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Mechanoelectrical Interactions and Their Role in Electrical Function of the Heart

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Integrated Cardiac Electromechanics

Introduction

The heart is an electrically controlled and chemically powered mechanical pump. There are complex interactions between cardiac electrophysiology, metabolism, and mechanics, with a multitude of interdigitating regulatory loops. This chapter will focus on the *cross-talk* between electrical and mechanical activity of the heart, and in particular its relevance for heart rhythm.

The cross-talk between cardiac electrics and mechanics can be viewed conceptually as a regulatory loop (Figure 7–1). In this loop, electrical control of cardiac contraction is afforded by excitation–contraction coupling (ECC)* while, in turn, the mechanical environment affects cardiac electrical activity via mechanoelectric feedback (MEF). This regulatory loop manifests itself at every level of structural integration, from whole heart to single cell. It supports the maintenance of steady-state cardiac performance, ensures adaptation to changing circulatory demands (even in the transplanted heart), and can contribute to both causation and termination of heart rhythm disturbances.[1]

Spatiotemporal Considerations

The heart is a spatially heterogeneous organ, both in terms of structure (e.g., variations in regional tissue architecture, cell distribution, coupling, innervation, blood supply) and function (active and passive tissue electromechanical properties). In addition, there are temporal gradients in key electromechanical behavior (e.g., activation, repolarization, shortening). Nonetheless, under physiological conditions the heart functions as a highly coordinated unit. This "externally homogeneous" mechanical performance at the organ level arises from, and necessarily requires, structural and functional heterogeneity at the (sub)cellular and tissue levels.[2]

While this appreciation has guided our thinking on structural and functional adaptation of the heart to (patho)physiological developments, it leaves the question as to how an individual cardiomyocyte inside this complex organization "knows" when and how to respond to beat-by-beat changes in electromechanical activity. The *when* is largely a function of the coordinated spread of electrical excitation (see Chapter 4 for details on the cardiac conduction system). The *how* requires subcellular regulatory pathways that match local mechanical performance to global mechanical demand; underlying processes are discussed next.

*Abbreviations: AP, action potential; ATP, adenosine triphosphate; $[Ca]_I$, free cytosolic Ca concentration; ECC, excitation–contraction coupling; ILCOR, International Liaison Committee on Resuscitation; LCC, L-type Ca channel; MEF, mechanoelectric feedback; NCX, Na/Ca exchanger; PT, precordial thump; RyR, ryanodine receptor; SAC, SAC_{NS}, SAC_K, stretch-activated channels of various ion selectivity; SERCA, sarcoplamsic/endoplasmic reticulum Ca^{2+}-ATPase; SL, sarcomere length; SR, sarcoplasmic reticulum; TnC, TnI, TnT, troponin C, troponin I, troponin T; VT,ventricular tachycardia; VF, ventricular fibrillation.

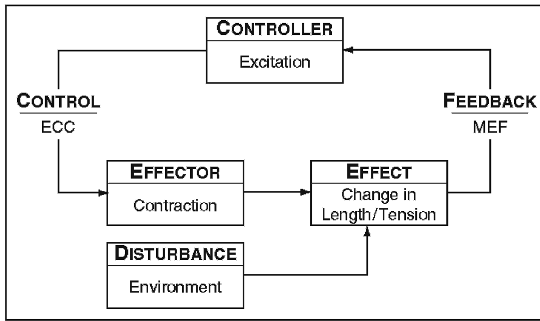

FIGURE 7–1. Conceptual scheme of cardiac electromechanical regulation. Electrical control of cardiac contraction is via excitation–contraction coupling (ECC), while the mechanical environment affects cardiac electrical behavior via mechanoelectric feedback (MEF). (From Kohl *et al.*,[1] with permission.)

Excitation–Contraction Coupling

Introduction

The process of ECC involves a transient rise in free cytosolic calcium concentration ($[Ca]_i$), as the intermediate signal between electrical depolarization of the cell membrane and activation of contractile myofilaments. The sequence is initiated by calcium (Ca) influx across the sarcolemma, which produces a secondary release of Ca from the sarcoplasmic reticulum (SR, a specialized Ca storage compartment in mammalian cardiac myocytes). The SR can rapidly release Ca in response to sarcolemmal Ca influx, a process termed "Ca-induced Ca release." The released Ca then binds to several intracellular Ca-binding proteins, including troponin, which in turn activates the myofilaments. The majority of Ca is resequestered back into the SR during each heartbeat, while the remainder (in steady state this is an amount equivalent to the initial transsarcolemmal influx) is extruded across the membrane.

In reality, the events involved in ECC are intimately connected and cannot be decomposed into discrete sets of spatially or temporally defined events. For example, SR Ca release occurs simultaneously with reuptake, with the net effect depending on the relative balance of the competing processes at any given time. Also, SR Ca storage involves "memory" mechanisms that render the amount of Ca stored in, and released from, the SR strongly dependent on stimulation history. Thus, the system shows complex behavior within single beats and between multiple beats. The following sections outline separate steps in the activation and relaxation sequence of cardiac muscle. However, care must be taken to remember that this decomposition into discrete steps is highly artificial and underestimates the complex dynamics of ECC.[3,4]

From Action Potential to Calcium Release

Figure 7–2 shows a conceptual model of Ca handling during a typical heartbeat. The trigger events (Figure 7–2A) involve sarcolemmal influx of Ca through L-type Ca channels (LCC; thick downward arrow), which produces a secondary and larger release of Ca from the SR (upward thick arrow), released via ryanodine receptors (RyR) into the diadic space (dotted box labeled DS). An important negative feedback pathway exists in that the released Ca, as well as LCC influx itself, causes Ca-induced inactivation of LCC, which reduces further influx (upward thin arrow with a "minus" sign). From the diadic space, Ca diffuses into the myoplasm (thick rightward arrow) to increase $[Ca]_i$ from approximately 0.1 µM to 1 µM (represented by the schematic Ca transient). The majority of this released Ca binds to intracellular buffers, including troponin and calmodulin (not shown). Ca can also enter the cell during the action potential (AP) upstroke and "notch" (rapid partial repolarization to plateau levels) via the Na/Ca exchanger (NCX), although this pathway is considered less important for ECC than Ca influx via LCC.

