

Regulation of Cardiac Muscle Contractility

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ABSTRACT The heart's physiological performance, unlike that of skeletal muscle, is regulated primarily by variations in the contractile force developed by the individual myocardial fibers. In an attempt to identify the basis for the characteristic properties of myocardial contraction, the individual cardiac contractile proteins and their behavior in contractile models *in vitro* have been examined. The low shortening velocity of heart muscle appears to reflect the weak ATPase activity of cardiac myosin, but this enzymatic activity probably does not determine active state intensity. Quantification of the effects of Ca^{++} upon cardiac actomyosin supports the view that myocardial contractility can be modified by changes in the amount of calcium released during excitation-contraction coupling. Exchange of intracellular K^+ with Na^+ derived from the extracellular space also could enhance myocardial contractility directly, as highly purified cardiac actomyosin is stimulated when K^+ is replaced by an equimolar amount of Na^+ . On the other hand, cardiac glycosides and catecholamines, agents which greatly increase the contractility of the intact heart, were found to be without significant actions upon highly purified reconstituted cardiac actomyosin.

Regulation of contraction in mammalian cardiac and skeletal muscle, which have many common biochemical and morphological features, is achieved by different physiological mechanisms. Rapid trains of stimuli delivered to a skeletal muscle fiber through its motor nerve enhance tension development by causing the summation of individual contractile responses or, in its fully developed form, a powerful tetanic contraction. In the heart, on the other hand, fusion of contractile responses does not occur because the refractory period persists almost to the end of the active state. Recruitment of increasing numbers of active motor units plays a major role in augmenting the tension developed by a skeletal muscle, whereas all fibers of the heart, which is a functional syncytium, are normally activated during each cardiac systole.

The tension generated by both cardiac and skeletal muscle fibers is influenced by initial fiber length (the length-tension relationship of skeletal muscle, and Starling's law of the heart), but the relatively less compliant myocardial fiber appears to operate with shorter sarcomeres than does that

of skeletal muscle (1). The finding that the cardiac ventricle does not normally function with extended sarcomeres, a condition where increasing fiber length decreases active tension by reducing the number of sites for interaction between actin and myosin (2), may reflect the geometrical constraints upon the performance of the intact heart (3, 4). Because the heart is a hollow muscular pump in which impaired contractile performance will increase the residual volume at the end of systole, a stable equilibrium can be achieved only when dilatation improves the ability to eject. Thus, the heart cannot function chronically on the descending limb of the Starling curve (5), while it is possible for a skeletal muscle to operate at lengths greater than rest length.

The heart's hemodynamic performance in the living animal is regulated primarily by changes in myocardial contractility, the potential of the myocardial fiber to perform work at any given rest length. These variations in myocardial contractility are paralleled by marked changes in shortening velocity (6-8), whereas alterations in skeletal muscle contractility, which are much less prominent and probably without physiological significance, are accompanied by little or no change in shortening velocity (9, 10). Examination of the biochemical characteristics of the cardiac contractile proteins permits evaluation of some of the mechanisms by which the intensity of the heart's contractile process can be modulated.

INDIVIDUAL MYOFIBRILLAR PROTEINS

Three proteins, actin, myosin, and tropomyosin, comprise most of the myofibrillar protein of both cardiac and skeletal muscle. Other proteins may belong on this list, but in most cases their function and anatomical location within the sarcomere remain uncertain. One exception is the recently discovered calcium-sensitizing protein (11), which appears to play a central role in the regulation by Ca^{++} of cardiac and skeletal actomyosin. The nature of this protein remains uncertain. It could be a native form of tropomyosin (11, 12), tropomyosin complexed with an additional protein (13, 13 *a*), or an additional protein unrelated to tropomyosin (14, 15).

Actin

Comparison of actins from cardiac and skeletal muscles has revealed no differences in physiochemical properties (16), amino acid compositions (17), or the number of sulfhydryl groups (18). The influences of cations and nucleotides on sulfhydryl reactivity, which appears to provide a sensitive index of conformational changes in the G-actin monomer (19), are similar in both cardiac and skeletal actins (18). Most significant from the physiological standpoint is the ability of actin to activate myosin ATPase activity. This property is the same for cardiac and skeletal actins (20, 21).

