Force-Velocity-Length-Time Relations of the Contractile Elements in Heart Muscle of the Cat

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ABSTRACT

The instantaneous force-velocity-length relations of the contractile elements of the cat papillary muscle have been obtained by determining the phase-plane trajectories of velocity of shortening relative to length during isotonic contractions and correcting these measurements for the series elastic extension during the isometric phase of contraction. The load-extension curve of the series elastic component was obtained by quick release. The velocity-length relations for a given load were independent of initial muscle length and largely independent of the time after stimulation. Velocity-length traces at varying lengths diverged only late in contraction because of a fall in the intensity of the active state. Thus the surface created by the instantaneous force-velocity-length relations serves to define a given contractile state for the contractile element of heart muscle. Further, the linear length-tension relations observed for the contractile element permits an estimation of the maximum development of isometric force with the creation of truly hyperbolic force-velocity curves. Limitations of velocities obtained following quick releases have also been noted.

ADDITIONAL KEY WORDS contractility contractile state myocardium force-velocity relation

In recent years a useful approach to evaluation of the contractility of the myocardium has been based on the fact that the velocity of muscle shortening decreases with increasing afterload—the force-velocity relation (1-3). However, such measurements are generally taken from the peak velocities of shortening of nontetanized twitches of heart muscle. Thus this analysis considers neither the instantaneous length of contractile elements during contraction nor the effects of the various times after the stimulus when measurements are made. To overcome these limitations, the instantaneous relations between force, velocity, and length or between force, velocity, and time have been considered (4), and a given contractile state of the myocardium has been characterized by the surface, or envelope, created by the instantaneous relations between force, velocity of shortening, and muscle length.

To correct for problems of time, quick-release experiments using the methods of Jewell and Wilkie (5) for skeletal muscle have also been performed. Immediately following the release of the isometrically con-
tracting muscle to different afterloads, the velocity of shortening has been determined and instantaneous force-velocity-time curves related to the times of release have been derived (4, 6, 7). While these quick-release experiments help to describe the course of the active state, absolute values may be altered by the procedure of quick release itself (6). Further, force-velocity-length-time relations of the myocardium have been obtained either from phase-plane analyses or quick-release studies, both of which require precise and meticulous analyses of the experimental data and determination of force-velocity relations at each particular length or at each particular instant during contraction.

Other difficulties are encountered when the data are analyzed in terms of a three-component model of muscle proposed by A. V. Hill (8), which consists of a contractile element in series with an elastic component and in parallel with another elastic element. At small preloads the parallel element can be ignored. The properties of the active contractile element can be studied indirectly from afterloaded isotonic contractions. Following stimulation, the contractile element shortens and stretches the series elastic component, developing force until the load is matched. The load then begins to move, and tension, and thus the length of the series elastic component, remains constant. However, although the external movement of the muscle directly reflects the shortening of the contractile element, even this analysis remains incomplete since no consideration is made for this shortening because of stretching of the elastic component during the isometric phase of contraction.

Accordingly, the present study was designed to analyze the mechanics of the contractile element as a function of instantaneous force, velocity of shortening, and length, with consideration of the effects of time after stimulation or of quick releases on these relations. By determining the simultaneous phase-plane trajectories of velocity and tension relative to length during afterloaded isotonic contractions and correcting these measurements for changes in length of the series elastic component, a three-dimensional relation for the force-velocity-length of the contractile element has been constructed and evaluated for the element of time.

Methods

Papillary muscles were removed from the right ventricle of cats anesthetized with sodium pentobarbital (25 mg/kg ip). The muscles were suspended in a bath containing modified Krebs-Ringer’s solution bubbled with a 95% O₂-5% CO₂ gas mixture. Experiments were performed at 29°C and 37°C. The lower nontendinous end of the papillary muscle was held in a spring-loaded lucite clip placed at the end of a fine steel tube which passed through the bottom of the bath and was attached directly to the force transducer. The upper, tendinous end of the muscle was held in a small spring-loaded metal clip which was attached by wire to the tip of the isotonic lever. To minimize the compliance of the equipment, neither ties nor knots of connecting silk threads were used. Electrical stimulation was provided through mass electrodes arranged along the entire length of the muscle. Electrical stimuli were 5 msec long and had an intensity slightly above threshold. A stimulation frequency of 12/min was employed throughout.

