A Theoretical Model of Regionally Ischemic Myocardium

Virgil B. Elings, George E. Jahn, and John H.K. Vogel

SUMMARY The isometric tension development of a one-dimensional regionally ischemic muscle was analyzed theoretically. The model consists of a one-dimensional normal segment in series with a one-dimensional ischemic segment. Each segment is modeled as a three-element muscle. The inputs to the various elements, except the contractile element in the ischemic segment, were obtained from published data for cat papillary muscles. To be consistent with segment length measurements on ischemic canine hearts, it was assumed that the ischemic contractile element contracted normally at the beginning of contraction and then at some tension, T_M, fell behind in its rate of tension development compared to the contractile element in the normal segment. Rate of tension development of the entire muscle and the stretching of the ischemic segment were calculated for various lengths of the ischemic segment and strengths of the ischemic contractile element. At the tension, T_M, the ischemic segment begins undergoing paradoxical expansion and, simultaneously, as a result of the expansion, the time derivative of the tension produced by the regionally ischemic muscle exhibits a sudden decrease.

CORONARY ARTERY disease directly affects localized regions of the heart because the various coronary arteries provide blood to discrete segments of the heart. Ischemia in the intact heart, therefore, usually occurs in isolated areas surrounded by normally contracting myocardium, giving rise to asynergy.1 Thus the effects of ischemia should be considered regional rather than global. This paper addresses the regional aspects of ischemia and their effect on the heart’s mechanical performance. In particular, a mathematical model of regionally ischemic muscle will be presented and analyzed. Such a model has been mentioned by Brady,2 but no qualitative or quantitative calculations were performed. Inputs to the model are based on published data from both normal and hypoxic papillary muscles. The stress development in the regionally ischemic fiber during isometric contraction and the paradoxical extension of the ischemic segment of the fiber are calculated. Examples of experimental observations will be presented for comparison with the results of the theoretical model.

Description of the Theoretical Model

Figure 1 shows a schematic representation of a heart. Several coronary arteries which supply blood to the heart are shown; the artery in the center of the ventricle is assumed to be occluded, causing ischemia in the region inside the dotted line. The one-dimensional muscle that is shown shaded will be examined in detail. The muscle is inside the dotted line. The one-dimensional muscle that is assumed to be of unit length and unit cross-sectional area will be presented and analyzed. Such a model has been mentioned by Brady,2 but no qualitative or quantitative calculations were performed. Inputs to the model are based on published data from both normal and hypoxic papillary muscles. The stress development in the regionally ischemic fiber during isometric contraction and the paradoxical extension of the ischemic segment of the fiber are calculated. Examples of experimental observations will be presented for comparison with the results of the theoretical model.

CHARACTERIZATION OF THE ELASTIC ELEMENTS

The length-tension relationships for the elastic elements of the normal section of the theoretical fiber were obtained from a nonlinear least squares fit to the data of Parmley et al.5 on isolated cat papillary muscles. The length-tension relation for the SE is described by:

$$T = C_{SE}/K_{SE}[\exp(K_{SE}-\Delta l) - 1]$$

where C_{SE} = 13.2 g/mm², K_{SE} = 31.95, and Δl is the percent change in length. This yields a stiffness of dT/dl = T / K_{SE} + C_{SE}.

The length-tension relation for the PE is described by the same expression with constants C_{PEM} = 2.6 g/mm² and K_{PEM} = 32.0. These length-tension relations are shown in Figure 3 and are identified by symbols A and B. Respectively, it is assumed that the elastic elements do not resist compression.

Tyberg et al.6 have shown that early anoxia has no
Figure 1 Schematic of a regionally ischemic heart showing a discrete one-dimensional muscle which extends from the normal region into the ischemic region. The one-dimensional muscle is shown modeled as two muscles in series.

The effect on the elastic properties of cat papillary muscle, whereas Henderson et al.\(^7\) have shown that in hypoxic rat papillary muscles, the stiffness, \(dT/d\varepsilon\), of the series elastic element increased when contracture occurred. In man, there is contradictory data on the effect of ischemia on the passive properties of the ventricle. McCans and Parker\(^8\) indicate that the passive pressure-volume relation of the ventricle is unchanged by ischemia. The data of Barry et al.\(^9\) indicate that, although the stiffness of the ventricle, \(dP/dV\), remains essentially unchanged, the pressure volume curve is shifted to higher pressures. They indicate that this could be due to a failure of relaxation of a portion of the left ventricular myocardium. In the calculations of the model presented here, it is assumed that the passive properties of the muscle are not affected by ischemia and therefore identical length-tension curves will be used to describe the elastic elements in both the normal and ischemic sections.

