

Mechanism and significance of early, rapid shortening in sensitized airway smooth muscle¹

Lincoln E. Ford and Susan H. Gilbert

Abstract: It has been reported that sensitization of animals to allergens increases both early shortening velocity and myosin light-chain kinase of their airway smooth muscle without increasing force generated by these muscles. Since early shortening sets muscle length for the duration of a contraction, these responses might be expected to produce greater airway obstruction. Here, it is explained how the more rapid early shortening without increased force production is predicted by the 2-stage process of activation followed by contraction posited by the crossbridge theory of contraction when the rate, but not the extent, of activation is increased. The experimental results are reproduced by a simple model in which activation rate is increased 1.6-fold without any other changes in contractile parameters. These results reinforce suggestions that sensitized animals are a model for reactive airway disease.

Key words: crossbridge, muscle activation, muscle force, asthma, airway obstruction.

Résumé : Des études ont indiqué que la sensibilisation des animaux aux allergènes augmente à la fois la vitesse de raccourcissement précoce et la kinase de la chaîne légère de la myosine de leurs muscles lisses bronchiques sans augmenter la force produite par ces muscles. Comme le raccourcissement précoce fixe la longueur du muscle pour la durée d'une contraction, ces réponses devraient vraisemblablement provoquer une plus grande obstruction des voies aériennes. Ici, on explique comment l'augmentation de la vitesse de raccourcissement précoce sans augmentation de la production de force est prédite par le processus d'activation en deux temps suivi d'une contraction, postulé par la théorie de la contraction par glissement des ponts transversaux, lorsque la fréquence et non pas l'ampleur de l'activation est augmentée. Les résultats expérimentaux sont reproduits par un modèle simple dans lequel la fréquence d'activation est augmentée d'un facteur 1,6 et constitue la seule modification dans les paramètres contractiles. Ces résultats viennent renforcer l'idée que les animaux sensibilisés sont un modèle pour l'affection respiratoire réactionnelle.

Mots-clés : ponts transversaux, activation musculaire, force musculaire, asthme, obstruction des voies aériennes.

[Traduit par la Rédaction]

Introduction

Those of us who study airway smooth muscle are blessed with an uncommon camaraderie that derives from these occasional, informal meetings organized by Dr. Newman Stephens in such idyllic surroundings that we cannot but find the good in each other's work. The ambience removes the tenacity associated with controversial issues and allows an enthusiastic exchange of ideas. In keeping with the felicitous spirit of the meeting, we will use our invitation to speak to discuss the mechanism and significance of Dr. Stephens' work on sensitized airway smooth muscle.

Dr. Stephens' colleagues developed a dog model of sensitized airway disease in which half a litter of puppies is given repeated injections of ragweed pollen or ovalbumin and the other half serves as "littermate controls" (Kepron et al. 1977). With students and colleagues, he has studied the con-

tractile responses of airway muscles from these 2 groups of dogs. When airway smooth muscles isolated from sensitized dogs are allowed to shorten under a low load early in a tetanus, they shorten faster and farther than muscles from the control dogs loaded in the same way (Stephens et al. 1986). Since shortening velocity in smooth muscle declines substantially during the rise of activation (Johansson 1973; Seow et al. 2000), this early rapid shortening sets a shorter muscle length. This is precisely the response that would cause airway narrowing and obstruction. Although we tend to think that asthma results from too much smooth muscle tone, in fact, the disease is not manifested until the muscles become too short.

Another seminal discovery by Dr. Stephens and his colleagues is that the rates of myosin light-chain phosphorylation (Jiang et al. 1991; Kong et al. 1990) and myosin light-chain kinase (Jiang et al. 1992) are both increased in sensitized muscle, providing a mechanism for the more rapid early shortening of sensitized muscle. This pioneering work suggests that sensitized airway muscle should become an important tissue for the study of reactive airway disease. Although chronic dog experiments have become prohibitively expensive, some of the participants here have extended this sensitized preparation to guinea pig (Ishida et al. 1990; Mitchell et al. 1993; Ndukwu et al. 1994), which is both less expensive and more amenable to gene manipula-

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L.E. Ford² and S.H. Gilbert. Krannert Institute of Cardiology, Indiana University School of Medicine, 1800 N. Capitol Avenue, Indianapolis, IN 46202, USA.

