CONTINUUM RHEOLOGY OF MUSCLE CONTRACTION AND ITS APPLICATION TO CARDIAC CONTRACTILITY

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ABSTRACT A set of constitutive equations is proposed to describe the mechanics of contraction of skeletal and heart muscle. Fiber tension is assumed to depend on the degree of chemical activation, the stretch ratio, and the rate of stretching of the fibers. The time rate of change of activation is governed by a differential equation. The proposed constitutive equations are used to model the time courses of isotonic and isometric twitches during contraction and relaxation phases of the muscle response to stimulation. Various contractility indices of the left ventricle are considered next by using the proposed constitutive equations. The present analysis introduces a new interpretation of the index of contractility $(dP/dt)/P$ used in cardiac literature. It is shown that this index may not be related at all to the maximum speed of shortening and that it may be dependent on both preload and afterload. The development of pressure during isovolumetric contraction of the left ventricle is shown to be governed by a differential equation describing the time rate of change of tension during isometric contraction of myocardium fibers.

INTRODUCTION

One of the fundamental areas of research in biomechanics is the mechanical analysis of biological organs such as the heart, ureter, and urinary bladder. Mathematical modeling based on the principles of mechanics is useful in relating bulk mechanical quantities such as pressure-volume diagrams to the geometry of the organ and orientation and strength of muscle fibers. A continuum theory of muscle contraction is needed to analyze the time-dependent behavior of these organs. Phenomenological continuum theories based on Hill's three-element model (1) have been extensively considered in the last few decades to describe the mechanics of contraction of muscle tissue. However, recent experimental and theoretical studies indicate the severe limitations of Hill's model both in concept and in empirical value (2, 3). During the last few decades, research on muscular contraction was influenced by the sliding filament model for cross-bridge action put forward by H. E. Huxley (4) and A. F. Huxley (5). In Huxley's kinetic model (5), cross-bridges are idealized as elastic springs when they form links between thick and thin filaments. Cross-bridge force is assumed to be a function of internal variable x, which is the distance from the stress-free configuration of the cross-bridge to the nearest actin site. The time rate of change of attachment is governed by a first-order kinetic equation. Since its introduction, this model has been revised considerably by its author and his co-workers (6) and by others (7, 8). The modifications have been considered to account for recent data on the short-time muscle response to a quick release. As a result, models with distinctly different mechanisms of cross-bridge action have been developed for skeletal muscle fibers.

A. F. Huxley's initial model (5) has also been generalized in several ways to partial activation and time variation of fiber extension to model the mechanical behavior of cardiac muscle fibers (9, 10). These kinetic models still contain the internal variable x in their equations, which introduces considerable difficulties in numerical computations. For example, analysis of isotonic contraction during a single twitch involves the numerical solution of several thousand coupled equations (10). Recently, Tözeren (11) developed a set of equations (free of x), governing the muscle contraction on the continuum level, based on an assumed cross-bridge mechanism similar to the one proposed by Podolsky and co-workers (7). The derived equations provide a useful means of evaluating the influence of cross-bridge parameters on the macromechanical behavior of muscle fibers, and enable the analysis of complex experimental data involving transients or sinusoidal oscillation. However, this continuum model may be considered unnecessarily detailed when simpler quasi-steady modes of contraction are considered. The aim of the present study is to develop a simple set of equations that describe approximately the mechanics of contraction on the macroscale. The present analysis incorporates the effects of the muscle length, fiber orientation, degree of activation, and the kinetic properties of the muscle during the development and relaxation phases of muscle contraction. The proposed

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constitutive equations are presented in the next section entitled Constitutive Equations and their application to cardiac contractility is discussed in the section entitled Application to Cardiac Dynamics.

