A Dominant Role of Cardiac Molecular Motors in the Intrinsic Regulation of Ventricular Ejection and Relaxation

Molecular motors housed in myosins of the thick filament react with thin-filament actins and promote force and shortening in the sarcomeres. However, other actions of these motors sustain sarcomeric activation by cooperative feedback mechanisms in which the actin-myosin interaction promotes thin-filament activation. Mechanical feedback also affects the actin-myosin interaction. We discuss current concepts of how these relatively under-appreciated actions of molecular motors are responsible for modulation of the ejection time and isovolumic relaxation in the beating heart.

In this review, we consider novel and, in our judgment, under-appreciated aspects of the role of sarcomeric myosin motors (cross bridges) in regulation of the heart beat. Relatively recent and compelling evidence has substantially expanded the limited textbook view of the role of cross bridges in the heart beat and in regulation of contractility. One aspect of this textbook view is that cross bridges react with actin and undergo state transitions powered by the free energy of MgATP hydrolysis that lead to a mechanical transition impelling thin filaments toward the center of the sarcomere. A second textbook view is that the actin cross-bridge reaction is inhibited at diastolic levels of sarcoplasmic Ca\(^{2+}\) and released from this inhibition when Ca\(^{2+}\) concentration increases in the sarcomeric space and Ca\(^{2+}\) binds to troponin C (cTnC). In basal metabolic states, not all available cross bridges are engaged in the actin-myosin interaction, and thus a third textbook view is that major control of contractility occurs with variations in the number of cross bridges engaged in the force-generating reaction with thin filaments. In this perspective, the level of contractility is governed largely by the amounts and rates of movements of Ca\(^{2+}\) to and from the sarcomeres.

Our expanded view of the role of the molecular motors in the heart beat includes processes intrinsic to the sarcomeres that are significant in sustaining myocardial stiffness during ejection and determining the rate of isovolumic relaxation. We discuss evidence indicating that these cooperative and mechanical feedback mechanisms are intrinsic to the sarcomeres and do not directly depend on membrane-controlled fluxes of Ca\(^{2+}\). We think this perspective of regulation of systolic mechanics and relaxation reorients thinking with regard to regulation of cardiac function from a focus on cellular Ca\(^{2+}\) fluxes to a focus on regulation of processes at the level of the sarcomeres. Central to these regulatory processes is a role of cardiac molecular motors beyond simple promotion of force generation and shortening. It is now evident that, following the triggering of activation by Ca\(^{2+}\) binding to cTnC, molecular motors are actively engaged in inducing and sustaining activation of the thin filaments. Moreover, the strain on active cross bridges, which occurs during ejection, and the rates of detachment of cross bridges are also important elements in determining the duration of systole and the rate of isovolumic relaxation. We discuss evidence that the kinetics of these sarcomeric processes are rate limiting during the cardiac cycle and modified by phosphorylation of regulatory proteins, especially cardiac myosin binding protein C (MyBP-C) and the thin-filament regulatory protein cardiac troponin I (cTnI). Finally, discussion is provided regarding evidence that the kinetics of molecular motors by drugs targeted to myosin represents a novel therapeutic approach in treatment of heart failure.

Structure and Regulation of Cardiac Molecular Motor Activity

The molecular motor of heart muscle is a highly asymmetrical protein consisting of two myosin heavy chains (MHCs) (FIGURE 1) and two pairs of myosin light chains (FIGURE 1 illustrates one MHC). The MHC has a globular head, containing both the actin binding site and the ATP binding and catalyzing site at the NH\(_2\) terminus of the protein. An \(\alpha\)-helical COOH-terminal tail interacts with another MHC in a coiled-coil motif that combines with rod portions of neighboring myosins to form the thick-filament backbone. There are two types of MHC expressed in mammalian myocardium, \(\alpha\)-MHC and \(\beta\)-MHC, existing as dimers first described by Hoh et al. (16) and termed \(V_1\), \(V_2\), and \(V_3\). \(\alpha\)-MHC generates about three times higher actin-activated ATPase activities, maximal filament
sliding velocity, and greater peak power output than those preparations containing β-MHC (4, 5, 13, 35, 37, 41, 47, 66, 67). β-MHC, however, has been reported to produce twice the cross-bridge force per ATPase cycle as α-MHC, meaning it consumes less energy to maintain a given force or a lower tension cost (12, 17, 31, 50, 58). Expression of these isoforms is species dependent and both developmentally and hormonally regulated (33) with V3 myosin, a ββ-MHC homodimer predominately expressed during early development of all mammals and remaining high throughout life in humans and other large mammals. The V1 cardiac myosin, a αα-MHC homodimer, predominates in mammalian hearts soon after birth and remains high throughout life in rats and mice (11).

