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Rate of force generation in muscle: Correlation with actomyosin ATPase activity in solution

(myosin/actin/contraction/velocity/force redevelopment)

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ABSTRACT **Crossbridge models of muscle contraction based on biochemical studies predict that there may be a relationship between the rate-limiting step in the actomyosin ATPase cycle *in vitro* and the rate of force development *in vivo*. In the present study, we measured the rate of force redevelopment in skinned rabbit muscle fibers following unloaded isotonic shortening and a rapid restretch. For comparison, ATPase activity was measured under identical conditions, using myosin subfragment-1 chemically crosslinked to actin. We found that the time course of force redevelopment is well fitted by a single exponential function, implying that force redevelopment is a first-order process, described by a single rate constant. The magnitude of this rate constant is in close agreement with the rate constant necessary to simulate the experimental force–velocity relation on the basis of a crossbridge model of the type proposed by A. F. Huxley in 1957. In addition, the observed close correlation between the rate constant for force redevelopment and the maximal actin-activated actomyosin ATPase rate under a variety of conditions suggests that the step that determines the rate of force generation in the crossbridge cycle may be the physiological equivalent of the rate-limiting step in the actomyosin ATPase cycle in solution.**

It is now widely accepted that skeletal muscle contraction occurs when the thin (actin) filaments slide past the thick (myosin) filaments. This process is driven by crossbridges that extend from the myosin filaments and cyclically interact with the actin filaments as ATP is hydrolyzed. This cyclic interaction causes maximal force development when the muscle is prevented from shortening (isometric contraction) and maximal shortening velocity when the actin and myosin filaments are allowed to slide freely past each other (unloaded isotonic contraction).

In 1957, A. F. Huxley (1) presented the first quantitative model of crossbridge action. In this model he suggested that crossbridges have a moderate rate of attachment (f) to actin to form the force-generating state, a very slow rate of detachment (g_1) during their work-stroke while they are exerting force, and a quite rapid rate of detachment (g_2) at the end of their work-stroke. This model was able to account quantitatively for the relationship between force and shortening velocity exhibited by the muscle (force–velocity curve) and also for the leveling off of energy utilization by the muscle at high velocity. However, it is not a unique model; a model with a very different set of values for f and g was also able to account for these physiological data (2).

Since these crossbridge models were proposed, considerable progress has been made in understanding the biochemistry of muscle contraction (3, 4). Studies on the interaction of actin, myosin, and ATP have shown that myosin can occur in two major conformations (5). With ATP or ADP·P_i bound, myosin occurs in a weak-binding conformation that binds very weakly to actin and attaches to and detaches from actin very rapidly. On the other hand, with ADP or nothing at the active site, myosin occurs in a strong-binding conformation that binds very strongly to actin and detaches much less rapidly (4, 5). Since crossbridges in the weak-binding conformation presumably exert relatively little force in muscle fibers compared to crossbridges in the strong-binding conformation, the rate of force generation, which in the Huxley model is mainly controlled by f, might be determined by the overall rate of the transition from the weak-binding conformation to the strong-binding conformation. In solution this same transition is the rate-limiting step in the ATPase cycle (6). This leads to the prediction that the rate of the rate-limiting step in the ATPase cycle will be equal to the rate of force development *in vivo* (6).

There have been previous studies on the rate of force development in muscle fibers. Moisescu (7) and Griffiths *et al.* (8) investigated the rate of force development in frog muscle fibers following step-wise activation. However, these measurements were complicated by slow steps which were found to occur as part of the calcium-activation process itself (7). To avoid this problem, the rate of force redevelopment following isotonic shortening can be studied. A. V. Hill (9) studied the rate of force redevelopment in frog muscle fibers following large releases that dropped the force to zero, but such measurements are complicated by the occurrence of considerable internal shortening. In addition, about two-thirds of the crossbridges remain attached during unloaded isotonic shortening of frog fibers, which complicates the measurement of force redevelopment (10, 11). In contrast, with rabbit fibers, only about 20% of the crossbridges remain attached during unloaded isotonic shortening (12). Rabbit fibers also offer the advantage that most of the ATPase studies have been done with rabbit muscle proteins, which facilitates comparison of biochemical and physiological data.