CONSTITUTIVE EQUATIONS

In the present study the muscle tissue is considered to be a fiber-reinforced material. The stress tensor for the striated muscle may be approximated in the form

$$\sigma_{ij} = -p\delta_{ij} + T_f a_i a_j, \tag{1}$$

where δ_{ij} is the unit isotropic tensor of the second order, p is the hydrostatic tissue pressure, T_f is the magnitude of the fiber stress (dyne/cm^2), and a_i denotes the unit-vector field specifying the fiber direction in the continuum (12). The basic contractile unit of muscle fibers is a serially repeating structure, the sarcomere. The sarcomeres are composed of an array of partially overlapping thick and thin filaments. According to the sliding filament hypothesis of muscle contraction, the developed tension increases with the number of cross-bridges that are formed between the thin and thick filaments. This number varies with the degree of overlap and hence depends on the sarcomere length. It is therefore convenient to introduce the concept of a macroscopic stretch ratio λ to study the length dependence of the actively developed fiber tension, T. Let the length of an infinitesimal fiber element in a reference configuration be denoted by $d\ell_o$. Let $d\ell$ be the length of the same fiber element in the present configuration. Then the stretch ratio λ is defined as

$$\lambda = \text{limit } (d\ell/d\ell_o)$$
$$d\ell_o \to 0. \tag{2}$$

Here the reference configuration, $\lambda = 1$, is assumed to correspond to the length of the fiber element in which maximum isometric active tension is achieved. Experimental observation indicates that during isotonic contraction fiber tension is inversely related to the speed of contraction (1). Hill's force-velocity relation is an hyperbolic equation between fiber tension and speed of contraction. In the present study, the rate of strain along the fiber direction is considered as a suitable kinematic variable analogous to the speed of shortening and will be employed in the constitutive equations. The rate of strain along the fiber direction is defined as

$$U = (\dot{\lambda}/\lambda) = \text{limit } [d(d\ell)/dt)]/d\ell,$$
$$d\ell \to 0 \tag{3}$$

where $\dot{\lambda}$ is the material time derivative ($\dot{\lambda} = d\lambda/dt$).

It has been well established that calcium ions (Ca^{++}) initiate the contraction by removing the inhibitory effect of the regulatory proteins on actin and myosin, the major components of thin and thick filaments, respectively. Isometric tension experiments on skinned muscle fibers show that no force is generated by the contractile proteins at a concentration of Ca^{++} ions $\lesssim 10^{-7}$ M, and force generation is maximal at a concentration of $\sim 10^{-5}$ M. Between these two values, the force increases steadily with the logarithm of the calcium ion concentration (13, 14). According to the steric models of activation, an increase in calcium-ion concentration increases the number of activated sites at which cross-bridges can be formed between the thick and thin filaments of the contractile unit or sarcomere (15). Here an internal variable, c, is introduced in formulating the constitutive equations of muscle fibers in order to incorporate the influence of the activating calcium ions on muscle contraction. Internal variable c reflects the amount of calcium bound by troponin and may be considered as a measure of the degree of activation of muscle fibers. In the following analysis, it will be convenient to express c as a product of the multiplication of two terms, namely $c = C \cdot c_o$. The parameter $C = C(t)$ is dimensionless and varies between 0 and 1.

The discussion presented above shows that the actively developed tension T, is a function of the stretch ratio λ, rate of strain ($\dot{\lambda}/\lambda$), and internal variable c

$$T = T(\lambda, \dot{\lambda}/\lambda, c). \tag{4}$$

The specific mathematical form of Eq. 4 varies in general with the muscle type and species. The kinetic model shown in Fig. 1 has been employed previously to model unsteady contractions after a quick release as well as sinusoidal oscillations of fully activated skeletal muscle fibers (11). During isometric tension (i.e., $U = 0$), the kinetic equation governing the fraction of attached cross-bridges and its first x-moment was integrated analytically with respect to x, yielding

$$\dot{T} = \alpha(C\,T_o - T), \tag{5}$$

where α is the sum of the rate parameters of attachment f_o and detachment g_o in the region of attachment ($0 < x < h$, $h = 110$ Å), respectively, and $\dot{T}$ denotes the time derivative of T. T_o is the isometric tension when $C = 1$. The parameter α is inversely proportional to the average dura-