L-Type Ca Channel Influx

The LCC is the major influx pathway for Ca during each heartbeat. This current has multiple roles in producing the Ca transient, both by directly increasing $[Ca]_i$ and by triggering a larger secondary Ca release from the SR. Moreover this current contributes to AP morphology, especially in sustaining the AP plateau in spite of repolarizing K currents (see Chapters 13 and 14). LCC are activated by voltage and inactivated by both voltage and Ca.[5]

The Ca-induced inactivation is thought to play a primary role in determining the amplitude and

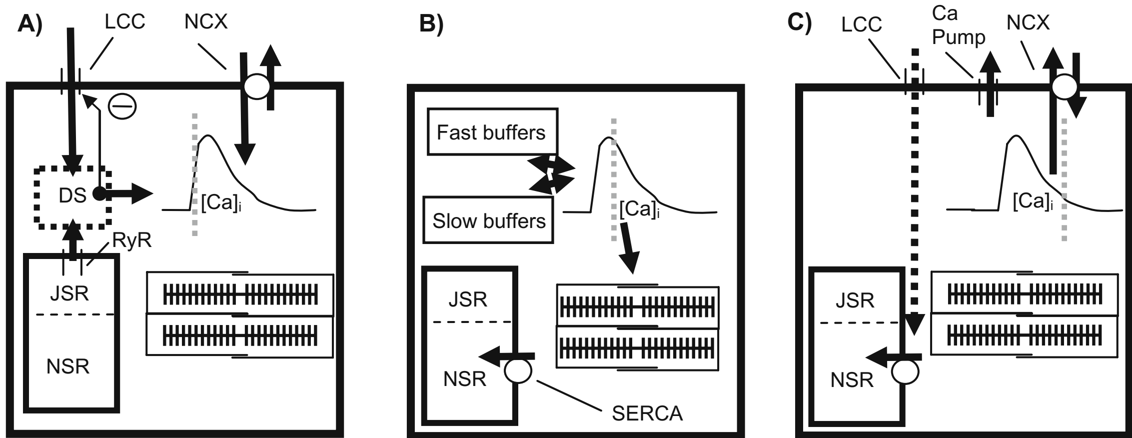

FIGURE 7–2. Schematic diagram of a cardiac cell, showing three conceptual steps in excitation–contraction coupling (ECC), with pseudorepresentative timing relative to cytosolic free Ca concentration ($[Ca]_i$) dynamics indicated by gray dotted lines. (A) Ca-induced Ca release; (B) cytosolic Ca buffering and contraction changes; (C) Ca reuptake and extrusion (for detail see text). DS, dyadic space; JSR, junctional sarcoplasmic reticulum; LCC, L-type Ca channel; NCX, Na/Ca exchanger; NSR, network sarcoplasmic reticulum; RyR, ryanodine receptor; SERCA, sarcoplasmic/endoplasmatic reticulum Ca-ATPase.

time course of LCC currents.[5,6] One potential role of this negative feedback (Figure 7–2A, thin arrow) is to limit Ca influx after triggering Ca-induced Ca release. However, longer-term roles in Ca homeostasis of both intracellular and SR Ca levels are also proposed.[4] Interestingly, LLC are generally assumed to sense diadic space Ca levels, determined largely by SR Ca release; this has a shorter latency, higher amplitude, and smaller overall duration than the cytosolic $[Ca]_i$ transient.[7] In contrast, Ca-induced LCC inactivation is generally seen to be prolonged, lasting as long as the AP.[5] These complex spatiotemporal dynamics may result from complicated molecular interactions with calmodulin, whose genetic manipulation to remove the negative feedback has surprisingly large side effects on AP duration (lengthening it by four or five times).[6] Thus, key electrophysiological parameters can be significantly more sensitive to Ca handling than customarily assumed.

Sarcoplasmic Reticulum Ca Release via Ryanodine Receptor Channels

Ca release from the SR via RyR has been shown to be roughly proportional to the trigger influx of Ca via LCC, although some variation exists, depending on how Ca flux is determined.[7] The system shows high gain, in that a small number of LLC will trigger release from a nearby cluster of RyR channels that open synchronously (see Chapter 15). As the discrete opening of LCC can modulate the number of activated RyR clusters, the large total Ca release tracks roughly linearly with total LCC Ca influx.

Another property of SR Ca release is that it appears to be a nonlinear function of SR Ca load. Essentially no SR release occurs below a threshold, after which SR release is usually a steeply increasing function of SR load.[7,8] Interestingly, there are indications that more than 100% of the original SR Ca content is released, suggesting that Ca is recycled back into SR during the release process, and rereleased again.[7] For a typical beat, though, the Ca release fraction is estimated at 60–80%.[8] Lastly, there appears to be a set maximum SR Ca load beyond which spontaneous RyR Ca release occurs, with potential for arrhythmogenesis (see Chapter 15). In addition, spontaneous RyR Ca release appears to also play critical roles in determining resting $[Ca]_i$.