Tropomyosin

No differences between the physiochemical properties and amino acid compositions of cardiac and skeletal tropomyosins (tropomyosin B) have been found, and there is no evidence that the heart contains significant amounts of tropomyosin A (paramyosin) (22). Mammalian skeletal tropomyosin has a dual action upon the Mg^{++} -activated reconstituted actomyosin made from skeletal muscle (23). At low ionic strengths tropomyosin stimulates the Mg^{++} -activated ATPase activity and abbreviates the clearing phase that precedes superprecipitation, whereas at high ionic strengths this protein inhibits this ATPase activity and delays superprecipitation (23). These phenomena have not been extensively studied in the case of the cardiac contractile proteins,

TABLE I
COMPARISON OF THE ATPASE ACTIVITIES OF RABBIT
RED SKELETAL, WHITE SKELETAL, AND CARDIAC MYOSINS

Cation	ATPase Activity		
	White skeletal	Red skeletal	Cardiac
	$\mu\text{mole } P_i/\text{min}/\text{mg}$	$\mu\text{mole } P_i/\text{min}/\text{mg}$	$\mu\text{mole } P_i/\text{min}/\text{mg}$
2.0 mM Mg^{++}	0.0097 \pm 0.0007*	0.0023 \pm 0.0005	0.0024 \pm 0.0004
1.0 mM Ca^{++}	0.600 \pm 0.038	0.130 \pm 0.005	0.106 \pm 0.016

Reactions were carried out at 25°C in 10 mM ATP, 0.1 M KCl, and 1.0 mM Tris acetate at pH 6.8. From Katz et al. (21).

* Standard error of the mean.

but preliminary findings indicate that cardiac tropomyosin, like its skeletal homologue, stimulates actomyosin at low ionic strengths (Katz, A. M. Unpublished observations).

Myosin

The over-all molecular dimensions of cardiac and white skeletal myosins are similar (24–26), as are several solvent-induced changes in secondary and tertiary structure (27). On the other hand, differences have been found in cysteine content (20), sensitivities to proteolytic enzymes (28, 29), immunological specificity (30, 31), and the amino acid sequence around one of the cysteine residues (32).

The lower ATPase activity of rabbit cardiac myosin, compared to that of rabbit skeletal myosin, was first reported in 1942 by Bailey (33), but the myosins examined in this pioneering study contained unknown amounts of actin, which was then an unrecognized protein. Subsequent comparisons of more highly purified rabbit skeletal myosins with myosins obtained from the hearts of larger mammals (dogs, cattle, sheep) confirmed the lower ATPase

activities of the latter. The possibility that these findings represented a species difference, rather than a true difference between cardiac and skeletal myosins, was raised by the finding that dog skeletal myosin had only slightly higher ATPase activity than dog cardiac myosin (26). However, a careful study of highly purified rabbit cardiac and skeletal myosins (20) confirmed Bailey's earlier finding. This discrepancy was resolved by the finding that the ATPase activity of rabbit red skeletal myosin was less than that of white skeletal myosin (34, 35), a conclusion suggested independently by histochemical studies of these muscle types in man (36), and by the observation that dog skeletal muscle is composed principally of red fibers. Examination of myosins purified from red skeletal, white skeletal, and cardiac muscle, all from the rabbit, revealed the ATPase activities of red skeletal and cardiac myosins to be similar to each other, but less than that of white skeletal myosin (Table I).

TABLE II
CALCIUM SENSITIVITIES OF THE INITIAL
Mg⁺⁺-ACTIVATED ATPASE ACTIVITY OF
RECONSTITUTED CARDIAC ACTOMYOSINS

Actomyosin made with	ATPase activity	
	0.1 mM CaCl ₂	0.25 mM EGTA
	$\mu\text{mole } P_i/\text{min}/\text{mg}$	$\mu\text{mole } P_i/\text{min}/\text{mg}$
Tropomyosin-free actin	0.0077	0.0066
Actin-tropomyosin complex	0.0142	0.0081

Results obtained with 0.5 mg/ml myosin and either 0.125 mg/ml tropomyosin-free actin or 0.167 mg/ml of the actin-tropomyosin complex in 1.0 mM MgATP, 0.10 M KCl, and 20 mM histidine, pH 6.8, at 25°C. The ATPase activity of the myosin alone in the presence of EGTA was 0.0039 $\mu\text{mole } P_i/\text{min}/\text{mg}$.