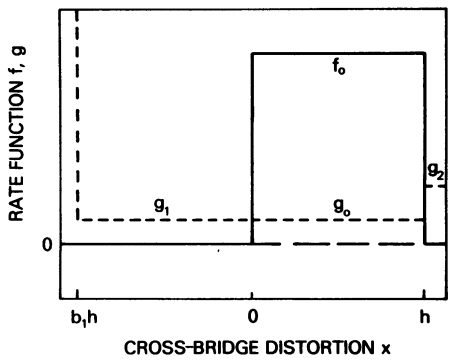

FIGURE 1 The variation of the rate constants f and g with respect to x for a simplified cross-bridge model is shown ($h = 110$ Å, $b_1 = 1.15$, $f_o = 1{,}000\ s^{-1}$, $g_1 = 30\ s^{-1}$, $g_o = g_1$, $g_2 = 0.1\,f_o$).

tion of a cross-bridge cycle. It is assumed that the number of active actin sites increases with C and that the rate parameters f_o and g_o are independent of C. These assumptions are in accordance with the elementary models of calcium regulation in muscle contraction proposed recently by Hill (16). During steady isotonic contractions (i.e., $T = 0$), the kinetic model shown in Fig. 1 can be fitted to experimental data well by adjusting the values of the constants g_1 and b_1 introduced in the model (11). Using the data of Podolsky and Teicholz (15), Hill's equation can be generalized to partial activation as follows

$$U = U_o (C T_o - T)/(C T_o + \gamma T), \tag{6}$$

where $\gamma = (T_o/a)$ is a dimensionless constant and U_o is the speed of contraction at zero load. According to Eq. 6 the speed of shortening during an isotonic contraction is insensitive to the degree of activation at each relative load. However, this formation has not been uniformly supported by the results obtained in other laboratories. For example, Julian (15) has found that the magnitude of U_o decreased with the degree of activation. Julian's data may be fitted with Eq. 6 provided that the CT_o term in the denominator be replaced by T_o.

Eqs. 5 and 6 can be generalized to partial activation and to the presence of relative motion (fiber shortening) with the following equation

$$\dot{(T/T_o)} = \alpha \{C[1 - (U/U_o)] - (T/T_o)[1 + \gamma (U/U_o)]\} \tag{7}$$

Eq. 7 can be shown to reduce to Eq. 5 when $U = 0$ and to Eq. 6 when $\dot{T} = 0$. Eq. 7 may be useful when the fiber extension λ and tension T vary with time. For example, the time history of shortening during a contraction in which the degree of activation varies with time may be predicted by using Eq. 7. If the drop in tension ΔT following a step decrease in length $(\Delta\lambda/\lambda)$ (calculated by Eq. 7) is plotted against $\Delta\lambda$, the resulting curve can be fitted easily to the experimental T_1 curve of Huxley and Simmons (6). The several time constants observed during short-time response after a quick release, however, cannot be reproduced with this equation because of the approximations inherent in Eqs. 5 and 6. Peak isometric tension T_o appearing in Eqs. 5–7 is a function of muscle stretch ration λ (16) as well as the electrochemical state variable c_o. Here $T_o = T_o(\lambda, c_o)$ is assumed to be determined experimentally.

To complete the analysis, Eq. 7 must be accompanied by an equation governing the time rate of change of the internal variable c. Note that c is not a measure of the intracellular Ca^{++} concentration, and its time course is slower (roughly equal to the time course of isometric tension). The slow rise in c might be considered to be due to the time necessary for Ca^{++} binding to troponin or the time necessary for a conformational change of troponin or tropomyosin. The rheological principle of equipresence suggests that the internal variable c must not only depend on electrochemical events, but also on the kinematic variables λ and $U = \dot{\lambda}/\lambda$. To model the length-dependent activation in the cardiac muscle (19, 20, 21), Panerai (10) introduced an activation measure defined as the instantaneous number density of actin molecules that are able to react with myosin. The rate equation proposed by Panerai (10) can be adopted to the present terminology as

$$\dot{c} = A(t)(c_o - c) - B(\lambda, \dot{\lambda}/\lambda)c, \tag{8}$$

where $A(t)$ is a function of the time-dependent calcium concentration in the sarcoplasm, B is the dissociation rate constant, and c_o is the maximum degree of activation corresponding to a given electrochemical state. The constitutive equations presented in this section state that active fiber tension T can be expressed as a function of three variables λ, $U = \dot{\lambda}/\lambda$, and c. An application of the present formulation to cardiac contractility will be presented in the next section.

