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EFFECTS OF ABRUPT LOAD ALTERATIONS ON FORCE–VELOCITY–LENGTH AND TIME RELATIONS DURING ISOTONIC CONTRACTIONS OF HEART MUSCLE: LOAD CLAMPING

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SUMMARY

1. Abrupt alterations in load (load-clamping) have been imposed on cat papillary muscles during the course of isotonic shortening, between the onset of shortening and peak shortening.

2. For any given total load, whether imposed during the course of shortening or before stimulation, the velocity of shortening is determined solely by the instantaneous length, and not by the sequence of length and tension changes through which it arrived at that length.

3. This unique force–velocity–length relation is independent of time from just after the onset of shortening until just prior to peak shortening.

4. These results suggest that a steady state exists for the maximum intensity of active state in heart muscle over a major portion of the time during which isometric force is rising, and that heart muscle always senses total load while shortening.

INTRODUCTION

In a previous study of the cat papillary muscle, it was shown that for any given total load, the velocity of shortening was solely determined by the instantaneous length of the muscle during the course of shortening (Brutsaert & Sonnenblick, 1969). These relations were shown to pertain in isotonic contractions, initiating from a wide range of initial muscle lengths where resting forces (preload) were present, so long as *total* load (preload and afterload) remained constant. Moreover, for a given state of contractility this velocity–length relation during isotonic shortening is largely independent of time except along the terminal portion of shortening, just before peak shortening, which approaches the time at which peak isometric force is reached. However, it could also be theorized that such

precise inter-relations of force, velocity and length during the phase of contraction between onset of shortening and peak shortening might be the fortuitous result of a slowly increasing intensity of active state and a decreasing muscle length. Accordingly, the present study was designed to explore such a possibility utilizing a new technique, termed *load-clamping*, which permits an abrupt alteration of load during the course of isotonic shortening so that the force–velocity–length relations may be explored over broad limits of time.

METHODS

Papillary muscles of the right ventricle of the cat were used for this study. The muscles were rapidly dissected free and mounted vertically in a bath containing a modified Krebs–Ringer solution (see below).

The lower non-tendinous end of the muscle was held by a light phosphor bronze muscle grip which was soldered in the middle of the spring of the force transducer as shown in Fig. 1. The tendinous end of the muscle was held by a second very light (30 mg) spring loaded stainless-steel clip extending upwards to the electromagnetic lever system. By the use of these clips series elasticity or viscosity due to the system could be minimized. The electromagnetic lever system was mounted on a Palmer stand and fixed immediately above the bath. In addition a force transducer system was designed for measuring force from the lower end of the muscle in the bath (see below). This system has the advantage that both force and displacement can be measured simultaneously with a muscle in a vertical position and without the disadvantages of previous force or displacement transducer devices which pass through the bottom of the bath.

The electromagnetic lever system (Fig. 1, panel III)

The lever (L) is fashioned from magnesium and is attached by epoxy cement to a coil (C) which is suspended in a strong field of a permanent magnet (magnetic induction = 1·2 Weber/m^2). This system is analogous to a pen drive motor and has a total compliance of 0·4 μ/g and a total equivalent moving mass of 225 mg. The equivalent mass of the lever itself is 40 mg. The current through the coil is controlled by two transistorized current sources, which are calibrated for step changes in force of 0·1 g, 1 g and 10 g, to a total of 30 g. The displacement of the lever is measured by means of a photo-electric system (P_2 and L_2), mounted on the magnet. The light emitted by the lamp (L_2) is modulated by the displacement of the lever and the resulting current alterations are amplified and recorded as indicated below. The non-linearity of the photo-electric system has been corrected electronically and a linear shortening of the muscle of 2·2 mm can be recorded without distortion. An active differentiator is used for deriving the velocity of displacement of the lever and thus for measuring the velocity of shortening of the muscle. The relation between the highest frequency component of the input signal of the differentiator to its critical frequency is of the order of 0·02.

