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Calcium and Arrhythmogenesis

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Abstract

Triggered activity in cardiac muscle and intracellular Ca^{2+} have been linked in the past. However, today not only are there a number of cellular proteins that show clear Ca^{2+} dependence but also there are a number of arrhythmias whose mechanism appears to be linked to Ca^{2+}-dependent processes. Thus we present a systematic review of the mechanisms of Ca^{2+} transport (forward excitation-contraction coupling) in the ventricular cell as well as what is known for other cardiac cell types. Second, we review the molecular nature of the proteins that are involved in this process as well as the functional consequences of both normal and abnormal Ca^{2+} cycling (e.g., Ca^{2+} waves). Finally, we review what we understand to be the role of Ca^{2+} cycling in various forms of arrhythmias, that is, those associated with inherited mutations and those that are acquired and resulting from reentrant excitation and/or abnormal impulse generation (e.g., triggered activity). Further solving the nature of these intricate and dynamic interactions promises to be an important area of research for a better recognition and understanding of the nature of Ca^{2+} and arrhythmias. Our solutions will provide a more complete understanding of the molecular basis for the targeted control of cellular calcium in the treatment and prevention of such.

I. Introduction

Membrane voltage and $[Ca^{2+}]_i$ changes have been linked for many decades. However recently, some human ventricular arrhythmias have been associated selectively with mutation of the ryanodine receptor (RyR), the primary release channel of intracellular Ca^{2+} stores in the cardiac cell (see sect. II*B2*). It is the goal of this review to discuss the role of cellular Ca^{2+} transport in cardiac arrhythmias. We review the basis for Ca^{2+}-dependent arrhythmias by reviewing the building blocks of excitation-contraction coupling. Then, we review what is known to date about the possible role of Ca^{2+} in different arrhythmias.

A. Overview of Ca^{2+} Transport in the Cardiac Cell

1. Structural aspects—The cell border is delineated by a glycoprotein layer overlying the sarcolemma, which invaginates the cell near the Z lines of the myofibrils. The resultant transverse tubules (t tubules) are rich in dihydropyridine-sensitive Ca^{2+} channels (DHPR) and Na^+/Ca^{2+} exchange proteins. The t tubules make contact with a longitudinal network of tubules with lipid membranes called the sarcoplasmic reticulum (SR), which is a prominent Ca^{2+} storage organelle. Terminal cisternae of the SR abutting the t tubules contain Ca^{2+} channels with a high affinity for ryanodine (RyRs) that are involved in Ca^{2+} release from the SR. The RyR are so large that they form ultrastructurally recognizable junctional “foot

proteins" in close proximity to the DHPR (Fig. 1). The longitudinal SR envelops the myofibrils and is densely covered by SERCA, SR Ca^{2+} pump molecules, which drive Ca^{2+} into the SR where it is buffered in the longitudinal SR by calreticulin and in the junctional SR by calsequestrin, a protein with intermediate affinity for Ca^{2+}. The pump rate of SERCA depends on the $[Ca^{2+}]_i$. The Ca^{2+} sensitivity of the pump is controlled by the degree of phosphorylation of the regulatory protein, phospholamban, in the SR membrane. The contractile proteins arranged in sarcomeres in the myofibrils occupy 60% of the intracellular space. Mitochondria adjacent to the sarcomeres occupy the remainder of the cell.

The ultrastructural elements underlying excitation-contraction coupling (ECC) in the heart are found in the coupling between SR and sarcolemma. Ca^{2+} are stored in the sarcoplasmic reticulum and can be released from the SR, thus activating the adjacent myofibrils over short diffusion distances (162, 518).

The action potential initiates the release of Ca^{2+} by mechanisms that are specialized in different cardiac tissues. The most well known specialization of the release units is found in ventricular myocytes, which is penetrated in a highly organized manner by transverse tubules of the cell membrane. The t tubules in these cells make contact with the terminal cisternae of the SR (70, 162, 518). The latter specialized junctional domains of the SR, containing calsequestrin (CASQ) and carrying protein "feet" on their cytoplasmic surface, contact t tubules in the form of dyads. Similar domains of the SR not associated with the cell membrane form so-called corbular SR. The molecular composition of the dyad is now beginning to be revealed. A linking protein junctophyllin is thought to be involved in the docking of t tubules on the dyads (518). While a majority of DHPR and RyR are colocalized in dyads (478), the observation that a significant fraction of RyR is not colocalized with DHPR (40% in adult rat myocytes) suggests that these RyR could be present in the corbular SR. On the luminal side of the junctional domains, the intra SR proteins, CASQ and junctin and triadin, are colocalized with RyR. Studies of the macromolecular protein assemblies have suggested that complete assembly of RyR/DHPR on the one side of the dyad and RyR/TrD (triadin)/JnC (junctin)/CASQ on the luminal side develops during maturation of the animal allowing efficient coupling between surface membrane depolarization and Ca^{2+} delivery to the myofibrils throughout an adult cardiac myocyte.

The ultrastructure of Purkinje and atrial cells differs from the above structure described for ventricular myocytes in that they have no t tubules and their SR presents in two forms, subsarcolemmal junctional SR and corbular SR located in the core of the cell (505) (Fig. 1). The diameter of a Purkinje cell is 30–40 μm. The diameter of a normal ventricular myocyte is 15–25 μm, whereas an atrial cell is 13–15 μm. Furthermore, the density of the myofibrils is lower in the Purkinje cell compared with that in ventricular myocytes. Accordingly, it has been shown that for both the small atrial myocyte and the large Purkinje cell, ECC relies on a process where surface membrane depolarization and Ca^{2+} delivery to myofibrils deep inside the myocyte depend on Ca^{2+} release by the SR, which starts at the cell membrane and which is propagated by chemical transmission to the depth of the cell (513).

2. Model of ECC—A descriptive model of ECC (Fig. 2) has been developed to explain the functional properties of the cardiac cell (476). During the action potential Ca^{2+} enter the cell

through a protein that is sensitive to dihydropyridine, a DHPR or "L-type Ca^{2+}" channels. In ventricular cells the number of Ca^{2+} channels is estimated to be 15/μm^2 and yet only 3% are open at peak currents (317). The amount of Ca^{2+} entering the cell per second depends on action potential duration and heart rate. Ca^{2+} influx at t tubules is 2.3× that of the cell surface, but more Ca^{2+} entry occurs per square micron at the cell surface than at t tubules (69). Ca^{2+} entering via L-type Ca^{2+} channels in the t tubules start ECC by triggering release of Ca^{2+} from the RyR in the terminal cisternae. In the rat (48), the ratio of RyR to L-type Ca^{2+} channels is 7:1 and would fit spatially with random coupling of the L-type Ca^{2+} channel to Ca^{2+} release via RyR (79). The ratio of superficial L-type Ca^{2+} channels versus t-tubular L-type channels is 1:3 (586), and it is anticipated then that one t-tubular L-type channel faces ∼10 RyRs. Ca^{2+}-induced Ca^{2+} release (CICR) is proportional to the free intra-SR Ca^{2+} content and dictates the force of the cardiac contraction. Free Ca^{2+} in the SR has recently been spatially resolved (484), and data show that intra-SR Ca^{2+} diffusion is rapid, and local Ca^{2+} in SR in normal ventricular cells is never less than 50% of the diastolic value. The released Ca^{2+} activates contraction of the sarcomere. This contraction is short lived due to the rapid elimination of Ca^{2+} from the cytosol (Fig. 3A). About two-thirds of the Ca^{2+} is resequestered by the SR (45); the remainder leaves the cell mostly via the low-affinity, high-capacity, Na^+/Ca^{2+} exchanger, while a low-capacity, high-affinity Ca^{2+} pump lowers the cytosolic Ca^{2+} level further during the diastolic interval (84). In the steady-state, the sum of the Ca^{2+} efflux through the membrane balances the influx during the action potential. It follows, then, that the Ca^{2+} content of the SR depends on the heart rate and on the duration of the action potential. Furthermore, a fraction of the Ca^{2+} involved in activation of the heartbeat recirculates into the SR and becomes available for activation of the next beat. Thus force of the heartbeat will depend on the force of the previous one. In addition, it takes time for the Ca^{2+} release process to recover completely from the last release so that sequestered Ca^{2+} can again be released from the SR. Therefore, the force of the heartbeat will also depend strongly on heart rate, on the duration of the diastolic interval, as well as on the duration of the action potential (594).

It is possible to load the SR excessively with Ca^{2+}. This may occur following damage of cardiac cells (115, 386) or after exposure to interventions that increase intracellular Ca^{2+} levels (digitalis, high $[Ca^{2+}]_o$, high stimulus rate). SR-Ca^{2+} overload is defined as the condition in which the SR releases Ca^{2+} spontaneously. Spontaneous uncoordinated Ca^{2+} release between heartbeats can be observed as spontaneous contractions of small groups of sarcomeres in cells of the myocardium and gives rise to fluctuations of the light-scattering properties of the muscle (287, 303). Spontaneous Ca^{2+} release increases the diastolic force generated by the contractile filaments and in so doing reduces Ca^{2+} release during the next heart beat (301, 510). Spontaneous release of Ca^{2+} is likely to lead to cell depolarization as a result of activation of Ca^{2+}-modulated channels and/or by electrogenic Na^+/Ca^{2+} exchange.