APPLICATION TO CARDIAC DYNAMICS

In this section, constitutive equations of the cardiac muscle fibers will be considered. These equations will then be employed in the analysis of isotonic contraction of a single fiber as well as isovolumetric contraction of a left ventricle during a single twitch.

The differential Eq. 7 governing active tension T can be simplified by noting that the time constant α is large ($\alpha = 1{,}000\ s^{-1}$) in comparison with the time constant governing variation of isometric tension during a single twitch. Therefore, as an approximation, the right-hand side of Eq. 7 can be set equal to zero, resulting in the simple equation

$$T = T_o C(t)\{1 - (\gamma + 1)(U/U_o)/[1 + \gamma(U/U_o)]\}. \tag{9}$$

During a cardiac cycle, the lengths of the myocardial fibers either decrease or remain constant in the active state. The term (U/U_o) is positive when the fibers shorten during contraction. A muscle fiber in the active state can be stretched if the applied force on the fiber is greater than the corresponding isometric force. In this case Hill's force-velocity relation employed in the derivation of Eq. 9 is not valid. Eq. 9 must be revised accordingly by replacing the term U/U_o appearing in the denominator by its absolute value. This revision assures that the change in active tension due to a step increase in fiber length is positive, as observed experimentally (6). This equation may be generalized to take into account the length-dependent activation observed in the ascending limb of the length-tension curve of papillary muscles of small mammals (20, 21) by expressing the isometric tension T_o as follows

$$T_o = T_m[1 + m(\lambda - 1)], \tag{10}$$

where the coefficients T_m and m are functions of the variable $c_o (c = Cc_o)$. In Eq. 10 the length-tension curves in the ascending limb are approximated by a family of

straight lines. A change in contractility not only influences the peak tension T_m but also the slope m of the length-tension curve. Experiments on cat papillary muscle (20) show that, with decreasing free-calcium concentration (Ca^{++}) of the bathing solution, peak tension T_m decreases but the slope m increases. In the present study, the parameter c_o plays a role in tension development similar to that of Ca^{++} concentration in the bathing solution.

In addition to Eq. 9, the dimensionless activation variable, $C = C(t)$, must also be prescribed. For this purpose Eq. 8 presented in the previous section may be employed. However, Blinks et al. (22) point out that aequorin luminescent may not be an accurate measure of the intracellular calcium concentration (function $A[t]$ in Eq. 8) during the rising phase of the twitch. Instead of introducing one more unknown function, $A(t)$, into the constitutive equations, it may be more suitable to express C as a function of λ and t directly, and determine the functional relation from isometric tension experiments. In the following analysis, the time variation of C during a single twitch is governed by the second-order differential equation and initial conditions

$$\ddot{C} + w^2 (C - 0.5) = 0, \qquad C(0) = \dot{C}(0) = 0, \qquad (11)$$

where the parameter w has two distinct values during the activation and relaxation phases of contraction. These values are denoted by w_c and w_r, respectively. It can be shown that

$$w_c = \pi/t_c, \qquad w_r = \pi/t_r, \qquad (12)$$

where t_c denotes the time required to reach peak tension and t_r is the duration of the relaxation phase during a single twitch. Experiments on cat papillary muscle (20) show that the maximum rate of tension development decreases appreciably with decreasing muscle length. For this reason the parameters w_c and w_r are assumed to depend on the stretch ratio λ. The rheological principle of equipresence suggests that internal variable C must also depend on the speed of shortening U. However, no attempt will be made to introduce the possible influence of U into Eq. 11, mainly because of lack of experimental data.

