Effect of External Force on Relaxation Kinetics in Single Frog Atrial Cardiac Cells

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SUMMARY. The effects of external force on relaxation kinetics were investigated in isolated single frog (Rana catesbeiana) atrial cells. We found that force decay occurred at a maximum and constant rate for a significant portion of auxotonic relaxation, and this rate was linearly related to the peak force developed during auxotonic contraction. The slope of the linear relationship between the maximum rate of auxotonic force decay and peak auxotonic force was not affected by changes in the level of contractile activation produced by activating the cell with different stimulus durations. The rate of force change during auxotonic contraction and relaxation in the isolated cell is directly related to the average sarcomere velocity within the cell. Thus, the results indicate that during auxotonic relaxation the velocity of sarcomere extension is directly related to the peak auxotonic force, and sarcomere extension, during relaxation, is therefore affected by external force. The direct effect of external force on relaxation kinetics was confirmed by the observation that force changes imposed on the cell during relaxation immediately altered the velocity of the extending cell from any given length. However, data are also presented which demonstrate that rapid sarcomere extension occurs during relaxation under conditions where external forces are negligible. Thus, rapid sarcomere extension during relaxation does not require large external forces, and internal forces must play a role in sarcomere extension during relaxation. An explanation is given for these apparently contradictory results. (Circ Res 52: 161-169, 1983)

RELAXATION has been defined as the process by which muscle returns to its initial tension and length following contraction (Hill, 1949). Accordingly, an understanding of relaxation requires, as a minimum, information about the time course of decay of the force-generating capacity ($P_o$) of the muscle as well as information about how external and internal forces affect sarcomere, cell, and tissue extension during relaxation.

Recent experiments have given some insight into the factors that affect the time course of $P_o$ decay in mammalian cardiac muscle. For example the rate of “isometric” tension decay during relaxation appears to be directly related to the magnitude of the peak force generated during the contraction (Krueger and Strobeck, 1978; Tamiya et al., 1977). Also, it has been clearly demonstrated that sarcomere length directly affects the duration of contractile activation in mammalian cardiac muscle as well as the rate at which contractile activation is removed during relaxation (Krueger and Farber, 1980). In contrast, the factors that affect tissue and/or sarcomere stiffening during relaxation are not well understood, and in some cases the results appear to be contrary to those expected. For example, one might expect that the velocity of tissue extension during relaxation would be proportional to the force tending to restore the muscle to its original rest length. Thus, it might be expected that the velocity of extension during relaxation would be directly related to the external force. In some cases an increase in external force does hasten relaxation. For example, Brutsaert et al. (1978a) demonstrated that an increase in external force at the peak of isotonic shortening in mammalian cardiac muscle causes a rapid extension of the tissue and a premature termination of the contraction. Also, the velocity of tissue extension during isotonic relaxation increases as external force increases provided isotonic relaxation follows isometric relaxation (Goethals et al., 1982). However, when isotonic relaxation precedes isometric relaxation (Strauer, 1973; Strobeck et al., 1975), the velocity of cell extension during isotonic relaxation increases as the load decreases. Also, rapid sarcomere extension occurs during relaxation in isolated single rat cardiac cells even when the cells are unattached and the external force is therefore negligible (Krueger et al., 1980). Thus, rapid sarcomere extension during relaxation does not require the existence of large external forces, and internal forces must play a role in returning the sarcomere to its initial rest length during relaxation. Certainly, clarification is needed as to whether or not external force directly affects sarcomere extension during relaxation.