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²Corresponding author (e-mail: lieford@iupui.edu).

tion. Thus, these sensitized animals could become important for the study of asthma, if one major obstacle could be overcome.

The issue arises because sensitized muscles do not develop more force. While no one disputes the finding that sensitized airway muscles shorten farther and faster than control muscles, for historical reasons discussed below, many physiologists equate force with activation, and the finding that force is unchanged makes it difficult for them to appreciate how the increased shortening occurs.

The explanation derives from Huxley's (1957) crossbridge theory, which predicts that the rise of isometric force during stimulation is expected to be slow, whereas the approach to steady shortening is likely to be rapid. For reasons discussed below, a failure to understand the disparity between slow force development and the rapid attainment of steady velocity derives from a flawed concept of active state, and a controversy over this same issue arose in cardiology several decades ago.

To test this explanation, we developed a mathematical model for simulating the time courses of activation, force development, and shortening in tracheal smooth muscle and used the model to test the extent to which the altered time courses of force development and shortening in sensitized muscle could be produced by simply increasing activation rate, without changes in other contractile parameters. The experimental data we have matched is from Antonissen et al. (1979), Jiang et al. (1992), and Stephens et al. (1986).

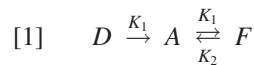
Methods

The time courses of activation, isometric force development, shortening velocity, and distance shortened were simulated using simple functions with constants derived either from Dr. Stephens' published work or from our own work on sheep tracheal muscle (Seow et al. 2000). One simplification was made to facilitate both the calculations and their description. Our experiments showed that activation, assessed as the maximum power capability of the muscle, rose to an early plateau and then declined slowly over the

duration of a 28-second tetanus (Seow et al. 2000). The equations below do not include the later fall, but instead define activation as rising monoexponentially to its final level. We have also shown that after activation begins to decline, force continues to rise at a greater rate than expected from the declining activation and that this continued rise of force occurs in a quantitative inverse relationship with a decline in velocity. As shown below, the continued rise of force was accurately simulated by the continued rise of activation. Velocity slowing was simulated independently of the rise of force.

Equations

Activation and force generation were assumed to progress by the following scheme:



in which detached, inactive bridges, D , on thick filaments, are first activated by phosphorylation to state A and then attach reversibly to thin filaments in a force-generating state F . The symbols designating the state of the bridges, D , A , and F , are also used to indicate the number of bridges in each state. The total number of bridges involved, A_0 , is the sum of bridges in each state, that is,

$$[2] \quad A_0 = D + A + F$$

Activation was assumed to rise exponentially beginning 0.1 s after the onset of stimulation, and its time course is described by the following equation:

$$[3] \quad A + F = A_0(1 - e^{-K_3 t})$$

The equation describing the approach to steady isometric force is then,

$$[4] \quad dF/dt = K_1 \{A_0(1 - e^{-K_3 t}) - F\} - K_2 F$$

which can be integrated to yield

$$[5] \quad F = K_1 A_0 \left[\frac{1}{K_1 + K_2} - \frac{e^{-K_3 t}}{K_1 + K_2 + K_3} + \frac{K_3 e^{-(K_1 + K_2)t}}{(K_1 + K_2)(K_1 + K_2 - K_3)} \right]$$

During shortening, the relationship between force, F , velocity, V , and activation, A , was defined by the Hill (1938) hyperbola:

$$[6] \quad (F + \alpha)(V + \beta) = (A + \alpha)\beta$$

where α and β are the asymptotes of the hyperbola and A , quantifying activated bridges, is also equivalent to the isometric force, F_0 , the muscle would generate in a steady state. In this equation, the ratios α/A and $\beta/V_{\max}$ are equal to each other and define the curvature of the hyperbola. We have shown that this curvature does not change during activation, so that these ratios also remain constant as velocity slows, and that β and maximum velocity decline in the same proportion. A decrease in velocity was therefore computed by diminishing the value of β without changing α .

