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THE INFLUENCE OF 'DIASTOLIC' LENGTH ON THE CONTRACTILITY OF ISOLATED CAT PAPILLARY MUSCLE

BY C. G. NICHOLS

From the Department of Physiology, The University, Leeds LS2 9JT

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SUMMARY

1. Isometrically contracting cat papillary muscles were studied. Muscle length was changed during diastole and returned to control just before the next contraction such that developed force was always measured at the same length.

2. When the diastolic length was increased from a control length, systolic force at the control length increased slowly over several minutes. When the muscle was then held at the increased length, there was an immediate increase in systolic force followed by a small secondary slow increase.

3. Conversely, a decrease in diastolic length from a control length resulted in a slow decrease in systolic force at the control length. When the muscle was then held at the decreased length there was an immediate decrease in systolic force followed by a small secondary decrease.

4. No change in the time course of contraction accompanied the slow force changes after a maintained change of length or a change of diastolic length alone.

5. The magnitude of the slow change of force was proportional to the duration of time in each diastole for which the length was altered and independent of the onset time of a given duration of diastolic length change.

6. The contractility changes were not linearly related to the amplitude of the diastolic length changes. The potentiating effect of a given stretch was greater than the depotentiating effect of a similar release.

7. The development of inotropic changes as a result of diastolic length changes occurred whether or not the muscle was stimulated during the period of the length changes.

INTRODUCTION

Many studies of isolated preparations of cardiac muscle have shown that force production depends on muscle length and that changes of length result in both immediate and delayed changes of force production (e.g. Parmley & Chuck, 1973; Allen, 1977; Lakatta & Jewell, 1977; Chuck & Parmley, 1980; Allen & Kurihara, 1982). However, the relative importance of the length of the muscle during and between contractions in governing its contractility has not so far been investigated. The specific aim of this study was to determine whether changes in the length of the muscle only for the interval between beats (diastole) could have any subsequent effects on contractility. A preliminary account of this work has already been communicated to the Physiological Society (Jewell & Nichols, 1984).

METHODS

Preparation

Cats weighing between 0·75 and 1·5 kg were anaesthetized with chloroform. The hearts were removed and washed free of blood with an oxygenated bathing solution containing the following (mmol l^{-1}): Na^+, 135; K^+, 4·0; Ca^{2+}, 1·8; Mg^{2+}, 1·0; Cl^-, 102·1; HCO_3^-, 20; HPO_4^{2-}, 1·0; SO_4^{2-}, 1·0; acetate$^-$, 20; glucose, 10. Insulin (5 u. l^{-1}) was added and the solution was bubbled with 95 % O_2, 5 % CO_2, gas mixture at 30 °C, giving a pH of 7·4. A papillary muscle of less than 1 mm diameter was removed from the right ventricle of each heart by cutting the chorda tendinae and undercutting the insertion of the muscle into the ventricular wall. The muscle was held in a Perspex clamp at its ventricular end. The tendinous end was tied with plaited silk to a stainless-steel connecting rod. The clamped muscle was lowered into a chamber (Blinks, 1965) containing well stirred and oxygenated bathing solution at 30 °C. The muscle was stimulated by punctate electrodes at its clamped end. The stimulus duration was 2 ms and the strength was maintained at just above threshold (usually less than 1 V). The preparation was stimulated to contract at a stimulus interval of between 3 and 15 s for several hours to allow stabilization of developed force. During this time the muscle was slowly stretched to the length at which active force development was maximal (L_{max}). At the end of the experiment the actual length of the muscle at L_{max} was measured and any length changes imposed during the experiment were expressed as percentages of L_{max}. The muscle was weighed and cross-sectional area calculated on the assumption that the muscle was a uniform cylinder with the density of water. All absolute forces presented here are given per unit cross-sectional area since this provides a means of standardizing the performance of muscles of different sizes.