The force transducer (Fig. 1, panel II)

The force transducer employs a photoelectric system. It consists of a flat brass spring (S) (compliance 6 μ/g) fitted with a shutter. The spring with shutter are in the bath and a phosphor bronze muscle clip is soldered to the spring. Any movement of the shutter modulates the light emitted by a miniature lamp (L_1) which is outside

the solution. This light signal is conducted to the shutter through the solution in the bath by means of optical fibres (OF). A second set of optical fibres conducts the modulated light to a silicon photodiode (P_1) which is also outside the solution. The

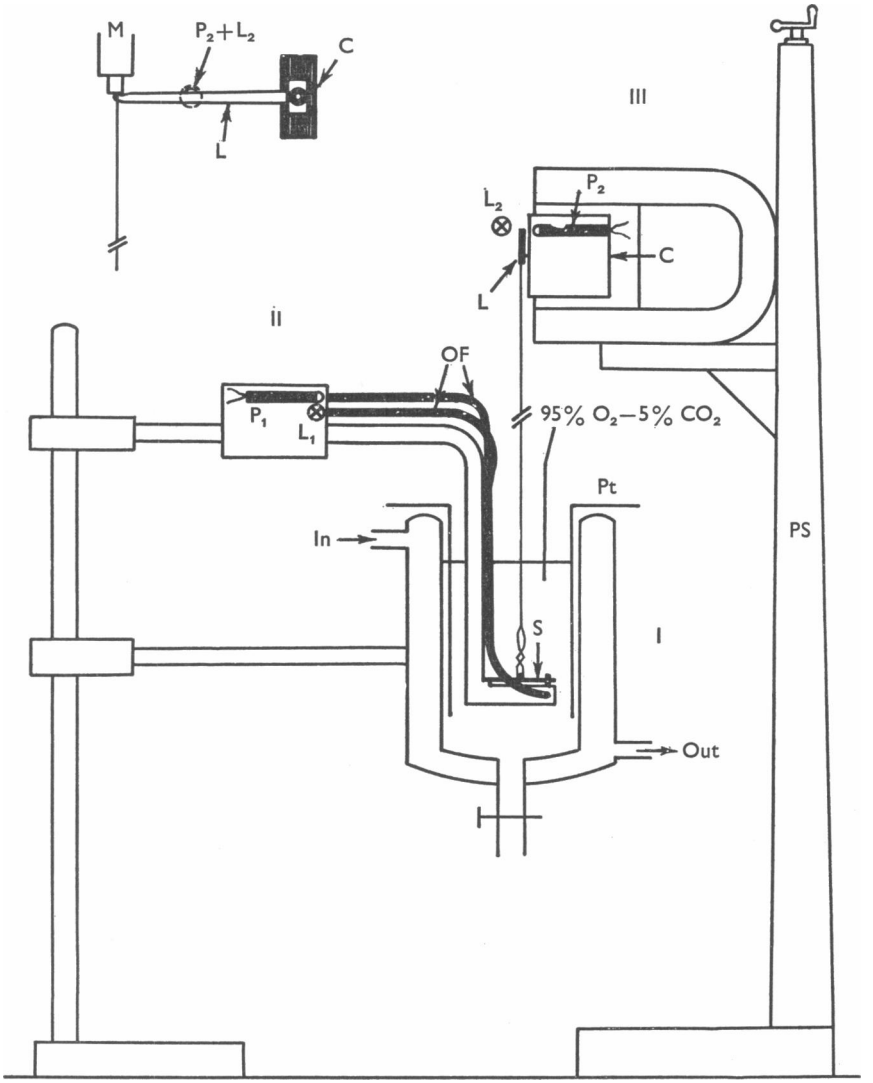

Fig. 1. Vertical section of the apparatus. Panel 1: cylindrical glass muscle bath with double wall. In: inlet; out; outlet, for temperature control. Pt: platinum electrodes for electrical stimulation. Panel II: force transducer. P_1: silicon photodiode. L_1: miniature lamp. OF: optical fibres. S: spring with shutter and muscle clip. Panel III: electromagnetic lever system. P_2: silicon photodiode. L_2: miniature lamp. L: lever. C: coil. Insert (upper left): front view of electromagnetic lever system. M: micrometer stop. PS: Palmer stand.

current through the diode is amplified and recorded as indicated below. An active linear phase filter (third order Paynter filter) (corner frequency 200 c/s) with a good step response is used to eliminate noise. The resonance frequency of the loaded transducer is 450 c/s, and the transient time after filtering is 4 msec.