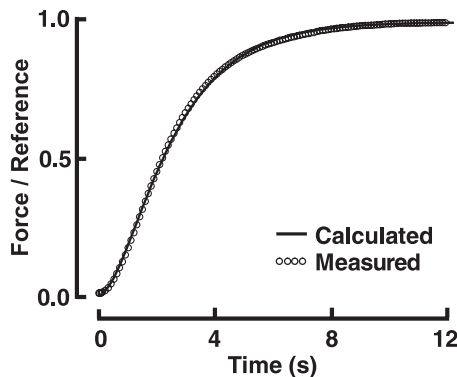
Two categories of velocity slowing must be incorporated in the simulation. The first is the slowing that occurs as shortening progresses. To mimic this, velocity was assumed to decline as an exponential function of time after shortening began, according to the following equation:

$$[7] \quad V = V_i e^{-K_4 t}$$

where V_i is the initial velocity achieved when the muscle is first released to an isotonic load.

The second category is the slowing of V_i that occurs later in a tetanus. We have found empirically that this initial velocity is nearly constant for the first 3 s of stimulation and then declines progressively when muscles are released at later times (Seow et al. 2000). Further analysis of the data showed that initial velocity, V_i , could be described as begin-

Fig. 1. Isometric force development during tetanic stimulation of sheep muscle at 37 °C. Open circles indicate force measured at 0.1 s intervals in 30 tetani of 16 muscles. The radii of the circles are equivalent to 1% of isometric force. The solid curve is a solution of eq. [4]. See text for details.



ning to decline abruptly at 3.2 s and following a course defined by

$$[8] \quad V_i = V_{i0} \{ 1 - 0.0067(t - 3.2) - 0.33(1 - e^{-0.27(t-3.2)}) \}$$

Both categories of velocity slowing were incorporated in the calculations below by multiplying β by the time-dependent multipliers in eqs. [7] and [8].

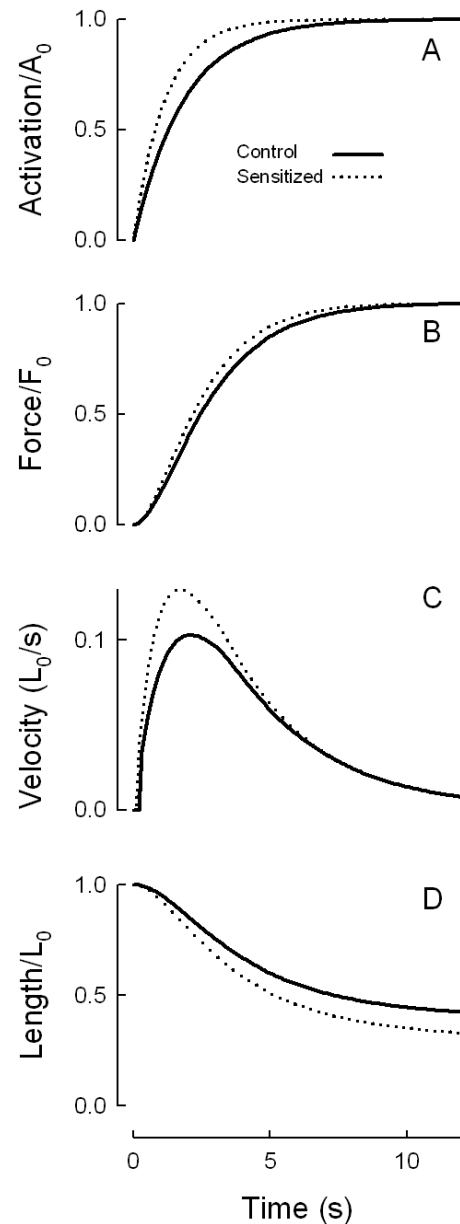
Results

To determine rate constants for activation, K_3 , and for crossbridge attachment and detachment, K_1 and K_2 , one of our published records for isometric force development (Seow et al. 2000) was matched with eq. [1], as shown in Fig. 1. The open circles represent the average force measured at 0.1 s intervals in thirty 12-second tetani produced by 16 muscles all treated identically. The radii of the circles are equivalent to 1% of the final level of force achieved. The solid curve is a plot of eq. [4] with $A_0 = 1$ and the following time constants: $K_1 = 0.23/s$, $K_2 = 0.874/s$, and $K_3 = 0.55/s$. These values were determined by repetitively substituting values in eq. [4] and superimposing the resulting curve on the data to obtain the best match. As shown, the solid curve touches all the circles. The ratio of K_2/K_1 , 3.8, indicates that in the steady isometric state, 21% of the activated crossbridges are attached in high force states. The effect of increasing phosphorylation rate without increasing the final level was then calculated by increasing K_3 without any other change in the contractile parameters.

