Mechanical Control of the Time-Course of Contraction of the Frog Heart

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ABSTRACT Changes in load during most phases of an isotonic contraction of the frog and turtle heart increased or decreased the duration of the twitch. It was abbreviated by a maintained increase or by a brief decrease in load. The relaxing effect of these procedures developed with a delay lasting more than a second under some conditions and will be called lengthening deactivation. The reverse procedures, a maintained diminution or a brief increase in load, increased the duration of the twitch. This effect will be called shortening activation. Although the termination of relaxation may be delayed or advanced by the mechanical interventions mentioned, the normal time-course of isotonic relaxation was always resumed later, regardless of the starting level and the load, making it possible to measure accurately changes in the duration of the twitch. The responses to changes in load produce positive feedback during the isotonic contraction and explain, at least in part, the difference in the time-course of isotonic and isometric contraction. The effects of changes in load were much smaller and briefer in the atrium than the ventricle.

That mechanical interventions can change the time-course of the heart beat has been demonstrated by the observation that stretching of cardiac and skeletal muscle during some phase of an isometric contraction depresses tension below that of controls at the greater length and abbreviates the contraction (4, 6, 11). This effect, which has been called "uncoupling" by Brady (4), was first observed in frog skeletal muscle by Jewell and Wilkie (9).

The effect of mechanical factors on contractile activity can be studied under simplified conditions during contractures induced by K or high Ca solutions. In such experiments changes in length or tension produce complex changes in activity, under certain conditions oscillations indicating the presence of a feedback mechanism (2, 3). Oscillations have previously been observed in activated insect fibrillar muscles and in various types of glycerol-extracted muscles (13, 14, 15), in which a moderate contraction was induced by a solution containing adenosine triphosphate. It has been concluded from these experiments, carried out under nearly isometric conditions, that changes in length produce a negative feedback. This has been demonstrated most conclusively by the oscillations which can be induced in activated insect...
flight muscles. It will be shown, however, that in living cardiac muscle
changes in length also produce a powerful positive feedback and that this
mechanism is the most important mechanical factor controlling the time-
course of the isotonic twitch.

METHODS

Rings of the ventricle and atrium of the frog (*Rana pipiens* and *Rana catesbeiana*) and
the ventricle of the turtle (*Chrysemys picta*) were used and prepared as described previ-
ously (1, 2). Mechanical changes were recorded with an inkwriting polygraph
(Grass Instrument Co., Quincy, Mass.) by using the apparatus illustrated in Fig. 1.

![Diagram of apparatus](image)

**Figure 1.** Diagram of apparatus. (A) Axis of lever, connected on one side to axis of
angular displacement transducer (not shown) on the other side to axis of penmotor (not
shown). (FT₁) A force transducer (Grass FT03) which can be attached to the lever by
a flexible connection for recording tension during afterloaded twitches. (FT₂) Force
transducer for recording isometric contractions. (R) A rod which can be moved hori-
zontally into a position above the lever to stop its upward movement.

A lever, which was 8 cm long, was mounted on the axis of an angular displacement
transducer (Harvard Apparatus Co., Inc., Millis, Mass.) The muscle was attached
to the end of the lever. A steady load was applied to the muscle by a long coiled spring
attached 0.6 cm from the fulcrum. The equivalent mass of the system was about
250 mg.

In experiments in which the load was changed quickly the axis of the transducer
was connected to that of a torque motor. A penmotor from which the springs were
removed was used. The load could be rapidly changed by a signal from a stimulator
acting through the driver amplifier of the motor. Although this system has a con-
siderable inertia, it was adequate for the slow muscles used. If the muscle was at
rest, the change in length produced by a signal suddenly applied to the torque motor
was 90% complete in 0.06 s. The lag is smaller during contraction because of a
smaller compliance of the muscle. In an earlier series of experiments changes in
length were produced by depressing or releasing the muscle lever a predetermined
distance by a vertical rod without using the torque motor and, therefore, with a
greatly reduced inertia. The same results were obtained.
A Grass force transducer (FT03) could be attached to the end of the lever for recording tension (FT2 in Fig. 1). Changes of tension at the beginning and end of an afterloaded contraction (Fig. 1) were recorded with transducer FT1 (Fig. 1) by the method of Jewell and Wilkie (9). The force transducer FT1 was connected to the isotonic lever by a light chain and determined the resting length. In some experiments the load was supported during part of relaxation. For this purpose rod R could be shifted horizontally along its axis by an electromagnet, so that movement of the lever was stopped briefly.