The isotonic lever was made of magnesium and had a 20:1 length ratio and an equivalent mass of approximately 45 mg. Displacement of the lever was measured with a photodiode system which was linear over 2 mm. The velocity of displacement was differentiated electronically using an RC circuit (time constant of 0.5 msec). Lever displacement and its differential (dl/dt) were displayed on a dual-trace storage oscilloscope (Tektronix model 564) and recorded on film. In this manner, velocity-length phase-plane trajectories of the total muscle were superimposed either for different loads at the same initial muscle length (Fig. 1, A) or for different muscle lengths at the same total load (Fig. 2). Simultaneously, the corresponding tension-length phase-plane trajectories were recorded using the second channel of the oscilloscope (Fig. 1, A). Contractions following a quick release were then superimposed either on the tension-length tracing for the study of the series elastic component or on velocity-length tracing for the study of the effects of quick release itself on the velocity-length relation.

Quick-release experiments were performed using an airjet system controlled by a solenoid valve and connected to the stimulator as previously described (4, 9). Quick release to zero afterload was accomplished in less than 10 msec. In
FIGURE 1

Force-velocity-length relations of the contractile elements. A, Tension-length (upper) and velocity-length (lower) phase-plane tracing of the whole muscle at increasing afterloads. A quick release (QR) to zero afterload from peak tension is superimposed on all tracings. By plotting the fall in tension as a function of length change, the load-extension curve of the series elastic component is obtained directly (10). B, Extension-load relation curve of the series elastic component, as obtained from the quick release in the upper panel of A. C, Velocity-length relations of the contractile element at increasing loads, obtained and redrawn from A by correcting for extension of the series elastic component. The range of contractile element lengths (% of L₀) at which this peak velocity occurs is also indicated. The times at which peak velocity occurred are shown on the right. The delay from stimulus to onset of tension development averaged 25 msec. D, A three-dimensional construct of the relations between force, velocity, and length of the contractile elements corrected for internal shortening due to stretching of the series elastic component, replotted from the phase-plane tracings obtained in A. Correction has been made on the force axis for the slight differences in weight of the added afterloads.

Each experiment, initial muscle length at a particular preload is indicated as L₀. Since only small preloads were used (<.6 g/mm²), the effects of the parallel element were negligible and were therefore ignored. By correcting for the extension of the elastic component during the isometric phase of contraction, the characteristics of the contractile element could be analyzed apart from those of the entire muscle.

The shortening of the contractile element during isometric contraction is equal to the extension of the series elastic component and was obtained from the load-extension curve of this component, which in turn was determined from quick releases (10). The extension curve of the elastic component was obtained either by multiple quick releases to different afterloads or by a single quick release to zero afterload. The curves obtained by these two methods were superimposed. Thus the shortening curves of the muscle...
Velocity-length phase-plane tracings. Starting from an isotonic contraction with no afterload, initial muscle length (6.2 mm) was decreased prior to each succeeding contraction. Total load was maintained constant at 0.35 g throughout the experiment. The results were fully reversible when the initial length was reestablished. Times after stimulation at which a common velocity-length relation (arrow) was achieved by contractions 1 through 7 are listed above the arrow. Note that over a wide range and independent of time, all curves follow a common pathway regardless of the initial length from which the shortening began. Also note the terminal velocity-length dissociation later during the contraction. Time to peak tension of a stable isometric beat of the same muscle at 0.35-g preload was 320 msec. The delay from stimulus to onset of tension development averaged 25 msec. Temperature, 29°C.