The α-helical tail region MHC interacts noncovalently with the light chains, consisting of one regulatory light chain (RLC) and one essential light chain (ELC). The light chains are located toward the neck region of S1 and help to stabilize the neck and may confer some regulation of functional activity (65), such as increasing Ca²⁺ sensitivity of force (56) and the rate of force development (59) (see Ref. 9 for a review). The thick filament also contains MyBP-C (FIGURE 1). It has been postulated that the presence of MyBP-C can alter Ca²⁺-sensitivity of force (28), rates of force development, and power output (27). These functional effects have been proposed to involve the interactions between the lever arm of MHC and MyBP-C, thereby constraining movements of the myosin head and affecting the probability of binding to actin (FIGURE 1).

Thick- and Thin-Filament States in the Cardiac Cycle

As depicted in FIGURE 1, myosin cross bridges cyclically interact with actin in a process coupled to the hydrolysis of ATP, which drives myocardial force generation and contraction. Cross bridges are initially in a weakly bound, non-force-generating “rest” state (state 1, FIGURE 1) during diastole. FIGURE 1 shows a thin-filament regulatory unit (RU) consisting of actin-troponin-tropomyosin in a 7:1:1 ratio. Troponin (Tn) is a hetero-trimer consisting of cTnC, cTnI, and cTnT. In the rest state, there is no Ca²⁺ bound to regulatory sites on cTnC; cTnI forms a complex with both actin and cTnT and thus reduces the reactivity of actin for myosin and holds tropomyosin in a position that blocks the cross-bridge binding sites on actin (30, 68).

The triggering of force generation and contraction is governed by Ca²⁺ fluxes determined by the dynamics of electrochemical coupling of Ca²⁺ release and Ca²⁺ binding to cTnC. Cross bridges and thin filaments now enter into a transition state (state 2; FIGURE 1)
determined by the on \((k_{on})\) and off rates \((k_{off})\) for \(Ca^{2+}\) exchange with cTnC. This “transition” state involves altered interactions between TnI and actin, increased binding of cTnI to cTnC, and a cTnT-dependent shift in Tm from its blocking position on the thin filament. These changes in the thin filament permit a shift in cross bridges toward strongly bound, force-generating states (state 3; FIGURE 1). The transition state is homologous to other cross-bridge models whereby a myosin head has a full compliment of ATP hydrolysis products (ADP and P) bound and \(Ca^{2+}\) bound at the thin filament. The state 2-to-state 3 transition (FIGURE 1; \(k_{on}\) and \(k_{off}\)) from weak-binding, non-force-generating cross bridges to strong-binding, force-generating states is regulated by the kinetics inherent to cross bridges. The rate-limiting kinetic transition determining the shift toward the “active” state appears to be dependent on the load on the muscle (18) with loads near peak power output (similar to those encountered during ejection) determined by the release of P (15) and loads more near isometric (such as occur during isovolumic contraction and relaxation) determined by ADP release (69). An important aspect of state 3 is that strongly bound cross bridges also induce cooperative activation of the thin filament by an increase in the affinity of cTnC for \(Ca^{2+}\) (10, 29, 43). In addition to this cooperative process within an RU, there is also a cooperative activation of neighboring RU transmitted through end-to-end interactions between contiguous Tm strands and possibly through actin-actin interactions (as reviewed in Refs. 9, 40, 63). This mechanism of propagated activation appears to be particularly important in cardiac compared with skeletal muscle, where relatively small changes in strongly bound cross bridges have significant effects on \(Ca^{2+}\) sensitivity of force and cross-bridge kinetics (6, 7).