Control unit

Two stimulators (Grass model S4) and two current sources with associated electronic circuitry are used to control the system. One of the stimulators provides the stimulus for the muscle and triggers the second stimulator with a pulse of variable duration and variable delay. This output pulse switches off the first current source of the electromagnetic system, and switches on the second one. In this way the load imposed on the muscle can be altered between various predetermined values within 3–5 msec. This provides the possibility of a *load clamp* technique in which total load can be programmed in a comparable way to the *voltage clamp* used in electrophysiological studies.

Stimulation

The muscles are stimulated at a rate of 12 pulses/min with rectangular pulses of 5 msec duration about 10 % above threshold. The stimulus is provided through two platinum electrodes arranged longitudinally along both sides of the muscle.

Solution

The composition of the modified Krebs–Ringer solution was (mM): NaCl, 118; KCl, 4·7; $MgSO_4.7H_2O$, 1·2; KH_2PO_4, 1·1; $NaHCO_3$, 24; $CaCl_2.6H_2O$, 2·4; glucose, 4·5; pH 7·38. The solution was bubbled with a 95 % O_2–5 % CO_2 gas mixture. The temperature of the solution was maintained at 29° C for all experiments.

Recording system

The output from the two photo-electric systems was transmitted to a multichannel recorder (Hewlett Packard 7848A). In this way the shortening of the muscle, the velocity of shortening and the force along with the stimulus artifact could be recorded simultaneously as a function of time. In addition, force and velocity of shortening were recorded as a function of length during shortening on a cathode-ray storage oscilloscope (Tektronix type 564) with a Polaroid Camera (Tektronix C12).

RESULTS

In Fig. 2, the effects of altering the load on the velocity of shortening during the course of an isotonic contraction are shown. In panel I are shown the velocity of shortening (above), shortening (middle), and total load (below) for a muscle with an initial preload of 0·3 g. Contraction 1 is a freeloaded contraction with the preload of 0·3 g alone. In contraction *ABCDEF*, an additional load of 0·4 g has been applied to the muscle at 70 msec after stimulation, maintained for 105 msec, and then removed. In contraction 2, the muscle contracts with a preload of 0·3 g and an afterload of 0·4 g, which are both maintained throughout. In panel II, velocity of shortening has been displayed as a function of muscle length during the course of shortening, while in panel III, panel II has been redrawn for

purposes of clarity. The velocity transients at the beginning and end of the load clamping have been omitted on this interpretative diagram. Although these transients are probably largely inertial, other phenomena may be involved (Civan & Podolsky, 1966; Armstrong, Huxley & Julian, 1966) and the redrawn tracings may thus be an oversimplification of the true transient. Further studies are in progress to elucidate this problem. The plot of velocity relative to length in panels II and III contain only the portion of shortening between onset and peak and not the phase of relaxation. In panel IV, the tracings of shortening as a function of time as shown in the 3 contractions of panel I have been superimposed. In panel V the times from the stimulus to the time at which each contraction reaches length X and length Y have been noted.

In panel III, the muscle contracting with the preload alone has an additional 0·4 g added at B. The contraction then proceeds from C to D, following the same velocity length pathway of the contraction which began shortening with the same total load from the same initial muscle length. Length X is reached by both modes of contraction with an identical velocity of shortening despite a 20 msec difference in the time at which this length is reached (panels IV and V). Length X is reached sooner by the load clamped contraction since the initial portion of the contraction proceeds with a light load and fast velocity. At D, the load of 0·4 g is removed, and the velocity length tracing rises to E and then declines to F. Length Y is reached with the same velocity for the same load despite a difference in time after stimulation of 45 msec.

In any given contraction, the velocity of shortening is determined only by the instantaneous load and length, independent of the sequence of length and tension changes through which it arrived at that length. This relation is independent of the time at which this length is attained, except late in the course of isotonic shortening, as noted later.

In order to investigate the generality and consistency of this finding, measurements were made at a series of loads and at a series of presentation times of the added loads. The same results have been obtained in the eleven papillary muscles used in the present study. For the purpose of comparison all illustrations (except for Fig. 4) are taken from the same representative muscle shown in Fig. 2.