Comparison of the dynamic constants of red and white skeletal muscle function suggests that myosin ATPase activity may determine V_{max} , the maximal shortening velocity of the unloaded muscle. In red skeletal muscle V_{max} is approximately $\frac{1}{3}$ that of white skeletal muscle (37, 38), a ratio similar to that seen between the myosin ATPase activities of these two muscle types (21, 34). On the other hand, it is unlikely that the ATPase activity of the contractile proteins influences P_0 , the maximal force-generating ability of the muscle, because the tetanic tensions per unit of cross-sectional area of red and white skeletal muscle do not differ significantly (38).

While precise quantification of the dynamic constants of cardiac muscle function is difficult (39), both the shortening velocity and force-generating capacity of the myocardium are less than in white skeletal muscle (8). The large mitochondrial content of heart muscle (40), which significantly reduces the fraction of cross-sectional area occupied by the myofilaments, appears to be partly responsible for the low tension generated by the myocardium.

The heart's slow contraction, like that of red skeletal muscle, probably reflects, in part at least, the weak cardiac myosin ATPase activity, but the myocardium, unlike red skeletal muscle, appears to have a variable V_{\max} (8). This latter property of cardiac muscle suggests that regulation of myocardial contractility is achieved by variations in the activity of cardiac actomyosin.

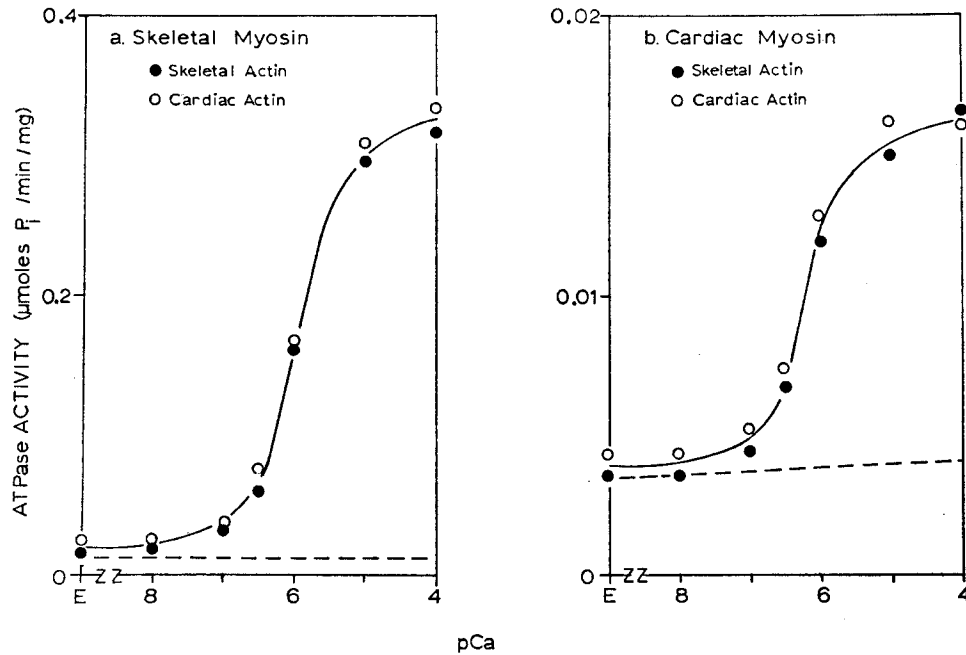


FIGURE 1. Influence of Ca^{++} on the initial Mg^{++} -activated ATPase activities of reconstituted actomyosins prepared from rabbit white skeletal myosin (a) and dog cardiac myosin (b). The myosin concentrations were 0.50 mg/ml and the concentrations of skeletal (●) and cardiac (○) actin-tropomyosin complexes were 0.167 mg/ml. All experiments were carried out at 25°C in 0.08 M KCl, 1.0 mM MgATP, and 20 mM histidine at pH 6.8. Free Ca^{++} concentration, expressed as p_{Ca} ($-\log [\text{Ca}^{++}]$), was buffered with EGTA and CaEGTA, the total EGTA concentration being 1.0 mM. The ATPase activities of the myosins alone are plotted by dashed lines. *Figure reprinted by permission of the American Heart Association, Inc., from Circulation Research, 1966, 19:1064.*