From Calcium Release to Contraction

The translation of $[Ca]_i$ to force generation occurs at the level of the sarcomere, i.e., the basic

subcellular unit of the contractile apparatus (Figure 7–3). The sarcomere is composed primarily of interdigitated thick myosin filaments that interact, when activated, with thinner actin filaments.[9,10]

While the basic interactions in the sarcomere are known, the underlying basis of several complex behavioral properties is still debated. For example, the myofilament system shows a high level of Ca sensitivity, as characterized by steep force–Ca relationships with a Hill coefficient equal to 7 or more (Figure 7–3B). Because each troponin binds a single Ca ion on the regulatory site of troponin C (TnC), a Hill coefficient of 1 is predicted; hence, the high Ca sensitivity is assumed to result from one or more cooperative mechanisms.[11]

Briefly, three types of cooperative interactions are most widely accepted. Attached crossbridges have been shown to increase the Ca affinity of TnC.[12–14] A second type of cooperativity among the regulatory proteins is thought to arise from nearest-neighbor interactions, produced by the overlap of adjacent tropomyosin units along the thin filament (Figure 7–3A).[9,10] A third proposed mechanism is that the binding of one myosin head increases the binding rate of neighboring heads by holding the regulatory proteins in a more permissive conformation.[15] Alternatively, the binding

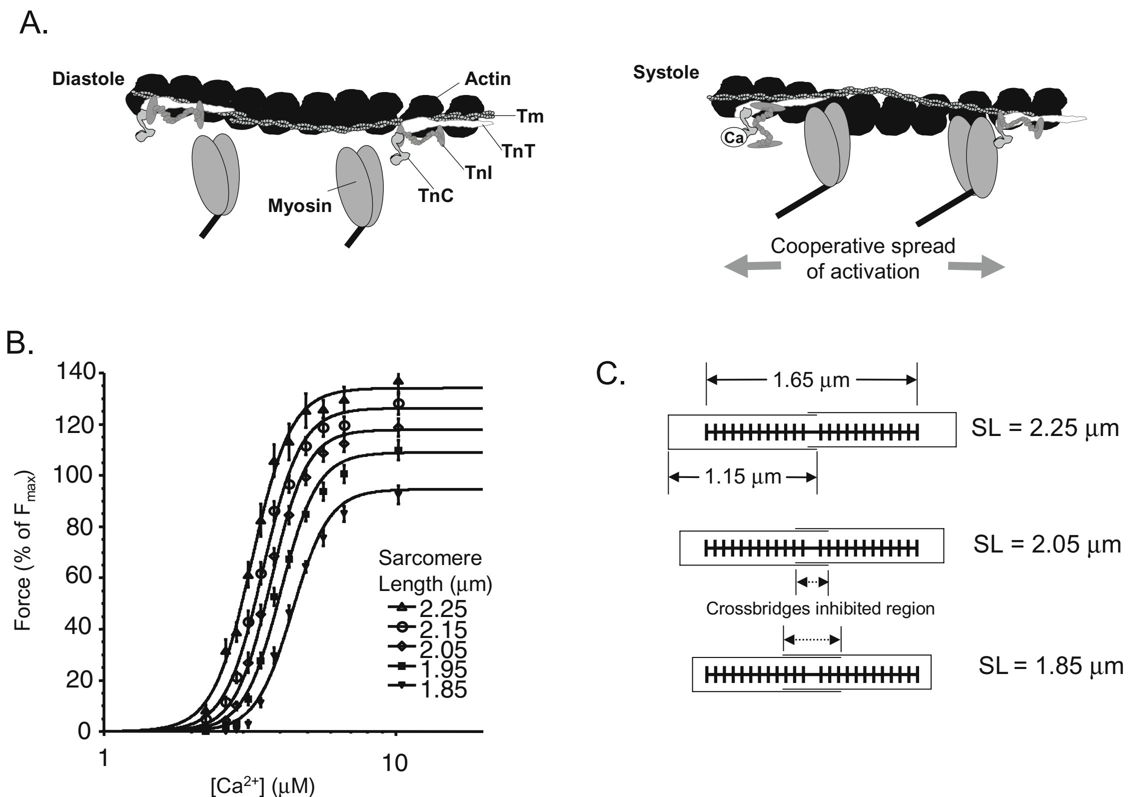

FIGURE 7–3. Contractile filaments and calcium. (A) Interrelation of a thin actin filament with nearby myosin heads. During diastole (left), tropomyosin (Tm) and troponin subunits (TnC, TnT, and TnI) sterically block crossbridge formation. During systole, elevated $[Ca]_i$ shifts the locations of tropomyosin/troponin to allow myosin head attachment and force generation. Note that cooperative activation can spread along the thin filament (see text for details). (From Bers,[3] with permission.) (B) Average force–Ca^{2+} relationships (pooled data, skinned rat cardiac trabeculae, $n = 10$) at five sarcomere lengths (SL); data are fitted to a Hill relationship. The level of cooperativity, assessed by the Hill coefficient, is not affected by SL. (From Dobesh *et al.*,[17] with permission.) (C) Diagram showing expected sarcomere geometry for three of the SL shown. Binding of crossbridges is assumed to be inhibited in the central region in which the thin filaments overlap.

of one crossbridge may pull binding sites on a compliant thin filament into register with myosin heads that have an inherently different characteristic distance in their repeating structure.[16]

Another complex phenomenon is the length dependence of force–Ca functions. Length-dependent effects can be separated into two main categories: changes in plateau force and changes in Ca sensitivity. As SL decreases, changes in plateau force may arise from overlap of thin filaments, which reduce the recruitable pool of crossbridges (Figure 7–3C; note that the lengths of the thick and thin filaments differ from the accepted values for skeletal muscle[11]). In support of this scheme, the developed force and ATPase rate of maximally activated cardiac muscle are linear functions of SL.[18] The second category is a decrease in myofilament Ca sensitivity, as shown by the rightward shift in force–Ca curves as SL shortens (Figure 7–3B). These length-dependent changes in Ca sensitivity are generally assumed to be the cellular basis of the Frank–Starling effect, although the biophysical mechanism is still under debate. One hypothesis suggests that SL changes the lattice spacing of the thick and thin filaments, with subsequent changes in crossbridge attachment.[19] Titin, a large protein that links myosin and actin lattices, could modify interfilament spacing[20] or act by additional mechanisms. However, other studies suggest that physiological changes in lattice spacing are insufficient to account for the observed changes in Ca sensitivity.[21,22] The changes in Ca sensitivity could result from cross-interactions of cooperative mechanisms and length-dependent changes in crossbridge recruitment as illustrated in Figure 7-3C.[11]

