# KINETICS OF FORCE REDEVELOPMENT IN ISOLATED INTACT FROG FIBERS IN SOLUTIONS OF VARIED OSMOLARITY

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ABSTRACT Isolated intact frog muscle fibers, while shortening with the intrinsic maximal speed, were stretched back to the original length to measure the kinetics of force redevelopment. These kinetics give information on the attachment rate constant in the cross-bridge cycle in vivo, and a value of ~25.6 $s^{-1}$ (0°C) is found in the present study. We find that these kinetics were slightly less sensitive to temperature than was the unloaded shortening speed. The effect of hyperosmolarity on force redevelopment was also measured in solutions with added sucrose or KCl. The rate constant was nearly halved with 120 mM sucrose, but there was practically no effect with isosmotic (60 mM) KCl. These results indicate that the rate constant of force redevelopment is insensitive to raised intracellular ionic strength. In sucrose, the fiber width was also compressed, and the attenuation of the rate constant of force redevelopment in this case is consequently attributed to the decrease in interfilament space. The order of magnitude of the rate constant found in this study suggests that tension transduction by a cross-bridge, during each turnover cycle, requires a series of elementary steps following the attachment.

## INTRODUCTION

It is now well accepted that the cyclic interactions between actin and myosin cross-bridges are responsible for the contraction of muscle (Huxley and Simmons, 1971; Podolsky and Nolan, 1973). There is also evidence that the cross-bridge cycle proceeds in a series of elementary steps, although much of this evidence comes from the biochemical kinetics of myosin and acto-myosin ATPase (Inoue et al., 1979; Lymn and Taylor, 1971; Trentham, 1977; Stein et al., 1985). Limited explorations of the kinetics of the elementary steps have also been done in situ on skinned fibers and these studies have been helpful in advancing the understanding of the chemo-mechanical transduction in muscle (Ferenczi et al., 1984).

The present study is an attempt to measure the attachment rate in the cross-bridge cycle of intact fibers, which in turn should give the information to decide whether force generation by a cross-bridge under physiological conditions occurs on immediate contact between actin and myosin or in a series of steps subsequent to the attachment. For the present study, the apparent attachment rate constant is estimated from the rate of tension redevelopment in fibers that had been briefly shortened under slack and were subsequently instantaneously restretched to the starting length, a protocol similar to that used recently on skinned fibers (Gulati and Babu, 1985*a*. This experimental approach is used also to investigate the effects of intracellular ionic strength and geometrical factors (radial compression of the myofilament lattice) on the attachment rate.

Parts of the results were presented at the 3rd colloquium of the New York Academy of Sciences, 1985 (Babu and Gulati, 1986).

## GLOSSARY

| | |
|---|---|
| $F$ | instantaneous force |
| $k$ | rate constant for tension development |
| $L_0$ | resting length of the fiber, corresponding to the sarcomere length of 2.2–2.3 $\mu$m |
| $\Delta L$ | slack step |
| $\Delta L_0$ | intercept on the $\Delta L$-$\Delta t$ plot for the slack-test data |
| $P_0$ | tetanic tension |
| $t$ | instantaneous time |
| $\Delta t$ | slack duration |
| $V_0$ | unloaded shortening speed ($L_0$/s) |

## METHODS

### Fiber Preparation

Isolation of intact single fibers from frog (*Rana temporaria*) tibialis muscles was as described before (Gulati and Babu, 1984). The Ringer solution used during dissection and electrical stimulation contained (in millimoles per liter): 2.5 KCl, 115 NaCl, 0.7 $CaCl_2$, 0.12 $MgCl_2$, 3.2 phosphate buffer, 5 dextrose. The control solution during the temperature step on the fibers contained (in millimoles per liter): 2.5 KCl, 100 NaCl,

10 $CaCl_2$, 10 imidazole. The osmotic pressure of these solutions is estimated as about 240 mOsmol/kg $H_2O$, and are referred to as 1.0T. The hyperosmotic solutions contained additional 60 mM KCl or 120 mM sucrose and the osmolarity of these solutions are 1.5 times. (The reason for 10 mM $CaCl_2$ in some of the solutions was that the fibers in high KCl were more stable, i.e., the force level was better maintained over a series of contractions). We also made checks in a number of fibers in 1.0T solution in the two solutions to see if the difference in buffers (phosphate vs. imidazole) affected the contraction properties. The results were identical in the two buffers, for both the electrical and temperature step activations employed here.