3. ECC coupling in atrial and Purkinje cells from normal hearts—In rabbit atrial cells, immunostaining for either RyR or the L-type Ca^{2+} channel can be seen near the cell's sarcolemma (84a). Nonjunctional SR elements visualized with RyR staining are in transverse arrays along the Z lines (284, 610). In rat atrial cells, a 0.5- to 1-μm gap exists between junctional and nonjunctional RyR (341). This is in contrast to the unique

ultrastructure of the latent atrial pacemaker cell, where subsarcolemmal SR cisternae are prominent and directly opposed to one another in adjacent cells. Differing from normal ventricular cell ultrastructure, where the presence of t tubules ensures reasonably synchronous Ca^{2+} release throughout the cell, atrial cells exhibit spatial Ca^{2+} gradients. In response to electrical stimulation, Ca^{2+} increases first at the cell's periphery and then after a 30- to 50-ms delay, increases in the central regions of the cell (38, 232, 284, 329, 341, 596). Preferential activation of Ca^{2+} sparks along the cell's periphery and then propagation to the cell's core (487, 596) is consistent with the biphasic nature of the human atrial Ca^{2+} transient under voltage clamp (198) and the ability of peripheral Ca^{2+} release to more efficiently regulate Na^{+}/Ca^{2+} exchanger function (328). Furthermore, in rat atrial cells, a set of "eager" Ca^{2+} release sites that have a fixed edge location and preset activation pattern are thought to reflect clusters of RyRs that are closely coupled to Ca^{2+} channels and display a high sensitivity to trigger Ca^{2+} (341). In voltage-clamped cAMP-stimulated atrial cells, L-type Ca^{2+} channel evoked peripheral Ca^{2+} release occurs within 1–4 ms, and this Ca^{2+} then propagates to the interior of the cell at $\sim$230 μm/s (596). The efficacy of Ca^{2+} currents to trigger peripheral Ca^{2+} release is fivefold greater than that needed for triggering center Ca^{2+} release. Thus, for rat cells, it is thought that the mechanism of Ca^{2+} release from junctional SR differs from that in nonjunctional SR. Recent spark data suggest that peripheral atrial Ca^{2+} sparks are brighter and occur more frequently than central sparks (597). The opposite appears to be the case in feline atrial cells (284) where under permeabilized conditions, Ca^{2+} spark frequencies in the two regions are similar (488). Thus, in the intact cell, mechanisms that cause Ca^{2+} release in central SR RyRs are not efficient, most probably because of structural components. An interesting report by MacKenzie et al. (343) states that inherent intracellular calcium buffers in the normal rat atrial cell (for instance, mitochondria and SERCA pumps) prevent global Ca^{2+} transients under normal-paced conditions. Furthermore, membrane depolarization evoked peripheral Ca^{2+} release only propagates to the cell's core when the cell is hormonally (e.g., endothelin) stimulated.

As a result of the different structure of the Purkinje cell, coupling of excitation of the cell membrane with Ca^{2+} release in the core of these (large) cells differs substantially from that of myocytes. Immunostaining experiments in rabbit Purkinje cells show that RyRs are subsarcolemmal as well as within the cell consistent with earlier reports (106, 256, 505, 513). In fact, canine Purkinje cells contain both RyR3 and RyR2 isoforms with the RyR3 protein being located in a subsarcolemmal region. Here the action potential of the Purkinje cell precedes rapid Ca^{2+} entry into the subsarcolemmal space. The latter induces Ca^{2+} release which in some species propagates into the core of the Purkinje cells (64). In rabbit Purkinje cells, experiments with ryanodine suggest that Ca^{2+} changes in the central core of cells are best explained by simple buffered Ca^{2+} diffusion and not Ca^{2+} propagation (106). However, in rabbit Purkinje cells, evoked Ca^{2+} transients and sparks are only seen to originate at peripheral cellular components, suggesting that RyRs in the cell center of this type of cell are "silent" (106). This is consistent with voltage-clamp studies of single rabbit Purkinje cells which show a single-component Ca^{2+} transient (497). However, in canine Purkinje cells, electrically evoked Ca^{2+} transients are multiphasic (61, 64). An action potential evokes a sudden increase in Ca^{2+} particularly along the periphery. In some Purkinje cells from normal hearts, if electrically evoked peripheral release is spatially and

temporally inhomogeneous, a local Ca^{2+} wave is produced and can propagate as a traveling Ca^{2+} wave the length of the aggregate as well as towards the cell's core (64, 513). Finally, while fundamentals of ECC have been described above, it is important to remember that the time course of the action potential (AP) of the cell can have significant modulatory effects on ECC efficiency. Not only does AP duration affect the time course of the evoked Ca^{2+} transient (58, 463), but altering the rate of early repolarization can affect both the magnitude and time course of SR Ca^{2+} release (464).

4. Reversal of ECC—In a ventricular myocyte, the distance between Ca^{2+} release sites on the terminal cisternae of the SR to the Ca^{2+} transport molecules at the surface of the t tubules is less than ∼300 nm (i.e., from 40 nm to DHPR to ∼300 nm to Na^+/Ca^{2+} exchangers). It follows that the transport molecules face the largest variation of $[Ca^{2+}]_i$ within the cell. This review discusses potential consequences of the SR-related $[Ca^{2+}]_i$ changes on function of membrane Ca^{2+} transport and how this feedback may be involved in modulation of action potential waveform and the development of arrhythmias. We anticipate that the cross-talk between the surface membrane and the SR is strongest in the working myocyte, given their high density of t tubules. In addition, it has become clear that rapid mechanical perturbations of the contracting cell may cause rapid Ca^{2+} dissociation from troponin C (TnC). Consequently, Ca^{2+} released from the myofilaments may also trigger Ca^{2+} release from the SR by CICR. While normal CICR occurs during the action potential, Ca^{2+} dissociation from the myofilaments may take place when the cell is repolarized. In that case, CICR could elicit a $[Ca^{2+}]_i$ transient that in turn affects a different set of membrane channels.

II. Molecular Building Blocks of Excitation-Contraction Coupling

A. Ca^{2+} Flux Through the Sarcolemma

1. Ca^{2+} entry through voltage-gated channels—There are several types of ion channels that are Ca^{2+} permeable. What has been termed as a background Ca^{2+} channel was originally defined in bilayer experiments (453, 454) (B-type Ca^{2+} channels). Under these conditions this channel spontaneously opens, has a relatively low conductance, is not blocked by nisoldipine, and is reasonably selective for Ba^{2+}. Further investigations into resting Ca^{2+} influx into adult cardiac cells have shown the existence of spontaneously active Ca^{2+}- and Ba^{2+}-permeable but Ni^{2+}-insensitive single channels in both cell-attached and inside-out patches (108). These latter channels are activated by phenothiazines such as chlorpromazine, trifluoperazine, and H_2O_2 but at very negative holding potentials (13, 314). A short report has stated that the voltage-independent B-type Ca^{2+} channel is regulatory in ceramide-induced rat myocyte apoptosis (201). While whole cell clamp data do not reveal such macroscopic inward currents in myocytes, some have suggested that this Na^+-independent Ca^{2+} channel contributes importantly to tonic Ca^{2+} entry in the quiescent rat trabecula (307). The molecular nature of these background Ca^{2+} channels is unknown at this time.

The L-type (L for long lasting, I_{CaL}) and T-type (T for transient, I_{CaT}) Ca^{2+} currents were initially described in neuronal tissues. Bean et al. (31) first described multiple cardiac Ca^{2+} channels in canine atrial cells. At that time two types of Ca^{2+} currents carried by Ba^{2+} were

recognized. Subsequently, I_{CaL} and I_{CaT} have been recorded in cardiac tissues of most species under various conditions. However, within the same species, the density of I_{CaL} and I_{CaT} varies depending on the location of the myocyte within the heart. Hagiwara et al. (189) first described the large density of both the L- and T-type channels in rabbit sinoatrial node (SAN) cells. Zhou and Lipsius (639) described large T-type currents in latent atrial pacemaker cells. Studies of cells dispersed from canine ventricles revealed a large peak T/L current density ratio in Purkinje cells dispersed both from free-running fiber bundles and the subendocardium of the left ventricle (LV) (212, 213, 548). In contrast, myocytes dispersed from mid and epicardial layers have a smaller T/L current ratio (548). Notably, T currents have not been observed in human atrial (366, 556), human ventricular (57, 366), or human Purkinje cells (P. Boyden, unpublished data).

Cardiac L- and T-type Ca^{2+} channels differ in the following biophysical properties. *1*) Voltage range of activation: the T-channel activation occurs at more negative voltages than the L channel, e.g., in 5 mM $[Ca^{2+}]_o$ the threshold for activation is −50 and −30 mV for T and L, respectively (548). *2*) Voltage range of inactivation: in 5 mM $[Ca^{2+}]_o$, the T channel can be inactivated by membrane depolarization positive to −70 mV. The L channel remains fully available for activation at potentials more negative than −40 mV. *3*) Mechanism of inactivation: T channel inactivates solely by membrane depolarization. For the L channel, both membrane depolarization and Ca^{2+} participate in the inactivation process.