In Fig. 3, the effects of four increments in the imposed load on the course of shortening and the velocity of shortening are shown. The protocol, notation and conclusions are as given in Fig. 2. The control contraction 1 with the preload (0·3 g) is the same throughout. The added load during the loadclamping has been increased progressively in contractions 2, 3, 4 and 5 from 0·1 g (panel I) to 0·5 g (panel II), to 1·0 g (panel III), and to 2·0 g (panel IV) respectively. The 0·4 g load step has been shown in Fig. 2.

In panels I and II the same timing was used as in Fig. 2. In panels III and IV a somewhat later onset of load clamping (*B* at 90 msec) and slightly shorter duration (100 msec) were used. The dissociation of length relative to time for a given load change when the clamped contraction is compared to its two non-clamped control contractions (Fig. 3, left tracing of panels I to IV) is again consistent with the time independence of the force–velocity–length relation during the major portion of the rising phase of force development.

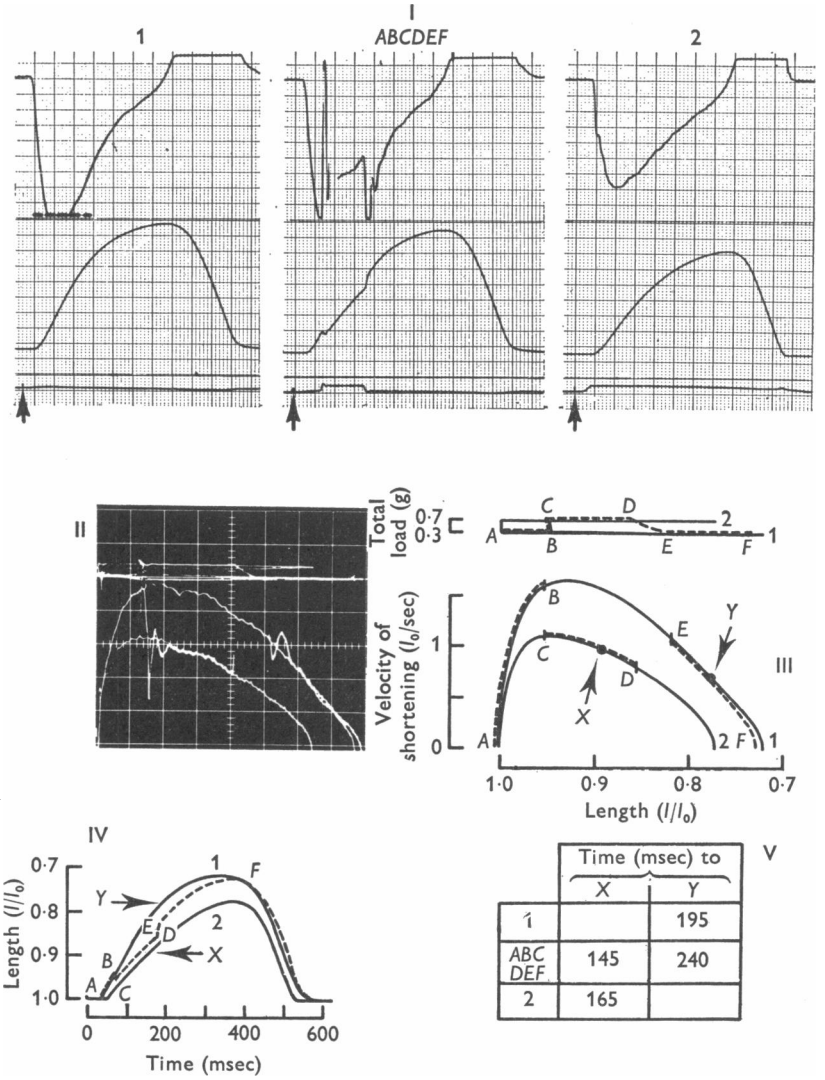

Fig. 2. For legend see facing page.