The transducer and the servo-motor were the same as before, except that the transducer beam was trimmed more closely and the natural frequency of the unloaded system was nearly 13 kHz. The motor arm was also shortened so that the step response was faster (<0.5 ms).

Experiments were carried out at 0°C except where indicated.

### Hyperosmotic (1.5T) Solution with Sucrose and KCl

These were used to examine the influences of ionic strength and lateral compression of the myofilament lattice on the contractile properties of intact fibers. Paired studies were performed in solutions with added sucrose and KCl.

The strategy here is based on the Boyle-Conway principles. The fibers are laterally compressed with sucrose (fibers shrink, but the length is being held fixed). Also, the intracellular solutes are simultaneously concentrated in this solution. In contrast, only the intracellular ionic strength is increased with KCl (Boyle and Conway, 1941; Palmer and Gulati, 1976).

The pH of all solutions was adjusted to 7.00 at room temperature.

### Fiber Stimulation

Since the fibers are also depolarized by high [KCl] (Hodgkin and Horowicz, 1960), the temperature step activation procedure was employed with this solution. Details for the techniques were the same as given earlier (Gulati and Babu, 1984). The control for this case was also done with the temperature step procedure.

All other activations, control and test, were by electrical tetanic stimulation.

### Slack Test

To obtain the unloaded shortening speed ($V_0$), the slack test method described earlier (Gulati and Babu, 1984) was used. Five to six slack releases ($\Delta L$) in the range of 5% to 10% $L_0$ were employed in separate contraction cycles, to obtain the corresponding slack duration ($\Delta t$). The value of the speed ($V_0$) for each fiber was obtained from the $\Delta L$-$\Delta t$ plot, as the inverse of the slope for the regression line. The intercept on the abscissa is defined as $\Delta L_0$, and is a rough measure of the overall fiber compliance including the contributions from the tendons and the knots.

### Inspection for Sarcomere Uniformity

The sarcomere length of the fiber was adjusted to 2.2–2.3 $\mu$m by laser diffraction and the diffraction pattern was monitored between contractions. This was particularly important at the start of the experiments, because they gave a check if the knots were securely placed on the tendons attached. Other precautions in the selections of the fibers were the same as before (Gulati and Babu, 1984).

For photographing the sarcomere patterns during contraction, a Zeiss compound microscope (Model ACM) was employed with a long working distance objective (50×; E. Leitz, Inc., Rockleigh, NJ). Polaroid pictures were taken by using a flash (≤3 ms exposure) and the shutter was set at the fastest speed (1/60th s; shutter control with Zeiss MC 63; Carl Zeiss, Inc., Thornwood, NY).

## RESULTS

### The Rate of Force Redevelopment in Tetanically Stimulated Fibers

Fig. 1 shows the design and the rationale for the experiment. The fiber was held isometric (length, $L_0$; top trace in Panel A) and stimulated. After the developed tension reached the plateau ($P_0$), the fiber was released by ~20% $L_0$ to a slack length while the stimulation sequence was continued. During the slack period, the fiber continued to shorten with maximum speed (Hill, 1970), and the active tension was zero. After at least half of the applied slack was taken up by active shortening, but force was still at the zero level, the fiber was stretched back by the amount equal to the above release (20% $L_0$) to return the length to $L_0$. The tension recovery after the length change was followed in this study (see also, Brenner, 1984).

Fig. 2 shows that the fiber contracted uniformly upon activation and that sarcomere uniformity was retained following the stretch. This indicates also that the shortening-stretching maneuver did not affect the fiber integrity.