In the present study, we investigated the rate of force redevelopment in single skinned rabbit psoas fibers following unloaded isotonic shortening and a rapid stretch to return the fiber to its original sarcomere length. Since we find that internal shortening of the fibers significantly slows the rate of force redevelopment, the sarcomere length of the fibers was kept constant during the redevelopment period by means of a servosystem using sarcomere length measured by laser light diffraction as the control signal. To compare the rate of force redevelopment with the rate-limiting step in the actomyosin ATPase cycle *in vitro*, the latter rate was measured with myosin subfragment-1 (S-1) crosslinked to actin (13, 14).

We observed that the value of the rate constant for force redevelopment agrees within a factor of 2 with the value of the rate-limiting step in the actomyosin ATPase cycle *in vitro*

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Abbreviation: S-1, myosin subfragment-1.

over a range of temperature and ionic strength. A preliminary account of this work has been presented (15).

MATERIALS AND METHODS

Fiber Preparation and Solutions. Single skinned rabbit psoas fibers were prepared as described (16). The fiber segments were attached to the mechanical lever system and to the force transducer by use of a cyanoacrylate glue (Histoacryl, Braun Melsungen, FRG). Solutions contained 10 mM imidazole, 2 mM $MgCl_2$, 3–5 mM MgATP, 10 mM creatine phosphate, and either 1 mM EGTA (relaxing solution) or 1 mM CaEGTA (activating solution). Ionic strength was adjusted by adding KCl. The temperature ranged between 5° and 35°C and the pH was 7.0.

Sarcomere Length Measurements. Sarcomere length was measured by laser diffraction using a Shottky barrier photodiode (PIN, SC/10D; United Detector Technology, Santa Monica, CA) to monitor the position of the centroid of the first-order maximum of the laser diffraction pattern. Sarcomere length was calculated from the angle between the zero- and first-order diffraction maxima, using the thin-grating equation as an approximation (17). To account for the domain structure (18) of single skinned rabbit fibers and its effects on the laser diffraction pattern, the output of the photodiode was monitored and compared at different beam incidence angles (18).

Force Transducer. Force was measured with a semiconductor strain gauge element (AE 801, Aksjeselskapet, Horten, Norway). The original silicone beam was modified to increase the natural frequency of the system (17). The resulting natural frequency was between 25 and 30 kHz with a fiber mounted and placed in solution.

Displacement Generator. The displacement generator was a modified moving-coil galvanometer (19) reinforced to avoid oscillations when used as part of a servosystem to control either overall length or sarcomere length of the fibers during isometric contraction. Load during isotonic shortening was set by applying a constant coil current. Initial overshoot of the coil movement when switching from isometric to isotonic mode, caused by the inertia of the moving parts, was reduced by a negative velocity feedback acting as a damping element.

Servosystem-Controlled Sarcomere Length. To control the average sarcomere length of the laser-illuminated fiber area during isometric contraction, the position of the centroid of the first-order diffraction maximum was monitored and used as the control signal in a servosystem. This servosystem had a "direct" and a "velocity" component. In addition, to reduce the remaining error of the direct component, an error-integrating unit was included in the feedback loop. The command signal used to keep sarcomere length constant during force redevelopment was the sarcomere length measured immediately before the period of isotonic shortening, stored in the "hold" mode of a sample-hold amplifier circuit. Due to deterioration of the laser diffraction pattern in activated fibers at temperatures ≥25°C, the feedback became unreliable; thus, overall length was controlled under these high-temperature conditions.

Measurement of Fiber Stiffness. Fiber stiffness was measured by applying fast displacements to one end of the fibers. Apparent fiber stiffness was taken as the slope when force was plotted vs. the change in sarcomere length during such displacements. The speed of displacement was variable up to about 8×10^5 nm per half-sarcomere per sec (17).

Experimental Protocol. Fibers were prepared and mounted while kept relaxed. Prior to activation, fibers were incubated for at least 15 min in relaxing solution containing the same amount of creatine phosphate and creatine phosphokinase as added to the activating solution, to allow the components of this ATP-regenerating system to diffuse into the fibers. To keep the striation pattern of the activated fibers well ordered and stable, fibers were cycled between periods of isometric contraction and unloaded or lightly loaded isotonic shortening (16). Force redevelopment was monitored following a period of lightly loaded isotonic shortening after fibers were restretched to their original isometric sarcomere length at the end of isotonic shortening. Either temperature or ionic strength was changed while fibers were fully Ca^{2+}-activated or fibers were relaxed between change of conditions. No significant difference in the results was observed with the two procedures.