Figure 2 The one-dimensional regionally ischemic muscle model is shown in both the Maxwell and Voigt configurations. In both configurations, the ischemic region is of length \(X\) and the normal section of length \(1-X\).

Figure 3 Passive length-tension relations for the elastic elements used in the model. Curve A is the length-tension relation for the series elastic element and curve B is the relation for the parallel elastic element.

CHARACTERIZATION OF THE NORMAL CONTRACTILE ELEMENT

In the Maxwell representation of heart muscle, all of the time-dependent, dynamic properties of the muscle have been assigned to the CE. Whereas the elastic elements were described in terms of length-tension relations, the CE will be characterized by a tension-velocity relation. The tension-velocity description means that, after stimulation, the CE shortens with a velocity that depends on the amount of tension produced by the CE. Force-velocity has generally been used as the input function to the CE in muscle models ever since A.V. Hill performed his classic experiments.\(^10\) Characterizing the CE with a force-velocity relation is simple and yields computational advantage. Viscosity is excluded from the CE in this formulation, but can be included in a separate viscous damping element in parallel with the contractile element.

The tension-velocity curve for the normal CE is chosen so that when the CE contracts along this curve, the calculated tension, \(T(t)\), and the rate of tension development, \(dT/dt\), match those measured from isometrically contracting isolated papillary muscles. The velocity of contraction of the CE is related to the rate of tension development, \(dT/dt\), by \(V_{CE}(t) = d\varepsilon/dt = dT/dt/dT/d\varepsilon\). The tension-velocity relation, \(V_{CE}(t)\), is then defined in terms of the measurable quantities, \(dT/dt\), and the stiffness, \(dT/d\varepsilon\), of the elastic elements. Since the stiffness of the elastic elements was described in the previous section, it remains to describe \(dT/dt\) for an isometrically contracting muscle in order to derive the tension-velocity relation, \(V_{CE}(t)\), for the normal CE.

Parmley et al.\(^5\) measured \(dT/dt\) vs. tension on isolated papillary muscle, then calculated \(V_{CE}\) (their Figure 8). The data in that figure were used to calculate \(dT/dt = V_{CE}(T \cdot K_{se} + C_{PE})\), shown in Figure 4. We subsequently obtained the original data from which they calculated their Figure 8. Their data indicate that within ±10%, the rate of tension development, \(dT/dt\), for a given developed tension is independent of muscle preload for preloads
from 0.1 to 2 g/mm² and for developed tensions from 0 to 3 g/mm². Others have found, again from measurements on isolated papillary muscles, that dT/dt at a given level of tension showed little change for changes in initial muscle length from Lₐₓ (the initial length at which the maximum active tension is produced) to 96% of Lₐₓ, a change in preload of a factor of about 3. Therefore, most of the model calculations were performed using a single tension-velocity curve that is independent of preload from 0.1 to 2 g/mm². Calculations were also performed using a preload-dependent tension-velocity curve with no effect on the qualitative results of the model. This point is considered in more detail in the Discussion. Shown in Figure 4 is a least squares fit to the data of the form dT/dt = A(1 - e⁻BT'), where T' is the developed tension of the muscle, A = 37.02 g/mm² per sec, and B = 2.304/g per mm². From this curve and the length-tension relationships for the elastic elements, the tension-velocity relationship for the normal contractile element was calculated and is shown in Figure 5.