The large amount of net stretch (~10% $L_0$) on the actively contracted fiber should have caused all the attached bridges to break instantaneously. The force recovery after the stretch was largely limited, therefore, by the rate of cross-bridge reattachment and the force stroke in the cycle. The time-course of force redevelopment following the length readjustment is shown on a faster time base in panel B of Fig. 1. Panel C (Fig. 1) shows the data for the force redevelopment on a semilog plot (log $[1 - F/P_0]$ vs. $t$) with a least-squares fit, from which a rate constant was calculated. The data on seven fibers at 0° and 10°C are given in Table I. The mean values for this rate constant ($k$) are 25.6 $s^{-1}$ (0°C) and 45.3 $s^{-1}$ (10°C), with a $Q_{10}$ of 1.8.

### Simultaneous Measurements of the Unloaded Shortening Speed ($V_0$) and the Rate Constant ($k$) of Force Redevelopment

The individual values from seven fibers at 0° and 10°C are shown in Table I. The main purpose of these experiments was to evaluate the possible correlations between the rate limiting steps for $V_0$ and $k$. The values of both parameters ($V_0$ and $k$) varied widely between experiments. The nearly twofold variation in $V_0$ was similar to that seen previously (Table III in Gulati and Babu, 1984). The variation in $k$ was about threefold. The data in Table I show, however, that these variations in the two parameters were independent. Furthermore, the $Q_{10}$ values were somewhat less scattered and the $Q_{10}$ value for $V_0$ was found to be consistently higher than that for $k$.

The inspection of the data in Table I also shows no significant correlation between the overall fiber compliance ($\Delta L_0$) and either $V_0$ or $k$.