It is now well recognized that anatomical, mechanical, and contractile nonuniformities can exist in intact cardiac preparations, and these nonuniformities can lead to uncertainties in data interpretation. There is, therefore, a recognized need for an investigation of many aspects of the contraction and relaxation properties of cardiac muscle in anatomically simple but
intact cardiac preparations. The isolated single intact cardiac cell represents the simplest intact preparation on which such an investigation can be undertaken. The progress that has been made by ourselves and by other investigators in investigating the mechanical and contractile properties of intact single cardiac cells has been reviewed recently (Tarr, 1983). There is now sufficient information (see Tarr, 1983) available to warrant the conclusion that the isolated cardiac cell can have normal force-generating capacity and sarcomere-shortening capacity, as well as normal electrical activity. In the case of the single frog atrial cell, there is also sufficient information available (Tarr et al., 1979, 1981c; Tarr, 1983) to warrant the conclusion that nondestructive attachment can be made to the single cell and that the contraction is homogeneous over the length of the cell segment between points of attachment. Also the sarcomere performance appears to be uniform across the width of the cell, and, therefore, the total force appears to be evenly distributed between the myofibrils. Thus, the forces acting at the sarcomere are known for the first time with a reasonable degree of certainty.

The purpose of the present investigation was to characterize various aspects of relaxation in the single frog atrial cell. To our knowledge, this investigation is the first investigation of relaxation in single cardiac cells that have intact cell membranes. Some aspects of relaxation have been investigated previously using skinned single cardiac cells (Brutsaert et al., 1978b). In this investigation, we were interested in determining (1) how the force developed during an auxotonic contraction affects the velocity of cell and sarcomere extension during relaxation, and (2) how the velocity of sarcomere extension during relaxation at external loads approaching zero compares to that which occurs during auxotonic relaxation at relatively large external forces. We hoped, by such experiments, to gain insight into the load dependency of sarcomere and cell extension during relaxation.

Methods

The techniques of cell preparation, the preparation and calibration of cantilevered glass force beams, the method of attachment of a single cell to the glass beams, the method of recording and determining sarcomere lengths and force development during a twitch contraction, and the methods used to electrically stimulate the cells have been reported previously (Tarr and Trank, 1976; Tarr et al., 1979, 1981a, 1981c). Briefly one end of a single cell is attached to a glass force beam of known compliance; the displacement of this beam is proportional to the force supported by the cell. When both ends of the cell are attached to glass beams (force beam and a noncompliant beam), the cell during a twitch shortens and develops force in an auxotonic fashion (see Figs. 1, 2, and 4). In this type of experiment, we secured the cell to the glass beams by performing end-to-end rotation of the cell about the beams in such a manner as to wrap each end of the cell around the beam by one to two turns. An alternative experiment is to attach one end of the cell to a glass force beam and draw the other end of the cell into a fluid-filled pipette with controlled suction. In this case, the cell shortens and extends during a twitch in a lightly loaded and relatively isotonic fashion, since the end of the cell in the suction pipette is relatively free to move (see Fig. 8 and Tarr et al., 1981a). In this type of experiment, the end of the cell attached to the glass beam is not wrapped around the beam. Conventional bright field light microscope techniques are used to view the cell, the sarcomere pattern within the cell, and the position of the calibrated compliant force beam. Synchronized stroscopic illumination is used to "freeze" the motion of the sarcomeres and the force beam at time intervals of 16.67 msec during the contraction. The data are recorded on a closed circuit TV-video tape system and analyzed using the stop frame capability of the video tape recorder in combination with a double TV cursor (see Tarr et al., 1979). By such an analysis, the time course of sarcomere length changes, cell segment length changes, and force development which occur during a twitch contraction can be analyzed (see Tarr et al., 1981a, 1981b, 1981c). For sarcomere length determinations, the length occupied by a small group of sarcomeres (usually 6–10) is determined and an average sarcomere length is calculated. The cell segment length is taken as the distance between the outside edges of the two glass beams.