Apparatus

The force transducer used in this study was a cantilever beam incorporating semi-conductor strain gauges (Akers AE801, Norway). A small hook was glued to the end of the beam and from this hook was suspended the stainless-steel connecting rod to which the muscle was tied. The force transducer was mounted on the mechanical output rod of a Ling series 100 vibrator. The position of the vibrator rod was sensed by a photodiode circuit of the kind described by Jewell, Kretzschmar & Woledge (1967). This signal was used as the feed-back to a length control system driven by a Hewlett–Packard model 6824A power amplifier. The resonant frequency of the servo-system was 1500 Hz, but velocity feed-back was used to produce just less than critical damping of the movement in response to a step change in the command signal. Muscle length could be electronically controlled over a range of 2 mm with this system. Isovelocity releases or stretches of up to 2 mm amplitude could be initiated at any time in the interval between stimuli. The time taken to release or stretch the muscle could be set digitally over a range from 1 ms to 10 s.

Recording and analysis of data

In all experiments a continuous record of force and length was obtained on slowly moving paper (Gould 2200 recorder). Force and length, along with a stimulus marker, were displayed on a Tektronix D11 storage oscilloscope which could be photographed with a Polaroid camera. The force signal to these recording devices was filtered at 100 or 200 Hz; length signals were not filtered. Unfiltered force and length signals were sometimes digitized by a (Zilog MCZ-105) microcomputer and measurements of peak force and other key data stored on floppy disk (Hanck, Jewell & Pinches, 1982). These data were transferred after experiments to a mainframe computer (AMDAHL VM470) for graphical analysis. In the results the term 'control length' is used to describe the length of the muscle in the pre-length change and post-length change control periods. Control length was varied in order to enable stretches and releases to be made over a similar range of lengths. For experiments involving stretches it was usually 80–90 % L_{max} and for releases usually 90–100 % L_{max}. Control length is specified in the legend to each Figure. The following measurements have been taken as indices of the magnitude and time course of changes in contractility.

1. Relative force, which is the developed force expressed as a fraction of the control isometric force.

2. Time to half-maximal effect ($t_{\frac{1}{2}}$), which is the time taken for the change in developed force to reach half of its final value.

RESULTS

The dependence of contractility on the diastolic length of the muscle

It is a characteristic feature of cat papillary muscle that when its length is changed, developed force changes immediately and then more slowly to a new level over about 10 min (Parmley & Chuck, 1973; Lakatta & Jewell, 1977; Chuck & Parmley, 1980; Allen & Kurihara, 1982). Fig. 1*A* illustrates this feature. After a release (*a*), there

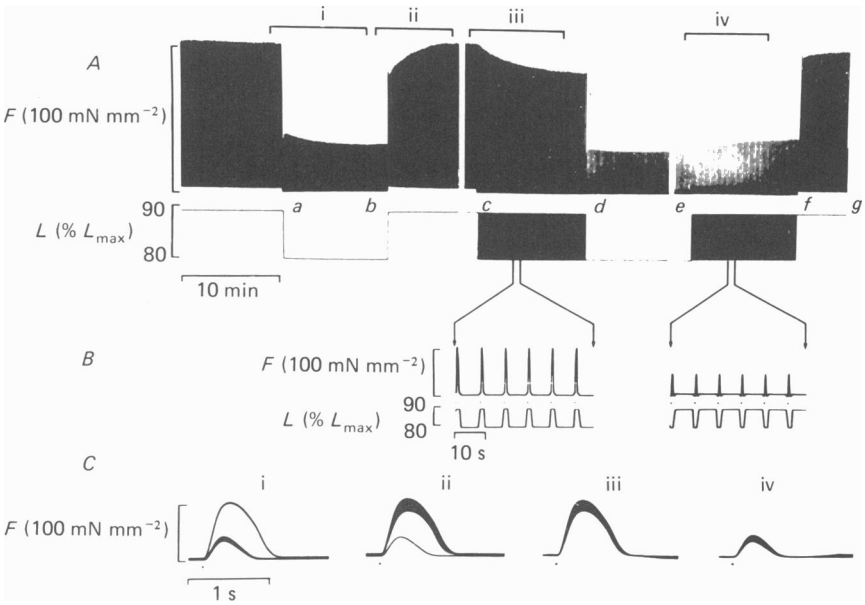

Fig. 1. Representative experimental records of the force changes associated with changes of muscle length in a cat papillary muscle at 30 °C. *A*, continuous record of force (*F*) and length (*L*). Length is expressed as a percentage of the length (L_{max}) at which force production is maximal. Length protocol: *a–b*, *d–e*, muscle contracted and rested at the short length (80 % L_{max}); before *a*, *b–c*, *f–g*, muscle contracted and rested at the long length (89 % L_{max}); *c–d*, muscle contracted at the long length but rested at the short length; *e–f*, muscle contracted at the short length but rested at the long length. *B*, force (*F*) and length (*L*) records to illustrate the protocols adopted in order to change diastolic length alone during the periods *c–d* and *e–f* in *A*. *C*, superimposed records of force during the contractions over the periods indicated in *A*. Dots beneath force records in *B* and *C* are stimulus markers. Stimulus interval 8 s, L_{max} 6·5 mm, muscle diameter 0·48 mm.