Figure 2 shows simulated records of activation, force, velocity, and shortening during 12-second tetani with the muscle shortening under an afterload equivalent to $0.01 F_0$. Table 1 lists the contractile parameters used to simulate the records, together with the contractile parameters from 3 studies by Dr. Stephens. The only difference between the control and sensitized muscle in these simulations is that the activation rate, defined by K_3 , is increased 1.6-fold. All of the other contractile parameters are the same.

Dr. Stephens has shown that muscles that begin shortening near their maximum velocity very early in a tetanus slow to near zero velocity after 12 s. This was simulated

Fig. 2. Calculated time courses of physiological parameters in tracheal smooth muscle from sensitized (broken curves) and control (solid curves) dogs. (A) activation, (B) force, (C) velocity, (D) shortening.



here using eq. [7] and 0.27 for the value of K_4 for both sensitized and control muscles.

As shown, there is very good agreement in almost all respects between the simulated records and Dr. Stephens' results listed in Table 1. The single exception is a large difference in the absolute maximum velocities, with the ratio of velocities for sensitized and control muscles passably similar and the extent of shortening well matched. The reason for this difference is that V_{max} has a different meaning in the two contexts. In experiments, it was the zero-force intercept of the Hill hyperbola fitted to experimental force-velocity data. In the simulated records, it was the maximum velocity achieved when the muscles were allowed to shorten under a low afterload. Thus, we did not attempt to match the

Table 1. Contractile parameters in 3 studies and the simulation in Fig. 2.

Study	α/F_0	β	$V_{\max}$ (S)	$V_{\max}$ (C)	$V_{\max}$ (S/C)	Sh S	Sh C	Sh S/C
Antonissen et al. 1979	0.219	0.062	0.35	0.23	1.48	0.62	0.53	1.17
Jiang et al. 1992	0.206	0.060	0.35	0.27	1.30	0.66	0.55	1.20
Stephens et al. 1986	—	—	0.44	0.36	1.25	0.74	0.67	1.10
Mean	0.212	0.061	0.38	0.29	1.34	0.67	0.58	1.16
Simulation ^a	0.21	0.061	0.13	0.10	1.26	0.67	0.58	1.16

Note: Sh, shortening; $V_{\max}$, highest velocity achieved during afterloaded shortening; S, sensitized; C, control; S/C, ratio of values of sensitized to control.

^aThese are the values used for the simulation shown in Fig. 2

different $V_{\max}$ values, but instead matched the ratio of the values in sensitized and control muscles.

Discussion

These calculations show that the results obtained by Dr. Stephens and his colleagues are expected of muscles that obey an inverse relationship between force and shortening velocity (Hill 1938) and that develop isometric force by a 2-step process (Huxley 1957), with activation by phosphorylation preceding crossbridge attachment in force-generating states. The 2-step process causes activation to rise more rapidly than force, so that force generation lags behind activation. Hastening phosphorylation rate increases the rate of activation, defined by the constant K_3 , but is not expected to alter the rates of attachment and detachment, defined by constants K_1 and K_2 . The increase in K_3 increases the rate of rise of force (Fig. 2B), but to a lesser extent than it increased the rate of rise of activation (Fig. 2A), so that the lag between activation and force production is increased. Thus, when force reaches the level of the same afterload in sensitized and control muscle, activation is higher in the sensitized muscle and it shortens faster (Fig. 2C). Since most of the shortening occurs during the early part of a contraction, this high early velocity causes the muscle to reach a shorter final length (Fig. 2D). This is the reason a muscle that has a more rapid rate of activation without any other change in contractile parameters is expected to cause airway obstruction in sensitized animals.