As shortening reaches towards the peak there is a terminal deviation of the velocity of shortening of the clamped contraction (portion between *E* and *F*) from control contraction 1. This deviation deserves special note since it increases as the magnitude of the load clamp is increased (panels I to IV). A consideration of the time course of the contraction suggests that at the terminal portions the velocity–length relation from the onset of shortening to peak shortening may be influenced by the time constraints of the course of active state. Thus peak shortening for the unclamped contraction 1 is reached at approximately the same time as the time from stimulation to peak isometric tension which in the same muscle at the same preload was 360 msec. However, the load clamped contractions which shorten for a defined period with a heavier load, and lower velocity, reach the terminal portion of the shortening curve considerably later in time. Thus *F* is reached at 390 msec (panel II) to 410 msec (panel IV) which is long after the time to peak shortening of the unclamped contraction 1 and after the time to peak tension.

In Fig. 4 the load has been removed during the course of shortening shortly after stimulation. Even in this early portion of the shortening, the velocity again adjusts perfectly to the instantaneous length and load. These

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Fig. 2. The effects of an abrupt change in load during the course of isotonic shortening.

In panel I are shown three contractions as a function of time. For each contraction are shown shortening (middle), velocity of shortening (pen limited in contraction 1) (above) and developed force (below). The arrows denote time of stimulation. Calibrations for force (total load) and velocity of shortening are noted in panel III, while length and time after stimulation are shown in panel IV— Contraction 1 represents an isotonic contraction with a preload of 0·3 g; in contraction *ABCDEF* an additional load of 0·4 g has been imposed abruptly on the shortening muscle at 70 msec after the stimulus, maintained for 110 msec, and then removed leaving the original load of 0·3 g; in contraction 2, the same load of 0·4 g has been added as afterload prior to the stimulus and maintained throughout the contraction.

In panel II, a polaroid photograph is shown with velocity of shortening and load as functions of shortening, between the onset and peak of shortening for the three contractions in panel I. The relaxation phase of the contraction does not appear.

Panel III portrays the tracings of panel II with their calibrations. The velocity transients due to acceleration and deceleration at the beginning and end of the load clamping have been omitted.

Panel IV shows the superimposed shortening traces of panel I. The letters denote the points at which common velocity-lengths of panel III have been measured.

Panel V, see text.

Muscle cross-sectional area 0·55 $mm^2 . l_0$, length with 0·3 g preload, is 7·33 mm. The time to peak isometric force of an isometric contraction at the preload of 0·3 g was 360 msec.

data support the view that the time independent force–velocity–length relation is attained already early in the course of the contraction.

In Fig. 5, the effects of altering the load on velocity of shortening during the course of an isotonic contraction are compared with a preloaded contraction carrying the same load. Contraction 1 is the control contraction with a preload of 0·3 g alone. In contraction *ABCDEF* of panel I an addi-