Biochemistry. S-1 crosslinked to actin was prepared using a slightly modified procedure of Mornet *et al.* (13) and Stein *et al.* (14). Iodoacetamide was used to quantitatively monitor the amount of S-1 crosslinked to actin (14). ATPase activity of the crosslinked S-1–actin was measured by the pH-stat method (20). The solutions contained 2 mM imidazole (pH 7.0), 2 mM $MgCl_2$, and 1 mM MgATP. The ionic strength was adjusted with KCl.

RESULTS

Force redevelopment can be characterized by following the increase in force that occurs when unloaded or lightly loaded isotonic shortening is stopped and the muscle fiber is held isometrically after a very small restretch. A typical trace is shown in Fig. 1*A*. Over a time period of about 0.5 sec, the force redevelops to a level about 75% of P_0 (the original isometric force level). It then slowly recovers fully to P_0 over a period of about 10 sec (not shown). In general, the force level reached during the initial phase of force redevelopment decreased somewhat as the amount of isotonic shortening increased. The cause of this phenomenon is not clear, but it may be related to the decrease in shortening velocity that occurs during isotonic contraction (19).

To avoid this problem as well as variations in the level of force redevelopment due to change in sarcomere length, fibers were rapidly restretched to their original sarcomere length before the rate of force redevelopment was measured. Fig. 1*B* shows that when such a maneuver was used in an experiment otherwise identical to that of Fig. 1*A*, the force recovered all the way to P_0 during the initial phase of force redevelopment. Further, it recovered with the same time course as in Fig. 1*A*. In numerous experiments we have found that although restretching the fiber affects the level of the redeveloped force, it does not affect the time course of the initial force redevelopment. Therefore, we restretched the fiber to its original sarcomere length in all further experiments presented here.

A factor that does affect the time course of force redevelopment is the occurrence of internal shortening. As shown in Fig. 1*C*, internal shortening of only about 2.5% significantly decreases the rate of force redevelopment compared to the rate with the sarcomere length held constant. In this experiment, the calculated rate constant for the force redevelopment decreased about 33% (see below for calculation method). This effect became even larger at 15°C, where we obtained a 50% decrease (data not shown). We therefore carefully controlled sarcomere length during the period of force redevelopment by using laser feedback wherever possible; as we discuss below, this was not possible at temperatures above 15°C.

To test whether force redevelopment reflects an increase in the number of myosin crossbridges bound to actin in the strong-binding conformation, the apparent fiber stiffness was measured during the period of force redevelopment (Fig. 2). To avoid detection of crossbridges in the weak-binding conformation, the stiffness measurements were performed at an ionic strength of 170 mM with a moderate speed of stretch (1000–5000 nm per half-sarcomere per sec). Attached cross-