Eqs. 9, 10, and 11 describe the fiber tension T as a function of the stretch ratio λ, the rate of strain U, and time t during a single twitch. The six parameters T_m, m, U_o, γ, w_c, and w_r must be specified for a complete description of active fiber tension. The parameters T_m and m can be obtained experimentally by measuring the peak and the average slope of the isometric length-tension data. The parameters w_c and w_r can be estimated by considering the time development of isometric tension during a twitch. The constants U_o and γ are obtained by curve fitting Hill's force-velocity relation to the isotonic data. For example, if the data on cat papillary muscle presented by Sonnenblick (23) is employed, $m = 4.75$, $U_o \simeq 1.2\ s^{-1}$ and $\gamma = T_o/a = 1.5$. Similarly, at optimum length ($\lambda = 1$), $w_o = 6.3\ s^{-1}$ and

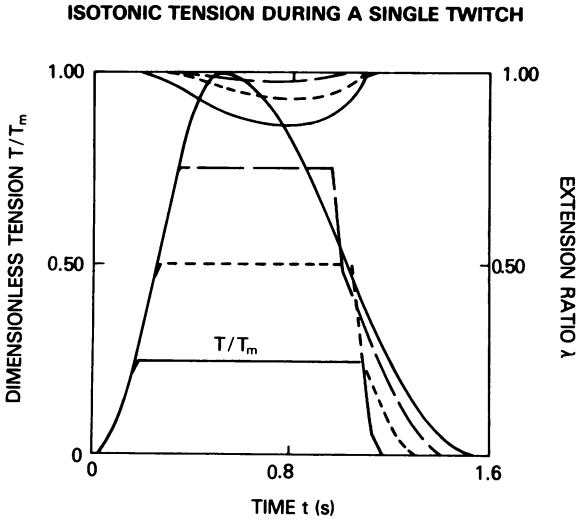

FIGURE 2 This figure shows the time variation of relative tension (T/T_m) and stretch ratio λ during isotonic contraction for (T/T_m) = 0.25, 0.5, and 0.75 ($U_o = 1\ s^{-1}$, m = 4.75, $a_2 = 3$, $w_c = 6.3\ s^{-1}$ $w_r = 3\ s^{-1}$, $\gamma = 1.5$).

$w_r = 3\ s^{-1}$. The present equations are useful in the analysis of contraction in which the degree of activation and muscle length changes with time. Fig. 2 shows the results of computations modeling isotonic contraction during a single twitch. The figure shows the time variation of fiber tension T as well as stretch ratio λ for three different values of afterload: $T/T_m = 0.25, 0.5, 0.75$. As shown in the figure, the fiber contracts isometrically at first until the fiber tension approaches the fixed afterload tension. The isotonic contraction is composed of fiber shortening followed by subsequent lengthening (relaxation phase). The phase lag between the peak tension and peak shortening shown in the figure is consistent with experimental results (23). The computations indicate that this phase lag is due to the presence of the last term in the tension (Eq. 9). Fig. 2 shows that isotonic contraction ends for small afterloads when the isometrically contracting fiber is still capable of bearing a tension greater than the isotonic tension. This behavior is modelled in the present computations by assuming that w_r increases with decreasing fiber length ($w_r = w_{ro}\ [1 + a_2(\lambda - 1)]$, $a_2 = 3$). The influence of the parameters m and U_o on the time history of shortening is illustrated in Fig. 3. The figure shows that an increase in the slope m of the isometric length tension relation results in less shortening for a given afterload. On the other hand, an increase in the speed U_o increases the amount of shortening as well as the maximum speed of shortening observed during an isotonic twitch contraction. If the duration of the contraction phase, $t_c (t_c = \pi/w_c)$ is increased, the amount of shortening increases while the peak speed of shortening decreases slightly. It is experimentally observed that an inotropic intervention (addition of norepinephrine, for example) is marked by increases in the rate of rise of tension w_c as well as the magnitude of the

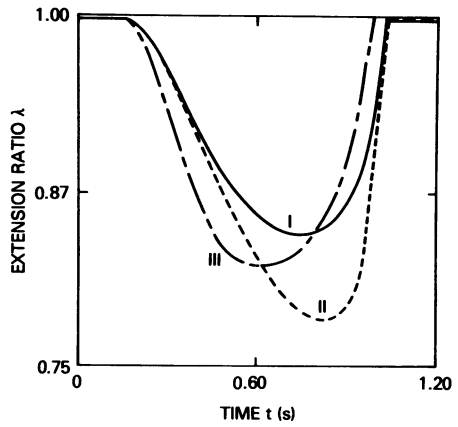

FIGURE 3 The influence of the parameters m and U_o on the stretch ratio $\lambda = \lambda(t)$ during isotonic contraction with constant relative load $(T/T_m) = 0.25$ is shown. Curve I $m = 2$, $V_o = -1\ s^{-1}$; and $m = 4.75$, $U_o = -2\ s^{-1}$, respectively. Other parameter values are the same as in Fig. 2.

isometric tension T_o accompanied by a decrease in the mean slope m of the length-tension curve in the ascending limb. In the present model a decrease in the slope m results in an increase in the speed of shortening during isotonic contraction. This prediction of the model is in agreement with the observed effect of norepinephrine on the cat papillary muscle (23).