is an immediate fall and then a further slow fall (*a–b*) in developed force. When the muscle is stretched (*b*), there is an immediate rise and then a further slow rise in developed force. In the periods *c–d* and *e–f* muscle length was changed only during the interval between contractions. Fig. 1*B* is an oscilloscope record to illustrate the protocol used. These intervals between contractions are not strictly analogous to the diastolic intervals of the whole heart because the mode of contraction is different but the term diastole provides a useful label to describe the period between the return of force to the resting level and the next stimulus. The remainder of the interstimulus

interval (i.e. the period occupied by contraction and relaxation) will be referred to as systole.

During the 10 min period *c–d* of Fig. 1*A*, diastolic length was decreased without change in systolic length (for protocol see Fig. 1*B*). Force production declined with a time course similar to that seen after the step decrease in length *a–b*. When the muscle was then held continuously at the short length (*d*) there was an immediate change in developed force but then almost no slow phase of force decline (cf. *a–b*).

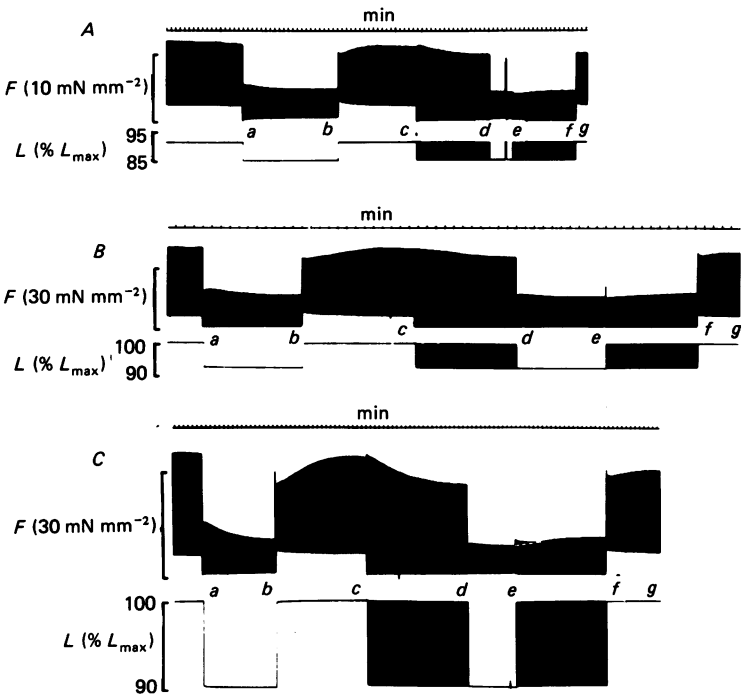

Fig. 2. Experimental records of the force changes (*F*) associated with changes of length (*L*) from right ventricular papillary muscles of *A*, rabbit; *B*, ferret; and *C*, dog. The sequence of length changes was the same as that in Fig. 1*A*. The experimental conditions were: *A*, Ca^{2+} 1·8 mmol l^{-1}, stimulus interval 6 s, L_{max} 3·5 mm, diameter 0·45 mm; *B*, Ca^{2+} 2·5 mmol l^{-1}, stimulus interval 5 s, L_{max} 4·5 mm, diameter 0·50 mm; *C*, Ca^{2+} 2·0 mmol l^{-1}, stimulus interval 10 s, L_{max} 11·0 mm, diameter 0·60 mm. Dashed line on force record in *C* (dog) marks active force when masked by greater resting force.