CHARACTERIZATION OF THE ISCHEMIC CONTRACTILE ELEMENT

An idea of how the ischemic contractile element should be characterized can be obtained from measurements of lengths on ischemic areas of canine ventricles. Measurements have been performed with both mechanical and ultrasonic crystal transducers. The measurements show that, upon occlusion of the coronary artery supplying blood to the measured area, a stretching of the ischemic muscle begins occurring late in systole, with little, if any, change in the contraction pattern in early systole. As time progresses and the ischemia becomes more severe, the stretching moves earlier into systole until, after a few minutes, the stretching has moved into the isovolumic phase of systole. This sequence of events has been described by both Theroux et al. and Tatooles and Rand. These data indicate that during initial contraction the ischemic muscle is able to produce tension at the same rate as the surrounding myocardium, otherwise it would begin stretching immediately at the onset of pressure development. In an intact heart in which the arteries are partially occluded, the stable severity of ischemia might correspond to any one of the contraction patterns shown by Theroux et al.; the more severe the ischemia, the earlier the appearance of the paradoxical expansion in systole. Measurements of tension development during isometric contraction of isolated hypoxic cat papillary muscles show that, as the hypoxia becomes more severe, the maximum tension and time to maximum tension both decrease, so that the initial rate of tension development decreases less slowly than the maximum force produced by the muscle. A simple approximation to all these results, therefore, is to assume that at the beginning of contraction the ischemic contractile element follows the same tension velocity relation as the normal contractile element until some maximum tension Tₓ is developed, at which point the tension produced by the ischemic contractile element begins to lag behind the tension produced by the normal contractile element. The tension Tₓ is a measure of the degree of ischemia. The more severe the ischemia, the lower the value of Tₓ. Calculations were performed for two cases in which, at the tension Tₓ, the tension produced by the ischemic element (1) remained constant and (2) continued to increase but at a rate less than the rate of the normal contractile element. Qualitatively, the results are essentially the same; therefore, quantitative results will be described only for case 1.

COMPUTER CALCULATIONS

The rate of tension development of the regionally ischemic muscle model shown in Figure 2 was calculated using the properties of the active and passive elements just described. The total length of the muscle was kept constant. The time derivative of the tension developed by the muscle and the length of the ischemic section of the muscle were both calculated as a function of the tension developed by the muscle.

The calculations were performed by incrementing in
small steps the tension in the two contractile elements up to a contractile element tension of $T_M$, after which the tension in only the normal contractile element was incremented. At each step in tension, the changes in length of the elastic elements were calculated so that the total tension in the normal and ischemic sections balanced and also so the entire muscle remained isometric. The time interval $\Delta t$ corresponding to an increment in tension was obtained from the tension-velocity relation of the contractile elements. The $dT/dt$ was calculated at each increment as the change in the tension in the muscle $\Delta T$ divided by the corresponding time interval $\Delta t$.

Results

QUALITATIVE RESULTS OF THE MODEL CALCULATIONS

The detailed results of the calculations can best be understood by first considering qualitatively what occurs in the regionally ischemic muscle during an isometric contraction. At the beginning of the contraction, both the normal and ischemic contractile elements contract at the same rate, producing a tension vs. time curve which begins the same as a normal homogenous muscle. During this period both the normal and ischemic sections remain isometric. When the tension produced by the ischemic contractile element reaches $T_M$, it ceases to produce more tension. Because the normal and ischemic sections are in series, the total tension in the ischemic section must at all times be equal to the total tension in the normal section. Therefore, the ischemic section must stretch so that its passive elastic elements can produce a tension which essentially makes up the difference between the tensions produced by the normal and ischemic contractile elements. Since the entire muscle is isometric, the normal section must contract slightly. Per muscle length, the ratio of the stretching of the ischemic section to the contraction of the normal section, is $(1 - X)/X$, which is normally much larger than 1. For small values of $X$, therefore, the normal section remains essentially isometric. As the ischemic section begins stretching, the rate of tension development of the overall muscle, $dT/dt$, undergoes a sudden decrease, since the contractile element in the normal section must now stretch both its own series elastic element and the parallel elastic element in the ischemic section. The general features of the results are unchanged and, therefore, for simplicity, the calculations presented in the following sections will be with the viscous elements absent.

stretching in turn causes the dip in the rate of tension development, $dT/dt$.

When a similar calculation is performed with viscous elements with a damping constant of 0.03 g·sec/mm² included in parallel with the contractile elements, the results in Figure 7 are obtained. When viscous elements are included in parallel with the contractile elements, one finds that the viscous elements smooth out the onset of stretching of the ischemic section and, therefore, smooth out and decrease the depth of the dip in the derivative of the tension. The reason for this is that, as the ischemic section begins to stretch, the contractile element and the viscous damper begin stretching. The damper produces a force proportional to the velocity of stretching but opposite in direction, hence slowing down the onset of stretching. The general features of the results are unchanged and, therefore, for simplicity, the calculations presented in the following sections will be with the viscous elements absent.

![Figure 6](image1.png)  
**Figure 6** Rate of tension development, $dT/dt$, vs. time after the beginning of isometric contraction for a normal and regionally ischemic muscle. Also shown is the stretching of the ischemic segment of the regionally ischemic muscle as a function of time.

