium influx. Similar electrophysiologic data are not available for the present phenomenon, but would be of great interest to see if there is a similar alteration.

In summary, the present study has quantitated a previously undescribed phenomenon in heart muscle, i.e., a length-dependent change in contractile state. The magnitude of this change is not inconsiderable in isolated muscle, and if also present in the intact heart, might provide an important regulatory mechanism for altering the contractile performance of the myocardium.

This investigation was supported, in part, by National Institutes of Health Grants HE-13297 and 5-801-RR-05468.

This work was done during the tenure of an Established Investigator, W. W. Parmley, of the American Heart Association.

Received for publication 12 June 1972.

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