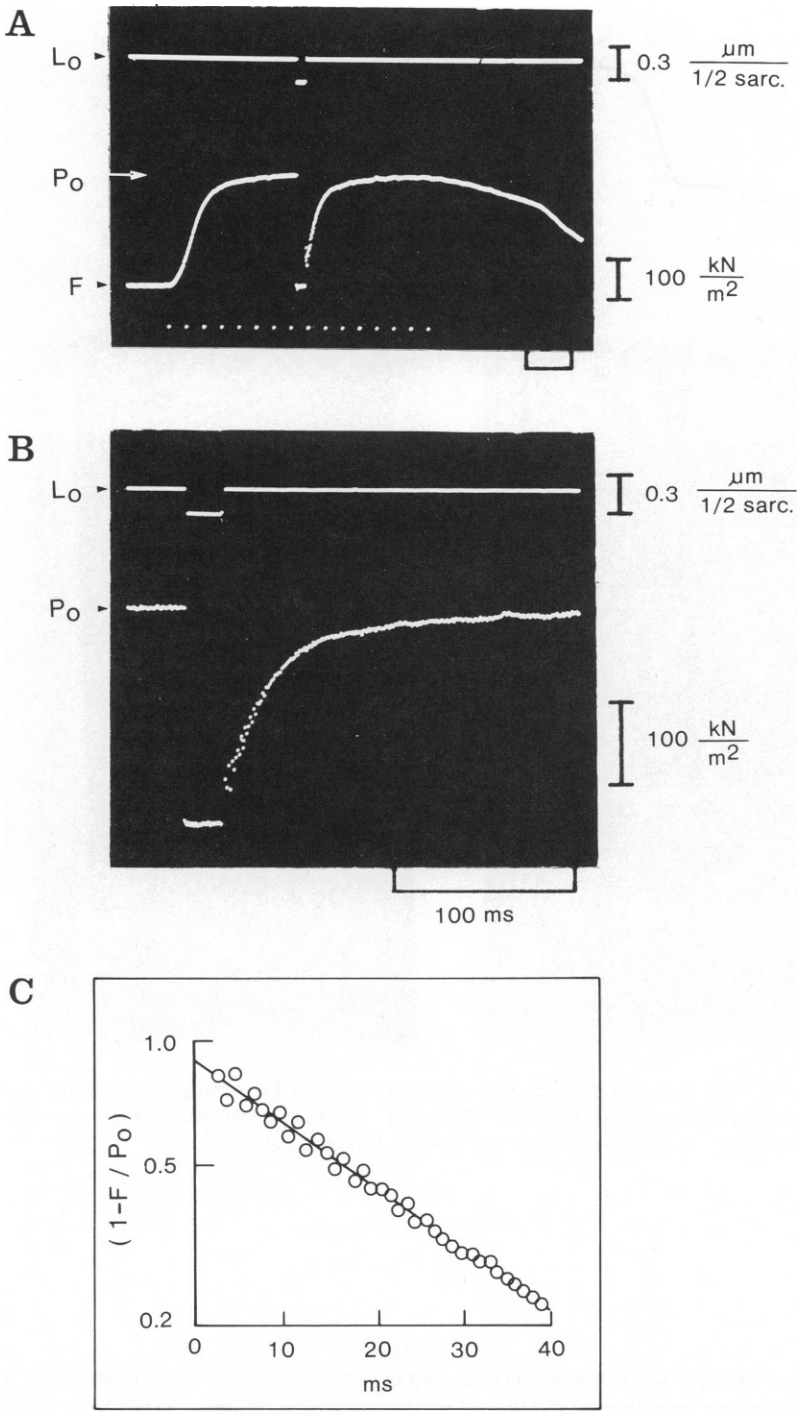


FIGURE 1 The rate constant for force redevelopment of tetanically activated intact fiber. (*A*) The fiber is held isometrically at the sarcomere length ($L_0$) of 2.2 μm and stimulated tetanically (40 Hz) shown by the dotted line at the bottom of the panel. When the force is steady, a shortening step of about 0.2 $L_0$ is applied to produce slack. Before the slack is taken up, the contracting fiber is restretched to the original length and the time course of force redevelopment is followed. (*B*) Shows the release-stretch response of the maximally contracting fiber on a faster time base. (*C*) Shows a semilog plot of the force redevelopment in *B*. The line is the least squares fit and rate constant is $0.693/t_{1/2}$. [Temperature: 0–1°C; fiber length: 7.34 mm; diameter: 126 μm].

## Possible Artifacts During the Force Recovery

In addition to the limitations by the cross-bridge attachment and the force stroke, the tension recovery could also be influenced by factors delaying the re-establishment of sarcomere length uniformity if this is affected by the stretching. Although sarcomere length non-uniformity cannot be completely ruled out, observations in the present results suggest that it was not a major factor.