Two techniques were used in the present experiments to alter the amount of external force existing in the cell at the onset of auxotonic relaxation. One technique was to position the beams so that the distance between the beams was less than the rest length of the cell. In this case, the cell had to take up slack before it became taut and developed force auxotonically. An increase in the amount of slack taken up before auxotonic force development led to a decrease in the amount of force developed auxotonically. The second technique was to impose quick stretches or releases on the cell at a time close to the peak of the contraction. To accomplish this, a Burleigh Incuborm Translator was used to translate the noncompliant glass beam, to which one end of the cell was attached, in the direction of the long axis of the cell. This translator is a piezoelectric electromechanical actuator which moved the noncompliant beam prescribed distances at a velocity of 600 μm/sec with very little oscillation or overshoot. The cells used in the present investigation were bathed in Ringer's solution having the following composition: NaCl = 89 mM, KCl = 4.3 mM, CaCl₂ = 1.8 mM, Tris = 10 mM, glucose = 4 mM, and HCl as required to adjust the pH to 7.3. All experiments were done at room temperature (~25°C).

Results

Figure 1 gives the force-vs.-time relationships obtained from one cell during auxotonic twitches in which the cell took up various amounts of slack prior to the onset of auxotonic force development. This figure demonstrates two consistent findings concerning auxotonic relaxation. First, for a considerable portion of each auxotonic relaxation, force decay occurs at a constant rate. Second, the rate of force decay during relaxation decreases as the peak force developed during auxotonic contraction decreases. It should be recognized that the apparent changes in the duration of the contractile event are misleading, since relaxation is not complete when force has returned to zero if the distance between the beams is less than the rest length of the cell. In this case, a period of unloaded shortening follows the auxotonic relaxation phase.

Figure 2 gives the force-vs.-time relationships ob-
that an increased rate of force decay during relaxation was associated with an increase in peak force developed during contraction. Furthermore, the similarity of results when different methods (periods of unloaded shortening prior to force development vs. quick stretch or release) were used to alter peak auxotonic force indicates that the rate of force decay during auxotonic relaxation is related more to the peak auxotonic force developed during the contraction than to the history of the contraction.

Figure 3 gives the relationship between the maximum rate of force decay (i.e., during the constant rate phase) during auxotonic relaxation and peak auxotonic force obtained from the same cell as the data presented in Figure 1. This figure demonstrates the consistent finding, obtained on all cells investigated, that the maximum rate of force decay (Y) during auxotonic relaxation is related linearly to the peak force (X) developed during contraction and is thus described by the equation $Y = mX + b$. The equations for this relationship obtained from six cells, the correlation coefficients ($r$) for the relationships, and the range of forces over which each relationship was obtained are given in Table 1. It is apparent that although there was some variability in the slopes (ranging from 1.60–4.82/sec) and zero force intercepts (ranging from $-10.4$ to $333.5$ nN) of the relationship...
TABLE 1
Relationship Between Maximum Rate of Force Decay (Y) and Peak Auxotonic Force (X)

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Equation</th>
<th>r</th>
<th>Force range (nN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-11681</td>
<td>Y = 4.82X + 98.2</td>
<td>0.93</td>
<td>31-122</td>
</tr>
<tr>
<td>3-52181</td>
<td>Y = 4.24X + 83.8</td>
<td>0.99</td>
<td>14-127</td>
</tr>
<tr>
<td>1-61181</td>
<td>Y = 1.71X + 209.2</td>
<td>0.92</td>
<td>105-450</td>
</tr>
<tr>
<td>1-61281</td>
<td>Y = 2.72X + 280.9</td>
<td>0.99</td>
<td>50-425</td>
</tr>
<tr>
<td>1-82781</td>
<td>Y = 2.10X - 10.4</td>
<td>0.90</td>
<td>115-355</td>
</tr>
<tr>
<td>1-82881</td>
<td>Y = 1.60X + 333.5</td>
<td>0.95</td>
<td>190-540</td>
</tr>
<tr>
<td>1-91881</td>
<td>Y = 2.45X + 41.5</td>
<td>0.97</td>
<td>13-312</td>
</tr>
</tbody>
</table>

Units are Y (nN/sec), X (nN).

there was always a high correlation coefficient (ranging from 0.92 to 0.99). It should also be emphasized that, for any given cell, the same relationship was obtained when quick stretches and releases were used to alter peak auxotonic force as when peak force was altered by allowing the cell to take up various amounts of slack prior to auxotonic force development.