Calcium-Sensitizing Proteins

When highly purified skeletal actin and myosin are combined, the resulting actomyosin is in a state analogous to permanent activation (11, 13) in that removal of calcium by EGTA [1,2-bis(2-dicarboxyethylaminoethoxy)ethane] or other calcium-chelating agents inhibits neither superprecipitation (11) nor ATPase activity (13). Reconstituted cardiac actomyosin made from highly purified cardiac actin and cardiac myosin is similarly insensitive to calcium

removal (Table II). Calcium sensitivity can be restored to both cardiac and skeletal actomyosin by "native tropomyosin" (41), or by preparing the actin under conditions that cause a tropomyosin-containing protein complex to be extracted from the acetone-dried muscle powder along with the actin (Table II) (13, 42, 43). This protein complex, isolated by virtue of its binding to F-actin, inhibits the activation of myosin by actin at low free Ca^{++} concentrations (13). The Ca^{++} sensitivities conferred by the tropomyosin-containing protein complexes extracted from cardiac and white skeletal muscles are the same (42) (Fig. 1).

CARDIAC ACTOMYOSIN

The mechanisms responsible for the control of myocardial contractility can be studied in highly purified cardiac actomyosin systems, which preserve many

TABLE III
COMPARISON OF THE MYOCARDIAL CALCIUM UPTAKE DURING
A POSITIVE RATE STAIRCASE AND THE CALCIUM REQUIRED
TO PRODUCE A SIMILAR INCREASE IN CARDIAC
ACTOMYOSIN ATPASE ACTIVITY

Myosin content of the heart	50-80 $\mu\text{moles/kg}$ wet weight
Sensitivity of actomyosin ATPase to changing level of bound calcium	An increase of 0.3 mole calcium per mole of myosin effects a 40% increase in activity
Estimated change in total myocardial calcium needed to effect a 40% increase in actomyosin ATPase	15-24 $\mu\text{moles/kg}$ wet weight
Calcium uptake accompanying 40% contractility increase	20 $\mu\text{moles/kg}$ wet weight

features of the contractile apparatus of the intact heart. Such actomyosins can be made to superprecipitate, an *in vitro* form of contraction (44); they hydrolyze ATP, which appears to provide the immediate source of energy for muscular contraction (45); and their activity is modified by low concentrations of calcium ion in a manner that appears analogous to the physiological role of this ion in effecting excitation-contraction coupling (42, 43, 46). Because changes in myocardial contractility are paralleled by changes in V_{max} , and because a direct relationship between V_{max} and the ATPase activity of the contractile proteins probably exists (47), enhanced cardiac actomyosin ATPase activity *in vitro* might be analogous to the accelerated shortening velocity that accompanies increased contractility *in vivo*. Two ionic mechanisms that could bring about such changes in the intact heart have been identified.

Variations in the amount of calcium released during excitation-contraction

coupling would be expected to modify myocardial contractility and shortening velocity if the heart's contraction is normally limited by the availability of intracellular calcium. The latter view is supported by the finding that the cardiac sarcoplasmic reticulum, which is presumed to contain this calcium, is less extensive than that of skeletal muscle (48-50). Because the sensitivities