The muscle was stimulated 5–10 times per minute, the frequency depending on temperature. The output of the stimulator was connected to the driveramplifier of the recording pen so that the stimulus, a rectangular shock lasting 3 ms, made a mark on the record of the contraction. Rise time was measured from the stimulus to the peak of the contraction.

To compare the time relations of contractions records of controls were traced on translucent paper. The copies were then shifted horizontally over the experimental records. Changes in the duration of a response could be determined accurately if the time-course of the final part of relaxation was the same. Because the ordinates of the recording system are curvilinear, such a comparison of the records is possible only if the base line of the records was adjusted to the same level.

In most experiments a load was chosen at the beginning so that increases in load produced only a moderate extension of the muscle. This was true for a load of about 60 g/cm². At the length so established, tension produced was about maximal. Under optimal conditions developed tension was about 400 g/cm² for the ventricle, 250 g/cm² for the atrium. Results of the experiments to be described were not essentially different if the load was as much as 10 times larger. All experiments were carried out with more than 10 muscles and were repeated many times with the same muscle.

The physiological solution, which will be called Ringer solution, contained in millimoles per liter: NaCl 114, KCl 3, CaCl₂ 1.5, glucose 2, Tris (hydroxymethyl) aminomethane chloride (Tris) 2, and had a pH of 7.2. Bicarbonate and other buffers were used occasionally and gave the same results. High Ca solutions were obtained by mixing Ringer solution with modified Ringer solutions in which all Na was replaced by 83 mM Ca. In K solutions all Na was replaced by K.

**RESULTS**

Results obtained with the frog and turtle heart were identical except for small quantitative differences. Unless specified otherwise, the description presented here refers to ventricle of the two species of frogs used.

How mechanical factors influence the time-course of contraction can be learned most directly from the effect of mechanical interventions. For an understanding of these effects, it is important first to compare the time-course of normal contractions under different mechanical conditions. Most remarkable is the finding that, except for the beginning, the speed of isotonic relaxation remained the same when the load was increased as much as 10 times, so that graphs of relaxation could be exactly superimposed, regardless of the
amplitude of the response, as shown in Fig. 2. Therefore, the duration of relaxation diminished with increasing load. Rise time usually remained the same, but sometimes diminished, as much as 10% in some muscles. To emphasize the agreement in the time-course of relaxation, on which the accuracy of the measurements depends, Fig. 2 and some later graphs were drawn so that the last phases of relaxation were superimposed.

In the isometric twitch, rise time was briefer, relaxation much slower than in the isotonic twitch (Fig. 3). If scaled to the same maximal height, graphs of the isometric twitch would be nearly the same over a considerable range of lengths (Fig. 2), in contrast to the isotonic twitch. If length was increased more than about 20%, rise time became increasingly shorter, but isometric relaxation became much slower, half time increasing several times, so that the duration of the twitch increased, as had previously been observed in frog skeletal muscle (9). In the following the effects of several types of mechanical interventions on the isotonic twitch and on contractures will be described.

**Interrupted Isotonic Relaxation**

To determine how mechanical force influences the speed of relaxation the muscle lever was briefly arrested by placing rod R (Fig. 1) over the lever. If relaxation were influenced significantly by force, one might expect that the completion of relaxation after withdrawal of the support would be delayed, but this was never observed. On the contrary, the ventricle was ex-
tended rapidly after the reaplication of the load beyond the level of the controls, as shown in Fig. 4. In the atrium, however, the normal time-course of relaxation was always resumed within less than 1 s at 4°C (Fig. 4). This phenomenon could be demonstrated most strikingly in high Ca solutions, in which relaxation was very slow (1).