Analysis of cardiac chamber dynamics may produce useful information about the mechanical behavior of cardiac muscle fibers in vivo. However, the transition from the time-dependent pressure-volume curves of the left ventricle to the mechanical properties of cardiac fibers is not easy and requires some simplifying assumptions on the three-dimensional geometry of the chamber and orientation of the fibers. The myocardium can be modeled as a fiber-reinforced material, as described in the section entitled Constitutive Equations. Equations governing the pressure variation in the myocardium can be obtained by substituting the constitutive equation (Eq. 1) into the vector equation of mechanical equilibrium (Eq. 12)

$$\nabla p = \mathbf{a}(T_f \nabla \cdot \mathbf{a} + \mathbf{a} \cdot \nabla T_f) + T_f(\mathbf{a} \cdot \nabla)\mathbf{a}, \qquad (13)$$

where ∇ is the gradient operator in the deformed configuration. Note that Eq. 13 is linear with respect to the fiber tension $T_f = T_p + T$ (T_p is the resting tension). The unit-vector field $\mathbf{a}$ describing fiber orientation evolves during the heart cycle. However, during isovolumetric contraction the shape of the left ventricle changes only slightly (24). Therefore, as a reasonable approximation, the vector field $\mathbf{a}$ describing fiber orientation may be considered to depend only on the chamber volume V. If the left ventricle is idealized as a thick circular cyclinder and the fibers form helices on cylindrical surfaces, the first two terms in Eq. 12 can be shown to be identically equal to zero and that sarcomere length throughout the thickness becomes approximately uniform (12). Under these conditions, left-ventricular pressure P and its time derivative $\dot{P}$ during isovolumetric contraction can be expressed in the form

$$P = P_p + P_a = P_p + C(t)P_q \qquad (14a)$$

$$\dot{P} = \dot{P}_a = \dot{C}(t)\, P_q, \qquad (14b)$$

where P_p and P_q and single valued functions of the chamber volume V, ($P_p = P_p(V)$, and $P_q = P_q(V)$, and P_a denotes the pressure term due to active fiber tension. During isovolumetric contraction, $\dot{V} = 0$.

The correlation between the functions P_p and P_q and the strength and orientation of cardiac fibers were considered recently (12). Numerical computations indicated that the assumed fiber orientation distribution of the left ventricle did not influence significantly the time-dependent pressure-volume relation. Eq. 14 is similar in form to the experimental pressure-volume relations based on the time-varying elastance (25). Various indices of cardiac contractility such as $\dot{P}/P$ and $\dot{P}/P_a$ may be given a clear meaning with the proposed constitutive equations. In the present analysis the time derivative of pressure P during isometric contraction is proportional to the time derivative of the internal variable C. Experiments on canine ventricles indicate that the durations of isovolumetric contraction and subsequent relaxation are not very sensitive to the end diastolic pressure (volume) (25). This would imply that the parameters w_c and w_r of the present formulation are not strongly length (λ) dependent at least for canine ventricles. Using Eq. 11, the variable C and its time derivative $\dot{C}$ may be written as

$$C = [1 - \cos(wt)]/2 \qquad (15a)$$

$$\dot{C} = w\,(1 - C)^{1/2} C^{1/2}, \qquad (15b)$$

where $w = w_c$. Eq. 15 is valid during the contraction phase where C increases from 0 to 1. Following relations for the indices $\dot{P}/P$ and $\dot{P}/Pa$ may be obtained by combining Eqs. 14 and 15