Slow force development versus rapid attainment of steady velocity

In contrast to the slow approach of isometric force toward its steady level, velocity achieves a steady level very soon after shortening begins, over the time required to shorten about 1–2 times the range of crossbridge movement, which in skeletal muscle is 1%–2% of muscle length. The rapid approach to a steady level occurs because muscle shortening by an amount equivalent to the reach of a single bridge, 1%–1.5% of muscle length (Ford et al. 1977), detaches all the bridges. If they did not reattach rapidly, force would drop to zero. Since the muscle reaches steady force and velocity rapidly, the approach to steady cycling rates must be rapid. By judicious choice of attachment and detachment rates, Huxley (1957) was able to account for both the slow rise of force and the rapid approach to steady shortening. As explained below, the lag of force development behind activation and the disparity between the slow approach to isometric force and the rapid approach to steady shortening has caused much confusion in muscle physiology.

This mechanistic explanation is relatively easy to understand, and, in my opinion, the conclusions of Dr. Stephens experiments would have been recognized as a major cause of reactive airway disease had not a different concept of activation clouded the issue for several decades.

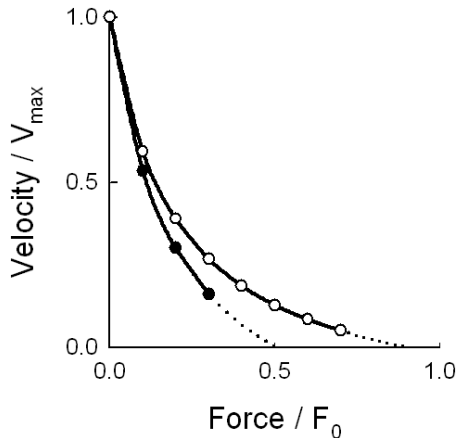
A brief history of the active state

A.V. Hill (1949) first proposed the concept of active state and defined it as equivalent to the force the contractile elements would generate if they were neither lengthening nor shortening, that is, if they were isometric. He illustrated the concept by showing that force could be brought to a nearly constant plateau when a muscle was stretched soon after the onset of stimulation. From this result he concluded that active state rose nearly instantly, and that the slow rise of force was due to internal shortening of the contractile elements as they stretched the series elastic elements. He made two further tests of this hypothesis. One was to slow the rise of force by adding compliant elements in series with the muscle. This result indicated that the force rise could be slowed by the internal shortening, and by extrapolation, that the slow rise of force normally observed was due to internal shortening. The other test was to calculate the isometric force using his previously described force–velocity hyperbola (Hill 1938) and the contractile element velocity inferred from the rate of stretch of the series elastic elements at each instant. These calculations showed that calculated isometric force rose nearly instantly and thus supported his conclusions: (i) that activation rose almost immediately and then remained constant for the duration of stimulation and (ii) that active state could be quantified as the isometric force the muscle would generate if the contractile elements were truly isometric. It is probably fair to say that most of the muscle physiology community accepted this conclusion, and I would accept it as well if “isometric force” is considered differently.

Defining differences in force–velocity curves

To understand the relationship between isometric force and activation, consider the idealized force–velocity curves in Fig. 3. They are idealized in that curves are Hill (1938) hyperbolae and the separate data points lie exactly on the curve. We have demonstrated similar experimental curves in striated muscle at different levels of activation. In skinned skeletal muscle fibers, activation was varied by altering the calcium concentration in the myofilament space (Podolin and Ford 1986). In cardiac muscle, it was varied by making the measurements at different times in a twitch (Chiu et al. 1987). The individual data points on the curves (circles)

Fig. 3. Idealized force–velocity curves showing extrapolation to isometric force at 2 times during the rise of activation. Individual data points (circles) derived from quick releases to different isotonic loads in different contractions, except that the rightmost point on each solid curve represents the force and velocity achieved in an afterloaded contraction. The solid curves representing fits to the data points are extrapolated as interrupted curves to 0 velocity to obtain the isometric force appropriate to each curve.



were derived from quick releases to different isotonic loads in different contractions, except that the rightmost point on each solid curve represents the force and velocity achieved in an afterloaded contraction (explained below). The solid curves representing fits to the data points are extrapolated as interrupted curves to zero velocity to obtain the isometric force appropriate to each curve.