From *e* to *f* the muscle continued to contract at the short length (i.e. no change in systolic length) but the diastolic length was increased according to the protocol illustrated in Fig. 1*B*. During this period there was a slow increase in developed force with a time course similar to that seen after the step increase in length (*b–c*). When the muscle was then held continuously at the long length (*f–g*) the immediate increase in force was followed by very little slow increase of developed force. Fig. 1*C* shows the time course of contractions in selected periods of the record in Fig. 1*A*. The time course of contraction remained essentially unaltered during the slow force changes whether they followed a step change in length (i and ii) or a change in diastolic length

alone (iii and iv). The results obtained in twelve similar experiments may be summarized as follows: diastolic stretch from 84±2% (control) to 95±2% L_{max} (mean±S.E. of mean) resulted in an increase in peak force of 41±8% (range 14–100%); diastolic release from 95±2% (control) to 85±2% L_{max} resulted in a maximum decrease in peak force of 22±2% (range 12–29%); $t_{\frac{1}{2}}$ was 3·1±0·3 min (range 2·5–5·5 min) for diastolic stretch, and 2·5±0·3 min (range 1·5–5·0 min) for diastolic release. As temperature was raised from 30 to 37 °C the $t_{\frac{1}{2}}$ was approximately halved. As bathing Ca^{2+} was raised, the magnitude of the effect was diminished.

This paper is concerned with cat papillary muscle but it is interesting to know whether diastolic length is a determinant of contractility in other preparations. Fig. 2 shows typical records of force changes associated with step changes of length and changes of diastolic length alone in rabbit, ferret and dog papillary muscles. Systolic force changes resulting from step length changes, or diastolic length changes, are similar to those shown for cat papillary muscle in Fig. 1.

The effect of the timing and velocity of length changes

It is important to know what aspects of the diastolic length change are important in determining the changes in contractility. The duration, onset and velocity of diastolic length changes have been varied in order to answer this question. The effect on contractility of changing the muscle length for varying durations in diastole has been studied in eight preparations. The results from a typical experiment are shown in Fig. 3. Note that if the slow change in contractility ($t_{\frac{1}{2}} \simeq 3$ min) is allowed to proceed to completion, an experiment of the kind illustrated takes so long that the condition of the muscle can change significantly during the experiment. To avoid this problem each change in contractility was measured after only 3 min of altered diastolic length and then the muscle allowed to recover.

Fig. 3*A* illustrates the protocol used to obtain the data shown in Fig. 3*B*. In the upper panel length was increased during diastole from a control length of 88% L_{max} and in the lower panel length was decreased from a control length of 98% L_{max}; the muscle was held at the altered length for differing durations (hold times) and then returned to control length. Fig. 3*B* shows relative force after 3 min at altered diastolic length as a function of the hold time at the altered length in each diastole. There is a roughly linear relationship between relative force and hold time, but note that the relationship is steeper for stretches than for releases. A similar relationship was found in all eight preparations.

This protocol does not allow one to say whether the determinant of the contractility change is the duration or the time of the return of the length to control. This point is resolved by the experiment shown in Fig. 3*C*, in which the onset time of a diastolic length change of fixed duration was varied. The relative force after 3 min of altered diastolic length was independent of the onset time of the diastolic length change. This result was obtained during the same experiment as Fig. 3*B* and was typical of seven preparations in which the relationship was investigated.

The experiments discussed above show that the absolute amount of time spent at an altered diastolic length is a critical determinant of the effect of such length changes on contractility. It is important to know what contribution, if any, is made by the velocity of the length change to the contractility changes. Fig. 4 illustrates the effect