The results presented in Figures 1-3 and Table 1 clearly demonstrate that the maximum rate of force decay during auxotonic relaxation is directly related to the peak force developed during the contraction. Whenever the cell is taut and the noncompliant beam is stationary, there is a direct relationship between the rate of change of force, rate of change of cell segment length (i.e., the distance between the points of attachment of the cell to the glass beams), and the average rate of change of length of the sarcomeres within the cell segment. Thus, the results indicate that the velocity of cell and sarcomere extension during auxotonic relaxation is directly related to the peak force developed during the contraction. The direct effect of external force on the velocity of cell extension during relaxation was confirmed by applying quick stretches and releases to the cell during relaxation. Typical results obtained on one cell are shown in Figures 4 and 5. A quick release applied during relaxation caused a reduction in force and in the velocity of cell extension following the release (Fig. 4). In contrast, a quick stretch (see Fig. 5) applied during relaxation caused an increase in force and a rapid extension of the cell. These results clearly demonstrate that cell extension during relaxation is dependent on the external force acting on the cell.

Changes in the inotropic state of cardiac muscle often result in not only an increase in rate of force development during contraction but also an increase in the rate of force decay during relaxation. We found this to be the case during auxotonic twitches in the single frog atrial cell when different stimulus durations were used to stimulate the cell. Typical results obtained from one cell are shown in Figure 6. In this case, an increase in stimulus duration from 10 to 50 msec caused a significant increase in the rate of force development, peak force, and rate of force decay. However, the relationship between the maximum rate of force decay and peak force was found to be the same for both stimulus durations (see Fig. 7). This result indicates that the increased rate of force decay associated with the long duration stimulus resulted entirely from a change in peak force rather than from a change in the kinetics of the relaxation process.

As stated previously, in our single cell experiments there is a direct relationship between the rate of force change (dF/dt) and cell segment length change (dL/dt) whenever the cell is taut and the noncompliant beam is stationary. This relationship is given by the equation dF/dt = KdL/dt, where K is the stiffness of the force beam. However, dL/dt is directly related to the average sarcomere velocity (dS/dt) within the cell segment by the relationship dL/dt = n dS/dt, where n is the number of sarcomeres within the segment. Thus, from the zero force intercept value of the rate of force decay vs. peak force relationship, it should be possible to predict typical values which would be expected for the velocity of sarcomere extension during relaxation at zero external force. Applying the above relationships to the data presented in Table 1
would indicate that sarcomere extension during relaxation at zero external load should occur at velocities below 0.5 μm/sec. However, we have found consistently that—during lightly loaded twitches—sarcomere extension occurs at velocities in excess of 1 μm/sec. Two examples are shown in Figure 8. In one case, sarcomere extension during relaxation occurred at a velocity of 1.8 μm/sec and in the other case at a velocity of 3.1 μm/sec. In both cases, the external force was very small (~2.5 nN). Thus, the actual velocity of sarcomere extension at small external force appears to be greater than that predicted from the auxotonic rate of force decay-vs.-peak force relationship.

Discussion

The data presented in this paper demonstrate the following. First, for a significant portion of auxotonic...
relaxation, force decay occurs at a relatively constant rate which is linearly related to the peak force developed during the contraction (see Fig. 1). Second, rapid force changes imposed on the cell during auxotonic relaxation immediately alter the velocity of the extending cell from any given length (see Fig. 5). Third, the slope of the linear relationship between the rate of auxotonic force decay and peak auxotonic force is not altered by changes in stimulus duration which alter the level of contractile activation in the cell (see Fig. 7). Fourth, the velocity of sarcomere extension during relaxation in lightly loaded twitches occurs at a velocity significantly greater than that predicted by the zero-force intercept of the linear relationship between the rate of auxotonic force decay and peak auxotonic force (see Fig. 8).