Results

Figure 1, A, shows the superimposed velocity-length traces (lower) and tension-length relations (upper) of the papillary muscle, which is shortening isotonically with increasing afterloads. In addition, a quick-release contraction is superimposed on the tension-length trace from which the load-extension curve of the series elastic component is derived (Fig. 1, B). From the series elastic load-extension curve, the isotonic shortening trace of the whole muscle has been corrected for the lengthening of the series elastic component, as shown in C. In D, a three-dimensional construct plotted from the data in C shows the relations between velocity of shortening (vertical axis), load (axis to left) and instantaneous length (axis to right) for the contractile element. In such a plot, the basal plane represents the true contractile element length-tension relation; the plane to the right, the velocity-length relation; and the plane to the left, the force-velocity relation.

For a given load, the force-velocity-length relation for the contractile element was found to be largely independent of the length from which shortening began, and was independent of the time during the course of the contraction at which the measurement of velocity was made. Thus, in Figure 2, the total load was maintained at 0.35 g while the initial muscle length was shortened mechanically
Velocity-length phase-plane tracings. In A initial muscle length was established at 5.7 mm with a preload of 0.35 g. Between beats the initial muscle length was then decreased and total load maintained constant. In B, initial muscle length was reestablished at 5.7 mm, an afterload was added prior to the next series of contractions, and initial length decreased again between beats. This same procedure was followed in each of the panels up to the isometric beat. In panels A-D, times after stimulation were selected along the common-velocity length relation as indicated by the arrow. In A and B, the time at which peak shortening occurred has been indicated for the longest and shortest muscle length. Note that in the early phases of contraction, the velocity-length relation is relatively independent of time, whereas, later in contraction—i.e. at peak shortening—time factor becomes a relatively important limiting factor. The delay from stimulus till onset of tension development averaged 25 msec. Temperature, 29°C.

before contraction. Velocity of shortening rose to a maximum in about 100 msec and after external shortening of about 2 to 3%. Velocity of shortening then decreased as the muscle shortened. When the muscle started from a shorter initial length, e.g., points 2, 3, 4, ..., 9, the velocity rose onto the same curve and then fell along the same velocity pathway or trajectory for a considerable distance, regardless of the point at which shortening began. That this essential identity of phase-plane trajectories for velocity relative to instantaneous length applies as well with increasing loads is shown in Figure 3 and plotted in a three-dimensional construct in Figure 4. These results are typical of those obtained in 33 experiments in 9 muscles.

Late in the course of contraction or at
shorter muscle lengths, i.e., at lengths <10% of the initial length, this identity of the velocity-length phase-plane trajectories did not persist, but the velocity of contractions initiated from longer lengths tended to fall. These deviations in the terminal end of the contraction are not the result of the shortening per se but appear to be better explained by the time in the contraction at which the measurements were made. On Figures 1 to 4, both the times after stimulation at which peak velocity of contraction was obtained and the times at which similar contractile element lengths were reached are noted. In Figure 1, C, the values to the right represent the time at which the peak velocity was reached. With correction for changes in length of the series elastic component, peak velocity is attained at nearly similar contractile element lengths, i.e., the length for peak velocity differs by only 2.2 ± 0.2% of initial muscle length. However, as the load is increased (Fig. 1, C), peak velocity is reached at progressively later times, increasing from 85 msec to 290 msec, while the time to reach peak isometric tension was 320 msec. When initial muscle length was altered (Fig. 4), the time to reach peak velocity was the same at smaller loads, but with greater loads occurred somewhat later when the muscle started shortening from the shorter initial length.