Voltage-dependent inactivation of the L-type Ca^{2+} current is clearly evident as channels incorporated into lipid bilayers inactivate even when Ca^{2+} is buffered (453) and as noted from the dependence of the time course of Ba^{2+} current decay on voltage (14, 187). In fact, inactivation of L-type Ca^{2+} current can occur at voltage steps where “apparent” activation is absent. The molecular determinants of voltage-dependent inactivation of Ca^{2+} channels are less well understood than those of K^+ or Na^+ channels. In studies using Ba^{2+} as a charge carrier, several critical locations throughout the channel protein have been implicated in the fast (tens to hundreds of milliseconds) voltage-dependent inactivation process. They are the I-II linker, the proximal COOH terminus, the EF hand area in IC, and all four S6 regions (37, 40, 41, 59, 202, 203, 504, 624, 628). One model proposed suggests that a domain of the I-II linker docks to one or all of the S6 segments at the cytoplasmic end (85, 512). Importantly, this mechanism is not involved in the channel's “recovery from inactivation,” only the channel's response to depolarization. Critical of course to these mechanisms is that Ba^{2+} permeating through these proteins show only voltage-dependent inactivation and no ion-dependent inactivation. However, recent data suggest that inactivation of the L-type Ca^{2+} channel when Ba^{2+} is the charge carrier may not be all due to a voltage-dependent process (157, 357).

The molecular basis of the cardiac L-type Ca^{2+} channel structure is due to the combination of the α_{1C}-subunit [$Ca_v1.2$; see Ertel et al. (146) for nomenclature] (four 6-transmembrane segments joined by intracellular linkers with cytoplasmic NH_2 and COOH termini) with β_2-, α_2/δ-, and γ-subunits. Alternative splicings of the α-subunit have been reported (for review, see Ref. 324) and two missense mutations in one exon appear to lead to abnormal Ca^{2+} current function in cells of patients with Timothy's syndrome (see sect. IV*A3*). Perhaps in some acquired diseases, alternatively spliced proteins constitute the remodeled Ca^{2+}

channels in arrhythmogenic substrates. The γ-subunit (33 kDa) is also expressed in skeletal muscle and in expression systems can have a modest effect on Ca^{2+} channel currents (112). Other studies have shown it can modulate $Ca_v3.1$, T-type Ca^{2+} channels (196). Its role in modulation of cardiac Ca^{2+} channels is minimal.

The $Ca_v1.2$ NH_2 terminus can act as an inhibitory particle (490) as well as a site for modulation by Ca^{2+}-binding proteins such as CaBP1 (635, 636), Ca^{2+}/calmodulin protein kinase II (CaMKII) (227), calmodulin (CaM) (227, 636), and Cavβ subunits (260). Some have suggested that a reduction in this inhibition can be caused by protein kinase C (PKC), which increases $Ca_v1.2$ Ca^{2+} currents (491); alternatively, phosphorylation of the NH_2 terminus by PKC has been proposed to decrease the L-type Ca^{2+} current (613).

Other major sites of modulation of the α_{1C}-subunit function are within the COOH terminus since it is the target of several kinases that regulate $Ca_V1.2$ L-type Ca^{2+} currents. Both PKA and CaMKII increase L-type Ca^{2+} current and change channel modal gating (139, 439, 621), and both effects are thought to be due to phosphorylation of the α_{1C} COOH terminus (227, 613). Additionally, Src kinase phosphorylation of the neuronal α_{1C}-isoform at a COOH-terminal residue leads to potentiation of the L-type Ca^{2+} current (36). However, the mechanisms by which specific kinases modulate L-type Ca^{2+} currents differ. For example, the major target for PKA in α_{1C} has been identified as Ser^{1928} (122, 370); however, recent data suggest that phosphorylation of this site may not be required for adrenergic stimulation of L-type Ca^{2+} currents (166). Although CaMKII activation leads to the same shift in modal gating as that caused by PKA stimulation (139), and CaMKII also phosphorylates the COOH terminus, the specific targets are unknown. One report suggests that Ser^{1517} may be the target (147), but definitive biochemical evidence is lacking. PKC also phosphorylates Ser^{1928} (613), although the effects of this phosphorylation on L-type Ca^{2+} currents are unknown.

The α_{1C} COOH terminus also contains a binding pocket for CaM (278), which mediates Ca^{2+}-dependent inactivation and Ca^{2+}-dependent facilitation of L-type Ca^{2+} channels (417, 643). The interaction between CaM and α_{1C} is constitutive (145, 278). T-type Ca^{2+} currents do not show Ca^{2+}-dependent inactivation (136, 213, 508); the α_{1G}- and α_{1H}-subunits lack the determinants for CaM binding in their respective COOH termini.

The voltage sensor for activation is the highly charged S4 segment. Ca^{2+} binding sites formed by glutamates in the pore loop of each repeat are critical for selectivity of the channel (144). Sections of the α_1-subunit pore-forming segments, intracellular loops, and COOH terminus all contribute to Ca^{2+} channel inactivation. Mutating single amino acids in IIIS6 and IVS6 domains have a significant effect on current decay, suggesting that an area in the inner channel mouth is a key player in channel inactivation. Further point mutations in the intracellular I-II loop and the IVS5-IVS6 linker both affect Ca^{2+} channel inactivation. Notably, these sections of the protein are also critical sites of β-subunit and/or G protein interactions.

Currently, four potential β-subunits (Ca_v β_1-β_4) have been recognized, but in cardiac cells the β_2-subunit predominates, providing a rate-limiting step in the expression of Ca^{2+} channel

proteins (102). $Ca_V\beta$ subunits are entirely cytoplasmic, and each subunit includes a variable NH_2 terminus, a conserved core that includes an interacting Src homology domain, a guanylate kinase (GK)-like domain (90, 361, 402, 526), and a divergent COOH terminus. Both the NH_2 terminus and SH3 domain contribute to isoform-specific regulation of channel inactivation (361). Interestingly, the GK domain contains the binding pocket for the α_1 interaction domain (AID) on the α_1-subunit. The role of the $Ca_V\beta$ COOH terminus is still largely unknown, but β_2 is a target for several kinases known to modulate L-type Ca^{2+} currents (e.g., the β_{2a} COOH terminus is phosphorylated by PKA on Ser^{478} and Ser^{479}). This phosphorylation appears to contribute to cAMP-dependent regulation of the channel (72).

The α_{1C}-subunit ($Ca_v1.2$) when expressed alone is sufficient for L-type channel activity, but when expressed with a cytosolic β-subunit (52), peak currents increase fourfold, apparently by accelerating the opening of the pore and reducing the rate of channel closure (295, 371, 389, 391, 415). Furthermore, there is a shift in the activation curve, a slowing of activation, and an enhancement of the inactivation process (415). β_{2a}-Subunits slow inactivation (243) due to palmitoylation of the NH_2-terminal residues, and subsequent tethering to the membrane (509). A region of I-II intracellular linker the AID of the α-subunit forms the primary binding site for the accessory β-subunits (429). It is thought that this AID region forms an α-helix that becomes buried within a conserved domain common to all β-subunits (90, 402, 555). Interestingly, functional studies have revealed that while the AID region is not necessary for β-subunit modulation of Ca^{2+} currents, the tethering of β subunits to the AID region optimizes subunit orientation which in turn increases local β-subunit concentration (346, 526). Finally, cardiac L-type Ca^{2+} current facilitation also occurs when the β_{2a}-subunit is coexpressed with the α_{1C}-subunit (113).

The two-component α_2/δ-subunit (170 kDa) remains linked in vitro, with α_2-subunit being an extracellular highly glycosylated protein; δ is the short membrane-spanning protein with a fully glycosylated extracellular portion. Several members of this family exist with α_2/δ and α_2/δ_2 being expressed in heart (170, 348). This subunit complex affects both ionic and gating currents of the expressed Ca^{2+} channels by increasing the number of functional channels at the cell surface (15, 25, 86, 281, 495). In one series of experiments, coexpression of α_2/δ with α_{1C} β_3-subunits prevented voltage-dependent facilitation (424). In these latter studies, this voltage-dependent facilitation was due to an increase in the number of channels that were able to produce gating current, as well as the number of channels that opened in response to voltage (424). Small molecules like the Ras-related G protein Gem have been shown to bind to β-subunits (33). Such binding apparently interferes with the subunit's ability to traffic the α-subunit to the membrane. Interestingly, gabapentin, a compound that has been shown to bind specifically to the $\alpha 2/\delta$-subunit (282), appears to have no consistent effect on expressed L-type Ca^{2+} currents (348).