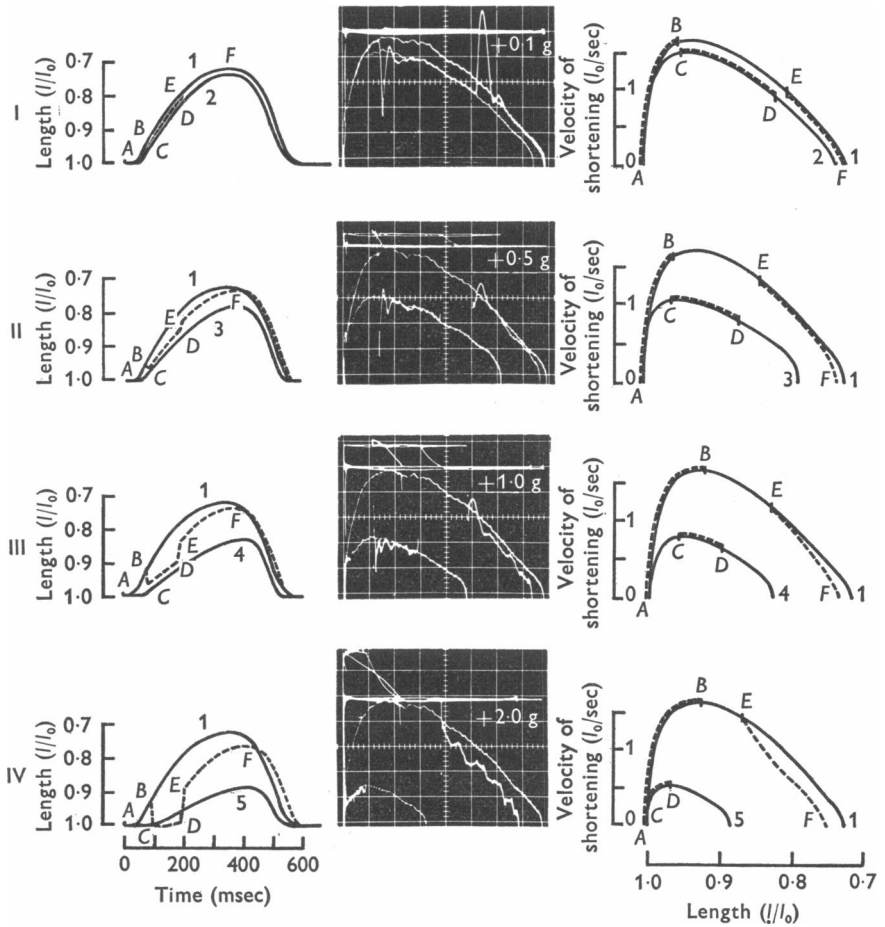

Fig. 3. Effects of four (panels I to IV) increasing load clampings during contraction. On the left of each panel are superimposed the shortening tracings of three isotonic contractions, obtained as in Fig. 2. In the middle, load and velocity of shortening are shown as a function of length as in Fig. 2 panel II. On the right, these velocity–length tracings have been redrawn. As in Fig. 2 and in all subsequent Figures, velocity transients due to acceleration and deceleration at the onset and end of the clamping have been omitted. The increments in load are indicated on the photographs in the middle. Characteristics of muscle as in Fig. 2.

tional load of 1·0 g has been applied to the muscle at 65 msec following stimulation and has been maintained for 85 msec. In contraction *ABCDEF* of panel II an identical load clamping of 1·5 g has been performed with

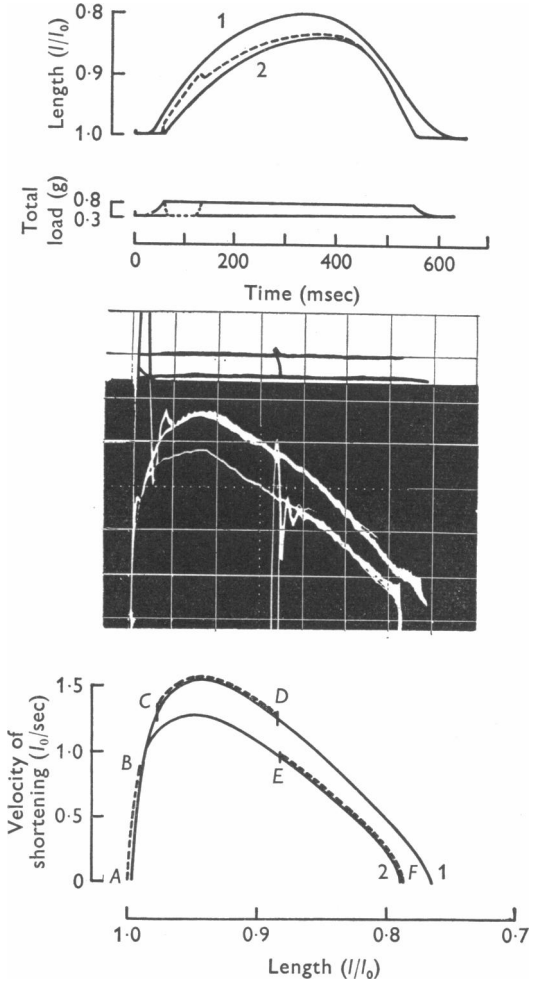

Fig. 4. The effect of removal of load during the early phase of the contraction on the course of shortening. Contraction 1 is a control contraction with a preload of 0·3 g only; contraction 2 has a preload of 0·3 g and an afterload of 0·5 g. In contraction *ABCDEF*, at 50 msec after the stimulus 0·5 g has been removed during the clamping period. Upper: length change and load are shown as a function of time after stimulation; middle: total load and velocity of shortening is shown as a function of shortening; below: the information shown in the middle has been retraced with the addition of the calibrations. Muscle cross-sectional area 1·2 mm^2. Length at 0·3 g preload is 7·5 mm. The time to peak isometric force of an isometric contraction at the preload of 0·3 g was 385 msec.

the same onset and duration. In contractions 2 and 3 the muscle contracts with a total preload of respectively 1·3 and 1·8 g added prior to the stimulus and maintained throughout.