Although the velocity of muscle shortening along the midportion of the velocity-length trajectory is identical at a given length, regardless of the starting length (Figs. 2 and 3), the time after stimulation at which this...
MEASUREMENTS OF THE CONTRACTILE ELEMENTS AT 37°C. A, Tension-length (upper) and velocity-length (lower) phase-plane tracings of the whole muscle at increasing afterloads, with a superimposed quick release (QR) to zero afterload at peak tension. B, Superimposed velocity-length relations of the contractile element for increasing afterloads after correction for the series elastic component. Note that the peak velocities of shortening occur within a very small range of contractile element lengths of 1.6% and regardless of a relatively wide range of time intervals after stimulation. C, A three-dimensional construct of the force-velocity-length relations of the contractile element with extension of the series elastic component at each afterload, replotted from the phase-plane tracings in A. Times of peak velocity and peak shortening are also indicated. Time to peak isometric tension was 240 msec. The delay from stimulus to onset of tension development averaged 20 msec. D, Velocity-length phase-plane traces at three initial muscle lengths with a constant total load. Initial muscle length was set at 5.37 mm with a preload of 0.6 g; initial length decreased between beats for the next two beats, and then was reestablished at 5.37 mm. Following the addition of increasing afterloads, identical series were superimposed on the same picture.

The given length is reached decreased progressively as the muscle started shortening from a shorter initial length. For example, in Figure 2, contraction 1, starting at 6.2 mm, reached 5.5 mm at 175 msec. Contraction 6, which started at 5.75 mm, reached the same 5.5 mm and the same velocity, but after only 125 msec. The same conclusion is evident from Figures 3 and 4. Thus the factor of time could not be a dominant factor in determining ve-
The force-velocity curve with linearization of the curve to obtain the Hill constants. A as in Figure 1 and B as in Figure 5. The Hill equation \((P + a) (V + b) = (P_o + a)\); \(b\) has been rearranged to the form \(\frac{P_o - P}{V} = 1/b(P + a/b)\). By plotting \(\frac{P_o - P}{V}\) against \(P\), the curve will be linear if the points from which it is taken form a true hyperbola. \(P = \) load, \(V =\) velocity of shortening, and \(a\) and \(b\) are constants. \(P_o\) is the experimental isometric tension while \(P_o\) is the tension calculated after correcting for the series elastic component. Utilizing \(P_o\), a linear relation is obtained (solid circles), while with \(P_o\) no meaningful plot is found (open circles). The slope of the linear plot equals \(-1/b\) while the intercept along the abscissa equals \(-a\). The derived constants \(a\) and \(b\) are shown on the curves.

In the terminal portions of the velocity-length trace, time does appear to play a role.
in bringing about a late fall in velocity for muscles which began shortening from a longer length. Thus, in Figure 4, the peak isometric tension is reached in 370 msec. However, the terminal portions of the external shortening trace are reached later in time than peak isometric tension. This was especially true with high loads. Since the maximum intensity of the active state must be starting to decline by the time maximum tension is reached, the active state would be less in the latter portions of contractions which initiate from longer lengths. Thus, the velocity-length relations would tend to deviate from a common pathway in the terminal portions of the velocity-length phase-plane trajectory. This is not the case, however, until the major portion of the trace is described.

Since the force-velocity-length relation has potential usefulness in the analysis of contractile activity in the intact heart, this relation was also studied at 37°C (Fig. 5). The results of 6 experiments on six papillary muscles were entirely comparable to those obtained at 29°C in that instantaneous velocity of shortening for a given load was largely

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**FIGURE 7**

The velocity-length (V-L) relations of a contraction following quick release (QR) to zero afterload compared to the velocity-length relations of isotonic contractions. Afterloads have been increased progressively in each panel as noted. Time after stimulation of the release is shown above each panel. Below is shown the time at which the common velocity-length relation is reached by the released contraction. (Terminal shortening of both the normal and quick released beat with no afterload is electronically cut off in this experiment.) Temperature, 29°C; preload, 0.35 g; muscle length, L₀ 8.7 mm; Cross-sectional area, 0.58 mm². Latency from stimulus to development of tension averaged 25 msec.