In addition to the immediate stretch-induced increase in cardiac force development, there is a secondary and more slowly occurring increase in force, which eventually reaches a plateau.[23] In contrast to the fast response, the slow force response involves an increase in Ca transient amplitude (Figure 7–4).[24] At the level of the myofilaments, there are no slow time-dependent changes in Ca sensitivity. In fact, length changes during the diastolic period alone are sufficient to generate a slow force response,[24,25,26] suggesting mechanisms that are independent of the ones discussed above. A full review of slow changes in force, and possible effects on membrane currents, is available elsewhere.[27] One obvious source of increased Ca is mechanically modulated ion channels (discussed below), which either directly conduct Ca ions or allow Na entry, which secondarily increases intracellular Ca, for example, via NCX. An alternative mechanism suggests Na influx via the Na/H exchanger, activated by a stretch-induced increase in angiotensin II and endothelin-1.[28,29]

Effects on the Ca Transient

While the exact mechanisms of length-dependent changes in Ca sensitivity are controversial, they may not be that important in understanding mechanical feedback on Ca transients. The amount of Ca bound to the myofilaments is generally assumed to be affected by the number of attached crossbridges (instead of length itself).[12–14] Hence, any feature that affects developed force can have secondary effects on Ca binding to troponin and on the Ca transient.

For example, increasing muscle length by 10% (see time points 3 and 4 in Figure 7–4) has a dramatic effect on developed force (see force in Figure 7–4B). This increase in developed force leads to greater Ca binding to TnC, initially lowering cytosolic $[Ca]_i$. Later, during the Ca transient, $[Ca]_i$ is slightly higher, as more Ca is slowly coming off TnC (compared with the low force case). Similar effects on the Ca transient have been seen elsewhere,[12,24,25,30,31] although details depend on the nature of mechanical perturbations and Ca monitoring agents used. Taken together, these results suggest that changes in force-dependent Ca binding to troponin have a noticeable, but not dramatic, effect on $[Ca]_i$ levels, which may restrict the role of this phase in mediating MEF effects.

Finally, a few more general comments should be made about Ca buffering. The cytosol of the cardiomyocyte is heavily buffered, and the vast majority of Ca ions are bound to several important buffers. For example, at diastolic $[Ca]_i$ of 0.1 μM, only ~2.5% of Ca ions are "free" in solution; this fraction increases to ~4.5% when systolic $[Ca]_i$ rises to 1 μM.[3] As shown in Figure 7–3B, fast and slow buffering systems exist in addition to troponin and the SR. Several fast buffers have dissociation constants near the operating range of

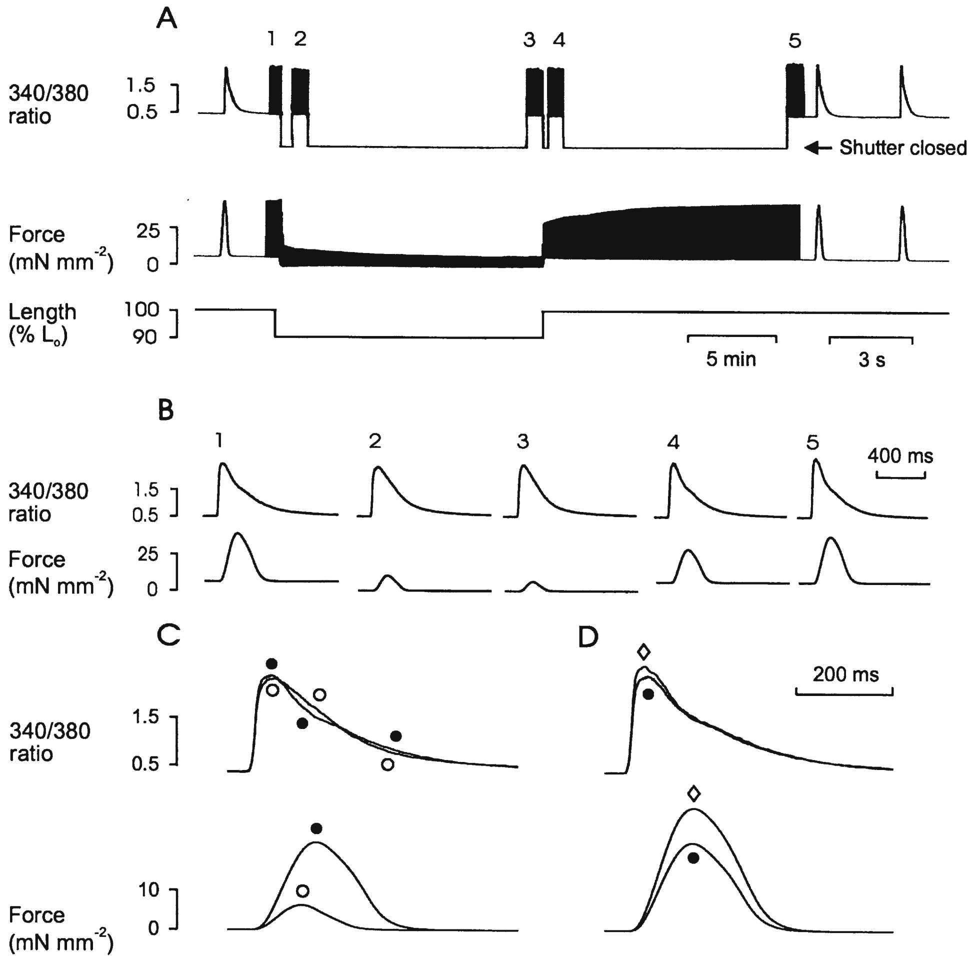

FIGURE 7–4. Illustration of immediate and slow changes in force after length changes. Records of the changes in fura2 fluorescence ratio and force produced by shortening a rat trabecula by 10% for 15 min. (A) Records of 340 nm/380 nm fluorescence ratio and force, with a representation of the length change from the initial length (L_0). A shutter in the excitation light pathway was opened only for discrete 48-sec recording periods (labeled 1–5) in order to avoid photobleaching of fura2. Note the slow changes in twitch force after the changes in muscle length. (B) Mean records (from 16 twitches) of fluorescence ratio and force measured during periods 1–5 in (A). (C) Overlaid traces of the fluorescence ratio and force averaged during periods 3 (○) and 4 (●) to illustrate the rapid effects of the length increase. Resting forces have been subtracted from these traces. (D) similar overlaid traces averaged during periods 4 (●) and 5 (◇) to illustrate the delayed effects of length increase. 24°C, 1 mM external Ca^{2+}, 0.33 Hz stimulation rate. (From Kentish *et al.*,[24] with permission.)