In the experiments described above the torque motor was not attached to

![Figure 3](image-url)  
**Figure 3.** Isometric and isotonic twitches of the same frog ventricle at the same resting length. Interrupted line: muscle unloaded for 0.15 s during isotonic twitch. Stimuli applied at time 0. Temp 11°C. *R. pipiens.*

![Figure 4](image-url)  
**Figure 4.** Effect of brief support of load during isotonic relaxation of ventricle and atrium. Experimental graph and control drawn so that rising phases are superimposed. Note slow time scale of graph on right representing contraction in high Ca solution. Ventricle of *R. pipiens*, atrium of *R. catesbeiana.*
the transducer. The maximal force produced by the movement after the release of the lever, calculated as the product of mass times acceleration, was found to be less than 0.1% of the load applied and, therefore, did not influence the results.

**Brief Diminution in Load**

In these experiments the load was diminished briefly during various phases of a twitch. In the atrium the time-course of contraction always continued unchanged after changes in load during the rising phase. During relaxation the muscle was subsequently extended beyond the controls, but later relaxation was resumed as it would have without the intervention (Fig. 5). If the twitch was made slower by increasing [Ca] of the medium the effect was still briefer in relation to the duration of the twitch.

In the ventricle the procedure produced much larger and longer lasting changes, which varied somewhat in different phases of the twitch and with the degree of unloading. After the load was diminished briefly by 50% or more, the muscle extended rapidly by as much as 10% of its length, then shortened again, but without reaching the peak of the controls; the relaxation was usually delayed (Fig. 6). During the last part of the rising phase and during relaxation the procedure caused rapid extension and a shortening of the twitch by as much as a third of the duration of the rising phase. After complete unloading near the peak, relaxation may be 90% complete in 0.2 s at 4°C (Fig. 3). An effect was observed after relaxation was more than

![Figure 5.](image)

**Figure 5.** Effect of complete brief unloading of atrium immersed in Ringer solution (left) and 60 mM Ca solution (right). The graphs are superimposed on a normal isotonic twitch (interrupted line). Procedure was applied twice during a twitch in high Ca solution. Note difference in temperature and time scale. Stimuli applied at time 0. *R. catesbeiana.*
The effect of briefly diminishing load from 3 to 1.5 g at different times during isotonic contraction of ventricle. In each graph a normal and a modified twitch (interrupted line) are drawn so that the beginning is superimposed. If the unloading started 1.1 and 0.4 s before the peak, relaxation was delayed 0.13 and 0.3 s, respectively; if started 0.24 s before the peak, relaxation was terminated 0.8 s sooner than in control. Note parallelism of relaxation with that of control about 1.5 s after intervention. Temp 15°C. *R. pipiens.*

Half completed. Near the peak a brief period could be found before which the procedure caused prolongation, after which the twitch was shortened.

The prolongation of the twitch after brief unloading was usually smaller than in Fig. 6 and diminished, sometimes disappeared, in the course of a long experiment. After the effect had disappeared, unloading before a critical phase near the peak was followed by rapid extension as before, but the normal time-course of the twitch was resumed later (Fig. 7). It should be noted that in Figs. 6 and 7 relaxation proceeded in two steps, except when the intervention occurred rather late during the twitch.

Immediately after a small brief diminution of the load, causing a shortening of less than 2%, the muscle first remained slightly shorter than the control because of shortening while the load was reduced. The maximal speed of relaxation then was reached only after a delay (Fig. 8). If the load is changed some time before the peak, the muscle may even shorten again after the change in load and begin to relax more than a second later, but earlier than the control. It is very important that in these experiments, as well as after other types of mechanical interventions, relaxation exactly paralleled the controls. The great accuracy of the agreement can be best verified by superimposing a tracing of a control over the experimental record. The normal time-course of relaxation was resumed about 1–1.5 s after the intervention at 4°C. The sensitivity of the muscle to movement near the peak of a twitch is remarkable; brief shortening by 0.5% may produce a striking relaxing effect.
Brief Increase in Load