Evidence suggests that the cardiac L-type Ca^{2+} channel protein in rabbit myocytes exists in two forms. One form is full length and comprises ~20% of all α_{1C}-subunits in rabbit membranes (122, 171, 173), while the other form, truncated at its COOH terminus, comprises ~80% of all α_1-subunits. The truncated form of the channel cannot be directly phosphorylated by PKA (122, 200), but remains in situ near the remaining α-subunit protein

(169). Functionally, it has been shown that removal of the COOH terminus from the full-length protein results in an increase in channel activity (280, 582). Several peptides designed to mimic residues of the distal COOH terminus of the $Ca_v1.2$ protein also inhibit expressed Ca^{2+} currents, illustrating that a specific domain of residues 2024–2171 of the subunit functions to inhibit channel conductance (170). It is unclear as to whether the truncated Ca^{2+} channel and its COOH terminus remain fully functional in the in situ myocyte. However, this mechanism of modulation of L-type Ca^{2+} current amplitude has the potential of being an important contributor to ECC. For example, activation of *N*-methyl-D-aspartate (NMDA) receptors and subsequent L-type Ca^{2+} channel-mediated Ca^{2+} influx induces such COOH-terminal truncation resulting in sustained changes in Ca^{2+} channel activity (200).

In addition to α_{1C} ($Ca_v1.2$), mRNA and protein from α_{1D} ($Ca_v1.3$) subunits have been measured in heart tissues (448, 530, 604). $Ca_v1.3$ Ca^{2+} channel proteins are sparse, but this type of Ca^{2+} protein may serve a specific functional role. Expression studies have shown that currents mediated by $Ca_v1.3$ proteins (plus β_{2a}-subunits) activate more quickly and decay more slowly than those of $Ca_v1.2$ proteins (288). Furthermore, steady-state inactivation and activation voltage relations of Ba^{2+} currents through $Ca_v1.3$ channels are shifted in the hyperpolarizing direction. These specific kinetic differences between $Ca_v1.2$ and $Ca_v1.3$ currents account in part for the decreased sensitivity of expressed $Ca_v1.3$ currents to dihydropyridine block (288). Finally, mice lacking α_{1D}-subunit proteins are deaf and exhibit sinoatrial dysfunction and bradycardia, suggesting a role for α_{1D}-proteins in SAN pacemaker activity (347, 425, 633). Interestingly, these mutant mice also show altered atrial Ca^{2+} currents and have inducible atrial fibrillation but no change in effective refractory period (ERP) (634). While Purkinje cells have not been studied in these mice, canine Purkinje cells express this protein, and two types of L-type Ca^{2+} currents have been described (548) suggesting that pacemaking in Purkinje cells may also involve Ca^{2+} currents through $Ca_v1.3$ channels.

The molecular basis of neuronal and cardiac T-type Ca^{2+} channels has been defined (111, 416). In both cases, the low-voltage T-type Ca^{2+} channel protein (α_{1H}, α_{1G}) ($Ca_v3.3$ and $Ca_v3.2$) has high sequence identity with the α_{1C}-subunit particularly in the membrane-spanning regions (416). Charged residues of the S4 regions are conserved between α_{1C} and α_{1H}, α_{1G} while a ring of glutamates important in α_{1C} channel selectivity has been partially replaced by aspartates. T-type Ca^{2+} currents inactivate with voltage but not by Ca^{2+} (136, 508). Some have suggested that a “ball-and-chain” type mechanism involving the amino side of the COOH terminus contributes to T-type channel inactivation (74, 508). Perhaps more importantly in terms of possible targets for pharmacological modulation, intracellular loop motifs involved in β-subunit binding (306, 429) or Ca^{2+} binding (124) of the L-type α_{1C} protein are missing in both the α_{1G} and α_{1H} proteins. In canine Purkinje cells, the large T currents most likely are due to $Ca_v3.2$ based on their kurtoxin sensitivity (448).

2. Na^+/Ca^{2+} exchange, Ca^{2+} entry, and Ca^{2+} efflux—The cardiac Na^+/Ca^{2+} exchanger protein transports Ca^{2+} across the sarcolemma in exchange for Na^+ and is important in maintaining Ca^{2+} homeostasis in the myocyte. Na^+/Ca^{2+} exchanger activity has been shown to affect various components of normal ECC [i.e., Ca^{2+} spark frequency, SR Ca^{2+} release, and SR load (47, 176, 331)]. Normally, Na^+/Ca^{2+} exchange works in the so-

called forward mode, i.e., extruding Ca^{2+} in exchange for extracellular Na^+. Reverse-mode operation of Na^+/Ca^{2+} exchanger could provide additional Ca^{2+} influx into the cell. In the forward mode, Ca^{2+} are being transported out against their electrochemical gradient, and therefore, this mode of activity requires an expenditure of energy. It is generally accepted that the Na^+ transcellular distribution indirectly provides the energy. Stoichiometric determinations have shown that three Na^+ are transported for one Ca^{2+}. Thus the exchanger is electrogenic. A recent study suggested that the stoichiometry may be closer to 4:1 Na^+/Ca^{2+} (163, 261), but these data have been challenged (211). Under normal conditions, the reversal potential of the Na^+/Ca^{2+} exchanger is −30 mV (279). Accordingly, negative to this potential Na^+ flux is inward and Ca^{2+} flux is outward generating an inward current. Positive to −30 mV, the Na^+/Ca^{2+} exchanger works in reverse mode, and outward current is generated. For the NCX1 transporter protein, it has been estimated that the turnover rate can be up to 5,000/s (209, 393) with a K_D for $[Ca^{2+}]_i$ of ∼6 μM (354). Recent data derived from the steady-state voltage and Ca^{2+} dependence of the Na^+/Ca^{2+} exchanger protein have suggested that within <32 ms of an action potential upstroke, peak Ca^{2+} in a submembrane space is >3.2 μM (578). Thus Na^+/Ca^{2+} exchanger current influences both the atrial and ventricular action potential (248). Furthermore, a component of observed transmural electrical heterogeneity of the left ventricle has been ascribed to basal differences in $I_{Na/Ca}$ currents across the wall (647).

The Na^+/Ca^{2+} exchanger protein is now considered to consist of nine transmembrane segments with a large (∼550 amino acids) intracellular loop (loop f) between segments 5 and 6 (392). The Na^+/Ca^{2+} exchanger gene *NCX1* undergoes alternative splicing (NCX1.1, NCX1.3) in the COOH terminus of its large intracellular loop. Splice variants function differently with respect to regulating properties, and expression of NCX1.3 was found to protect against severe Ca^{2+} overload conditions (230). Distinct regions of the protein have been shown to be involved in the Na^+/Ca^{2+} translocation process (135), while other regions, particularly loop f, are involved in the intrinsic regulation of the Na^+/Ca^{2+} exchanger by Na^+ and Ca^{2+} (355). Ca^{2+}-dependent regulation of exchanger activity is via a high-affinity binding site (0.022–0.4 μM) that is distinct from the Ca^{2+} transport site (354), is ∼130 amino acids in length, and is located in the center of loop f (316). Ca^{2+}-dependent regulation of Na^+/Ca^{2+} exchanger activity is apparently allosteric in ferret cells such that when $[Ca^{2+}]_i$ levels are reduced (approximately <150 nM) Na^+/Ca^{2+} current deactivates (577). A corollary is that when $[Ca^{2+}]_i$ is elevated, steady-state activation of Na^+/Ca^{2+} exchanger current increases, by as much as 67% for a doubling of $[Ca^{2+}]_i$. Such activation in normal cells promotes Ca^{2+} efflux with concomitant production of inward currents. If Ca^{2+} transients occur as traveling Ca^{2+} waves between cells, activated Na^+/Ca^{2+} exchanger current would contribute to the occurrence of Ca^{2+}-activated membrane currents.

Binding of the regulator Ca^{2+} decreases Na^+-dependent inactivation of the Na^+/Ca^{2+} exchanger (208). Intrinsic regulation of the Na^+/Ca^{2+} exchanger by Na^+ originally observed by Hilgemann (206) was termed Na^+-dependent inactivation. This process is enhanced at low intracellular pH and diminished by micromolar Ca^{2+} (207). Mutagenesis studies suggest that the exchanger inhibitory peptide (XIP) binding site is located on loop f of the protein and is involved in the Na^+-dependent inactivation of the exchanger (355). However, recent

work with split exchanger proteins suggests that endogenous XIP region is not located between amino acids 265 and 672, since the activity of split exchanger with these loop residues deleted is still blocked (405). Other regulators of exchanger function include free radicals, pH, lipid products, as well as several kinases.