One issue in these types of experiments was to define the difference between the two curves. Hill's formulation suggests that it might be quantified as the "isometric" force, defined as the zero velocity intercept of the curve, and this would be a perfectly valid measure, at least in theory. In practice, this parameter is subject to error because it is determined by extrapolation and because the curve approaches the axis at a small angle. We have found empirically that maximum power, defined as the product of force multiplied by velocity, is a more robust index because it is determined by interpolation rather than extrapolation (Podolin and Ford 1986).

The difference between the Hill (1949) and Huxley (1957) interpretations of the slow force rise can be illustrated by the way they explain the meaning of the zero velocity intercepts. The Hill interpretation suggests it is the value that would be achieved if internal shortening caused by series elastic element stretch were stopped abruptly. The Huxley interpretation is that it is the level that would be achieved after a time lag if the level of activation were held constant and attachment of additional crossbridges increased the number appropriate to the level of activation. The curves themselves illustrate how these two possibilities can be distinguished. Hill's hypothesis predicts that the two curves obtained in quick-release experiments should superimpose. Huxley's theory predicts that the curve obtained later in the tetanus will lie above that obtained earlier. Our experiments showing two distinct curves in skeletal (Podolin and Ford, 1986), cardiac (Chiu et al. 1987), and smooth muscle (Seow et al. 2000) greatly favor the Huxley interpretation.

These curves also demonstrate the use of A to represent isometric force in eq. [6]. It is equivalent both to the number of activated crossbridges at the level of activation designated A and to the isometric force that they would generate in the steady isometric state.

Measurement of force–velocity properties

The belief that activation was instantaneous was embraced by some because it led to an easier method of measuring force–velocity properties of muscle. Before the advent of modern servo motors for the study of muscle, shortening velocity at constant load was measured with an isotonic lever system originally developed by Magnus Blix (1895). The muscle was held vertically with its lower end fixed and its upper end attached to a lever balanced on a fulcrum. Weights were hung from the lever arm opposite the muscle attachment. A small weight, called the "preload," stretched the muscle to its starting length. A stop was then set above the muscle attachment to prevent further stretch, and an additional weight, called the "afterload," was added to the preload and the muscle was stimulated. When the force rose to the level of the afterload, the muscle began to shorten.

A problem with these experiments is that velocity for each afterload is measured at a different time during the rise of force. It would be much more satisfactory to make all the measurements at the same time after the onset of stimulation. But such measurements require that the muscle be released abruptly to a lower load, causing a technical difficulty with oscillations. The lever has inertia that, when combined with the compliance of the muscle and its attachments, causes it to oscillate when the muscle is suddenly released to a lower load. Blix introduced several clever innovations to reduce the inertia and the oscillations, and these innovations were used in later experiments for more than 75 years, but even these innovations did not completely eliminate the oscillations produced by an abrupt load change. The conclusion that activation rose nearly instantly was therefore welcomed as a justification for studying afterloaded contractions that did not greatly excite the oscillations.

The belief that activation rose to its final plateau level nearly instantly and that the lag in force development was due to internal shortening led MacPherson (1953) to develop a method for calculating the complete force–velocity relationship from the time course of force development during a single isometric twitch and a knowledge of the compliance of the contractile elements. The rationale for this method was that the speed of contractile element shortening, dL/dt , is equal to the rate of force development, dF/dt , multiplied by the compliance of the series elastic elements, dL/dF , so that,

$$[9] \quad dL/dt = (dL/dF)(dF/dt)$$

Subsequent experiments invalidated this method by showing that activation rises relatively slowly, but the consequences for our understanding of skeletal muscle were not great compared with that of cardiac muscle, which alters its rate and extent of activation during normal function.

Studies of cardiac muscle

Because cardiac muscle normally produces only twitches, it cannot normally be studied during a period of constant ac-