The reverse procedure, briefly increasing the load, prolonged the twitch if carried out near the peak, but the change was rather small (8–12% of the duration of the rising phase under favorable conditions). The magnitude of the effects was about twice as large after a stretch lasting 0.3 s than after one lasting 0.1 s, and was largest if the extra load was removed shortly after the peak. That the normal height of contraction was usually not regained does not argue for a diminution in activity, because contractile activity can be assumed to be weak near the peak, so that the extra energy needed to lift the load back to its normal height was not available. Actually in the experiment illustrated in Fig. 9, in which the stretch was very brief and applied early, the subsequent contraction surpassed the control for a short time. This effect was usually not obtained, and only at temperatures above 12°C. In all experiments, however, shortening after the release was much larger than that which would have taken place at that time without the intervention. This shortening was at first very rapid, then the tracing became nearly parallel to the controls. Even if the rapid phase, which is presumably due to elasticity, was disregarded, the amount of shortening was still much larger after the intervention than in controls. This fact and the prolongation of the response show that contractile activity was increased by a brief increase in load.
Figure 8. Effect of a small and brief diminution of load. Load was diminished from 3 to 2.4 g for 0.2 s, producing changes in length of about 2%. In each panel a normal (solid line) and a modified (interrupted line) twitch are drawn so that the beginnings are superimposed. During an early phase the procedure produced only a transient diminution of contraction. Later relaxation was advanced, but was exactly parallel with normal relaxation about 1.5 s after change in load. Temp 4°C. R. pipiens.

Maintained Increase or Decrease in Load

The experiments just described left open the question whether the effects observed were due to shortening or lengthening. Therefore, in other experiments the load was suddenly increased or decreased during a twitch and maintained at this level for the rest of the contraction. The duration of this twitch was then compared with that of the next twitch with the new load. Increasing the load induced rapid relaxation and shortened the twitch; reducing the load had the opposite effect. The largest effects were obtained near the peak of the twitch (Fig. 10). If the increase in load was moderate the relaxing action of passive extension developed gradually.

Even without change during contraction, the duration of the isotonic twitch varied with the load, decreasing as the load was increased, as shown in Fig. 2. Therefore, if the load was increased between two twitches, the
Figure 9. Effect of a brief increase in load. (Left) Increase in load from 2 to 3.5 g for 0.06 s. (Right) Increase from 2 to 5 g for 0.3 s. In both panels one experimental twitch and one control drawn so that the beginnings are superimposed. Temp. 13°C. *R. pipiens.*

Figure 10. Effect of a maintained change in load during twitch. In each of the lowest panels two successive twitches are drawn so that relaxation is superimposed. (Left) Shortly after the peak of the first twitch the load was increased from 2 to 2.6 g, as shown in middle panel. The next twitch was obtained at the higher load, and was 1.05 s longer. (Right) Same experiment, but load was diminished from 2.6 to 2.0 g. The control twitch was 0.85 s shorter. In the same experiment the timing of the change in load was varied. The changes in the duration of the twitch so produced are plotted in the upper panel. Temp 4°C. *R. pipiens.*
second was briefer than the first. However, if the increase occurred during the first twitch, the second twitch was longer than the one during which the load was changed. The opposite was true if the load was diminished during a twitch. Therefore, the actual effect of changes in load during a twitch can be assumed to be larger than the direct measurements indicate. In the experiment illustrated in Fig. 10 the differences in load, and therefore also the differences in the duration of normal twitches, were small.

Afterloaded Isotonic Twitch

Tension and length were recorded simultaneously by the method of Jewell and Wilkie (9). In experiments with the frog sartorius, these authors found that the last part of isometric relaxation of the afterloaded twitch proceeded exactly as during an isometric twitch, but occurred earlier, the more so the larger the degree of shortening. The first part of the isometric phase was faster than during an isometric twitch. Both changes were also found in the frog heart, but they were much smaller in the atrium than in the ventricle (Fig. 11). With small afterloads, permitting a large degree of shortening, the duration of the twitch of the ventricle was 1.5–2.0 s shorter than the isometric twitch, 0.2–0.4 s shorter in the atrium, both at 5°C. Furthermore, the first accelerated phase of isometric relaxation was very brief in the atrium, and was not detectable with high preloads and at temperatures above about 12°C.