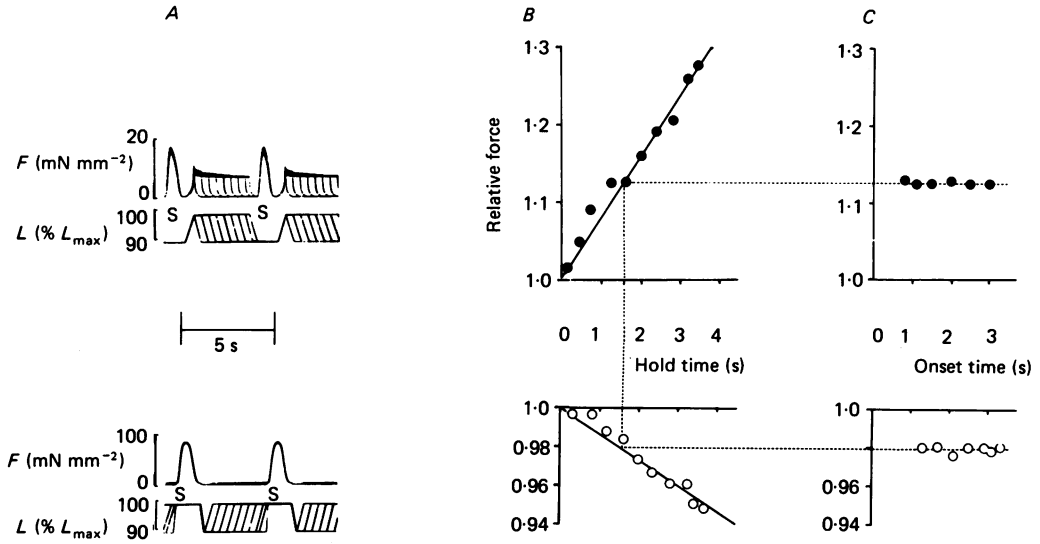

Fig. 3. *A* and *B*, the effect on contractility of varying the proportion of diastole for which length is changed. *A*, superimposed records of force (*F*) and length (*L*) to illustrate the protocol adopted for varying the proportion of diastolic time spent at a length longer than control (upper panel, control = 88% L_{max}) and at a length shorter than control (lower panel, control = 98% L_{max}). The onset time of the initial length change was held constant and the hold time at the altered length varied. S, stimulus marker. *B*, graph showing the relative force after 3 min of diastolic stretch (upper) and release (lower) as a function of the hold time (and hence the duration of diastolic time) at the altered length (note that the ordinate scales are different for the two graphs). *C*, graph showing the relative force after 3 min of diastolic stretch (upper) and release (lower) as a function of the time of onset (after the stimulus) of a diastolic length change with a fixed hold time (in this case 1·6 s). Ordinate scales as in *B*. Cat papillary muscle, L_{max} 3·2 mm, muscle diameter 0·35 mm.

on contractility of varying the velocity of diastolic length change. Fig. 4*A*, where the muscle underwent rapid release and stretch during diastole, shows that simply changing length in diastole without holding the muscle at the altered length does not influence contractility. In Fig. 4*B* the time taken to restretch the muscle after diastolic release was varied between 0·1 and 1·5 s while a constant length–time integral was maintained. After 10 min of diastolic release the change in contractility was the same whatever the velocity.

The effect of the amplitude of length changes

Fig. 5 shows the effect on contractility of varying the amplitude of stretches and releases from a control length of 90%. The hold time of the length change was the same for each amplitude. The relationship between the amplitude and the effect on contractility is non-linear with stretches having a proportionately greater effect than releases (Fig. 5*B*). This result was typical of four muscles studied.