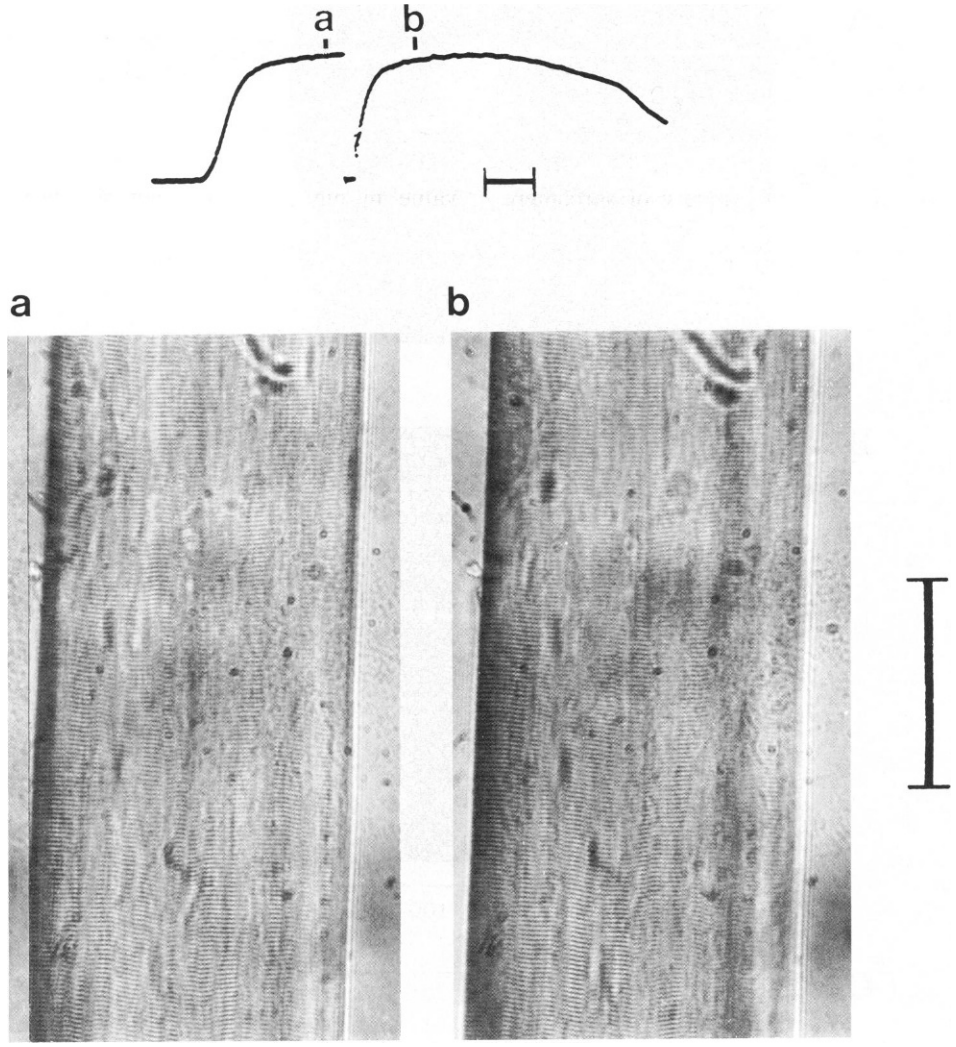


FIGURE 2 Uniformity of the sarcomere pattern during force redevelopment. (*a*) The pattern during steady force prior to the length step (mean S. L. = 2.28 $\mu$m). (*b*) The pattern following the stretch (mean S.L. = 2.26 $\mu$m). The markers in the force trace show the instants where the flash was turned on. Horizontal bar: 100 msec; verticle bar: 100 $\mu$m. Temperature: 0–1°C.

TABLE I
EFFECT OF TEMPERATURE ON UNLOADED SHORTENING SPEED AND FORCE RATE CONSTANT

| Experiment | Slack-test | | | | Rate constant for force redevelopment, $k$ ($s^{-1}$) | | |
|---|---|---|---|---|---|---|---|
| | Unloaded shortening speed, $V_o$ ($L_o$/s) | | | $\Delta L_o$(% $L_o$) | | | |
| | 0°C | 10°C | $Q_{10}$ | | 0°C | 10°C | $Q_{10}$ |
| 14 vi 85 | 2.7 | 6.1 | 2.3 | 2.17 | 27.6 | 50.0 | 1.8 |
| 12 vi 85 | 2.9 | 10.0 | 3.5 | 2.63 | 22.4 | 41.1 | 1.8 |
| 6 vi 85 | 3.1 | 7.8 | 2.5 | 1.27 | 34.0 | 61.8 | 1.8 |
| 5 vi 85 | 3.1 | 7.0 | 2.3 | 3.76 | 29.9 | 49.4 | 1.7 |
| 3 vi 85 | 2.0 | 6.1 | 3.1 | 2.00 | 32.2 | 54.4 | 1.7 |
| 20 v 85 | 2.2 | 5.5 | 2.5 | 2.43 | 20.0 | 40.7 | 2.0 |
| 18 v 85 | 2.8 | 5.0 | 1.8 | 2.31 | 13.1 | 19.7 | 1.5 |
| Mean ± SEM | 2.7 ± 0.2 | 6.8 ± 0.9 | 2.5 ± 0.3 | 2.37 ± 0.88 | 25.6 ± 3.8 | 45.3 ± 6.9 | 1.8 ± 0.1 |

First, the semilog plot of tension recovery was linear over nearly the entire range, indicating that the property expected of the first order reaction-kinetics was retained throughout the tension recovery.

Secondly, we find that the apparent fiber compliance ($\Delta L_0$) was quite variable in different experiments (Table I) and this could have affected the recovery of sarcomere uniformity during the tension recovery. But, as mentioned above, there was no obvious correlation between $\Delta L_0$ and $k$, which suggests that the variation in fiber compliance was probably not a significant factor in the sarcomere readjustment following the stretch, and/or that the resulting sarcomeric changes occurred relatively rapidly.