Our results demonstrating that the rate of force decay during auxotonic relaxation is linearly related to the peak force developed during the contraction are similar to those reported by Krueger and Strobeck (1978) and Tamiya et al. (1977) for tension decay during isometric relaxation in which the maximum rate of decline of isometric tension is linearly related to the magnitude of the peak isometric tension developed during contraction. Tamiya et al. (1977) reported slopes for this linear relationship for isometric relaxation ranging from 2.4 to 8.5/sec which are similar to our values of 1.6-4.8/sec for auxotonic relaxation. Tamiya et al. (1977) also reported that the slope of the linear relationship was independent both of preload and the amount of shortening which occurred prior to the onset of isometric relaxation. Our results indicate that the linear relationship for auxotonic relaxation is also independent of preload, since the same relationship was obtained from twitches initiated from sarcomere lengths above the resting sarcomere length at zero external force as from twitches in which the cell took up various amounts of slack prior to auxotonic force development. This finding also implies that the linear relationship for auxotonic relaxation is independent of the amount of shortening the cell undergoes during contraction, since the amount of shortening is directly related to peak auxotonic force in contractions initiated at sarcomere lengths above the zero external force resting sarcomere length but is inversely related to peak auxotonic force development in twitches where the cell takes up various amounts of slack prior to auxotonic force development. Our results also indicate that the linear relationship is not affected by the history of force changes which occur during contraction, since the same relationship was obtained from twitches in which peak auxotonic force was changed by allowing the cell to take up various amounts of slack as when peak force was altered by imposing quick release or stretches on the cell just prior to the peak of the contraction.

Our finding that the slope of the linear relationship did not change when the contractile state of the cell was changed by stimulus duration indicates that the relationship between the rate of auxotonic relaxation and peak auxotonic force need not be dependent on the contractile state of the cell. This finding is contrary to that presented by Tamiya et al. (1977) for isometric relaxation in which a change in contractile state produced either by drugs or changes in extracellular calcium concentration changed the slope of the linear relationship. Our results on auxotonic twitches support the results of other investigators who have found that there is not always a tight coupling between myocardial contraction and relaxation as evidenced by the fact that inotropic interventions that alter the kinetics of contraction do not always alter the kinetics of relaxation (see Blaustein et al., 1981). Thus, our data do not support the suggestion of Tamiya et al. (1977) that relaxation kinetics can be used as a useful index of contractility.

The finding that the maximum rate of auxotonic force decay is related to the peak auxotonic force is compatible with a relaxation mechanism in which external force affects the rate of relaxation. However, this relationship by itself does not prove that this is the case. Furthermore, the interpretation of auxotonic data can be complicated by the fact that both force and length are changing with time. In the case of the
linear relationship between the maximum rate of force decay and peak force, the peak force is measured at a different time and at a different length than is the maximum rate of force decay. Thus, it is possible that length and time factors may have in some manner contributed to the apparent close correlation between the maximum relaxation rate and peak external force.

Time does not appear to be a critical factor, however, since the rate of force decay is constant and maximum for a significant portion of auxotonic relaxation. Thus, the time at which the maximum rate of force decay is determined is not critical for establishing that the maximum relaxation rate is related to the peak auxotonic force. Also, a linear relationship is obtained if the maximum rate of force decay is plotted as a function of force at a given time during the period when the rate of force decay is constant. Thus, the relaxation rate at a given time is also linearly related to the external force at that time.