3. Stretch-sensitive Ca^{2+} flux—Stretch-activated ion channels have been described in both atrial and ventricular cells of several species (34, 226, 626). The channel is permeable to monovalent cations and Ca^{2+} (275) and thus can provide a source of Ca^{2+} influx. In single cells and isolated tissues from normal hearts, stretch has been observed to lead to a gradual (10 s) increase in $[Ca^{2+}]_i$ (167, 533) as well as increases of inositol trisphosphate (IP_3) and inositol tetrakisphosphate (IP_4), both of which may modulate $[Ca^{2+}]_i$ levels (119) and subsequent force development. In adult guinea pig cells, large stretch-induced $[Ca^{2+}]_i$ changes are blocked by streptomycin (34, 168), a blocker of mechanosensitive transduction currents in hair cells (399), are not sensitive to ryanodine or tetrodotoxin (TTX), but sensitive to extracellular Ca^{2+}. Interestingly, streptomycin also blocks stretch-induced atrial tachyarrhythmias in the isolated heart (19a), presumably by inhibiting mechanosensitive cation channels in atrial myocytes (168, 275, 276). In rat cells, stretch produces a slow increase (minutes) in the electrically evoked Ca^{2+} transient (222). Stretch of either rat myocytes or trabeculae increases both the frequency of SR Ca^{2+} release (seen as Ca^{2+} sparks) as well as the level of Akt and endothelial nitric oxide synthase (eNOS) phosphorylation. Thus it has been proposed that in response to stretch, myocytes generate nitric oxide (NO), which acts locally to modify ECC efficiency (419). Interestingly, sensitivity of a myocyte to stretch increases with age and degree of cellular hypertrophy (258).

B. Intracellular Ca^{2+} Cycling

1. SR Ca^{2+}-ATPase pump—Two Ca^{2+} can be transported by the cardiac SR Ca^{2+} pump for each ATP molecule consumed (524), although other stoichiometries have been reported. ATP binds to high-affinity binding sites on the cytoplasmic side of the pump. The terminal phosphate of ATP is transferred to aspartate-351 on the pump protein, and the bound Ca^{2+} are "occluded." ATP hydrolysis of the protein alters the structure such that Ca^{2+} cannot return to the cytoplasmic side. Phosphorylation also reduces the Ca^{2+} affinity of the pump such that Ca^{2+} can be released into the lumen of the SR.

The cardiac Ca^{2+} pump protein is the same as that from slow-twitch muscle (66, 67, 344) and has 10 membrane-spanning regions where each region, M1-M5, has additional α-helical "stalk" regions on the cytoplasmic side. Most of the 96-kDa protein is on the cytoplasmic side of the SR membrane including a β-strand, phosphorylation (aspartate-351) and nucleotide binding sites, stalk domains, and a hinge region. The crucial high-affinity Ca^{2+} binding sites were initially proposed to reside in the highly anionic stalk region (67); however, more recent data suggest that they are not in the stalk, but within the transmembrane regions M4-M6 and M8 (99, 100). It is likely that in the membrane these transmembrane domains may be arranged in a cylinder to form an ion channel through the SR bilayer (344).

The rate of the cardiac SR Ca^{2+} pump is highly regulated by phosphorylation of the protein phospholamban (522). In the dephosphorylated state, phospholamban interacts with the SR Ca^{2+} pump near the phosphorylation site of the pump (246), acting as an inhibitor of the Ca^{2+} pump activity. Phosphorylation removes the inhibitory effect and increases the pumping rate (205). Phospholamban is a homopentamer; the monomer has 52 amino acids and exhibits one hydrophobic and one hydrophilic domain. A proposed structural model states that the pentamer could have a hydrophilic pore through the SR membrane with phosphorylation sites on the cytoplasmic surface (494). Kovacs et al. (290) have obtained evidence that dephosphorylation of phospholamban can form Ca^{2+}-sensitive channels in lipid bilayers. However, it is not clear whether or how the ionophoretic property might be related to the function of phospholamban in cardiac SR.

Phospholamban is phosphorylated by cAMP-dependent protein kinases (523). Studies from the intact perfused hearts show that β-adrenergic stimulation via PKA reduces the K_m for Ca^{2+} and thus accelerates relaxation of the muscle (362). Ca^{2+}-calmodulin dependent protein kinases and protein kinase C (PKC: Ca^{2+}/phospholipid dependent) (244) also phosphorylate phospholamban at threonine-17 (579). The PKC site on phospholamban is Ser-10, but there is no evidence that this site is ever phosphorylated physiologically. Whether Thr-17 phosphorylation increases V_{max} or Ca^{2+} affinity is controversial. This stimulation can result in an increase in SR content. The cardiac Ca^{2+} pump has two ATP binding sites: a high-affinity site ($K_d \sim 1\ \mu M$) that is the substrate site and a second lower affinity site ($K_d \sim 200\ \mu M$) that serves as a regulatory role (127, 138). The substrate for the Ca^{2+} pump is probably MgATP, but other nucleotides can be used (525). Therefore, the ATP level would have to be low to prevent ATP binding to the substrate site. However, decrease of the ATP level during ischemia slows SR Ca^{2+} pumping and relaxation.

2. Ryanodine-sensitive SR-Ca^{2+} release channels (RyR)—Two kinds of Ca^{2+} release channels found in the SR membrane, a Ca^{2+}-activated channel and an IP_3-activated channel, are proteins that form a distinct, highly conserved gene family. It is thought that the major mechanism regulating Ca^{2+} release in cardiac cells is CICR. CICR requires that Ca^{2+} provided by the activated L-type Ca^{2+} channel bind to the SR-Ca^{2+} release channel and cause opening of a high-conductance channel allowing rapid Ca^{2+} efflux from the SR. Studies of the SR-Ca^{2+} release channel have been greatly accelerated by the recognition that ryanodine, a plant alkaloid, is a selective and specific ligand for this channel. The RyR functionally constitutes the Ca^{2+} release channel of the SR and structurally represents the "foot" structure linking the t tubules to the SR. The recognition of selective ryanodine binding has allowed purification of several isoforms of RyR (RyR1, RyR2, RyR3) from skeletal (236, 239, 298) and cardiac (238, 297) muscle. Most of what is known about RyR comes from electrophysiological experiments on the channels after they have been incorporated into lipid bilayers (298, 456, 457, 502). Such experiments have suggested a biphasic response of the open probability of the channel (P_o) to activating [Ca^{2+}]. RyR2 P_o increases up to micromolar concentrations of $[Ca^{2+}]_i$ and then decreases at higher [Ca^{2+}] (606, 609) (Fig. 4, A and B). Luminal [Ca^{2+}] versus P_o of RyR activity slightly differs between control wild-type RyR and mutated RyR (251) (Fig. 4C). Furthermore, the probability that a single RyR will be activated is determined by the amplitude and duration

of Ca^{2+} trigger signals (623). The channel has a high Ca^{2+} conductance but can also conduct other divalent cations such as Ba^{2+} and Mg^{2+} (42, 97, 455) as well as monovalent ions in the absence of Ca^{2+} (502). Compared with the sarcolemmal Ca^{2+} channel ($Ca_v1.2$) under similar conditions, the SR Ca^{2+} release channel has lower selectivity for Ca^{2+} and 10-fold higher conductance (42). The ability of Ca^{2+} to cause release depends on $[Ca^{2+}]_i$, the rate of rise of $[Ca^{2+}]_i$ at its receptor (151), as well as the presence of various nucleotides and Mg^{2+}. RyR channels close rapidly either by deactivation (192) or decrease in trigger Ca^{2+}. An increase of SR luminal $[Ca^{2+}]$ causes a marked increase in the P_o of the Ca^{2+} release channel as well as the cell's resting Ca^{2+} spark frequency (27, 339, 500). Human atrial RyR share similar biochemical properties compared with ovine or canine ventricular counterparts (107). Refractoriness of SR release may be due in part to SR Ca^{2+} refilling mediated by the SR Ca^{2+} pump (521). Ryanodine, at low concentrations (<30 μM), opens the cardiac SR Ca^{2+} release channel in either vesicles or bilayers to a stable subconducting state and the channel no longer responds to Ca^{2+}, ATP, Mg^{2+}, or ruthenium red (363, 459). This probably is due to the occupation of the high-affinity ryanodine binding sites (K_d ~10 nM). Very high concentrations of ryanodine (>100 μM) appear to lock the Ca^{2+} release channel in a closed state.

RyR is a homotetramer with a molecular mass of the monomer of ~320–450 kDa (238, 239, 297). The three-dimensional architecture of RyRs, reconstructed using image processing, matches that of the junctional “feet” observed by electron microscopy in muscle (54, 568). The gene product of cardiac RyR is smaller than, but homologous to, that of skeletal RyR (564,711 Da) (404, 529). The COOH termini of the isoforms are well conserved and contain highly hydrophobic segments probably forming 4 of the ~10 transmembrane domains (M1-M4), with 2 additional transmembrane sequences near the center of the molecule. Recently, it has been shown (89) that substitution of alanine-3885 for glutamine near the putative transmembrane sequence of the M2 region of RyR3 reduced Ca^{2+} sensitivity of the channel 10,000-fold. Thus it has been proposed that glutamates of each RyR monomer cooperatively form the Ca^{2+} sensor of the RyR binding protein. Negatively charged residues within a transmembrane sequence are involved in binding and translocation of cations across the SR membrane (99, 611). This arrangement is attractive because it might confer Ca^{2+} sensitivity to RyR both at the cytoplasmic as well as the luminal side of the SR membrane.

Novel high-resolution imaging electron microscopic techniques have allowed exciting progress in the structural understanding of SR Ca channels IP_3R as well as RyR1, -2, and -3 (468, 481). Future progress will be facilitated by the development of crystallization procedures for these protein complexes (619). These studies have revealed that SR Ca^{2+} channels are strikingly similar tetrameric structures. We will review here the structure of SR Ca^{2+} release channels based on data from both cardiac RyR2 (629) and skeletal RyR1 (468).