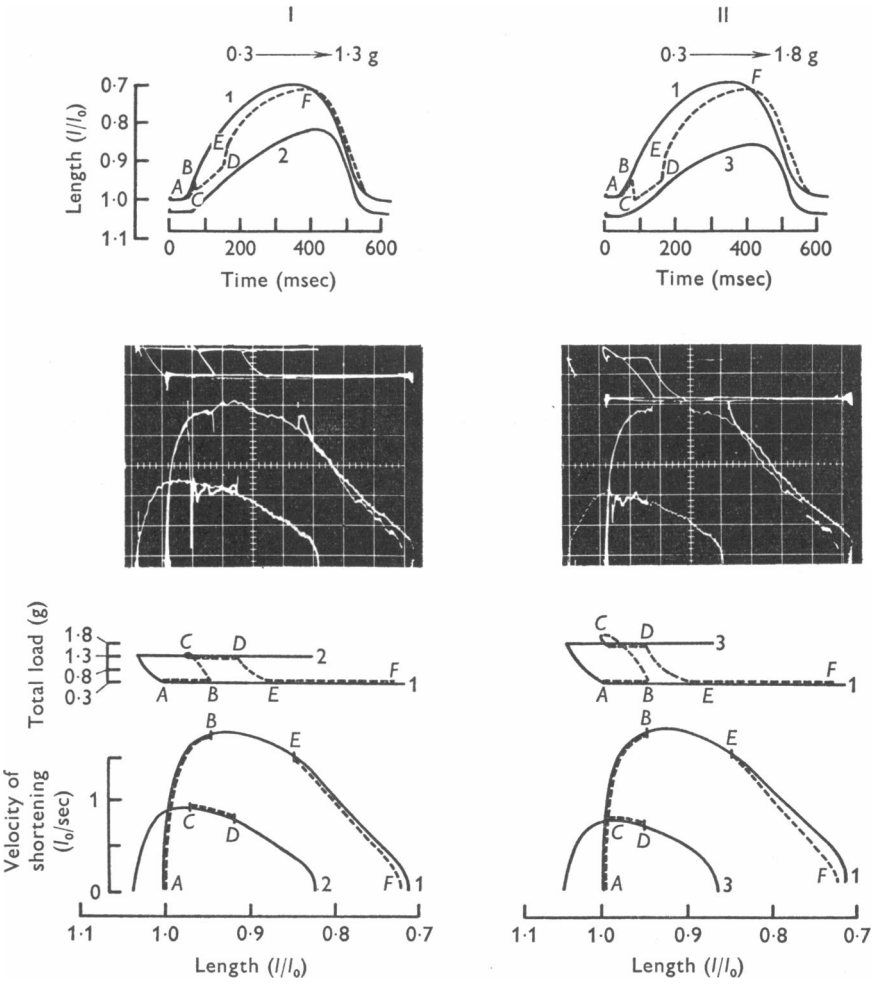

Fig. 5. Alterations of total load during the course of contraction are compared with preloaded contractions carrying the same load throughout shortening. Format as in Fig. 4. See text. The characteristics of the muscle were as in Fig. 2.

The similarity between panel I of this Fig. 5 and panel III of Fig. 3 is striking. The records are virtually identical apart from a slight difference in the timing of the clamp period. The total load is changed from 0·3 to 1·3 g in both cases, and the only real difference between the two figures is

in the type of contraction with which the clamped contraction is compared. In Fig. 3 it is an afterloaded contraction against 1·0 g (with 0·3 g of preload), and in Fig. 5 it is a preloaded contraction against a load of 1·3 g. This finding indicates that muscle always senses 'total' load whether present as preload alone or as preload and afterload, and that for any given 'total' load velocity of shortening depends only on the muscle length.