Length effects can be of three types: (1) the amount of shortening which occurs during contraction, (2) the history of shortening during contraction, and (3) the sarcomere length at the onset of relaxation. As discussed previously, neither the amount of shortening nor the history of shortening affects the relationship between maximum relaxation rate and peak force. The sarcomere length (or cell segment length) at the onset of auxotonic relaxation is determined primarily by the isotropic state and the associated isometric tension-sarcomere length relationship which exists at the peak of the auxotonic contraction. A change in peak auxotonic force for a given isotropic state will therefore be associated with a change in sarcomere length at peak force. Thus, for a given isotropic state under auxotonic conditions, there is a good correlation between the maximum relaxation rate and the sarcomere (or cell segment) length at the onset of relaxation. However, changes in isotropic state which alter the isometric tension-sarcomere length relationship and thereby alter the relationship between the maximum relaxation rate and sarcomere (or cell segment) length at the onset of relaxation do not alter the relationship between the maximum relaxation rate and peak auxotonic force. Thus, the sarcomere length at the onset of relaxation does not appear to be the primary determinant of the maximum relaxation rate during auxotonic relaxation.

If length and time factors are not critical in producing the close correlation between the maximum relaxation rate and peak auxotonic force, then it seems reasonable to conclude that the close correlation occurs because of a cause and effect relationship between the maximum relaxation rate and peak external force. However, it must be recognized that peak auxotonic force is also an isometric force (Po), and a significant correlation between the maximum rate of force decay and Po could occur if relaxation were a purely active process governed simply by the rate of decay of Po. This possibility cannot be ignored, since it has been demonstrated previously that the maximum rate of isometric force decay is linearly related to the peak isometric force (Krueger and Strobeck, 1978; Tamiya et al., 1977). It is possible, therefore, that changes in peak auxotonic force produce changes in the maximum rate of relaxation simply because the time course of Po decay is directly related to the maximum Po obtained during the contraction. However, there are two lines of evidence which indicate that this is not the case. First, if Po were the sole determinant of relaxation kinetics and the maximum rate of Po decay were directly related to the maximum level of Po, then the relaxation rate under lightly loaded conditions should have been very slow, since relaxation would have started from a low Po. Clearly, this is not the case, since the velocity of cell extension under lightly loaded conditions occurred at a velocity significantly higher than that predicted by the zero-force intercept of the linear relationship between the rate of auxotonic force decay and peak force. Second, if relaxation were entirely an active process determined solely by the time course of Po decay, then a force change imposed during the time course of relaxation should not affect the velocity of relaxation. This also is clearly not the case (see Figs. 5 and 6). Thus, it seems reasonable to conclude that the velocity of relaxation during auxotonic relaxation is related to peak auxotonic force because external force is one of the factors which affects the rate at which the cell returns to its initial resting length during relaxation. This conclusion is directly confirmed experimentally by the observation that a force change imposed on the cell during relaxation immediately alters the velocity of relaxation.

Although the data clearly demonstrate that external force is one of the factors affecting relaxation kinetics, the data also clearly demonstrate that external force is not the sole determinant. This is evident by the fact that, for a significant portion of auxotonic relaxation, the rate of relaxation remains constant even though external force is decreasing. Also, the velocity of sarcomere extension under very lightly loaded conditions occurs at a high velocity. Thus, rapid sarcomere extension during relaxation does not require the existence of large external forces. It might seem that the finding of a high relaxation rate at light loads is not compatible with the auxotonic data in which relaxation rate is linearly related to peak force. However, as will be discussed later, these findings are indeed compatible and can be simply explained if the velocity of sarcomere extension during relaxation is governed by a Hill-type force velocity relationship.

Recently, Brutsaert et al. (1976a) proposed that relaxation in cardiac muscle be classified as being either activation-dependent or load-dependent. However, Brutsaert’s classification is based primarily on how loading conditions affect the overall duration of the contractile event rather than on how loading conditions affect the velocity of tissue extension during relaxation. Accordingly, a cardiac tissue was classified by Brutsaert et al. as having an activation-dependent relaxation when the total duration of the twitch was found to be relatively insensitive to loading.
conditions as evidenced by (1) the superimposition of the isometric relaxation phases of afterloaded isotonic twitches and (2) little or no change in the duration of the twitch when load changes were imposed during the contraction phase. By this classification scheme, frog cardiac muscle is classified as having a relaxation phase which is primarily controlled by an activation-dependent mechanism. In contrast, mammalian ventricular tissue is classified as having a relaxation phase which is primarily controlled by a load-dependent mechanism, since the overall duration of the contraction is highly sensitive to loading conditions.