![Figure 7](image2.png)  
**Figure 7** Rate of tension development, $dT/dt$, vs. time for a regionally ischemic muscle model in which viscous elements have been included in parallel with the contractile elements.
In Figure 8 is shown the rate of tension development of the regionally ischemic muscle vs. the total tension across the muscle using the Maxwell configuration for both the normal and ischemic sections. The fraction of the muscle that is ischemic was given the values 1%, 5%, 10%, and 20%. The size of the dip in the rate of force development increases as the ratio of ischemic to nonischemic muscle increases. For these calculations the preload was fixed at 0.25 g/mm², and the maximum tension produced by the ischemic CE, $T_M$, was 0.5 g/mm². The curves for different values of $X$ tend to be parallel to one another for developed tensions greater than $T_M$.

Figure 9 shows the effect on the $dT/dt$ vs. $T$ curves as $T_M$; the maximum tension developed by the ischemic CE is given the values 0, 0.25, 0.5, and 1.0 g/mm². In these calculations, 10% of the muscle was ischemic and the preload was again 0.25 g/mm². The results show that as the strength of the ischemic contractile element decreases, the dip moves to lower developed tension and the magnitude of the dip in the rate of tension development decreases. Figure 9 also shows the stretching of the ischemic section as a function of developed tension as $T_M$ is varied. These curves have the same shape for different values of $T_M$ and are simply shifted from each other along the tension axis. When the ischemic contractile element is completely inactive, $T_M = 0$, there is no dip at all in the rate of tension development, although the stretching of the ischemic section is at a maximum. Although with $T_M = 0$ there is no dip in the derivative, the stretching of the ischemic section causes the rate of tension development at any given tension to be less than normal. If the elastic elements in the ischemic section were very stiff, such as might occur in an old infarction in the intact heart, the ischemic section would not stretch, the normal section would remain isometric, and the entire muscle would exhibit a normal isometric tension development curve.

**Discussion**

In the Results just presented, it has been assumed that the ischemic contractile element produces a constant force during paradoxical systolic expansion. The formation of the dip in the derivative depends only on the fact that the ischemic section begins contracting normally (or approximately normal) and then at some tension undergoes a rapid expansion. The formation of the dip does not depend on what is explicitly assumed for the tension development of the ischemic contractile element during this stretching, but the depth (size) of the dip does. Figure 10 shows calculations from the theoretical model using the Maxwell configuration in which it is assumed...
that, after the active tension $T_M$ is reached, the ischemic contractile element (1) produces constant tension and (2) increases its tension at a rate of 50% of the normal contractile element. The dip is produced in the derivative in both cases but is one-half as deep in the second case. The depth of the dip, therefore, is dependent on the size of the ischemic region, the preload of the muscle, the strength of the ischemic contractile element, and the tension generated by the ischemic contractile element as it undergoes stretching.

It is assumed in the model that the ischemic region is uniformly ischemic, and therefore all portions of that section began stretching simultaneously. If the ischemic section were assumed not to be of uniform strength, then various portions of it would begin stretching at different developed tensions. The result of this would be to broaden the dip in the derivative and decrease its depth.

For the regionally ischemic muscle model calculations, the initial portion of the $dT/dt$ vs. $T$ curves up to the onset of the dip are identical, independent of the strength of the ischemic section, $T_M$, or the size of the ischemic region, $X$, as illustrated in Figures 8 and 9. This is a result of the assumption that, at the beginning of contraction, the ischemic contractile element contracts normally.

Any measurements made on such a hypothetical muscle before the onset of stretching of the ischemic segment would therefore not be affected by the ischemia. Such a measurement is $V_{max}$, the velocity of contraction of the contractile element at zero developed tension. In the intact heart, the tension in the heart wall is proportional to the ventricular pressure, the proportionality constant depending on the size of the ventricle and the wall thickness. During isovolumic contraction in the intact

**Figure 11** The rate of left ventricular pressure development and the ischemic segment length as a function of left ventricular pressure for an open-chested dog. The data are shown before occlusion, 60 and 100 seconds after occlusion, and 1 minute after termination of a 2-minute occlusion. At 60 seconds after occlusion, there is a systolic bulging in the ischemic segment length accompanied by a dip in the pressure derivative. At 100 seconds after occlusion, the bulging and dip have both moved to lower pressure. One minute after the 2-minute occlusion was terminated, the derivative and segment length returned essentially to normal although, after recovery, the maximum pressure was slightly lower than before occlusion.