the Ca transient (0.1–1 μM), and these bind and release Ca on each heart beat. This group includes calmodulin, adenosine triphosphate (ATP), creatine phosphate, and the phospholipids of the sarcolemma. Slow buffers have dissociation constants that are much lower than the operating range of $[Ca]_i$, and hence Ca remains largely bound to these buffers throughout the heartbeat. Slow buffers include myosin and two high-affinity, nonregulatory sites on TnC. In addition, the mitochondria comprise roughly 35% of cytosolic volume and can potentially contain large amounts

of Ca. Their large volume, coupled with close proximity to myofilaments and RyR, suggests a potentially significant active role for mitochondria in ECC.[3] However, most findings suggest little net Ca transit between mitochondria and cytosol on a beat-by-beat basis. In fact, mitochondrial Ca exchange may be an epiphenomenon of mechanisms that match ATP production to cellular demand, using intracellular Ca as a proxy for the energetic demand of a cell.

From Contraction to Relaxation

While “contraction” tends to be at the focus of attention, the process of relaxation is just as important for cardiac performance, yet is less well understood.[32] As diastolic filling occurs under low pressure, any residual force from incomplete relaxation can severely affect cardiac function. Relaxation is more than just elastic recoil of tissue, and complexities arise from the interplay of Ca release from the myofilaments, Ca reuptake into the SR, and crossbridge detachment (Figure 7–2C).

Besides serving as a trigger, LCC Ca influx also serves to load the SR (Figure 7–2C, dotted down arrow). This influx of Ca is thought mainly to influence the amount of Ca releasable by the SR on the subsequent beat (rather than the current beat). In steady-sate conditions, net loading is zero, as the amount of Ca extruded by NCX (and sarcolemmal Ca pumps) matches that of LCC influx.

The majority of $[Ca]_i$ (60–80%, depending on species) is recycled back into SR via the sarcoplasmic/endoplasmic reticulum Ca-ATPase (SERCA). Factors such as heart rate, inotrophic stimulation, or pathologies affect reuptake rates (heart failure can decrease SR uptake by 50%).[3,33] The major sarcolemmal efflux pathway is the NCX, extruding ~20–40% of Ca during the transient, whereas the sarcolemmal Ca-ATPase and mitochondrial uptake are generally thought to contribute less.[34]

With the decline of $[Ca]_i$, Ca ions unbind from TnC, starting the relaxation process. If TnC were a simple buffer, the process could be easily described. However, complexities arise from the presence of activated thin filaments and attached crossbridges, which increase TnC affinity for Ca (as described previously). Moreover, a small number of attached crossbridges are thought to be able to hold the thin filament in an activated state, even if Ca has dissociated from neighboring binding sites (Figure 7–3A). Thus, attached crossbridges can slow relaxation both by increasing Ca affinity of TnC and by holding the thin filament activated after Ca has dissociated from a fraction of TnC.

Because of these features, contractions involving high levels of developed force (and many attached crossbridges) are slower to relax than those with lower force development. This affects especially final relaxation, past 50% of maximum force.[35,36] Thus, a larger force transient as observed after application of stretch (see Figure 7–4C, lower panel) is noticeably slower to relax than a low force transient (note that for the two runs shown in Figure 7–4C, the activating Ca transients are very similar). Interestingly, increased force due to larger peak Ca transients also produces a slowed final relaxation, suggesting that the effect results from slow unbinding kinetics of crossbridges, not upstream Ca activation events.[32,36]

Finally, and as noted previously, complete relaxation is important for competent diastolic filling. Here, the steep Ca sensitivity of the myofilaments contributes to keeping the developed force minimal at diastolic $[Ca]_i$. Other features that may promote relaxation include the ability of myosin to detach under isometric or lengthening conditions (by quickly reversing the steps of attachment and head rotation) in a manner that retains most of the energy of ATP hydrolysis.[11,32] In contrast, the typical forward cycling scheme requires ADP dissociation and new ATP binding for a crossbridge to detach (if this slower detachment mechanism dominated, the relaxation rate would be greatly slowed). In fact, recent characterizations of isolated myofibrils suggest that relaxation is a nonuniform biphasic process,[32] and while isolated myofibril behavior may differ from intact muscle, the point is clear that relaxation is complex and is not just the reverse of activation.

Mechanoelectric Feedback

Diastolic Stretch Effects

As shown above, the heart is an exquisitely mechanosensitive organ. This also applies to mechanoelectrical transduction, as will be obvious

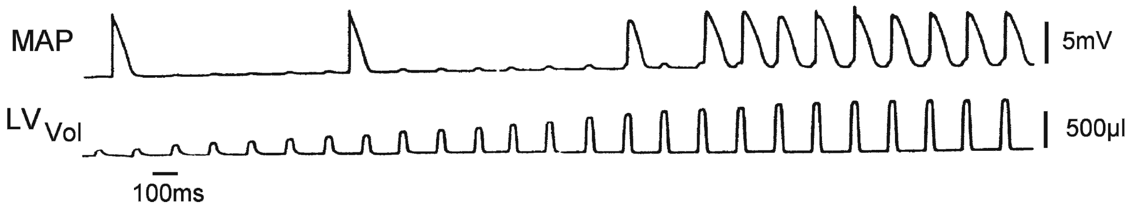

FIGURE 7–5. Diastolic stretch causes membrane depolarization. Monophasic action potential recordings (MAP) from an isolated rabbit heart (AV node disrupted) shows that injection of increasing amounts of fluid into a left ventricular balloon (LV_{Vol}) causes matching diastolic depolarizations that, once threshold is reached, will mechanically pace the preparation (note: the first two action potentials are spontaneous escape beats not related to mechanical stimulation). (From Franz *et al.*,[37] with permission.)

to anyone whose training involved the use of Langendorff-style heart preparations that can be stopped or started "by the flick of a finger." Mechanisms underlying these acute electrical responses to mechanical stimulation include stretch-activated ion channels (SAC), mechanical modulation of Ca handling, and effects mediated via communication with other cells.