A consequence of these cooperative mechanisms is illustrated by state 4 in FIGURE 1, which indicates a population of cross bridges that remain in the active, force-generating state despite the loss of bound \(Ca^{2+}\). As discussed below, the lifetime of state 4 is an important determinant of the duration of ejection. Inasmuch as the kinetic transition between states 3 and 4 (and state 2 to 3 to some extent) is dependent on cross-bridge feedback, mechanisms that alter the number of active cross bridges will alter this transition. Processes that may potentially modify the number of active cross bridges include the sarcomere length, as determined by the end-diastolic volume, the strength of the interaction energies determining cooperativity within and between RU, and stretch-induced activation (54). Mechanical feedback associated with sarcomere shortening also controls the transition from the strong binding state 4 to the weak binding state 1, thereby determining the duration of state 4. The mechanical feedback, which is indicated as a unidirectional rate constant \((k_{val})\) in FIGURE 1, occurs as a result of strain imposed on active cross bridges with shortening, a process known as shortening-induced deactivation (20, 36, 39). Thus the balance of the intensity of the cooperative mechanisms, which promote the transition to state 4, and the mechanical feedback, which promotes dissipation of state 4, determine the population of cross bridges in state 4. Therefore, these mechanisms are likely to be important determinants of the time to the end of systole.

Another more controversial possibility to increase cross-bridge availability permitting feedback would be to allow individual cross bridges to interact with the thin filament multiple times during activation. The cross-bridge cycle described by FIGURE 1 assumes cross bridges driving cardiac pump function are tightly coupled to ATP hydrolysis (i.e., one ATP per cross-bridge cycle). However, questions remain as to the validity of this assertion. Evidence for a more loosely coupled system comes from observations by the Yanagida laboratory (23) and Lombardi et al. (32) that a single cross bridge can move actin many times the length of a single cross-bridge swing on an individual ATP and that cross bridges can reprimed following a power stroke without binding additional ATP, respectively. In agreement, based on experimental data concerning length-tension area (analogous to pressure-volume area) vs. oxygen consumption, Taylor et al. (62) concluded the cross-bridge-to-ATP ratio may be variable with tightly coupled usage at high loads becoming more loosely coupled at low loads where muscle may shorten (reviewed in Ref. 57).

**A Dominant Role of Processes Involving Cardiac Molecular Motors in Left Ventricular Ejection and Isovolumic Relaxation**

Ultimately, the reactions of molecular motors in the left ventricle (FIGURE 1) are responsible for the ejection of blood into the peripheral circulation. During a beat of the left ventricle, pressure rises for a time with no change in ventricular volume and limited internal shortening of the sarcomeres. During this phase, cross bridges are recruited into action as \(Ca^{2+}\) rises in the sarcomeric space. When the aortic valve opens, ejection begins and the sarcomeres shorten. In this phase, cross bridges impel the thin filaments toward the center of the sarcomere. Shortening imposes a strain on reacting cross bridges and alters the kinetics of the actin-myosin reaction. As systole progresses and blood flows to the periphery, left ventricle pressure falls, the valve closes, pressure falls with no change in ventricular volume, and the strain dependence of actin cross-bridge kinetics is greatly relieved. Unfortunately, much of our understanding of the cellular mechanisms governing these processes (such as the dynamics of excitation contraction coupling and relaxation) is based on determinations of intracellular \(Ca^{2+}\) and mechanics with myocytes shortening against zero loads or not
shortening at all. In the following, we expand governance of these processes to include prominent, intrinsic sarcomeric regulation of these processes and alterations occurring with changes in load.

**Differences in kinetics of sarcomeric-bound Ca\(^{2+}\) and pressure during a heart beat**

A major challenge in the investigation of molecular control mechanisms in regulation of the heart beat is how to connect the action of the cardiac molecular motors to global ventricular function. These actions include state transitions leading to development of force and shortening, promotion of the activated state of thin filaments, response to the prevailing pre-load and afterload, and the relative amounts of Ca\(^{2+}\)-bound to cTnC (related to contractility) that ensures efficient ejection of the blood added to the ventricle during diastole. **FIGURE 2** depicts the time course of Ca\(^{2+}\) bound to cTnC in a region of the A band of sarcomeres at various time points during pressure changes during a beat of the left ventricle. The figure illustrates our perception of the state of the A-band region at various time points during the beat. Estimation of Ca\(^{2+}\) binding to the thin filaments is based on a computational model of Burkoff (2), which is in general agreement with experimental findings (60) and other models of transitions in thin-filament RUs during left ventricular pressure development in a beat of the heart (29). These models are driven by experimental determinations of the transient change in Ca\(^{2+}\) (29, 44) and by determinations of kinetics and steady-state binding of Ca\(^{2+}\) to Tn in myofilaments (43, 49). The estimate is
also based on studies by Peterson et al. (44), who applied a mechanical assay to determine the time course of the amounts of Ca\(^{2+}\) bound to cTnC, and by Ishikawa et al. (19), who used a quick-release protocol and intracellular aequorin to determine cTnC-bound Ca\(^{2+}\). These studies both demonstrated that the fall in thin-filament-bound Ca\(^{2+}\) precedes the fall in force in an isometric twitch of heart muscle.