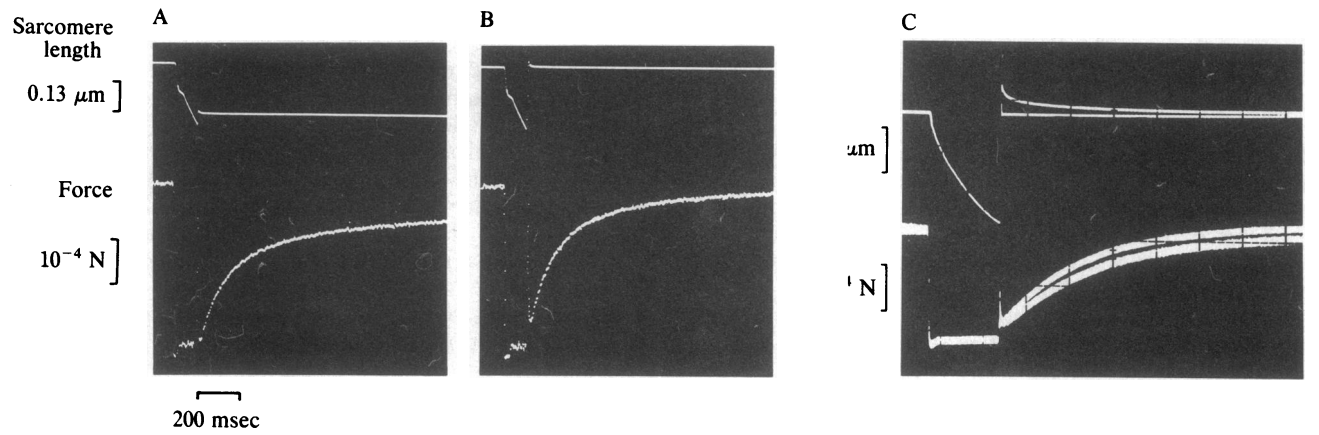

FIG. 1. (*A*) Force redevelopment after isotonic shortening, followed by only a small stretch (20% of full restretch). The upper trace shows sarcomere length, and the lower trace, force, for a single skinned rabbit psoas fiber (length 7.4 mm, cross-section 85 × 95 μm) at 5°C and pCa 4.5. Although this experiment ideally should be without any restretch at the end of the isotonic shortening, a small stretch had to be allowed since at that moment, switch-over from load control to sarcomere-length control occurs. This switch-over is always accompanied by a small transient. To avoid transient slackening of the fiber with subsequent destabilization of the feedback in sarcomere-length control, parameters of the feedback were adjusted so that a small stretch occurred. (*B*) Force redevelopment after isotonic shortening, followed by restretch to original isometric sarcomere length (conditions as in *A*). After a 120-msec period of isotonic shortening under relative load near zero ($P/P_0 \leq 0.06$), the fiber was restretched to its original isometric sarcomere length, and force redevelopment was followed while the fiber was held at constant sarcomere length. The spike in the force trace indicating the end of the isotonic period is the result of the transient increase in force during the restretching of the fiber to the initial sarcomere length. The time for restretch is 10–20 msec. (*C*) Effect of internal shortening on force redevelopment (conditions as in *A*). Traces of experiments with and without laser-controlled feedback are superimposed. Note that internal shortening of only about 2.5% causes a delay in force redevelopment of ≈150 msec at the time of half-maximal redevelopment.

bridges in the weak-binding conformation, such as are observed in relaxed rabbit muscle fibers at low ionic strength, would not be detected in these measurements (17, 21). Fig. 2 shows (*i*) that during unloaded isotonic shortening, only about 20% of the crossbridges are attached in the strong-binding conformation, which facilitates measurement of force redevelopment, and (*ii*) that there is a close correlation between isometric force and apparent fiber stiffness. Assuming that there is no exponential series compliance within the sarcomere, this suggests that the increase in force reflects an increase in the number of crossbridges attached to actin in the major force-generating state.

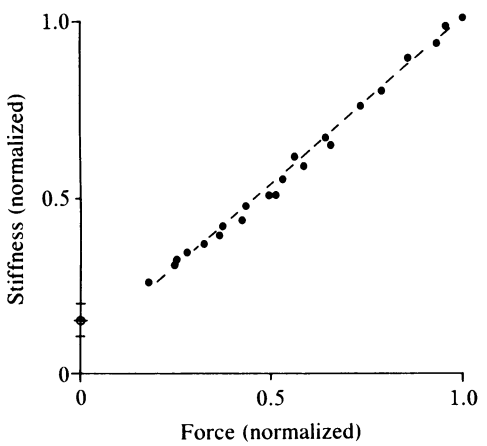

FIG. 2. Apparent fiber stiffness during the period of force redevelopment. Each point represents a single stiffness measurement during the course of force redevelopment. By application of the cycling technique (16), several stiffness measurements were possible from one fiber, although only one stiffness measurement was done during each cycle. Apparent fiber stiffness is defined as the resulting slope when force is plotted vs. the change in sarcomer length observed during rapid stretches. Speed of stretch, 1000–5000 nm per half-sarcomere per sec. Symbol on ordinate (⊕) shows apparent fiber stiffness during lightly loaded ($P/P_0 \leq 0.03$) isotonic shortening [0.16 ± 0.05 (mean ± SD, $n = 4$)]. Conditions were as described in the legend to Fig. 1.

We next determined whether the rate of force redevelopment is a first-order process that can be fitted by a single exponential function. Fig. 3*A* shows the time course of force redevelopment at both 0.05 M and 0.17 M ionic strength. This experiment was performed at 5°C, where the sarcomere length-control system works well. Fig. 3*B* shows first-order plots of these data. As can be seen, both plots are linear, which means that the rate of force redevelopment is well fitted by a single exponential function; from the slopes of the linear plots, we find that the rate constants in these particular experiments are 5.0 sec^{-1} at 0.05 M and 5.9 sec^{-1} at 0.17 M (see Table 1 for average values).