Change in Load During a Contracture

In previous work it was found that changes in load during contractures induced by K or high Ca solutions induce complex changes in activity. The

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**Figure 11.** Records of tension during isometric and afterloaded twitches of ventricle and atrium with different afterloads, drawn so that the last part of relaxation is superimposed. Temp 5°C. *R. catesbeiana.*
first effect of a sudden increase in load or brief unloading was a large extension; it was followed by shortening to a new level, under some conditions by oscillations (Fig. 12). Unloading produced the opposite effects. An important new result was obtained if the changes in load were rather small. The extension after brief unloading or an increase in load then proceeded in two distinct phases, a small instantaneous, evidently passive, increase in length, then a much larger, gradually accelerating lengthening (Fig. 12 B). No delay was observed with larger changes in load.

**Figure 12.** Effect of changes in load (indicated by upper line in each panel) during contracture induced by K_{2}SO_{4} solution. *R. pipiens.* (A) Record at low speed. (B) Same, but with smaller change in load and recorded first at high speed, then continued at low speed. Falling base line because of decrease in contracture. (C) Same procedure at higher temperature. Same muscle, but after recovery in Ringer solution and during second immersion in K_{2}SO_{4} solution.

**DISCUSSION**

*Lengthening Deactivation and Shortening Activation*

The effects of mechanical interventions during the isotonic contraction described above show that movement, depending on its direction, can produce a delayed increase or decrease in activity. Such responses can be demonstrated most easily during contractures. Under isometric conditions a stretch produced a delayed, transient rise in tension; release had the opposite effect (11). Similar delayed responses have been observed in activated insect fibrillar (and other types of muscle (10, 13, 14, 15) and can be expected to produce a negative feedback during contraction. However, under isotonic conditions
changes in load first produced much larger effects in the opposite direction. An increase in load first produced extension (1, 2). That this was not purely passive is shown most clearly by the observation that after the immediate elastic effect the maximal speed of extension was reached only after a delay, if the change in load was moderate (Fig. 12 B). This delayed relaxing action will be called lengthening deactivation. The reverse effect, which will be called shortening activation is demonstrated by a slow shortening beyond the final length.

These responses are closely related to the effect of changing the load during twitches. Lengthening deactivation accounts for the shortening of the twitch after an increase in load and after supporting the load briefly during relaxation. Shortening activation is similarly responsible for the opposite effect of diminishing the load.

Alteration of the time-course of a twitch by movement can be shown most easily by experiments in which the load is changed briefly. A relaxing effect is produced by a brief diminution in load, that is by allowing the muscle to shorten, then extending it by restoring the load. Because an increase in load has the same effect, relaxation can be assumed to be due to extension. The same explanation can be applied to the relaxing effect of the isotonic phase of an afterloaded twitch, demonstrated by the fact that during the final isometric phase tension dropped very rapidly at first and that the relaxation was completed earlier, the larger the degree of shortening (Fig. 11). That extension, not shortening, caused these effects has been shown in special experiments by Jewell and Wilkie (9) for frog skeletal muscle. Applying the same interpretation, it can be assumed that the reverse effect, produced by a brief increase in load, is due to shortening.

The responses to all types of interventions applied were several times smaller and briefer in the atrium than in the ventricle. This result supports the assumption that the effects of all mechanical interventions are due to the same mechanism.

An increase in activity was never the first effect of extension in experiments in which step changes in force were applied. In the ventricle, however, a large and brief diminution in load during the rising phase of the twitch, after first causing partial relaxation, usually delayed the final part of relaxation. This effect may correspond to the secondary active shortening after a brief diminution in load which was found during contractures and is essential for the oscillations observed under certain conditions (1, 2).