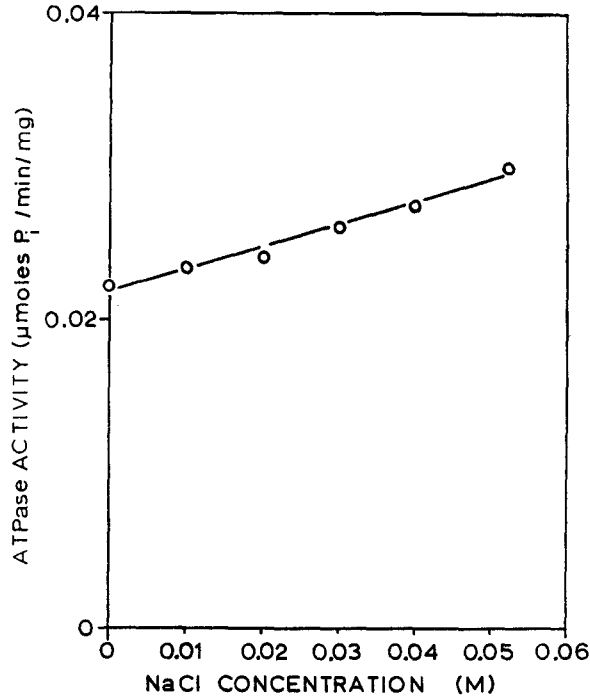


FIGURE 2. Stimulation of cardiac actomyosin ATPase activity when Na^+ is substituted for K^+ . The initial Mg^{++} -activated ATPase activity of a Ca^{++} -sensitive reconstituted cardiac actomyosin, made with 0.50 mg/ml myosin and 0.167 mg/ml of the actin-tropomyosin complex, was measured at 25°C in 1.0 mM MgATP, 0.1 mM $CaCl_2$, and 10 mM histidine buffer at pH 6.8. In each reaction the total concentration of Na^+ and K^+ was 0.08 M. *Figure reprinted by permission of the American Heart Association, Inc., from Circulation Research, 1966, 19:1066.*

of cardiac and skeletal actomyosins to changing levels of Ca^{++} are similar (42, 43, 51), these anatomical findings indicate that the heart's sarcoplasmic reticulum may normally contain less calcium than is needed to activate the cardiac actomyosin fully. If the degree of activation of the heart's contractile proteins is, in fact, limited by the availability of calcium in the sarcoplasmic reticulum, a net gain in intracellular calcium could increase contractile force. Calcium uptake has been noted during a number of inotropic interventions, for example, during the positive staircase that accompanies an increased frequency of stimulation (52-54). In the dog papillary muscle per-

fused through its arterial vessels, a 40% increase in isometric tension is accompanied by a net gain of approximately 20 μ moles of calcium per kg wet weight, which appears to be in a homogeneous, kinetically defined compartment (54). The myosin content of the ventricle is 50–80 μ moles/kg wet weight (see reference 42 for details of this calculation), and, where the sensitivity of actomyosin to changing Ca^{++} concentration is maximal (55), an increase of approximately 0.3 μ mole of calcium per mole of myosin would effect a 40%

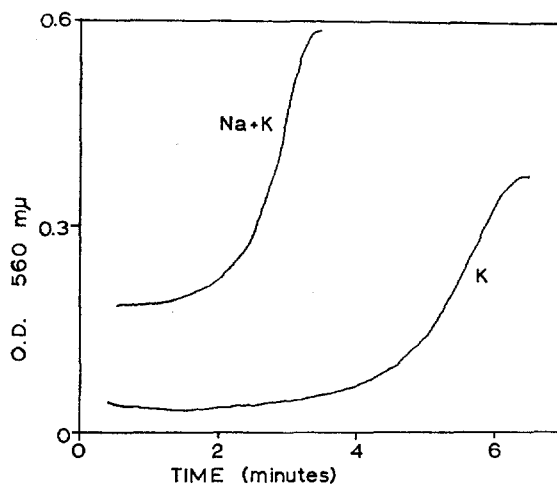


FIGURE 3. Stimulation of the superprecipitation of cardiac actomyosin when Na^+ is substituted for K^+ . The changes in absorbancy at 560 $\text{m}\mu$ of 0.667 mg/ml cardiac actomyosin, containing 0.50 mg/ml myosin and 0.167 mg/ml of the actin-tropomyosin complex, were measured in 0.080 M KCl (lower curve) and 0.045 M KCl plus 0.035 M NaCl (upper curve). Reactions were carried out at 25°C in 0.1 mM CaCl_2 , 0.33 mM MgATP, and 20 mM histidine at pH 6.8. *Figure reprinted by permission of the American Heart Association, Inc., from Circulation Research, 1966, 19:1067.*

increase in ATPase activity (Table III). The relationship between free Ca^{++} concentration and actomyosin-bound calcium has been carefully defined for white skeletal actomyosin; in the case of cardiac actomyosin, a similar distribution appears to exist (51, 55). The additional calcium needed to increase cardiac actomyosin ATPase activity by 40%, 15–24 μ moles/kg wet weight, is thus the same as that actually taken up by the heart during a comparable gain in contractility. Calculations such as these cannot establish that the observed myocardial calcium uptake provides an increased quantum of calcium to be released during the heart's contraction, thereby enhancing myocardial contractility. On the other hand, the data now available fit well with this postulated relationship.