A significant outcome of these measurements and models is that they indicate that, during a “heartbeat,” the time course of Ca\(^{2+}\) bound to the thin-filament cTnC is nearly over at a time when ejection is ongoing and isovolumic relaxation has not yet begun. We interpret this difference in time course of thin-filament Ca\(^{2+}\) binding and pressure to mean that much of ejection and relaxation of the ventricle depends on molecular processes intrinsic to the sarcomere. These intrinsic molecular processes involve the following significant actions of the cardiac molecular motors: 1) activation of the thin filaments by cooperative mechanisms sustaining thin-filament activation despite a fall in thin-filament-bound Ca\(^{2+}\), 2) sensing the sarcomere length (preload) in a mechanism explaining the Frank-Starling law, 3) sensing the load in a mechanism related to the inverse relationship between force and velocity, and 4) relaxation kinetics related to rates of cross-bridge detachment and intersarcomere dynamics [as described by Stehle et al. (46)].

**Processes intrinsic to the sarcomere control systolic mechanics and relaxation**

Consideration of the change in the state of the A-band sarcomeric proteins during the transition from diastole to systole and the return to diastole during a heart beat serves to describe the interplay between control mechanisms extrinsic (such as membrane-dependent regulation of Ca\(^{2+}\) fluxes) and mechanisms intrinsic to the sarcomere. In the diastolic state, cross bridges are either blocked from reacting with actin or in a weak, non-force-generating state (FIGURE 1). The molecular motors of the heart are not completely passive in diastole in that they are likely to sense the preload. There is evidence that the state of stretch of the myocardium at the end of diastole is transmitted to the cross bridges by titin, which is responsible for the passive force of the myocyte (8). Pre-load determines the strain on titin, and it is plausible (although not fully documented) that the net effect of the longitudinal and radial strain on titin alters interfilament spacing or provides a signal acting through a titin-MyBP-C-cross-bridge interaction by which the molecular motors sense sarcomere length (8). In general, it has been thought that the motors sense sarcomere length via a length-dependent change in interfilament spacing, which in effect alters the local concentration of cross bridges at the actin binding sites and thereby alters the myofilament response to Ca\(^{2+}\) (25, 26, 38). This “length-dependent activation” of the sarcomeres provides the cellular mechanism for the Frank-Starling law. Yet the theory that length dependence of activation is well correlated with changes in interfilament spacing has not stood the test of direct determination of the interfilament spacing by X-ray diffraction (25, 26).

With release of Ca\(^{2+}\) into the sarcomeric space, Ca\(^{2+}\) binds to cTnC, and systole begins. The transient change of intracellular Ca\(^{2+}\) in the sarcomeric space, as detected by intracellular fluorescent probes, demonstrates only ~2% of the total cellular Ca\(^{2+}\) that moves from the extracellular space and sarcoplasmic reticulum (SR) and back during a heart beat (52). Thus the bulk of these Ca\(^{2+}\) ions is bound to buffers including TnC and other regulatory Ca\(^{2+}\)-binding proteins such as calmodulin (64). With the rise in cTnC-bound Ca\(^{2+}\), which is shown in FIGURE 2, cross bridges make the transition from the blocked or weak binding state to a strong force-generating state. A reasonable estimate is that ~20–25% of available cross bridges are recruited into the systolic state during resting levels of cardiac output (24). The reactions of these cross bridges generate the wall tension responsible for the rising phase of left ventricular pressure; shortening is limited until sufficient pressure is generated to open the aortic valve.