tivation. The rate of force development and peak twitch force can also be made to vary separately using different inotropic agents. In a classic study in which they introduced the papillary muscle preparation, Abbott and Mommaerts (1958) showed that "maximum shortening velocity," assessed using afterloaded contractions, was increased by inotropic interventions such as increasing stimulation rate and postextrasystolic potentiation. Sonnenblick (1962), using the same methods, later showed that "maximum velocity" was not altered by changes in muscle length. Extending MacPherson's (1953) method for assessing entire force-velocity curves during a single isometric tetanus, Levine and Britman (1964) developed a method of assessing maximum velocity in the intact ventricle during the isovolumic phase of a single contraction and showed that it was increased by inotropic interventions. These findings produced a large literature in cardiology and cardiac-muscle physiology. It would have been the perfect way of assessing inotropic state in the intact heart, something that is not well done even today, if the physiological underpinnings had been correct. Unfortunately, none of the conclusions leading to each new method were correct. When a method was developed for tetanizing cardiac muscle so that all the force-velocity data were collected at the same level of activation, maximum velocity was found to depend strongly on muscle length (Forman et al. 1972). When servo motors were used to impose rapid, critically damped releases to isotonic loads, maximum velocity was found to vary only slightly with time in the twitch (Chiu et al. 1987) and not to vary with inotropic state (Chiu et al. 1989; Ford 1991).

These misunderstandings of cardiac muscle derived partly from the belief that activation was instantaneous, partly from the use of afterloaded contractions, and partly from a failure to appreciate the significance of a lag between activation and force development. Had these factors been understood, the work might have been used to better purpose. It could, for example, have been used to quantify the adrenergic state of the heart if it had been realized that no agent increases maximum velocity but that increased adrenergic tone increases the rate of activation and the lag between activation and force development.

Crossbridge models

Huxley's original theory (1957) posited only 2 states for the crossbridges, attached in high-force states and detached. Subsequent, simultaneous discoveries that (i) myosin undergoes a series of chemical reactions as it interacts with actin (Lymn and Taylor 1971) and (ii) crossbridges attach in low force states and then undergo a "power stroke" to high-force states (Huxley and Simmons 1971) have led to multi-state models (e.g., Huxley 1980, p. 94). In these models, work is extracted from ATP hydrolysis in an orderly cycle where chemical reactions (ATP binding, hydrolysis, and release of products) alternate with physical transitions (cross-bridge attachment, power stroke, and detachment). Much research on muscle in the past few decades has been directed toward discovering the sequence and nature of these transitions, mainly by studying "transients," i.e., the approach to a new steady state when the system is perturbed. The focus of this research has created the incorrect perception that the original, 2-state model is outdated. This is not

the case. It can still provide accurate descriptions of steady-state phenomena such as isometric force, shortening velocity, and the rate of isometric force development, and has been used recently by Mijailovich et al. (2000) to examine the effect of length oscillations on crossbridge distributions. The calculations presented here are simplified substantially from the original model because they did not need to account for shortening velocity and predict only the rate of rise of isometric force. Quasisteady shortening was then determined by using the Hill (1938) hyperbola.

Velocity slowing

One aspect of muscle physiology that is not yet well understood and that has not been studied extensively is the velocity slowing that occurs during isotonic shortening. Slowing to a stop must eventually occur if muscles are to maintain a finite length, and so the issue is not whether it occurs, but rather the onset, extent, and cause of the slowing. Published records suggest that it is least in skeletal muscle and greater in both smooth and cardiac muscle. At least three mechanisms are likely to contribute to it: deactivation, internal compression, and substrate depletion. Perhaps it is the multiplicity of likely contributing mechanisms and the difficulty in distinguishing among them that has led to a paucity of studies quantifying the slowing. As a result of this dearth of data and multiple possible mechanistic explanations, velocity slowing here was estimated from two sources. The first source was a published record (Stephens et al. 1986, Fig. 2) showing that shortening had nearly stopped after 10.5 s of stimulation. The second was a table showing that, at this time, control muscles had shortened by 67% and sensitized muscles by 74%, distances likely to cause both substantial internal compression and stimulation of other protective mechanisms likely to limit shortening. We therefore arranged that the calculated shortening would occur over this same distance and nearly stop after 12 s of stimulation. To do this, we used a monoexponential function with the same rate constant for both muscle types, thereby avoiding any bias favoring more extensive slowing in either type of muscle.

Conclusion

The calculations presented here show that the experimental findings of Dr. Stephens and his colleagues are entirely in keeping with predictions of the crossbridge theory of muscle contraction and suggest that airway obstruction caused by hyperreactive airway disease can be explained on the basis of more rapid activation of sensitized airway smooth muscle without other changes in contractile parameters.

Acknowledgements

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