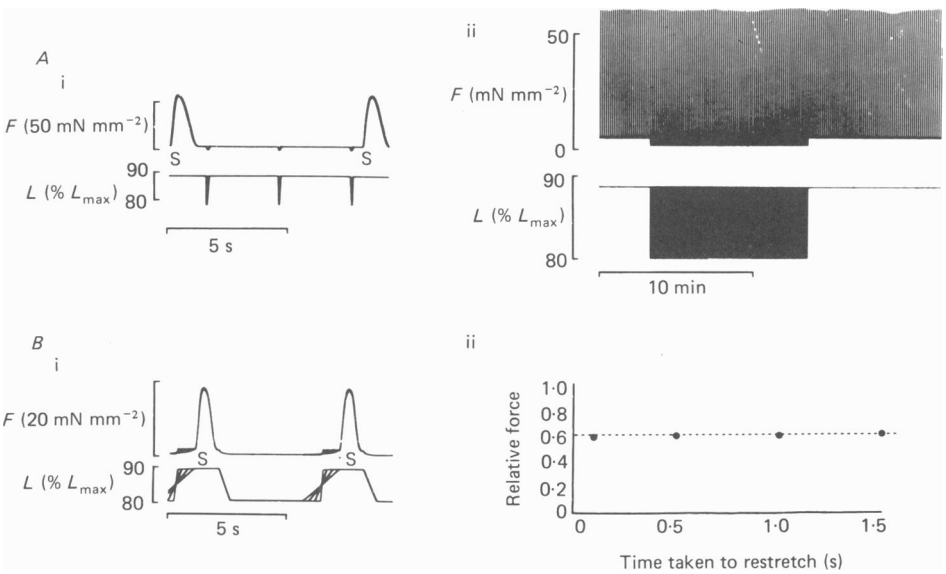

Fig. 4. The effect of velocity of diastolic length changes on the associated contractility changes. *A*, the muscle underwent rapid release and stretch at the beginning, in the middle, and at the end of the diastolic period such that the effect on the length–time integral was minimal: i is a record of force (F) and length (L) to illustrate the protocol (S, stimulus) and ii is a continuous record of the force (F) and length (L) over the period in which these rapid length changes were imposed and during the period of recovery. Control length 89 % L_{max}. Same muscle as in Fig. 1. *B*, the velocity of restretch at the end of diastole was varied between 100 % L_{max} s^{-1} and 7 % L_{max} s^{-1} such that the length–time integral was held constant. i, force (F) and length (L) records to illustrate the protocol (S, stimulus; control length 90 % L_{max}), and ii, graph showing the relative force after 10 min of diastolic release as a function of the time taken to restretch the muscle at the end of each diastolic period. Cat papillary muscle, L_{max} 6·5 mm, muscle diameter 0·70 mm.

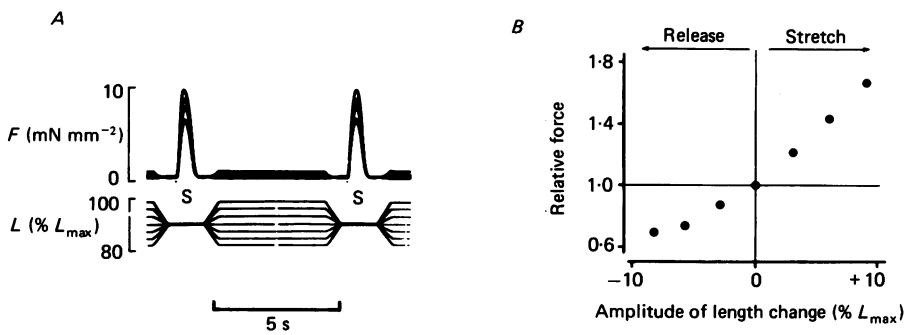

Fig. 5. The effect of varying the amplitude of diastolic stretch or release on the associated contractility changes. *A*, records of force (F) and length (L) to illustrate the protocol adopted in order to stretch or release the muscle during diastole from an intermediate control length (90 % L_{max}); S, stimulus. *B*, graph showing relative force (after 10 min of altered diastolic length) as a function of the amplitude of the length change. Same muscle as in Fig. 4*B*.

Does the effect of diastolic length change on contractility require regular activation of the muscle in order to accumulate?

The results presented in Figs. 1 and 3 suggest that changes in the level of activation take place as a result of changes in diastolic length over a period of about 10 min. Such inotropic changes may require the processes of activation in order to accumulate. To investigate whether this is so the following experiment was performed on six