DISCUSSION

In the present study the effects of sudden alterations of load (load clamping) during isotonic shortening on shortening and velocity of shortening of cat papillary muscles have been examined relative to length and time. These abrupt alterations of load have been imposed in the interval between the onset of shortening and peak shortening, and have been compared with isotonic preloaded and afterloaded contractions in which the load remains the same throughout contraction.

From the present findings certain facts have become clear.

First, for any given total load, whether this load is imposed during the course of shortening or prior to the stimulus, the course of velocity of shortening is determined solely by the instantaneous total load and length, independent of the sequence of length and tension changes through which it arrived at that length. These findings obtained from abrupt load alterations confirm and support the observation made in a previous study (Brutsaert & Sonnenblick, 1969) that the surface created by the three-dimensional plot of instantaneous force, velocity and length between the onset of shortening and peak shortening is unique for a given state of contractility.

Secondly, this unique relationship between the force–velocity–length characteristics is independent of the time over the largest portion of the shortening from shortly after the onset to near peak shortening. Load alterations to relatively small loads imposed early in the course of the shortening have shown that this unique relationship is indeed attained shortly after activation. Load clampings imposed at later time intervals demonstrate that this relationship is maintained over a large portion of the shortening phase. These results are consistent with the view that the capacity of shortening with light loads or with no load (V_{max}) must be at its maximum very early in the course of the contraction and must be maintained at the same value during the major portion of the shortening phase up to near peak shortening. The early onset of V_{max} which occurs, at approximately 20 % of the time from the stimulus to peak developed force has been demonstrated already in a previous study (Brutsaert & Sonnenblick, 1971; Brutsaert, Vermeulen & Sonnenblick, 1970).

From the present considerations it can thus be concluded that the maximum intensity of active state is 'turned on' relatively early in the contraction and is maintained at a stable level until just before the peak tension development. While it is well known that the duration of the maximum intensity of active state and its subsequent course during relaxation may be altered by the mode of loading (Hill, 1970), this does not appear to be the case during the period in which the major portion of force is being generated or shortening is proceeding. On the other hand the present findings are in contrast to earlier work (Brady, 1965; Sonnenblick, 1965; Edman & Nilsson, 1968) that indicated a more gradual onset of the active state in heart muscle with no plateau of the sort required to explain the main results of the loadclamping. This difference may be partly due to the use of quick stretch or quick release methods which both may alter the course of the subsequent active state (Brady, 1968; Brutsaert & Sonnenblick, 1969).

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REFERENCES

ARMSTRONG, C. F., HUXLEY, A. F. & JULIAN, F. J. (1966). Oscillatory responses in frog skeletal muscle fibers. *J. Physiol.* **186**, 26–27*P*.

BRADY, A. J. (1965). Time and displacement dependence of cardiac contractility: problems in defining the active state and force-velocity relations. *Fedn Proc.* **24**, 1410–1420.

BRADY, A. J. (1968). Active state in cardiac muscle. *Physiol. Rev.* **48**, 570–600.

BRUTSAERT, D. L. & SONNENBLICK, E. H. (1969). Force-velocity-length-time relations of the contractile elements in heart muscle of the cat. *Circulation Res.* **24**, 137–149.

BRUTSAERT, D. L. & SONNENBLICK, E. H. (1971). The early onset of maximum velocity of shortening in heart muscle of the cat. *Pflügers Arch. ges. Physiol.* **324**, 91–99.

BRUTSAERT, D. L., VERMEULEN, F. E. & SONNENBLICK, E. H. (1970). The early occurrence of maximum velocity of shortening in heart muscle. *Archs int. Physiol. Biochem.* **78**, 563–565.

CIVAN, M. M. & PODOLSKY, R. J. (1966). Contraction kinetics of striated muscle fibres following quick changes in load. *J. Physiol.* **184**, 511–534.

EDMAN, K. A. P. & NILSSON, E. (1968). Mechanical parameters of myocardial contraction studied at a constant length of the contractile element. *Acta physiol. scand.* **72**, 205–219.

HILL, A. V. (1970). *First and Last Experiments in Muscle Mechanics.* Cambridge: Cambridge University Press.

SONNENBLICK, E. H. (1965). Determinants of active state in heart muscle: Force, velocity, instantaneous muscle length, time. *Fedn Proc.* **24**, 1396–1409.