## EFFECT OF HYPEROSMOLARITY

Sucrose and KCl solutions were used to evaluate the effects of intracellular ionic strength and of radial compression of the intact fiber on the kinetics of force redevelopment.

### 120 mM Sucrose

The values of the rate constant for force redevelopment, steady-state isometric force and fiber width in sucrose solution are given in Table II. Force, speed of shortening and width are all reduced in this solution, and these effects are similar to earlier results (Gulati and Babu, 1982, 1984). The rate constant of force recovery was found in the present study to decrease to 0.54 of the control value.

### 60 mM KCl

In the KCl solution, which has the same osmolarity as the sucrose solution above, fiber width was unchanged (Table II). The fibers in this case were activated by the temperature-step activation procedure described earlier (Gulati and Babu, 1982; 1984). Because the steady-state force with temperature step activation is less than the tetanic force (Gulati and Babu, 1985*c*), the control in 1.0T solution was also determined by the same activation procedure (i.e., by temperature step).

The results in Table II show that the relative force level in high KCl was reduced by the same factor as in sucrose, but the speed of shortening was unaffected in KCl (and hence by the increased intracellular ionic strength), and these findings are consistent with the previous results on intact fibers (Gulati and Babu, 1984). Also, in contrast to the result in the presence of sucrose, the rate constant for force redevelopment in KCl was 1.19 times the control value (the difference between the control value and the test value in high KCl was not significant), showing that increased intracellular ionic strength had relatively little effect on the force rate constant of intact fibers.

## DISCUSSION

The rate of force redevelopment after re-stretching the actively shortening intact fiber gives the lower limit for the cross-bridge attachment rate constant in vivo. The mean value of 25.6 $s^{-1}$ at 0°C in the frog fiber (Table I) may be compared with the value of ~10–20 $s^{-1}$ (15°–20°) measured by the same restretching technique on Ca-activated skinned rabbit and hamster fibers (Brenner, 1984; Gulati and Babu, 1985*a*). Goldman et al. (1984) found the value of 50–100 $s^{-1}$ (20°C) from the kinetics of force redevelopment when rabbit fibers were instantaneously switched from rigor to the normal state by photogeneration of ATP. These values are remarkably similar to the estimate for the attachment rate constant arrived at by Huxley (1957) to explain Hill's force-velocity relation and the Fenn effect, by a cross-bridge model assuming that force is made in a single step immediately upon attachment. Explanation for the contraction transients (Civan and Podolsky, 1966; Huxley and Simmons, 1971), and retaining the above assumption, required a high attachment rate (2,000 $s^{-1}$, Podolsky and Nolan, 1973). Alternatively, with a low attachment rate, the contraction transients still could be explained if the force development was completed in a series of steps in the cross-bridge cycle (Huxley and Simmons, 1971; Julian et al., 1974). The present results provide direct support for this view and suggest that force transduction by the cross-bridge is a multistep process.

### Effects of Radial Compression and High Ionic Strength

Paired experiments in hyperosmotic solutions of sucrose and KCl make it possible to evaluate the contractile effects

TABLE II
EFFECTS OF HYPEROSMOLARITY ON CONTRACTION PARAMETERS

| | Sucrose hyperosmolarity* | | | KCl hyperosmolarity* | | |
|---|---|---|---|---|---|---|
| | 1.0T | 1.5T | Ratio | 1.0T | 1.5T | Ratio |
| Fiber width | 1.00 ± 0.01 | 0.84 ± 0.01 | 0.84 | 1.00 ± 0.01 | 1.00 ± 0.01 | 1.00 |
| Force ($kN/m^2$) | 306 ± 30 | 210 ± 20 | 0.69 | 221 ± 3 | 149 ± 5 | 0.67 |
| Unloaded shortening speed ($L_o/s$) | 2.9 ± 0.1 | 1.5 ± 0.1 | 0.52 | 2.4 ± 0.2 | 2.3 ± 0.2 | 0.96‡ |
| Rate constant for force redevelopment $k(s^{-1})$ | 26.7 ± 2.1 | 14.5 ± 1.5 | 0.54 | 24.1 ± 2.6 | 28.8 ± 5.5 | 1.19 |

*Five fibers were used to test the sucrose effect and an additional four for the KCl effect.
‡The speed in this case was on 13 fibers separate from those used for the $k$ values.

of ionic strength and radial compression in the intact fiber (Gulati and Babu, 1982). The results with KCl suggest that increasing the intracellular ionic strength has relatively little effect on the particular rate constant for cross-bridge reattachment. This indicates that the initial interaction between actin and myosin at the cross-bridge sites is primarily nonionic, implying that at least one of the reacting species at this stage of interaction is electrically neutral.