Three-dimensional reconstruction of RyR1 has revealed a transmembrane domain and a large cytoplasmic assembly (Fig. 5A). The transmembrane domain is shaped as a square prism that is linked by columns in a narrower region to the cytoplasmic assembly (468). The cytoplasmic assembly itself forms a square that is rotated 45 degrees with respect to the prism. The center of the assembly gives access to a trough that connects to the Ca^{2+} channel in the depth of the transmembrane domain. The corners of the cytoplasmic assembly form

the so-called “clamp.” The sides form the “handle.” A series of interconnected tubular structures form a rhomboid structure on the t-tubular surface of the clamp linking four domains (337).

The transmembrane domain is formed of four columns, each of which forms an internal branch and an external branch. The arrangement of the internal and external branches forms a central cavity and four peripheral chambers. The resulting constricted axial structure provides direct continuity between cytoplasmic and transmembrane assemblies. The transmembrane assembly has probably at least six transmembrane α-helices per monomer and closely resembles a closed K^+ channel atomic structure (253, 337, 468) and may serve as the single Ca^{2+} channel formed by the tetramer.

Four columns arise from the external peripheral branches of the transmembrane prism. Each column consists of two connections to the handle; in addition, two adjacent monomers are structurally linked. This creates a connection between each rhomboid structure with a column of the prism via a direct pathway as well as via an external arm of the handle. If the structures in this link exhibit elastic properties, one would expect a torsional force on the prism that should depend on the integrity of the rhomboid structure on the t-tubular surface of the clamp. The twist of the transmembrane prism (as in Fig. 5), observed in the closed state of the channel, is consistent with this notion. Releasing the torque on the molecule, by dissociation of the internal connections in the rhomboid structure, would be accompanied by untwisting the transmembrane prism as has been observed during opening of the channel (480).

The peptide sequences involved in the transmembrane domains are known to some extent, although the exact number of transmembrane sequences ($\geq$6) is still under study. Similarly, the location of the peptide sequences in the cytoplasmic domains is only partially known. The location of the peptide chains in the structure of the Ca^{2+} channel is still far from complete and even farther from conclusions regarding control mechanisms of the P_o of the channel, and therefore, a detailed review of their location (cf. Refs. 332, 334, 350, 466; see also Refs. 35, 191, 333, 334, 465, 467, 629) is beyond the scope of this review. However, the proximity of mutations that affect the channel in skeletal muscle in malignant hyperthermia and central core disease and arrhythmogenic mutations in cardiac muscle suggests that the bridge in the rhomboid structure in the clamp is important to regulation of opening of the channel. The central domain of mutations that is involved in arrhythmias is again found in the bridge within the rhomboid structure of the clamp, suggesting that this structure in the clamp is important in the regulation of the opening probability of the channel.

Similar to what has been hypothesized for RyR1 channel proteins (609), it appears that RyR2 structure involves a critical interdomain interaction that plays a role in modulation of the channel's ability to release Ca^{2+}. In this hypothesis, specific domains of the NH_2 terminus interact to “zip” shut regions of the central core region. This zipped conformation has been linked to RyR2 channels with no Ca^{2+} “leak” (235). In disease and with RyR2 mutations, these regions can become unzipped to “leak” Ca^{2+} (see sect. IV*A1*). However, recent data also suggest that highly reactive free radicals destabilize these interdomain

interactions and by themselves can cause partial dissociation of the FKBP12.6 binding protein (616).

Several studies have elucidated the sites for modulation of CICR (see reviews in Refs. 44, 88). Smaller modulatory proteins that have been found to copurify with RyR proteins are triadin (68, 183), sorcin, FKBP12.6 (249), PKA catalytic and regulatory subunits, MAKAP anchoring proteins, protein phosphatase (PP) 1 and PP2A (349), and calmodulin/CaMKII (44, 182). Recently, it has become known that RyR2 can be phosphorylated by at least two kinases, PKA and CaMKII, but each has a distinctive effect on RyR2 function. Ca^{2+} spark frequency of a normal myocyte increases with CaMKII stimulation due to a direct effect of phosphorylation of RyR2 (182). On the other hand, PKA-mediated effects to increase spark frequency appear to be related to an effect on SR load. The role of each of these kinases in abnormal Ca^{2+} spark frequencies accompanying disease awaits further study. It has been suggested that the FKBP12 protein is required for normal function of RyR2 playing a key role in the efficient so-called coupled gating between neighboring RyR2 channels (401). An immunosuppressant agent, FK506, binds to FKBP12 presumably inhibiting its modulation of RyR1, thereby increasing spontaneous $[Ca^{2+}]_i$ transients by increasing the rate of release from the SR (358). FKBP12 null mice have RyR2 channels that exhibit abnormal gating in that there is a high occurrence of subconductance states (492). However, others have reported that removal of FKBP12.6 from RyR2 has no effect on RyR single-channel function (26). In rapamycin- or FK506-treated ventricular cells, presumably the loss of association of FKBP12 from RyR2 underlies the substantial increase in resting Ca^{2+} spark frequency (358).

A) Potassium and Chloride Channels in the SR Membrane: The presence of large Ca^{2+} fluxes through the membrane of the SR requires the existence of other channels which allow large countercurrents to protect against electrical instability of the SR membrane. A large-conductance (150–200 pS) K^+ channel exists in both ventricular and atrial SR membranes and provides counter ion transport for Ca^{2+} release (1, 107, 159). Activation kinetics are slow with open times of 100 ms (455). There is no inactivation process. Typical K^+ channel blockers (4-aminopyridine, iberiotoxin, amiodarone) are without effect (420). Ca^{2+} and Mg^{2+} do not alter the channel's activity (455), but its P_o is reduced in low pH. The molecular identity of this protein is unknown at this time.

Additionally, a large-conductance (120 pS) Cl^- channel exists in SR membrane and can be also permeable to Ca^{2+} (516). This Cl^- channel's activity is altered with phosphorylation (125, 270, 458), and some have suggested that phospholamban modulates its conductance (125). The molecular identity of this protein remains unknown.

B) Ryanodine Receptors and Calcium Overload of the SR: Spontaneous SR Ca^{2+} release was first observed by Fabiato and Fabiato (153) in the form of spontaneous oscillatory contractions in skinned fibers. The spontaneous contractions were initiated by loading the SR using low $[Ca^{2+}]$; the $[Ca^{2+}]$ used for the loading was by itself insufficient to induce Ca^{2+} release. The observation that skinned myocyte fragments started to contract in an oscillatory fashion led to the concept that a heavily Ca^{2+}-loaded SR is characterized by spontaneous Ca^{2+} release. The importance of this phenomenon is that spontaneous

contractions, caused by cytosolic $[Ca^{2+}]_i$ oscillations (403, 588), are accompanied by spontaneous oscillations in current and membrane potential in both single myocytes as well as nondriven multicellular cardiac preparations (80, 264, 287). Agents that reduce Ca^{2+} load of the SR (e.g., ryanodine, caffeine, EGTA buffer) abolish spontaneous $[Ca^{2+}]_i$ oscillations as well as the oscillatory potentials, current, and contractions (4, 353, 519). Therefore, it is thought that spontaneous $[Ca^{2+}]_i$ oscillations are not secondary to transmembrane potential changes but, given the correct initiating conditions, may cause depolarization and give rise to nondriven action potentials (61, 64, 81, 353) (Fig. 6).

As stated, Fabiato's work on the properties of cardiac SR (152) has provided a potential explanation for spontaneous Ca^{2+} release in mechanically skinned cells in which the SR was intact. The mechanism for increased probability of opening of the SR Ca^{2+} channel when the SR is heavily loaded with Ca^{2+} is still uncertain, but suggests that the channel is directly or indirectly sensitive to the luminal $[Ca^{2+}]$ of the SR. The localization of the Ca^{2+} sensor in the transmembrane domain of the RyR channel could make it suitable as a sensor of both luminal and cytosolic $[Ca^{2+}]$. Intact normal cells with a high SR Ca^{2+} load show similar phenomena (82, 287). Hence, the oscillatory character of a triggered arrhythmia in myocardium with a high cellular Ca^{2+} load may be due to further increase of Ca^{2+} entry into the cells during the action potentials of the arrhythmia causing even more Ca^{2+} loading of the SR. Consequently, as soon as the release process has recovered after an electrically induced Ca^{2+} release, the overloaded SR again releases a fraction of its Ca^{2+}. The requirement that the Ca^{2+} release mechanism must recover first would explain the presence of a delay between aftercontractions and afterdepolarizations and the preceding beat.