As a rule, mechanical stimulation of resting cardiac tissue (during "electrical diastole") causes membrane depolarization (Figure 7–5).[37] This behavior can be observed across the whole range of structural integration, from whole organ to single cell, and it is understood to be largely mediated by depolarizing transmembrane currents through SAC.[38,39]

The SAC were discovered in mammalian cardiomyocytes about two decades ago,[40] and a number of channels with varying ion selectivity and gating properties have subsequently been described. Despite two decades of research, a uniform SAC classification has yet to emerge.

Meanwhile, SAC can be distinguished based on ion selectivity. The first group is composed of SAC that show little selectivity for the various cations normally present in physiological solutions (SAC_{NS}; for nonselective). The second group preferentially conducts potassium (SAC_K). A third group of chloride-selective channels[41] has been described in settings that involve centrifugal membrane deformation (most commonly in the context of pathophysiologically increased cell volumes). These channels show significant lag times between mechanical stimulus and increased channel open probability (1 min or more), rendering them less likely to underlie acute mechanical effects on heart rate and rhythm.[†]

The SAC_{NS} usually have reversal potentials between 0 and −20 mV. This is more positive than the membrane potential of resting cardiomyocytes, so that diastolic activation of SAC_{NS} will tend to depolarize cardiac cells. In working cardiomyocytes, SAC_{NS} activation may cause ectopic AP generation,[38] while in pacemaker cells a positive chronotropic response may be observed.[42]

The SAC_K will tend to shift the membrane potential toward the potassium equilibrium potential (negative to −90 mV), so their activation will oppose depolarization.

Given that diastolic stretch tends to depolarize myocardium, SAC_{NS} are generally assumed to be the leading contributors to acute electrophysiological responses of cardiac cells to stretch. In support of this idea, block of SAC_{NS} prevents mechanically induced extrasystoles.[43] In contrast, SAC_K appear to play secondary roles, at least under physiological conditions.

Systolic Stretch Effects

The AP upstroke, whether triggered by mechanical or electrical stimulation, is firmly governed by the fast sodium current. Any additional stimuli, including mechanical, have little appreciable effect.

[†]Mechanosensitive chloride channels are likely to affect electrophysiology predominantly in settings such as ischemia, reperfusion, or hypertrophy (where they are constitutently activated); for further detail see Baumgarten and Clemo.[41]

During the subsequent AP plateau, cardiomyocyte membranes are more positive than the reversal potentials of either SAC_{NS} or SAC_{K}, and stretch tends to have a repolarizing effect, which often leads to an overall reduction in AP duration.[44] However, AP lengthening[45] and crossover of repolarization[46] have also been observed. In particular, stretch applied during late repolarization often prolongs the AP, potentially giving rise to early or delayed afterdepolarization-like behavior. These afterdepolarizations may trigger extra beats, such as seen in patients during balloon valvuloplasty.[47]

Even when the immediate outcome of mechanically induced effects on systolic electrophysiology is less prominent, MEF can still affect electrical load, excitability, and refractoriness of cardiac tissue. This has implications for heart rhythm maintenance, as illustrated below.

Mechanisms

Most acute electrophysiological responses to mechanical stimulation, observed in cardiac cells, can be reconciled with SAC activation. That said, mechanically induced changes in Ca handling[27] and second messengers such as nitric oxide[48] are also likely to directly or indirectly contribute.

With respect to Ca handling, large changes in developed force or length produce generally small changes in the cytosolic Ca transient under normal conditions (see discussion of Figure 7–4). As such, mechanical perturbations alone are unlikely to produce large enough cell-wide perturbations in intracellular Ca concentration to be proarrhythmic by activating Ca-dependent inward currents (e.g., NCX), similar to that proposed in heart failure.[49] However, *in vitro* evidence suggests that stretch of locally weakened muscle regions can produce release of Ca from SR near the boundary of strong and weak cells.[50] Mechanically inhomogeneous myocardium (whether locally weakened, or stiffened, say by scarring or fibrosis) may give rise to proarrhythmic Ca release.

Finally, mechanosensitivity is not restricted to cardiomyocytes. Various mechanosensitive cell populations affect cardiac electrical responses to mechanical stimulation, either by paracrine pathways (e.g., neurons, endothelial cells, connective tissue),[51] or through direct electrotonic interaction via connexin-based coupling (fibroblasts).[52] Furthermore, several connexins have been found to exhibit mechanically modulated opening[53] that, if applicable to the heart, would have implications for signal propagation.

This dynamic area of research will benefit from the recent identification of a highly selective peptide blocker of SAC,[54] so that significant new insight into mechanisms of cardiac MEF can reasonably be expected in the next few years.[55]

Relevance for Electrical Function of the Heart

Mechanosensitivity of the Normal Heart

Manifestations of both the Frank–Starling effect (mechanically induced positive inotropy)[56] and the Bainbridge effect (stretch-induced positive chronotropy)[57] can be observed in human heart, even after denervation (e.g., recently transplanted heart). While the Frank–Starling effect is a well-established and efficient means of matching cardiac output to venous return, manifestations of the Bainbridge effect in humans are less evident. This is related to the fact that most interventions that temporarily raise venous return (e.g., tilt-table or orthostatic challenges) are associated with corresponding changes in arterial pressure. These, via reflex pathways, slow down (rather than accelerate) pacemaking. However, studies using autotransfusion (passive elevation of the legs) found that an isolated increase in venous return does indeed raise the heart rate in humans.[58] This response is believed to underlie the nonneural component of respiratory sinus arrhythmia (inspiration increases venous return, which raises beating rate), or the sometimes observed phase-inverted sinus arrhythmia during positive pressure ventilation (when forced inspiration impedes venous return, which reduces beating rate).