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independent of initial muscle length (Fig. 5, D) and the three-dimensional force-velocity-length relation was readily generated to define a given contractile state. Although the time at which peak velocity was reached was somewhat dependent on the load (Fig. 5, B), the contractile element lengths at which this occurred were quite similar. Further, the time at which a given length was reached for a given load depended on the length from which the contraction began (Fig. 5, D). Nevertheless, as at 29°C, the contractile element velocities were identical for the same load regardless of initial length. Thus, even at 37°C, time is not a limiting factor for contractile element velocity over the major portion of the shortening and does not vitiate the uniqueness of the force-velocity-length relation.

From an analysis of the force-velocity-length relations of the contractile element (Figs. 1 and 5), certain observations are clear. First, the plot of the maximum shortening of the contractile element against load is linear. Since this portion of the three-dimensional construct forms the ascending limb of the length-tension curve, its extrapolation to the load axis may provide the force of contraction which the contractile element would produce were there no shortening of the element during contraction due to extension of the series elastic component. This correction for contractile element shortening also helps to explain the deviation of the force-velocity curve from a true hyperbola at high loads. In Figure 6, the force-velocity relation is plotted and the linearization of the Hill equation attempted using the directly obtained isometric tension (P_o') and the calculated isometric tension (P_o) had no shortening occurred during isometric contraction. The data in Figure 6, A, were derived from Figure 1, D, and Figure 6, B, from 5, C. It is apparent from Figure 6, A, that a true hyperbolic relation between force and velocity of shortening for the contractile element is obtained when the isometric force corrected for shortening (P_o) is utilized. The same results were obtained in 36 experiments on 8 papillary muscles. Deviation of the force-velocity curve from a true hyperbola as shown by the inability to linearize the curve when utilizing P_o' for the isometric tension, is thus attributable to the effects of contractile element shortening during isometric contraction rather than to a limitation of the time for contraction. The same conclusion applies at 37°C (Fig. 6, B).

The effects of quick release itself on the subsequent course of contractile velocity is shown in Figures 7 and 8. Figure 7 shows quick releases (QR) with increasing afterloads and at various times after stimulation. Following quick releases, a finite time is required for the rapidly declining velocity to reach the velocity-length phase-plane trajectory of the isotonically contracting muscle. If the velocity following quick release reaches the velocity-length trajectory at less than 200 msec after stimulation (at 29° and 12/min), the subsequent paths of velocity as a function of length are identical, at least for a significant
portion of the velocity-length trace. However, when quick releases are produced more than 150 to 200 msec after stimulation, the subsequent velocity of shortening falls quite rapidly relative to the velocity-length trace of the unreleased isotonically shortening muscle (Fig. 7, C and D; Fig. 8). Thus, at later times in contraction, no steady-state velocity-length relation could be obtained following quick releases. Accordingly, the velocity obtained at any of these later times during contraction depended more on the release itself than on the activity of the muscle when the release was induced. Thus a unique relation between force, velocity, and length could not be obtained by using quick releases, and this limits their direct application to evaluating the contractile state of the myocardium. Also, the velocity of shortening following the quick release reaches the isotonic velocity-length curve at approximately the same length, despite wide variations in the times of release.

Discussion

In the present study, the relations between velocity of shortening, load, and instantaneous length of the contractile elements of heart muscle have been defined. This has been done by determining the phase-plane velocity-length trajectories of contractions with varying initial muscle lengths and loads, and then correcting these traces for the extension of the series elastic component during force development. From these findings at both 29° and 37°C, certain facts appear to be clear.

First, the surface created by the three-dimensional plot of instantaneous force, velocity, and length is unique for a given state of contractility. Thus the course of velocity of shortening with a given load is largely independent of the initial length from which the contraction began. Further, this phase-plane trajectory of velocity vs. length is largely independent of time except at the terminal portions of shortening, where the active state is declining.

Second, the extent of shortening of the contractile element forms a linear relation relative to tension. This fact permits an estimation of the maximum shortening the contractile element can accomplish with no load and further permits an estimation of the maximum tension this element could develop were there no extension of the series elastic component and hence shortening of this component during the development of force. Viewed in this light, the nonlinearity of the length-tension relation of the whole muscle reflects a linear force generator, the contractile element, being arranged in series with a nonlinear spring, the series elastic component.