The released Ca^{2+} constitutes a “leak” from the SR that tends to reduce the “overload.” This phenomenon has been observed in different forms, which all fall under the general definition of a Ca^{2+} leak, e.g., increased probability of opening of RyR in lipid bilayer experiments (252), a biochemically detectable loss of Ca^{2+} from the SR (615), Ca^{2+} sparks in isolated cells and muscle (485, 590), micro Ca^{2+} waves in isolated cells and muscle (252, 615) and Purkinje cells after infarction (61), Ca^{2+} waves that travel inside myocytes but are limited to single cells (396), and multicellular cellular Ca^{2+} waves (308, 372, 513). The threshold for Ca^{2+} “leak” appears to be reduced in some arrhythmogenic mutations of the RyR (252) and in the acquired dysfunction of the RyR such as in congestive heart failure (49, 581, 614) and the first days after infarction (61).

3. IP_3-dependent Ca^{2+} release—By immunohistolocalization techniques, the IP_3 receptor (IP_3R) has been identified in cardiac cells. Its density is less than that of RyR2 but particularly high in Purkinje and atrial cells (178, 342, 513). Most studies show it is located to a region of the intercalated disc (160, 384) with little or no fluorescence in longitudinal SR or mitochondria (274). Three isoforms of IP_3R have been identified, with IP_3R2 occurring in working cardiac muscle (414) and IP_3R2 in the atrial and IP_3R1 in the Purkinje fiber system (178, 325). IP_3R2 staining in atrial cells is mostly discontinuous, but of a different distribution than that of RyRs. Double-labeling experiments show that RyRs and IP_3R2s overlap in subsarcolemmal regions of rat atrial cells (325, 342), and IP_3R1 resides mostly with RyR2 in peripheral regions of the Purkinje cell (513). While there are more

IP_3R2s in atrial versus ventricular cells, binding studies suggest IP_3 binding affinities in atrial (K_d = 7.2 nM) and ventricular cells (K_d = 6.8 nM) are similar (325).

IP_3R is a tetramer (either homomeric or heteromeric) with a binding site on each subunit. IP_3-induced Ca^{2+} release is regulated by Ca^{2+} with a biphasic sensitivity (188); that is, IP_3-induced opening and subsequent release are augmented with a modest increase in cytosolic Ca^{2+} (<300 nM) but are inhibited at higher [Ca^{2+}]. However, the predominant cardiac IP_3R type 2 is resistant to the inhibitory effects of high Ca^{2+} (437). IP_3R2 has the highest affinity for IP_3 (0.10 μM) followed by IP_3R1 and then IP_3R3 (0.40 μM). ATP modulates IP_3R1 and IP_3R3 but not IP_3R2 (550). For the rat IP_3R2, amino acids 1915 to 2175 appear to bind Ca^{2+} (367). The Ca^{2+} sensor region is conserved between the various IP_3R isoforms [i.e., E2100 is critical for Ca^{2+}-induced changes of IP_3R1 (376)]. Isoforms appear to have similar gating and conductance properties and show the bell-shaped sensitivity to Ca^{2+} (551). These sites are located near the FKBP12, PKA, ATP, and CaM binding sites, all within the regulatory domain of the molecule (71). PKA, while effectively phosphorylating IP_3R1, is a weaker modulator of IP_3R2 and IP_3R3 (595). Residues of the COOH-terminal tail are thought to be a site where ligands bind to transduce activation of the channel (553).

Accessory proteins have been implicated in the Ca^{2+} regulation of IP_3-induced release (627). For example, IP_3R2s bind Ca^{2+}/CaM (608), which subsequently inhibits Ca^{2+} release (2). This interaction is Ca^{2+} independent, suggesting a role for CaM in tonic inhibition of IP_3Rs. One family of Ca^{2+} binding proteins (CaBPs) are direct ligands of the IP_3 channel (612), suggesting that IP_3 release channel can become activated by a rise in Ca^{2+} without the necessity for IP_3 and Ca^{2+} coincidence. Recent studies have shown that the brain IP_3R1 complexes with PKA, PP2A, and PP1 (132). PKA increases the sensitivity of IP_3R1 to activation by IP_3 (595), while PP2A and PP1 would be expected to inhibit channel activity. Other high-affinity, low-capacity calcium binding proteins, such as NCS-1, have been shown to directly increase IP_3R1 single-channel activity (473), which subsequently leads to dysregulated intracellular Ca^{2+} via IP_3Rs. Interestingly, this interaction between NCS-1 and IP_3R1 is attenuated with lithium.

The role of IP_3 Ca^{2+} release in cardiac ECC is unknown, but IP_3R2s from ferret ventricle when incorporated into planar bilayer are Ca^{2+} selective, IP_3 activated, blocked by heparin, and not altered by ryanodine (414). Interestingly, in skinned cardiac fibers, IP_3 can induce tension oscillations and enhance submaximal caffeine induced CICR (641) without increasing the Ca^{2+} sensitivity of Ca^{2+} release channel (641). Presumably this is because luminal Ca^{2+} can bind to cytosolic IP_3R sites and modulate function. Recent work has linked a highly specialized local Ca^{2+} pathway between IP_3, IP_3R, CaM, and CaMKII and nuclear transcription (599). In adult ventricular cells, endothelin-1 increases IP_3, which binds to its nuclear membrane receptor. This IP_3 receptor is associated with CaM and CaMKII, which then activates type II histone deacetylases (HDACs), leading to the derepression of transcription factor MEF2 (599). Thus IP_3Rs appear to play a role in excitation-transcription coupling in the native cell.

In rat atrial cells preincubated in the cell-permeant analog of IP_3 ($InsP_3BM$), an IP_3 receptor agonist, the number of spontaneous Ca^{2+} sparks increases significantly, particularly in the

subsarcolemmal regions where IP_3R2s and RyRs colocalize (325). Furthermore, $InsP_3BM$ increases electrically evoked atrial Ca^{2+} transients suggesting that Ca^{2+} released from activated IP_3Rs activate RyRs mimicking the effects of endothelin in atrial cells (342, 343). IP_3-evoked Ca^{2+} release in ventricular cells is modest compared with that of atrial cells (325). Initial evidence had suggested that IP_3 receptor function is critical for the positive inotropic effects of α-adrenergic agonists in guinea pig (378), but these results should be taken with caution since the inhibitor used, xestospongin C, may have other effects. Recent studies using permeabilized atrial cells suggest that IP_3 and adenophostin can trigger elementary nonpropagating Ca^{2+} events that can be prevented by both heparin and 2-aminoethoxy-diphenylborate (2-APB) (642). Furthermore, IP_3R2-deficient atrial cells failed to show endothelin-1-induced spontaneous Ca^{2+} transients (322), suggesting that IP_3-dependent Ca^{2+} release enhances atrial intracellular cell signaling. 2-APB also affects the incidence and frequency of spontaneous Ca^{2+} events in Purkinje cells from the infarcted heart (62), again suggesting a modulatory role of IP_3 in Ca^{2+} release in Purkinje cells from diseased hearts.

As discussed, Ca^{2+} waves in cardiac cells depend on the regenerative production of a diffusible molecule that triggers Ca^{2+} release from adjacent SR stores. Cytosolic Ca^{2+} may be one such diffusible molecule, but IP_3 could also serve as a propagating signal within and between cardiac cells. IP_3-dependent Ca^{2+} waves have been reported in airway epithelial cells (56) and other nonexcitable cells (77, 175). In these latter cells, an endoplasmic reticulum Ca^{2+} binding protein, calreticulin, clearly inhibits IP_3-evoked repetitive Ca^{2+} waves (77). At this time, no apparent role has been defined for IP_3-dependent Ca^{2+} release in cardiac cell wave propagation.

4. Mitochondria Ca^{2+} transport—Mitochondria can accumulate a large amount of Ca^{2+}, aided in the presence of inorganic phosphate by the precipitation of insoluble Ca^{2+}-phosphate deposits in the matrix (84). Ca^{2+} enters via a uniporter pathway down a large electrochemical gradient (~180 mV) set up by proton extrusion linked to the electron transport system. The uniporter can be blocked competitively by physiological $[Mg^{2+}]_i$ and also potently by ruthenium red and lanthanides (45). Ca^{2+} extrusion occurs mainly via Na^+/Ca^{2+} and Na^+/H^+ exchangers and thereby is $[Na^+]$ dependent (181).

Ca^{2+} uptake by the mitochondria is too slow to contribute significantly to intracellular Ca^{2+} transient and myocyte relaxation (46), but may have an important role in the regulation of the $[Ca^{2+}]_i$ over periods of many seconds and could, therefore, be expected to contribute to the mechanical restitution of cardiac muscle preparations. This postulate would require that there would be an interaction between the SR and the mitochondria, as observed in skinned rat cardiac trabeculae. In skinned rat fibers, the mitochondria have been observed to decrease the maximally Ca^{2+}-activated force (557). Miyata et al. (377) developed a new approach to measure mitochondrial free $[Ca^{2+}]$ within a living cell by using a fluorescence Mn^{2+} quenching technique. A dependence of mitochondrial free $[Ca^{2+}]$ on the frequency of electrical stimulation suggests that mitochondria can accumulate Ca^{2+} under physiological conditions. Also a study by Wendt-Gallitelli et al. (585) on the changes of total mitochondria Ca^{2+} using electron probe X-ray microanalysis supports the results of Miyata et al. (377). Recent data suggest mitochondrial Ca^{2+} uptake is apparent only after a

progressive Ca^{2+} load (cytosolic threshold ~30–500 nM) and is sensitive to the mitochondrial Ca^{2+} uniporter blocker Ru360 (640). Further direct evidence has been reported for a role of mitochondria in clearing subsarcolemmal Ca^{2+} near the L-type Ca^{2+} channels and subsequent inactivation (469).