Mechanical Pacing in Asystole and Bradycardia

Precordial percussion of the asystolic heart was among the first documented mechanical interventions for heart rhythm management. As reported in 1920, Stokes–Adams syndrome patients could

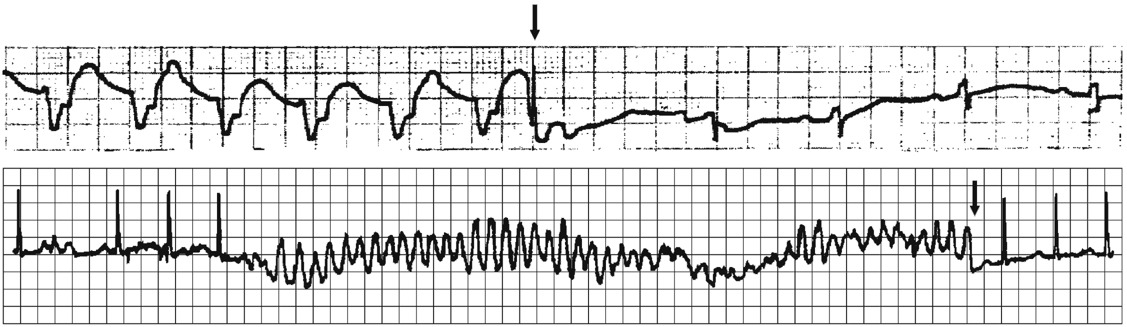

Figure 7–6. Tachyarrhythmia termination by precordial thump in humans. Case reports showing termination of ventricular tachycardia (top) and early ventricular fibrillation (bottom) by application of a fist thump to the precordium (arrows). (From Pennington *et al.*[66] and Barrett,[69] with permission.)

be kept conscious during periods of ventricular standstill by pacing the heart using fist impacts to the chest.[59]

Further applications include precordial thumps (PT) for the management of severe bradycardia, such as in the context of spinal anesthesia, or direct epicardial stimulation by "finger tap," which is regularly employed by surgeons to reinstate rhythmic activity in hearts that are weaned from cardiac bypass. The majority of case studies, conducted mainly in the 1970/1980s,[60,61] concluded that the fist is a suitable mechanical pacemaker, in particular in emergency situations where no alternative treatment modalities are available.[62] Of note, the impact energies required to trigger premature ventricular beats in humans are low,[‡] ranging from 0.04 to 1.5 J.[63] Underlying mechanisms of mechanically induced cardiac contractions are believed to be similar to those seen in isolated heart or tissue experiments, where diastolic stretch causes cardiomyocyte membrane depolarization that, if large enough, triggers AP generation (Figure 7–5) and subsequent ECC.

Of note, PT-induced ventricular contractions have significantly greater hemodynamic value than chest compressions, where blood is passively squeezed out of the heart (rather than actively ejected by the heart itself). In fact, the hemodynamic efficacy of mechanically induced beats matches that achieved with electrical pacing in patients.[64] Since adverse side effects are uncommon in this setting, the 2005 International Liaison Committee on Resuscitation (ILCOR) guidelines recommend fist pacing (at a rate of 50–70 bpm) for hemodynamically unstable bradyarrhythmias, until more enduring solutions (e.g., electrical pacemakers) can be employed.[65]

Mechanical Cardioversion in Tachycardia and Fibrillation

Single PT have been employed successfully as emergency resuscitation measures to terminate ventricular tachycardia and fibrillation (VT and VF, respectively; see Figure 7–6).[66,67] They are applied as a sharp impact to the lower half of the sternum, delivered from a height of 20–30 cm, using the ulnar edge of the tightly clinched fist, followed by active retraction after full impact (to emphasize the impulse-like nature of the stimulus).[68]

To date, no prospective study has evaluated the clinical utility of PT.[§] Case reports suggest that PT can be efficient in terminating witnessed cardiac arrest in about one-third of cases, and that VT is more amenable to mechanical cardioversion than VF.[67,68] However, severe preexisting hypoxia may render PT less efficient (which has implications for out-of-hospital PT success rates).[70]

Mechanisms underlying successful PT are believed to involve SAC_{NS}, which, via depolariza-

‡For comparison: 1 J of impact energy is released by dropping a standard can of soda from a 30 cm height.

§An out-of-hospital evaluation of PT for unwitnessed cardiac arrest is currently underway in the Pordenone region of Italy; results are expected in 2007.

tion of excitable gaps, may terminate reentry. The reduced efficacy of mechanical interventions in severely hypoxic hearts has been linked to the fact that reduced ATP levels preactivate at least some SAC_K.[71] This changes the overall electrophysiological response to mechanical stimulation, making it less efficient in depolarizing the excitable gap. In addition, more pronounced AP shortening may potentially render PT arrhythmogenic in severely ischaemic tissue.

Energy levels involved in PT termination of tachyarrhythmia range from 2 to 8 J.[68] This can be sustained by the conscious patient, in contrast to external electrical defibrillation involving more than one order of magnitude higher energy levels.

As PT is usually the fastest possible resuscitatory intervention "at hand,"[72] current ILCOR recommendations suggest considering it after monitored cardiac arrest, if no electrical defibrillator is immediately available.[73]

Mechanical Induction of Arrhythmia

Both acute and sustained stretch have been linked to atrial and ventricular arrhythmogenesis.[74,75]

The specific contribution of *sustained stretch* to cardiac arrhythmogenesis is difficult to clearly isolate, as pathologies that give rise to pressure and/or volume overload often carry an increased risk of heart rhythm disturbances via other mechanisms.