This experiment not only shows that the rate of force redevelopment is a first-order process, it also suggests that it actually increases slightly as the ionic strength is increased. This is somewhat surprising because the affinity of myosin for actin markedly decreases as the ionic strength is increased. Apparently this decrease in affinity does not have a significant effect on the rate of force redevelopment.

We next determined how the rate constant for force redevelopment compares with the maximal actin-activated ATPase rate determined in biochemical experiments (Table 1). The latter rate was measured under conditions identical to those used in the fiber experiments by using S-1 crosslinked to actin (13, 14). Unless S-1 is crosslinked to actin it is not possible to accurately determine V_{max}, the maximal actin-activated ATPase rate, under these conditions because the binding between S-1–ATP and actin is too weak. Comparison of the ATPase rate of crosslinked acto-S-1 with the maximal actin-activated ATPase rate of uncrosslinked S-1 at $\mu = 12$ mM, where the latter rate can be accurately measured by extrapolation, shows that the ATPase rate of crosslinked S-1 is about 18% lower than the maximal actin-activated ATPase rate of uncrosslinked S-1. In Table 1, the measured ATPase rates of crosslinked S-1 have been corrected for this 18% discrepancy.

Table 1 shows that at 5°C, the rate constant for force redevelopment is about twice the maximal actin-activated ATPase rate both at $\mu = 0.05$ M and at $\mu = 0.17$ M. As the

Table 1. Comparison of the rate constants for force redevelopment and crosslinked acto-S-1 ATPase activity

Conditions*	Rate constant, sec^{-1} Force redevelopment† (mean ± SEM)	ATPase‡
5°C (μ = 0.05 M)	3.8 ± 1.3 (n = 4)	1.82
5°C	4.5 ± 1.9 (n = 13)	1.92
15°C	14.5 ± 2.4 (n = 5)	11.41
25°C	26.1 ± 4.0 (n = 9)	49.40
35°C	50.7 ± 8.2 (n = 3)	137

*All experiments were at μ = 0.17 M except where otherwise noted. See *Materials and Methods* for compositions of solutions.
†Measurements at 25° and 35°C with overall-length control, all others with sarcomere-length control during the period of force redevelopment.
‡All rates are corrected for the 18% reduction of the ATPase activity of S-1 crosslinked to actin compared to that of uncrosslinked S-1 (see text).

temperature is increased to 15°C, the rate constant for force redevelopment increases about 3.5-fold while the maximal actin-activated ATPase rate increases about 5-fold, so that at 15°C, the two rates are nearly equal. As the temperature is further increased to 25°C and 35°C, the rate constant for force redevelopment appears to increase less than the maximal actin-activated ATPase rate so that, at 25°C and 35°C, the measured rate constant for force redevelopment actually becomes about a factor of 2 slower than the maximal actin-activated ATPase rate. However, it is likely that the true rates of force redevelopment at these higher temperatures are at least a factor of 2 higher than the measured values. Both at 25°C and 35°C, the laser-controlled feedback is not reliable; there is deterioration of the laser diffraction pattern in active fibers at these high temperatures. Hence, rather than controlling the sarcomere length, the overall length of the muscle was controlled. Due to internal shortening, this very likely reduced the observed rates of force redevelopment by at least 50%, the decrease we observed at 15°C when laser-controlled feedback was not used. Therefore, the results in Table 1 suggest that from 15° to 30°C, the rate constant for force redevelopment is about equal to the rate-limiting step in the ATPase cycle, whereas at 5°C there is a factor-of-2 difference between the two rate constants. Although we cannot explain the latter discrepancy, overall our data do suggest that the same step in the biochemical cycle determines both the maximal actin-activated ATPase rate *in vitro* and the rate of force redevelopment in muscle fibers.