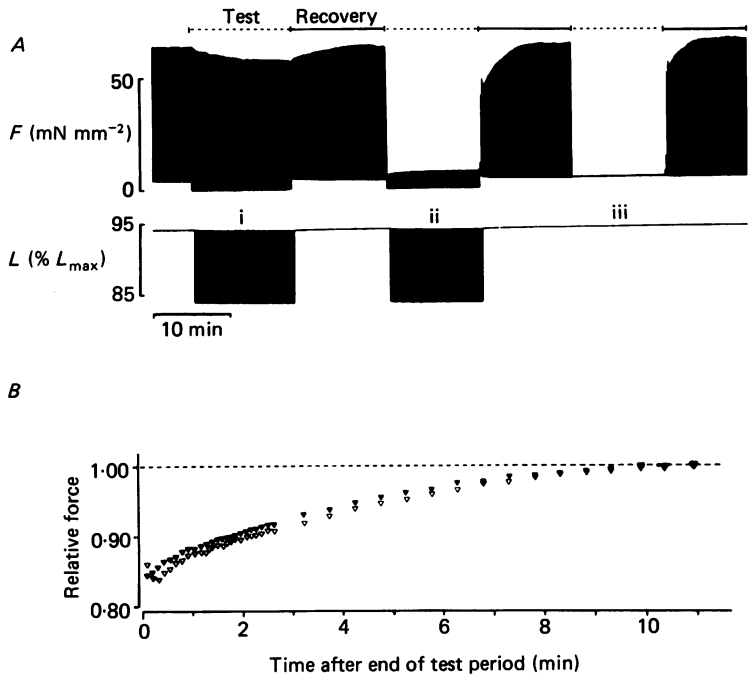

Fig. 6. The stimulation independency of the effects of diastolic length changes. *A*, experimental record of force (*F*) and length (*L*) to illustrate the protocol adopted in order to compare the recovery from a test period of diastolic release with (i), and without (ii), stimulation during the test period. iii is a control test period without stimulation or length changes. *B*, force produced in each contraction of the recovery from test period (ii) is plotted as a fraction of the force produced in the corresponding contraction of the recovery from test period (iii) against time after end of test period (open triangles). This is to be compared with the recovery from i (filled triangles) where each contraction has been normalized to the post-control force. Stimulus interval 6 s, control length 94 % L_{max}. Cat papillary muscle, L_{max} 4·0 mm, muscle diameter 0·80 mm.

muscles. For test periods of 10 min the muscle was: i, allowed to develop a reduced contractility as a result of diastolic release; ii, not stimulated although it underwent the same length changes as in test period i; iii, stimulated but underwent no length changes. This protocol is illustrated in Fig. 6*A*. The recovery of force production after each 10 min test period includes recovery from any contractility changes occurring during the test period.

From Fig. 6*A* it is clear that the staircase of recovery from the rest with length

changes (ii) is not the same as that from the rest without length changes (iii). By expressing the force of each contraction in the recovery from ii as a fraction of the force of the corresponding contraction in the recovery from iii one obtains a 'residual' recovery which is independent of the staircase resulting from the rest itself and must be the recovery from contractility changes resulting from the imposed length changes. This 'residual' recovery (open triangles) is plotted against time after the end of the test period in Fig. 6*B*, together with the normalized recovery from i (filled triangles). Recoveries from test periods of diastolic stretch with and without stimulation gave complementary results which are not shown. The 'residual' recovery from altered length during the rest is remarkably similar to the recovery from altered length between contractions except in the first few beats after the rest.

DISCUSSION

The dependence of contractility on diastolic length

The work reported in this paper has shown that the contractility of isolated cat papillary muscle is influenced by the length of the muscle during the interval between contractions (diastole). The change in contractility that occurs over about 10 min (at 30 °C) when diastolic length is changed accounts for much of the slow change in contractility that follows a maintained change in length (Fig. 1). The demonstration that similar behaviour can be observed in rabbit, ferret, and dog papillary muscle (Fig. 2) shows disastolic length dependence of contractility to be a property of isolated ventricular muscle in general. It has already been shown that the contractility changes following step changes of length are unrelated to muscle diameter (Parmley & Chuck, 1973) and so it is unlikely that adequacy of oxygenation is a critical factor. Furthermore, it has recently been reported that very similar changes in developed pressure occur following step changes of volume in isovolumically contracting blood-perfused dog ventricles (Tucci, Bregagnollo, Spadaro, Cicagna & Ribeiro, 1984). These experiments were carried out at physiological temperature and frequency (37 °C, 56 beats min^{-1}) and so it seems that such length dependence may also be a feature of fibres in the intact ventricle.

Cardiac muscle has visco-elastic properties, so it is possible that stretching and releasing the muscle (or vice versa) may cause a transient change in sarcomere length which takes more time to recover to its control. Therefore it is possible that force changes resulting from repeatedly changing muscle length about a control (as in these experiments) are a manifestation of transient changes in sarcomere length and not a reflexion of a change in the level of activation. The results of Fig. 4 argue against this suggestion. Simply changing length and rapidly returning to control (Fig. 4*A*) does not result in any slow changes in contractility. Similarly, Fig. 4*B* shows that variations in the time taken to change length, which might be expected to affect any processes dependent on visco-elastic properties, do not affect the slow contractility changes under discussion. Measurements of sarcomere length at the peak of contraction show that during the slow increase of force after a step stretch in rat papillary muscles there is a small decrease in sarcomere length ruling out the possibility that changes in sarcomere length could be responsible (J. C. Kentish & H. E. D. J. Ter Keurs, personal communication).