Since the intersection of the length-tension curve of the contractile element with the load axis represents the maximum tension the contractile element could produce for that length without the contribution of the series elastic component, this tension constitutes the theoretical maximum intensity of the active state, i.e., the "maximum" force development at a constant length of the contractile element, as initially proposed by Gasser and Hill (11). Consequently, although the myocardium cannot be tetanized, the determination of the length-tension curve of the contractile element permits a useful estimation of maximum tension of this element. Use of this "true" maximum isometric tension for the contractile element yields a hyperbolic force-velocity relation. This finding supports the view that the failure to obtain a hyperbolic curve from the force-velocity relations of the heart does not depend on a limitation of time for contraction but rather on the presence of a series elastic component that reduces the length of the contractile element, and hence force and velocity at high loads. It is significant that this is true at physiologic temperatures (37°C) as well as those generally employed for in vitro studies (29°C).

It has been demonstrated that there are peak velocities of shortening with increasing afterloads at almost the same length of the contractile element regardless of a relatively wide range of times after stimulation at which they occur (Figs. 1, C, and 5, B). These findings imply that in studying the whole muscle, the use of peak velocity of shortening with increasing loads (1, 2) still provides a useful method for obtaining force-velocity relations.
Length corrections are not required, since the contractile element length difference at which peak velocities occur, especially at the heavier loads, is negligible. Furthermore, a correction for time is not required since peak velocities for all loads are reached during the contraction when the velocity-length relation is still independent of time.

In the terminal portions of the velocity-length trajectories, the intensity of the active state tends to fall, and some dissociation of the traces from different lengths becomes evident (Figs. 2 to 4). These limitations of time later in the course of contraction take on added significance in quick-release measurements. Determination of the force-velocity relations at various times in contraction has been attempted by quick release methods (4, 9). More recently, Edman and Nilsson (7) have attempted to correct such curves for contractile element shortening. Furthermore, Jewell and Blinks (12) have asserted that force-velocity curves obtained from quick releases at different times after stimulation allows the most accurate and closest determination of the high velocities. However, this approach is less reliable at high loads, since quick releases at 200 msec or more after excitation may result in S-shaped instantaneous force-velocity curves (4). Finally Brady (13) claims that a release after the midpoint of the rising phase of the contraction tends to facilitate relaxation, and the velocity of shortening immediately after the release may be prematurely reduced. The present study lends support to this view.

Despite the theoretical advantages afforded by the force-velocity curves obtained following quick releases, certain difficulties largely limit their usefulness. (1) Following the release, a substantial period of time is necessary to reach a steady state in which valid measurement can be made, and at this point the intensity of the active state may be altered relative to the time of release. (2) The quick release itself, with its rapid shortening, may somehow disrupt the initial course of the active state, as suggested by Brady (13). (3) Accurate measurements of shortening velocities following quick releases are exceedingly difficult to make with assurance. (4) Both time and length of the contractile element cannot be kept constant simultaneously, and changes in the intensity of active state due to time may readily alter the results.

In summary, the surface created by a three-dimensional construct of the instantaneous force-velocity-length relations of the shortening contractile element provides a useful method for evaluating the contractile state of heart muscle. By correcting for extension of the series elastic component, the force-velocity-length relations for the whole muscle as previously defined (4) have been refined so that true hyperbolic force-velocity curves can be obtained. These observations also support the view that the duration of the active state is not a serious limitation to maximum force development in heart muscle. This is also supported by the observations that prolongation of contractile activity in heart muscle by voltage clamp techniques does not further increase twitch tension (14). The identity of the velocity-length traces for a given load, regardless of initial muscle length and time after stimulation, as shown, strongly argues that a varying intensity of the active state is not an important consideration through most of the shortening phase of contraction. However, during the later stages of the shortening contraction, which occur later than peak tension development, the intensity of the active state is undoubtedly declining and a deviation of the terminal portion of phase-plane velocity-length traces is thus observed.

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