A second ionic mechanism by which myocardial contractility could be regulated has been suggested by the observation that exchange of intracellular

K^+ with extracellular Na^+ accompanies a variety of interventions which increase myocardial contractility (56–59). The possibility that the cardiac myofibril is more active in the presence of Na^+ than K^+ is supported by the finding that both ATPase activity (Fig. 2) and superprecipitation (Fig. 3) of highly purified cardiac actomyosin are stimulated when K^+ is replaced by an equimolar amount of Na^+ (42). The relatively small effects of Na^+ - K^+ exchange on actomyosin are seen only when large quantities of Na^+ are substituted for K^+ , however, so that the physiological significance of this phenomenon remains uncertain.

The different effects of Na^+ and K^+ on cardiac actomyosin ATPase activity

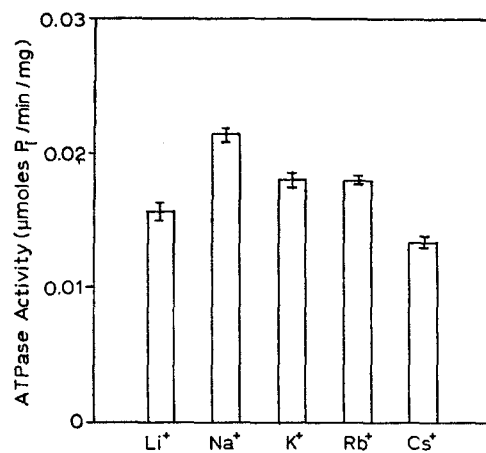


FIGURE 4. Effects of alkali metal ions on the initial Mg^{++} -activated ATPase activity of rabbit white skeletal actomyosin. Reconstituted actomyosin, consisting of 0.5 mg/ml myosin and 0.125 mg/ml tropomyosin-free actin, was studied in 0.026 M KCl, 1.0 mM MgATP, 0.1 mM $CaCl_2$, and 10 mM histidine, pH 6.8, at 25°C. Each alkali metal ion was added as the chloride to give a total (KCl + MeCl) of 0.100 M. The vertical bars represent one standard error of the mean of three determinations.

do not appear to be related to the structure-disrupting actions of higher concentrations of these cations. The higher actomyosin ATPase activity in the presence of Na^+ is the converse of the greater inhibition by Na^+ than by K^+ of the ATPase activity of myosin alone (60). Furthermore, the effects of other alkali metal ions on the Mg^{++} -activated skeletal actomyosin ATPase activity (Fig. 4) do not parallel their abilities to perturb the secondary and tertiary structures of proteins (61). It is thus more likely that these ions act at a specific site on the actomyosin complex, perhaps by competing for Ca^{++} (55).

During the past 20 years many attempts have been made to demonstrate an action of inotropic drugs upon the heart's contractile proteins. The results of most of these studies have been negative, but occasional positive results have been reported (see reference 62 for a review of some of this literature). We have found no effects of either cardiac glycosides (62) or norepinephrine (63)

upon the highly purified, calcium-sensitive, reconstituted actomyosin. While these negative findings do not exclude such a direct action of these drugs, they are in accord with physiological evidence suggesting that these agents act indirectly upon the contractile proteins. Most significant is the finding that, after maximal contractility is achieved by any of a number of agents or ionic manipulations, additional inotropic interventions of a different class bring about no further enhancement of myocardial contractility (64).

Miss Doris I. Repke, Miss Barbara R. Cohen, Mrs. Kathleen D. Clarke, Mrs. Bonnie B. Rubin, and Miss Anne Sanders participated in these studies.

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Discussion

Dr. Sandow: I think, Dr. Katz, that you have short-changed skeletal muscle in stating that it has little capacity for having its contractility altered. It depends on what you do with it. For example, the zinc ion, which has a depressive effect on heart muscle, can greatly prolong the active state of skeletal muscle and so cause it to produce a much bigger twitch output.

Now, this difference between heart and skeletal muscle raises some questions as to mechanism. The available evidence indicates that this is fundamentally a problem involving difference in membrane function, which, though very interesting, will not be discussed further since our interest here is essentially in the contractile process.

Dr. Katz: I certainly agree. I am aware of these findings, but I didn't mention them because they are probably of little physiological importance. My main point is that changes in cardiac muscle contractility, unlike those which occur in skeletal muscle, are paralleled by changes in V_{\max} . This strongly suggests that these functionally important variations in myocardial contractility are due to changes in the extent of activation of the heart's contractile proteins.