Removal of Ca\(^{2+}\) from the sarcoplasm by the SR pump and the Na\(^{+}\)/Ca\(^{2+}\) exchanger sets into motion a process whereby Ca\(^{2+}\) is released from cTnC, and this is in part responsible for the decay in Ca\(^{2+}\) bound to the thin filaments. However, as illustrated in FIGURE 2, this fall in thin-filament Ca\(^{2+}\) binding precedes the fall in left ventricular pressure, thus indicating that the actin cross-bridge reactions are sustained even in the face of a decline in Ca\(^{2+}\)-dependent activation. Moreover, at the time the aortic valve opens, cooperative mechanisms in which thin filament RUs remain active without Ca\(^{2+}\) bound sustain ejection (FIGURE 2). Computational models indicate that this state occurs by cooperative mechanisms within an RU in which cross-bridge binding to the thin filament increases the affinity of cTnC for Ca\(^{2+}\) (step 4 in FIGURE 1) and by near-neighbor cooperative mechanisms acting longitudinally along the thin filament (9, 48). As ejection proceeds against the afterload, cross bridges enter into a new state in which the strain imposed by shortening promotes release of ADP from the cross bridges, an increase in ATP turnover, and an increase in cross-bridge detachment rate. The effect of
strain on cross bridges is well accepted to affect nucleotide binding. For example, in slow skeletal muscle, ADP release is sensitive to the load; the lighter the load, the greater the shortening velocity, the faster the release of ADP, and the faster the ATP turnover (51). This strain dependence of cross-bridge kinetics is the basis for the Fenn effect. This “mechanical feedback” thus promotes the transition of cross bridges from strong to weak binding states (step 4 in FIGURE 1) and lowers the affinity of cTnC for Ca$^{2+}$. As a result, rate of loss of bound Ca$^{2+}$ is enhanced. Thus systolic mechanics reflect a balance between cooperative activation of thin filaments and shortening-induced deactivation (29). It is evident that the dissipation of the cooperative activation is relatively slow. In shortening from a long to a short length, Chandra and Campbell (3) suggest that the sarcomeres “remember the higher force attained at the longer length” and shortening (ejection) is prolonged in comparison to the situation with no cooperative mechanisms. The kinetics of the cross-bridge cycle and the relative time the cross bridges are strongly bound, especially the rate of detachment of cross bridges, is also an important determinant of the time in ejection and the isovolumic relaxation rate.

Mechanisms at the level of the sarcomere that affect relaxation include the dissipation of the cooperative activation of the thin filament and forward detachment of cross bridges as ATP binding to cross bridges reestablishes the actin-myosin-ADP-P$_i$ weak binding state (state 1 in FIGURE 1). A third mechanism is a strain-dependent reversal of the power stroke transition from the actin-myosin-ADP state to the actin-myosin-ADP-P$_i$ state (a transition from state 3 to state 2, as illustrated in FIGURE 1). In the case of myofibril preparations, relaxation is accelerated by small stretches and by increased P$_i$ concentration (46). These common effects have been interpreted by Poggesi et al. (46) to indicate that, in relaxation, both P$_i$ binding to cross bridges and altered cross-bridge strain during relaxation may result in reversal of the power stroke. If a significant number of the cross bridges undergo this reversal of the power stroke, then a significant potential outcome is that weak binding cross bridges are reestablished without splitting ATP and ready to engage in the cross-bridge cycle in the next beat.

Direct tests of the relative significance of processes extrinsic to the sarcomere (Ca$^{2+}$ uptake by the SR) and these processes intrinsic to the sarcomere indicate that the intrinsic processes can be rate limiting. For example, in the experiments of Peterson et al. (44), the derivative curve of bound Ca$^{2+}$ fell to low levels, whereas force remained high during the onset of relaxation in an isometric twitch. This result indicates that factors other than the velocity of SR Ca$^{2+}$ uptake are rate limiting in loaded ejections with shortening. Sys and Brutsaert (60) reached the same conclusion using a different experimental approach. On the other hand, when Peterson et al. (44) used ryanodine to slow Ca$^{2+}$ uptake by SR, the fall in force and cTnC-bound Ca$^{2+}$ occurred in parallel. Thus, when SR Ca$^{2+}$ uptake is slowed down as in heart failure (45), the role of processes intrinsic to the sarcomere becomes relatively blunted.