Our data indicating that sarcomere extension during relaxation in the single atrial cell is highly load-dependent is not incompatible with Brutsaert's data indicating that the overall duration of contractile activation in frog cardiac tissue is not affected by the loading conditions during contraction. Loading conditions affect the extent of shortening which occurs during contraction and, in turn, affect the sarcomere length which exists at the onset of relaxation. Recently, Krueger and Farber (1980) demonstrated that the duration of contractile activation in rat ventricular tissue is sarcomere length dependent; an increase in sarcomere length increases the duration of activation. Thus, loading conditions could alter the time of onset of relaxation simply by altering the sarcomere length at peak contraction. Under such conditions, it seems likely that the overall duration of the contraction would be highly load-dependent, since the timing of the onset of relaxation would be load-dependent. This is most likely the case for mammalian ventricular tissue. In contrast, it might be possible for the duration of the contraction to be relatively independent of loading conditions if the duration of contractile activation were independent of sarcomere length. Perhaps this is the case for frog cardiac tissue. In both systems, however, the velocity of sarcomere extension during relaxation may be highly load-dependent in the sense that an increase in external load at any given sarcomere length and level of contractile activation during relaxation would increase the velocity of sarcomere extension.

As discussed previously, there is a diversity of results concerning the effects of external force on the velocity of tissue extension during relaxation. For example, sarcomere extension can occur at high velocity even when external load is zero, yet our data indicates that the velocity of extension during auxotonic relaxation is directly related to the peak force developed during contraction. In contrast, the velocity of extension in afterloaded isotonic twitches is inversely related to isotonic load provided isotonic relaxation follows isometric relaxation (see Strauer, 1973, and Strobeck et al., 1975). Computer simulations (Tarr et al., 1982) suggest that these apparently contradictory results may have a rather simple explanation. If sarcomere velocity is at all times during the twitch controlled by Hill's force-velocity relationship, then the sarcomere velocity at any time will be to a large extent determined by the difference between the force-generating capacity of the sarcomere (P₀) and the force (P) tending to oppose sarcomere shortening or aid sarcomere extension: P being the sum of external load (Pₑ) and internal restoring force (Pᵢ). In this situation, when Pᵢ < P, the sarcomere will extend by a velocity proportional to Pᵢ. A change in Pᵢ at any instant during relaxation will affect the velocity of extension simply because it will alter Pᵢ. In this sense, sarcomere extension will be load-dependent and it is reasonable to assume that such a load-dependent mechanism exists in all cardiac tissue. However, a diversity of results concerning apparent relationships between external force and relaxation kinetics can result simply because the force tending to extend the sarcomere is not directly related to P but rather it is related to Pᵢ. Thus, factors that affect the time course and magnitude of Pᵢ will also affect relaxation kinetics. In this sense, the load-dependency of sarcomere extension is intimately linked to the time course of activation, and relaxation may under some circumstances appear to be more nearly related to the time course of activation (i.e., activation-dependent) than to the external loading conditions. It is possible, therefore, for the velocity of sarcomere extension at a light external load to exceed that at a heavy external load simply because the sarcomere extension in the lightly loaded case will generally begin at a shorter sarcomere length and a much lower Pᵢ, than will be the case for relaxation with the heavy load. As the sarcomere extends through longer and longer lengths during relaxation, the high velocity can be maintained even in the presence of a small external force simply because the time-dependent decrease in Pᵢ offsets the length-dependent increase in Pᵢ which would have occurred if Pᵢ were time-independent. However, it is important to recognize that a change in external force imposed on the sarcomere at any given time during relaxation will immediately alter the velocity of sarcomere extension, since it will alter the value of Pᵢ. In that sense, relaxation in frog cardiac muscle (and probably all cardiac muscle) is load-dependent.

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