$$(\dot{P}/P_a) = w(P_a)^{1/2}/(P_a^* - P_a)^{1/2} \qquad (16a)$$

$$(\dot{P}/P) = w\,(P_a)^{1/2}\,(P_a^* - P_a)^{1/2}/(P), \qquad (16b)$$

where P_a^* is the peak active pressure during isometric contraction. The term $\dot{P}/wP$ is plotted in Fig. 4 as a function of P_a/P_a^*. In the cardiac literature $\dot{P}/P$ has been considered to represent the speed of shortening of muscle fibers. If Hill's three-element model were employed in the mechanical analysis of cardiac fibers, $\dot{P}/P$ would be directly proportional to U_o (25). However, the present analysis indicates that $\dot{P}/P_{max}$ is directly proportional to w and increases with decreasing end-diastolic pressure. The dependence of the contractility index $\dot{P}/P_{max}$ on the end-diastolic volume (pressure) has been investigated in patients with aortic valve disease by Mirsky et al. (26). Their results indicate a similar dependence of $\dot{P}/P_{max}$ on

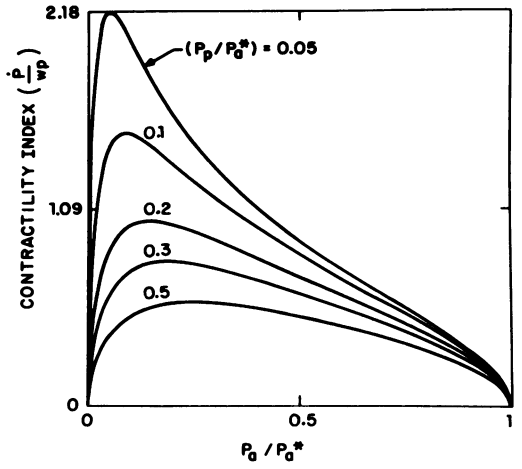

FIGURE 4 The contractility index $(\dot{P}/wP)$ as a function of relative active pressure (P_a/P_a^*) for various values of the end diastolic pressure Pp is shown.

the end diastolic pressure. Fig. 4 shows that the term $\dot{P}/wP$ is zero at zero afterload and at peak active pressure. The family of curves shown in the figure are similar to the experimental curves on mongrel dogs (27).

This analysis also shows that the contractility index $\dot{P}/P_a$ is equal to w when $P_a = P_a^*/2$. Hence, the value of $\dot{P}/P_a$ at half point is not dependent on the preload or afterload, but is an indicator of the electrochemical state of the muscle tissue. In the intact heart the contractions are not isovolumetric, and therefore it is not possible to measure P_a^*directly. An approximation to w in this case may be obtained by evaluating the term $\dot{P}/P_a$ just before the aortic valve opens. However, then the index $\dot{P}/P_a$ would depend on the afterload, namely $(\dot{P}/P_a) > w$ if $P_a < 1/2\ P_a^*$, and $(\dot{P}/P_a) < w$ if $P_a > 1/2\ P_a^*$, where P_a is the pressure when the aortic valve opens. A simpler method of assessment of w would be to measure the duration of ventricular contraction and then to use Eq. 12 to calculate w. Experiments on isolated canine hearts (29) and analysis of coupling between left ventricle and large arteries (30) indicate that cardiac contractility cannot be assessed with a single index of contractility. The rate of rise of pressure and the rate of decrease of volume in the left ventricle are approximately doubled when w is doubled, however, stroke volume and peak systolic pressure decrease only slightly with this intervention (30). Nevertheless, an accurate measure of w may be important in the assessment of cardiac contractility, because a change in w due to an inotropic intervention is usually accompanied by significant changes in T_m and m (see Eq. 10). The perturbation in the isometric length-tension curve of cardiac muscle fibers strongly influences the cardiac output for a given heart rate 25, 29, 30).

The proposed rheological model is useful in relating the experimental data on whole organ behavior of the left ventricle to the orientation and mechanical properties of cardiac fibers. Here, fiber tension is assumed to depend only on three variables: λ, U, and c. The detailed mathematical formulation depends on the kinetic model adopted for cross-bridge action as well as data on isotonic and isometric tension during partial activation. Therefore, the formulation may be revised by further developments of muscular mechanics at the cross-bridge level.

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