**Control of Cardiac Molecular Motors by Modulation of Thick- and Thin-Filament Regulatory Proteins**

Phosphorylation of thin- and thick-filament regulatory proteins that modulate the actin-cross-bridge reaction also affect duration of ejection and relaxation. Although multiple sarcomeric proteins are modified by phosphorylation (reviewed in Refs. 24, 53), we focus here on MyBP-C and cTnI inasmuch as the state of these proteins has been reported to affect systolic mechanics. Both proteins are phosphorylated by protein kinase A at sites unique to the cardiac variants. In the case of MyBP-C, compared with controls, mouse hearts lacking cMyBP-C demonstrate a significantly abbreviated time course of systolic elastance (42). There is little change in the early phase of systole, but hearts lacking MyBP-C relax prematurely. Sarcomeres lacking MyBP-C also have faster unloaded shortening velocity than controls (42). Importantly, PKA-dependent phosphorylation of MyBP-C, which occurs at a site that interacts with myosin S2, mimics the effects of its ablation (55). Thus it is apparent and likely that the state of MyBP-C modifies the transmission of force across the sarcomere as well as shortening-induced deactivation. This finding may be of significance regarding the pathology of mutations in MyBP-C, which are a common cause of familial cardiomyopathy (1).

Among Tnl variants, cTnI is unique in having an NH$_2$-terminal extension of 30 amino acids that contain PKA-dependent phosphorylation sites. Phosphorylation of these sites appears pivotal in the positive inotropic response to β-adrenergic stimulation (22) and to changes in frequency (61). However, the demonstration of both of these effects is most evident in auxotonically loaded, ejecting hearts and much less evident in isovolumic hearts, isometric muscle preparations, or unloaded isolated myocytes. The increases in ejection indexes, such as stroke work and the end-systolic pressure-volume relation, are significantly blunted in hearts expressing slow skeletal Tnl (which lacks the PKA sites) in place of cTnl (22). However, myocytes from these hearts or isovolumic hearts demonstrated nearly the same inotropic responses to β-adrenergic stimulation as the controls. Phosphorylation of cTnl has also been reported to increase unloaded shortening velocity and power generation by isolated, skinned cardiac myocytes (14) and to enhance the effect of sarcomere length on force-Ca$^{2+}$ relation (26). Taken together, these results indi-
cinate a significant involvement of the cTnI phosphorylation in cardiac systolic mechanics and relaxation in response to β-adrenergic stimulation by its effects on the cooperative activation and mechanical feedback.

Hearts of transgenic mice (TG-cTnIDD) expressing cTnI, in which the PKA-targeted Ser are mutated to Asp as a phosphorylation mimetic, also show responses to increases in frequency, indicating an effect of cTnI phosphorylation on rate-dependent increases in systolic function (61). Moreover, there was a prolonged relaxation associated with increased afterload in nontransgenic control hearts beating in situ when compared to the TG-cTn-IDD hearts. This difference was not evident when the hearts were treated with isoproterenol. As with the studies on the TG-ssTnI hearts, frequency-dependent responses in isometric trabeculae from the TG-cTnIDD hearts did not demonstrate differences from controls (61). These studies reinforce the role of cTnI phosphorylation on systolic function and relaxation kinetics and also indicate that the mechanism is revealed when cross bridges function against a load as in the ejecting ventricles. It has been reported that there is a diminished TnI phosphorylation in that, which is likely to be an important mechanism in the blunted force-frequency relation of failing human hearts.

**Novel Pharmaceutical Therapies Targeting Molecular Motors**

Translation of the detailed understanding of sarcomeric regulation to therapeutics is an important research objective, and there is evidence that pharmacological modification of molecular motors may be useful as a therapeutic approach for heart failure. One aim has been the discovery of small molecules that directly modify sarcomeric proteins and improve cardiac function. Early phases of the search for such compounds that enhance myofilament sensitivity to Ca²⁺ targeted thin-filament proteins. Examples of these agents are levosimendan and EMD 57033, which bind to cTnC, and pimobendan, which promotes Ca²⁺ binding to cTnC. These agents improve systolic function in animal models of heart failure (as reviewed in Ref. 21), and levosimendan and pimobendan have progressed into clinical use. More recently, there has been a search for agents directly affecting the molecular motors of the heart. Although further studies are required to establish the value of these agents in human therapeutic application, the initial data are promising (34). It is apparent that modification of the myosin by these agents prolongs systolic ejection. This indicates that these agents alter the balance of cooperative mechanisms and shortening induced deactivation such that systolic mechanics are enhanced. Whether modification of troponin and/or MyBP-C by drugs may also affect this balance appears possible but has not been investigated explicitly.

**References**