DISCUSSION

In this work, we studied the time course of force redevelopment in single skinned rabbit fibers. Our results show that the time course of force redevelopment following a period of unloaded isotonic shortening and a rapid restretch can be fitted by a single exponential function. In most earlier experiments, the redevelopment of force was studied following a release in an isometric transient (22). When we measured force redevelopment following an isometric release in a preliminary experiment, we found that in skinned rabbit fibers, as in intact frog fibers (22), the recovery of force during phase 4 of the isometric transient could not be fitted by a single exponential. Of course, the recovery of force during an isometric transient is a very different phenomenon from the recovery of force following unloaded isotonic shortening. During an isometric transient, the crossbridges are not in a steady-state distribution; most of the crossbridges remain attached during the release phase of the transient (22) and considerable detachment of crossbridges may occur during the recovery of force. In contrast, following unloaded isotonic shortening, the crossbridges are in a steady-state distribution, and in rabbit fibers most of the crossbridges are detached from actin (Fig. 2) (12). This may explain why the recovery of force in our experiment can be fitted by a single exponential.

The magnitude of the observed rate constant for force redevelopment after a period of isotonic shortening and a restretch agrees reasonably well with the rate constant for force redevelopment required to simulate the shape of the experimental force–velocity curve on the basis of a Huxley (1957)-type crossbridge model (1, 23, 24). In such a model, the rate constant for force development, which is mainly determined by f, the rate of crossbridge attachment, is significantly lower than the rate constant for detachment of crossbridges at the end of the crossbridge cycle. On the other hand, our data are in conflict with an alternative explanation of the force–velocity curve which postulates a very fast rate constant for force generation but slow detachment of the crossbridges at the point in the cycle where they exert zero

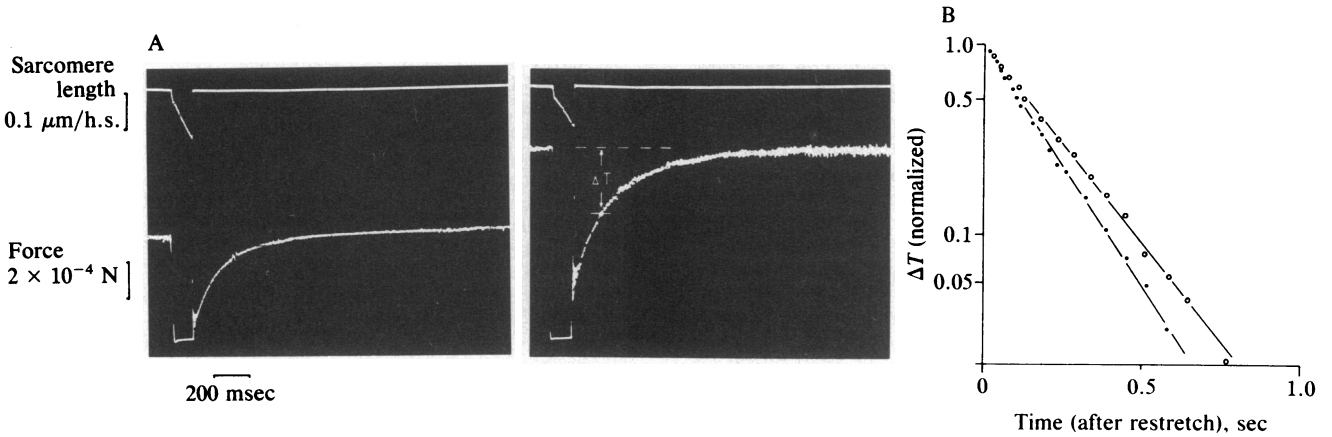

FIG. 3. Effect of ionic strength on force redevelopment. (*A*) Experimental records. Upper traces, sarcomere length (h.s., half-sarcomere); lower traces, force. Fiber length 8.7 mm, cross-section 65 × 85 μm; temperature 5°C; pCa 4.5; ionic strength 0.17 M (*Left*) or 0.05 M (*Right*). (*B*) Approximation of force redevelopment by a single exponential function. The difference between steady-state isometric force and instantaneous force during redevelopment (see ΔT in *A*) is plotted (logarithmic scale) against the time after restretching of the fiber to the original isometric sarcomere length; for ionic strength 0.17 M (●) and 0.05 M (○). The approximately linear relation between ΔT and time after restretching indicates that force redevelopment is satisfactorily fitted by a single exponential function. The rate constant k, the slope of the linearized relation, equals 5.9 sec^{-1} at 170 mM and 5.0 sec^{-1} at 50 mM ionic strength.

force (2). Therefore, our data are consistent with a Huxley-type model.