**Figure 12** The rate of left ventricular pressure development and the ischemic segment length as a function of left ventricular pressure for an open-chested canine before occlusion and at 100, 140, and 190 seconds after occlusion of the left anterior descending coronary artery. At 140 seconds after occlusion, a pulsus alternans developed, and the solid and dotted lines are data for alternate beats. They are each averaged over five beats. The other curves in the figure are averaged over 10 beats.
heart, the geometry remains essentially fixed and the proportionality between wall tension and ventricular pressure remains constant. The rate of change of pressure, dP/dt, therefore, will exhibit the same characteristics as dT/dt, the rate of change of tension in the heart wall. Peterson et al. computed $V_{\text{max}}$ from left ventricular (LV) pressures measured in normal and diseased human hearts and concluded that there was essentially no difference in the average value of $V_{\text{max}}$ obtained from each group. This observation is consistent with the results of the present theoretical model.

In the present model, if the elastic elements in the ischemic region were very stiff, such as might be the case in an old infarction, the isometric tension development curve would be normal, giving a normal $V_{\text{max}}$. Such a stiff section in the intact heart would not contribute to ejection of blood and, therefore, ejection phase indices would not be normal. This result is again consistent with the findings of Peterson et al. in which, although they found no difference in $V_{\text{max}}$ between the two groups with normal and diseased hearts, they did find a difference in ejection indices such as ejection fraction and mean velocity of fiber shortening.

Examples of the phenomena described by this model are shown in Figures 11 and 12. Data were obtained from open-chested dogs before and after occlusion of the left anterior descending (LAD) coronary artery. The LV pressure was measured with a 7F transducer-tipped catheter (Edwards Laboratories) with an electronic system which had a time constant of 2 msec. Two miniature ultrasound crystals were implanted approximately midwall in the ischemic zone to measure simultaneously the contraction of a segment length. The distance between the crystals was measured by means of the technique described by Franklin et al. The derivative of the pressure and the segment length, averaged over 10 beats before occlusion and 60 and 100 seconds after occlusion, are shown in Figure 11. At 60 seconds after occlusion, a distinct stretching of the ischemic segment occurs, accompanied by a dip in the derivative. At 100 seconds after occlusion, the onset of stretching of the segment and the dip in the derivative have both moved to lower pressure. Also shown in Figure 11 are the derivative and segment length 1 minute after the end of the 2-minute occlusion. Both the stretching of the ischemic segment and the dip in the derivative have disappeared. After occlusion, but earlier than 60 seconds after occlusion, irregularities occurred in the negative portion of the derivative.

Figure 12 shows data from another dog for which the LV pressure derivative and segment length in the ischemic region are shown before occlusion, and 100 seconds, 140 seconds, and 190 seconds after occlusion of the LAD artery. The data are again averaged over 10 heart beats. Before occlusion, the segment length exhibits a shortening up to a pressure of about 30 mm Hg and then remains isometric up to a pressure of 100 mm Hg. At 100 seconds after occlusion, the segment length again shortens at the beginning of contraction but then begins stretching at a pressure of 60 mm Hg. The pressure derivative exhibits a large dip which begins forming at 60 mm Hg.

At 140 seconds after occlusion, a pulsus alternans developed, forming two distinctly different segment-length contraction patterns and derivatives every other beat. These are shown as solid and dotted lines in Figure 12. During the "weak" beat (dotted line) the stretching of the segment length and the dip in the derivative both begin at 50 mm Hg, whereas on the "strong" beat (solid line) the stretching of the segment and the dip in the derivative begin at 60 mm Hg. This beat-to-beat correlation between the onset of stretching and the dip in the derivative suggests that the stretching in the ischemic region causes the dip in the derivative.

At 190 seconds after occlusion, the ischemic segment begins stretching immediately at the beginning of isovolumic contraction and the dip in the derivative has almost completely disappeared. This is consistent with the model calculations shown in Figure 10A, except that the percent stretching of the ischemic segment is about twice that calculated by the model, i.e., 10% instead of 5%.

In summary, a theoretical model of regionally ischemic myocardium has been developed which predicts irregularities in the derivative of the left ventricular pressure during isovolumic contraction caused by paradoxical expansion of the ischemic region. Examples of this phenomenon in open-chested dogs are shown. The model may explain why isovolumic indices such as $V_{\text{max}}$ are not as sensitive as indicators of heart disease as are ejection phase indices.

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