An interesting insight has been obtained, though, from the reverse conceptual approach, where volume overload was temporarily eliminated by conducting the Valsalva maneuver. This caused a reduction in venous return and cardiac dimensions, with subsequent temporary (while cardiac dimensions were reduced) termination of ventricular and supraventricular tachyarrhythmias,[75] even in heart transplant recipients,[76] suggesting that maintained stretch is proarrhythmogenic.

Underlying mechanisms are likely to involve SAC, whose pharmacological block prevents overload-mediated atrial fibrillation in isolated heart.[77] Similarly, activation of SAC has been implied to contribute to reduced defibrillation efficacy during volume overload.[78,79]

Acute mechanical stimulation of the heart can cause a range of electrophysiological responses, from single ectopic beats, to conduction abnormalities, runs of VT, and VF.[80] In the context of nonpenetrating extracorporeal impacts without cardiac structural damage, this is referred to as *Commotio cordis*.[81] Determinants of *C. cordis* outcome include impact type, location and energy,[82] as well as timing.[83]

The vulnerable window for mechanical induction of VF coincides, in a domestic pig model, with a 20-msec period prior to the peak of the ECG T-wave.[83] This vulnerable window is narrower than for electrical stimulation, and may explain why *C. cordis* is relatively rare.

Underlying mechanisms are likely to involve SAC activation, although the exact nature and individual contribution of subpopulations remain unresolved.[84,85] At the cellular level, mechanical stimulation during the T-wave affects cardiomyocytes differently, depending on their actual state of AP repolarization at the given point in time (Figure 7–7A–C). This may provide both trigger (ectopic AP) and sustaining mechanisms (heterogeneity of repolarization) for arrhythmogenesis.

The need to avoid both sustained overload (hemodynamic unloading, active and passive cardiac assist) and untoward acute mechanical stimulation of the heart (chest protectors) identifies important targets for prevention of arrhythmia.

Outlook

Cardiac mechanics is not merely an endpoint of heart rhythm management, but it is a rhythm moderator in its own right. Mechanical interventions affect the pace and force of cardiac contractions, and they may contribute to the induction, sustenance, and termination of arrhythmias.

Many of the links between electromechanical cross-talk, tissue and organ structure, and temporal organization of cardiac function are still poorly understood. This ranges from basic science questions, for example, regarding the modalities and mechanisms underlying mechanosensing, to clinical issues, such as the effects of various pathological factors (e.g., inhomogeneities, fibrosis) and treatment regimes (drugs, exercise) on mechanical arrhythmogenesis.

A better understanding of the cardiac electromechanical riddle will lead to more intelligent treatment strategies. This includes pharmacological leads,[77] as well as device development/

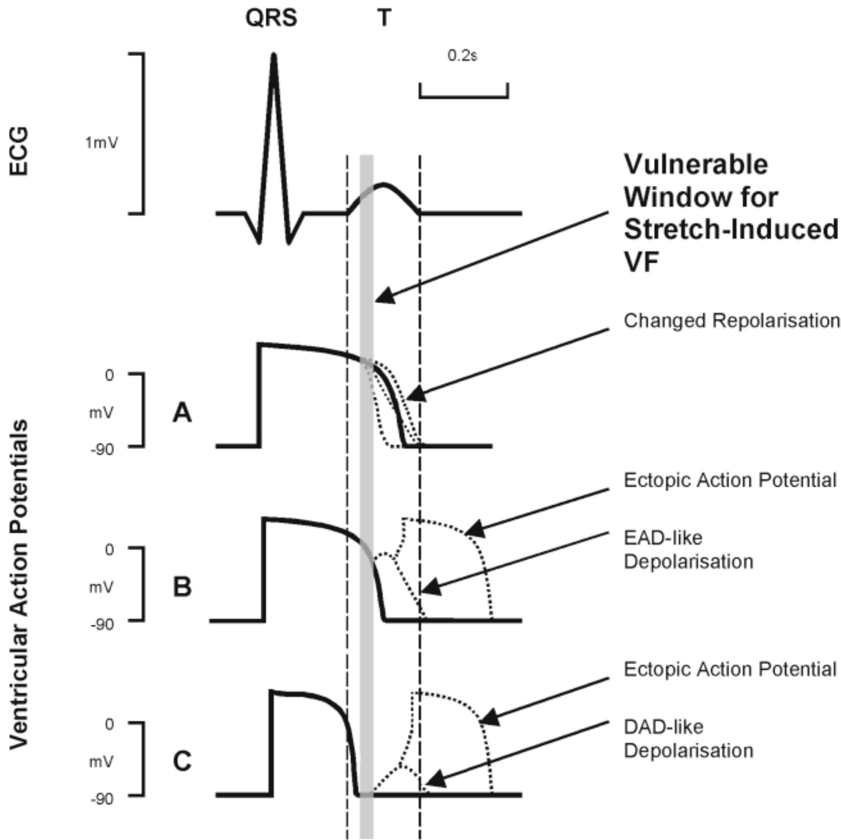

FIGURE 7–7. Schematic representation of cellular correlates of mechanical impacts during early repolarization (upstroke of the T-wave, see the gray band). Effects depend on the actual membrane potential of cardiomyocytes in different regions of the heart (A–C) and include (A) changes in action potential duration (shortening, prolongation, crossover of repolarization); (B) early afterdepolarization (EAD)-like behavior; or (C) delayed afterdepolarization (DAD)-like events, both of which may trigger extra beats. (From Kohl *et al.*,[85] with permission.)

improvement opportunities ranging from the use of ultrasound for cardiac pacing,[86] over active and passive cardiac assist technologies,[87] biventricular pacing/resynchronization,[88] and cardiac contractility modulating electrical stimulation,[89] to application of electrical defibrillation during peak chest compression and mechanical cardioversion, to name but a few.

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