Biochemical studies suggest that in a Huxley-type cross-bridge model, the overall rate constant for force redevelopment following a large isotonic release *in vivo* will be determined by the first-order rate constant which governs the rate of the transition from the weak-binding conformation to the strong-binding conformation *in vitro* (23–25). This first-order rate constant is also the rate-limiting step in the acto-S-1 ATPase cycle *in vitro* (6). Therefore these models predict that there will be a close correlation between the rate constant for force redevelopment and the rate-limiting step in the acto-S-1 ATPase cycle under a variety of conditions. The results presented in this paper support this prediction. However, there is still disagreement about the nature of this rate-limiting step *in vitro*.

Two biochemical models have been proposed to account for the kinetic behavior of acto-S-1 *in vitro*, the four-state model (scheme 1) and the six-state model (scheme 2) (5, 26). In the following schemes, A = actin and M = myosin.

$$\begin{array}{ccccc} & & \mathrm{M{\cdot}ATP} & \rightleftharpoons & \mathrm{M{\cdot}ADP{\cdot}P_i} \\ & & \downarrow\uparrow & & \downarrow\uparrow \\ \mathrm{A{\cdot}M} & \rightleftharpoons & \mathrm{A{\cdot}M{\cdot}ATP} & \rightleftharpoons & \mathrm{A{\cdot}M{\cdot}ADP{\cdot}P_i} \rightleftharpoons \mathrm{A{\cdot}M} \end{array}$$

Scheme 1

$$\begin{array}{ccccccc} & & \mathrm{M{\cdot}ATP} & \rightleftharpoons & \mathrm{M{\cdot}ADP{\cdot}P_i^I} & \rightleftharpoons & \mathrm{M{\cdot}ADP{\cdot}P_i^{II}} \\ & & \downarrow\uparrow & & \downarrow\uparrow & & \downarrow\uparrow \\ \mathrm{A{\cdot}M} & \rightleftharpoons & \mathrm{A{\cdot}M{\cdot}ATP} & \rightleftharpoons & \mathrm{A{\cdot}M{\cdot}ADP{\cdot}P_i^I} & \rightleftharpoons & \mathrm{A{\cdot}M{\cdot}ADP{\cdot}P_i^{II}} \rightleftharpoons \mathrm{A{\cdot}M} \end{array}$$

Scheme 2

In the four-state model, either the ATP-hydrolysis step or the P_i-release step with S-1 bound to actin are thought to be rate-limiting (6, 26). Both of these steps have very different rates depending on whether S-1 is bound to or dissociated from actin; the ATP-hydrolysis step is considerably faster when S-1 is dissociated from actin, whereas the P_i-release step is much slower. On the other hand, in the six-state model, the rate-limiting step is the transition from $M{\cdot}ADP{\cdot}P_i^I$ to $M{\cdot}ADP{\cdot}P_i^{II}$ which is postulated to have about the same rate whether S-1 is bound to or dissociated from actin (6). The data presented in this paper cannot be used to determine which kinetic model is valid. However, these data do place a restriction on the models. To be valid, a model must account for our observation that increasing ionic strength does not decrease the rate of force redevelopment *in vivo*, despite the fact that the binding of the crossbridge to actin is weakened as the ionic strength is increased. The six-state model can account for this behavior in a simple way, since the rate-limiting step is about the same whether S-1 is bound to or dissociated from actin. The four-state model can also account for this behavior, but it must do so in a more complex way because the possible rate-limiting steps have such different values when the crossbridges are bound to or dissociated from actin.

Whichever kinetic model is valid, the data presented here show that there is a close correlation between the rate constant for force redevelopment and the maximal actin-activated ATPase rate. Barany (27) was one of the first to document the correlation between ATPase activity and the velocity of muscle contraction. However, it is important to note that although the rate constant for force redevelopment controls the curvature of the force–velocity curve, it does not control the maximal velocity of shortening. This is presumably controlled by the rate of crossbridge detachment (23, 24). The studies of White and his collaborators (28) suggest that this detachment rate, in turn, may be controlled by the rate of ADP release from actomyosin. Therefore, the studies that have found a correlation between actomyosin ATPase activity and the maximal velocity of shortening may, in reality, be reflecting a tendency for the rate-limiting step in the ATPase cycle and the rate of ADP release to change in parallel for different types of muscle. Such a parallel change could ensure that the same general shape of the force–velocity curve is maintained for fast and slow muscles.

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