The mechanism of potentiation

The demonstration by Parmley & Chuck (1973) that the effects of maintained step changes of length were much reduced in high bathing Ca^{2+} concentrations, and by Allen & Kurihara (1982) that the Ca^{2+} transient changes with the force production, together suggest that changes in the distribution of Ca^{2+} between an intracellular store and the external medium may be the underlying cause. Several lines of evidence have suggested that the rise in intracellular Ca^{2+} responsible for the staircase of force after a maintained stretch may be derived from an enhanced inward Ca^{2+} current during the action potential: the action potential gets longer after a stretch (Allen, 1977); the slow changes of force show a partial beat dependence (Lakatta & Jewell, 1977); the slow force changes can be reduced in the presence of verapamil (Lakatta & Jewell, 1977); the staircase of force recovery from a long rest differs with muscle length (Lakatta & Spurgeon, 1980). However, the observation that the contractility effect of a change in diastolic length is directly proportional to the amount of time spent at the altered length in each diastole (Fig. 3), and the demonstration that the development of contractility changes is independent of muscle activation (Fig. 6), seem to exclude the possibility that changes of a Ca^{2+} flux *associated with the action potential* can be the principal mechanism responsible for these slow changes.

The observation of Chuck & Parmley (1980) that caffeine blocks or even reverses the slow changes of force which follow a step change of length provides an alternative explanation of the slow changes that is consistent with the excitation and contraction independence of the slow effects reported here. Chuck & Parmley (1980) suggest that Ca^{2+} uptake or release from the sarcoplasmic reticulum may be affected by length. It has been suggested that in cat papillary muscle the sarcoplasmic reticulum loses stored Ca^{2+} during a long rest (Allen, Jewell & Wood, 1976). Unless length can affect the 'rested-state' sarcoplasmic reticular Ca^{2+} level, any effects of diastolic length on sarcoplasmic reticular Ca^{2+} loading would be lost during a long rest, so the results of Fig. 6 would suggest that the potentiation due to diastolic length change is not a result of altered sarcoplasmic reticular Ca^{2+} loading. Alternatively, Ca^{2+} bound to, and released from, the sarcolemma, or diastolic cytoplasmic Ca^{2+} may be affected by muscle length and these might alter the trigger to subsequent Ca^{2+} release from the sarcoplasmic reticulum (Fabiato, 1983).

The greater effect of diastolic stretch on contractility as compared to a release of the same magnitude (Fig. 5) is interesting. If a given muscle is assumed to be an extensible cylinder of constant volume, a given release would cause a smaller change in surface area than would stretch of the same magnitude. This might be taken as suggestive evidence that the change in surface area of the muscle causes alterations in the accessibility, orientation, or number of ionic exchange sites on the sarcolemmal membrane.

Systolic and diastolic contributions to the slow changes

Although it has been shown in this paper that much of the effect on contractility of a maintained length change may be a result of the incorporated change in diastolic length (Fig. 1), the possibility that systolic length may have some effect is not discounted. Indeed, as can be seen in Fig. 1*A* (*d–e*, *f–g*), a change in systolic length

alone does result in some slow contractility change. If it is postulated that separate diastolic and systolic mechanisms contribute to the slow contractility changes that result from changes of length, then some of the apparently contradictory results of previous authors could be explained. The interplay of an action-potential-dependent and a diastolic (action-potential-independent) inotropic change could result in an apparently partially beat-dependent effect of step change of length (as observed by Lakatta & Jewell, 1977). In this case, blocking the systolic component by verapamil may (Lakatta & Jewell, 1977), or may not (Chuck & Parmley, 1980), be judged to block the combined slow contractility changes following a step change of length. The time course of the change in action potential duration reported by Allen (1977) is rather shorter than the time course of the force changes that result from a step change of length (Fig. 1 *A c–d, e–f*) but may correspond to the time course of the force changes that result from the change in systolic length alone (Fig. 1 *A d–e, f–g*).

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