Lateral compression of the fiber by raising the sucrose in the bathing solution attenuated the force rate constant. The fiber width was reduced by 16% in 1.5T sucrose solution. Converting this radial factor to calculate the accompanying change in filament lattice, the interfilament space is estimated to decrease from the control value of ~13.2 nm to 10.0 nm (Gulati and Babu, 1984). The effect on the kinetics of force redevelopment is attributed to this decrease in filament separation, because the associated increase in ionic strength alone would not influence the force constant. If the force rate constant in the compressed fiber also is assumed primarily to be the representation of the attachment step, the results suggest that the cross bridge might experience steric hindrance during this step prior to the force stroke, due to the space restrictions within the myofilament lattice. But the force per bridge, in steady state, was constant at compression levels comparable to those in this study, and also the number of cross-bridge attachments in the rigor configuration remained high with compression (Gulati and Babu, 1982; 1985*b*). These findings suggested that the force stroke following the attachment is completed without significant movement of the cross-bridge. However, because the attachment rate appears to be decreased, considerations of reversibility suggest also that the detachment rate in the cross-bridge cycle is similarly attenuated by lateral compression.

## Effects on Unloaded Shortening Speed

The results of $V_0$ in KCl and sucrose solutions are the same as before (Gulati and Babu, 1984), indicating that the speed is unaffected by high intracellular ionic strength but decreases with lateral compression. This conclusion of the ionic strength effect contradicts Edman and Hwang (1977). They attributed the sucrose effect to ionic strength, but our studies indicated that the results in sucrose are correlated instead with lateral compression.

In the present experiments in sucrose and KCl a similarity is apparent in the effects of $V_0$ and $k$; $V_0$ and $k$ decreased simultaneously in sucrose, but both were apparently unaffected in KCl (Table II). This suggests that the decrease in $V_0$ in the compressed fiber may be due to the alterations in the cross-bridge kinetics. On the other hand, since the speed of shortening can be depressed by internal load that may increase under compression also (Gulati and Babu, 1984), the similarity in the effects on $V_0$ and $k$ in sucrose may be fortuitous. Additional experiments would be useful to test this point.

## Effects of Temperature and Relation to Other Studies

The $Q_{10}$'s for $V_0$ and $k$ are shown to be different. Consequently, the attachment step is not the rate limiting step for shortening. The order of magnitude of the $k$ value suggested that the force stroke is separate from the attachment step as well. Furthermore, it was argued that the force and shortening strokes are associated with different elementary steps in the cross-bridge cycle (Gulati and Babu, 1985*a*). More recent studies have suggested that the $P_i$ release step is associated with the force stroke and the subsequent ADP release step is associated with the shortening stroke (Hibberd et al., 1985; Siemenkowski et al., 1985).

The present approach for stretching the isolated fiber while actively shortening at the maximum intrinsic speed is analogous to the approach by Katz a number of years ago (Katz, 1939; Huxley, 1971), where the interest was to study the contraction response to loads greater than the isometric force. Katz found that Hill's force-velocity relation for shortening (loads less than $P_0$) did not apply for loads above $P_0$ and also that the temperature sensitivity ($Q_{10}$) for shortening was higher than that for lengthening with loads above $P_0$. In light of the present result, that $Q_{10}$ for the shortening speed is also higher than for the rate constant for force redevelopment, an explanation is suggested for the force-velocity relation above $P_0$. That is, unlike the isotonic shortening, muscle contraction for the higher loads ($>P_0$) is rate limited by the cross-bridge reattachment.

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