**Mechanism of Activation and Deactivation**

It has been reported previously that stretching as well as release during an isometric twitch depresses contractility (4, 5, 12). Kaufmann et al. (12) have pointed out that this effect, which has been called uncoupling by Brady (4),
can be explained on the basis of the statistical theory of cross-bridge activity of A. F. Huxley (7). If the time constant of establishing new cross bridges is rather long, as assumed in this theory, movement diminishes their number and has, therefore, a relaxing effect.

This theory is in conflict with two observations reported above. It is not consistent with the fact that changes in length can increase activity and prolong the twitch (Figs. 9, 10), effects which have been called shortening activation. Thus extension and release produced opposite effects. This result disagrees with conclusions derived by previous authors (5, 12) from an experiment, in which the muscle was quickly released during the second half of the rising phase of an isometric twitch. From the observation that tension subsequently did not rise as high as during a twitch at the shorter length it was concluded that activity was diminished by the shortening. However, the amplitude of the rise was actually much larger than it would have been during a normal twitch (12, Fig. 2), perhaps an indication that activity was actually increased by the release.

The theory mentioned above also does not explain that lengthening deactivation is a delayed effect. If movement acted primarily by breaking bonds, the relaxing effect should be strongest at the very beginning, whereas extension beyond the controls may not begin until more than a second after the passive movement (Fig. 8).

The fact that the rapid extension, produced by a large, brief diminution in load, had no delay (Figs. 6, 7) remains to be explained. Under these conditions the mechanism suggested by Kaufmann et al. (12), mentioned above, may play a role. However, subsequent events, maintenance of partial relaxation with early or late completion of relaxation, depending on the timing of the intervention, must be considered as delayed effects. That two mechanisms come into play is supported by the presence of two stages of relaxation. Smaller passive movements, on the other hand, produced only delayed effects. The terms lengthening deactivation and shortening activation refer specifically to these delayed effects.

The observations reported here show that the absolute speed of isotonic relaxation is independent of force and length and that, therefore, only chemical processes control the making and breaking of cross bridges during relaxation. It seems reasonable to assume that changes in length influence these processes. This may apply also to other phases of the twitch. That this type of control is not an essential part of the force-generating mechanism is suggested by the large quantitative differences between atrium and ventricle.

That changes in the membrane potential play an essential role, as suggested by the work of Kaufmann et al. (11), is ruled out by the experiments on contractures. The relaxing effect of movement has also been explained by assuming intracellular movements of Ca (12, 16), but studies on the effect of
movement on glycerol-extracted muscles immersed in Ca buffers make this hypothesis unnecessary (10, 13, 14, 15).

Time Relations of the Twitch

Shortening activation acts as positive feedback during the rising phase of a twitch; lengthening deactivation acts similarly during relaxation. This interpretation agrees with the fact that in the isotonic twitch the rising phase is longer, relaxation is shorter than in the isometric twitch. However, a quantitative evaluation of the influence of activation and deactivation on the time-course of contraction is not possible because neither isotonic nor isometric contraction represents accurately the changes in contractile activity.

Another difference between isometric and isotonic contraction is the fact that variations in amplitude due to different loads or lengths have very different effects on the time-course of the twitch. That the speed of isotonic relaxation does not vary with amplitude may result from the effect of extension on the chemical processes governing relaxation. The absence of this factor during isometric relaxation may explain why its time-course, if scaled to the same amplitude, is nearly independent of the amplitude. However, small movements take place also during the isometric twitch. Because of the great sensitivity of the muscle to movement, it must be assumed that isometric relaxation would be still slower under strictly isometric conditions. Actually A. F. Huxley and Simmons (8) have reported that the relaxation of segments of isolated skeletal muscle fibers became much slower when the length was kept very constant by the spot follower method.

That the time-course of isotonic relaxation is independent of the amplitude of contraction and is resumed, although advanced or delayed after some interventions, is difficult to explain on the basis of our present knowledge of cross-bridge activity. It appears that the breaking of the bridges proceeds according to a pattern which is only briefly disturbed by sudden changes in length. Such a behavior suggests that some of the processes controlling relaxation are rather rigidly programmed and that a high degree of cooperation between the cross bridges exists.

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