Instead of mediating cardiac Ca^{2+} fluxes during the contraction-relaxation cycle, mitochondrial Ca^{2+} fluxes regulate intramitochondrial processes and thus ATP production. Some matrix enzymes, e.g., pyruvate dehydrogenase, α-oxoglutarate dehydrogenase, and the NAD-dependent isocitrate dehydrogenase, can be activated by Ca^{2+} in the low micromolar range (128, 129, 359). Therefore, an increase of $[Ca^{2+}]_i$ would lead to an increase of $[Ca^{2+}]$ in mitochondria that would increase oxidative metabolism and thereby increase ATP production to meet increased demands caused by high cytosolic $[Ca^{2+}]$, e.g., contractile activation and Ca^{2+}.

Under pathological conditions, mitochondria can also accumulate a large amount of Ca^{2+}. When Ca^{2+} overload occurs, mitochondria will temporarily compensate for a cellular Ca^{2+} load by taking up large amounts of Ca^{2+}, which may prevent cell damage. However, Ca^{2+} accumulation by mitochondria diminishes ATP production and may eventually compromise the mitochondria by inducing the permeability transition. It seems that mitochondrial Ca^{2+} transport is important in the regulation of intramitochondrial dehydrogenases and in coping with cellular Ca^{2+} overload. However, beat-to-beat fluctuations in mitochondrial $[Ca^{2+}]$ are small during normal ECC (640).

C. Intracellular Ligands and Buffers

1. Sarcolemmal Ca^{2+} binding—The interaction between Ca^{2+} and the sarcolemma is pivotal in the feedback mechanisms described in section III*C* The actual $[Ca^{2+}]$ close to the sarcolemma is determined by the cell's buffering systems, one of which is formed by phospholipids, mostly the phosphatidylserines and phosphatidylinositols of the cell membrane. The density of phosphatidylserine and phosphatidylinositol (427) permits substantial Ca^{2+} binding (585); the number of sarcolemmal binding sites is estimated at 42 μM (42). The K_d for Ca^{2+} binding (0.3–1.5 μM) allows these phospholipids to act as a powerful dynamic buffer during the contractile cycle. Hence, feedback of subsarcolemmal $[Ca^{2+}]$ on protein function in the sarcolemma depends critically on this buffer system. Given the low K_d of this buffer, it would be expected that in Ca^{2+} overloaded cells, the buffer may saturate and cease to buffer $[Ca^{2+}]$ variations near the sarcolemma.

2. Intracellular ligands—Table 1 shows important intracellular Ca^{2+} ligands in the cardiac cell. It is unlikely that these ligands reflect all intracellular binding sites as was shown by electron microprobe analysis of rapidly stimulated and frozen isolated guinea pig myocytes. Wendt-Gallitelli et al. (585) have shown that the total $[Ca^{2+}]$ rises and falls in the A band of the myofibril from ~2.6 to ~5.5 mmol/kg dry wt following a voltage-clamp pulse (from −80 to +5 mV for 180 ms). The rise and fall nearly parallels the free $[Ca^{2+}]_i$ transient itself, indicating that binding and dissociation of Ca^{2+} occur extremely rapidly and that the contractile proteins are responsible for the threefold slower rise of force. These values of total $[Ca^{2+}]$ in the presence of a $[Ca^{2+}]_i$, which ranges between 100 nM at diastole and 1 μM

at peak systole, reinforce the notion that the Ca^{2+} is tightly buffered in the cardiac cell. The concentrations of buffers in the cell indicated in Table 1 are not enough to explain that in excess of 99% of Ca^{2+} is buffered (585). Hence, Wendt-Gallitelli et al. (585) have postulated an additional 600 μM of rapid Ca^{2+} binding sites in the cell. Precise knowledge of the properties of these latter buffers is required to assess their modulation of protein function.

III. Functional Consequences of Calcium Cycling

A. Macroscopic Events

1. The cardiac cycle: cytosolic Ca^{2+} transients and force development—Figure 3A shows force and the estimated cytosolic [Ca^{2+}] (with a peak of ~1 μM) as a function of time during a twitch in a muscle loaded by microinjection of fura 2 salt (22). The results are representative of contractions at long and short end-systolic sarcomere length (SL), i.e., at the extremes of the function curve of cardiac muscle. Figure 3A shows a typical behavior of mammalian cardiac muscle, i.e., peak and time course of the Ca^{2+} transients are remarkably independent of length, albeit that the relaxation phase differs between the short and long muscle. The interpretation of $[Ca^{2+}]_i$ transients and their relation to force development requires caution, since it is known that full activation of the contractile system requires saturation of all Ca^{2+} sites on TnC (requiring ~60 μM) with simultaneous binding of another 25 μM Ca^{2+} to calmodulin (43). Hence, even activation of the muscle at only 25% of its maximum, such as in Figure 3A, is accompanied by Ca^{2+} turnover of ~30 μM. It is clear that only a small fraction of this Ca^{2+} is "visible" in the cytosol. With these considerations the cytosolic Ca^{2+} transient can teach us about a number of important properties of the ECC process. The changes in the kinetics of the transient with stretch are consistent with the hypothesis that force-length relation is determined principally by the length-dependent sensitivity of the contractile system, which resides in the relation between Ca^{2+} affinity of TnC and stretch (204, 272). This also implies that in the stretched myocardium more Ca^{2+} is bound (221). The molecular mechanism underlying length dependence of Ca^{2+} binding to TnC remains unknown, but one current hypothesis is that force exerted on the actin filament deforms the TnC molecule, thus retarding the dissociation of Ca^{2+} from TnC. This effect is bound to be length dependent since the number of myosin cross-bridges that can attach to actin increases with SL over the operational range of cardiac muscle (1.6 to 2.3 μm). Thus the mechanical load on a sarcomere will influence the dissociation of Ca^{2+} from TnC. In fact, it has been shown that rapid removal of an external load on a muscle causes a robust additional $[Ca^{2+}]_i$ transient (224). This phenomenon can be important when the ECC properties of the myocardium are nonuniform (such as in disease), since nonuniformity of contraction of myocytes may be accompanied by such unloading-related $[Ca^{2+}]_i$ transients. Thus the relaxation phase of the $[Ca^{2+}]_i$ transient depends on the rates of Ca^{2+} binding and dissociation to and from TnC, the rate of Ca^{2+} binding to the sarcolemma Na^+/Ca^{2+} exchanger, and the Ca^{2+} pump of the SR and on the rate of removal of Ca^{2+} by these transporters.

B. Microscopic Events

1. Ca^{2+} sparks in normal cardiac ventricular muscle—Spontaneous release of Ca^{2+} from the SR is evident in single ventricular cells as spatially localized increases in $[Ca^{2+}]_i$, termed Ca^{2+} "sparks" (92). Ca^{2+} sparks are also triggered during voltage-clamp pulses (335) and during action potentials (79), where they have been termed "evoked Ca^{2+} sparks" or "local $[Ca^{2+}]$ transients." Local $[Ca^{2+}]$ transients or evoked Ca^{2+} sparks were originally proposed to be triggered by Ca^{2+} entering via single L-type Ca^{2+} channels (78, 336, 574). It is thought now that a cluster of L-type Ca^{2+} channels is involved in triggering a cluster of RyRs at least in rabbit ventricular cells (237). Even during periods of no electrical activity, Ca^{2+} released from RyR can occur and is due to the low probability of opening of RyR at diastolic Ca^{2+} levels (92). Ca^{2+} sparks may also trigger each other to produce Ca^{2+} waves, which propagate through the cell (91). It now seems unlikely that a Ca^{2+} spark arises from a single ryanodine receptor (92, 574) because smaller SR Ca^{2+} release events can be observed under some conditions (326) and because Ca^{2+} sparks can sometimes be observed directly to have multiple sites of origin (407). Numerous experiments have suggested that sparks are due to the coherent release of Ca^{2+} by a cluster of RyR and that Ca^{2+} sparks evoked by L-type Ca^{2+} currents summate, spatially and temporally, constituting the electrically evoked whole cell $[Ca^{2+}]_i$ transient (78, 79, 335, 336, 589) that couples excitation to contraction.

The relevance of Ca^{2+} sparks to normal ECC was proven recently by similar observations using confocal microscopy of working ventricular trabeculae under physiological conditions ($[Ca^{2+}]_i$ and temperature). Similar to the situation with Ca^{2+} sparks, Ca^{2+} waves had been recorded previously only in single isolated cells (511, 528, 588), although waves of sarcomere shortening, limited to single cells, had been reported in multicellular preparations. A possibly related phenomenon, scattered light intensity fluctuations (SLIFs), has been recorded in ventricular muscle but had been related only indirectly to fluctuations in $[Ca^{2+}]_i$. In addition, rapidly propagating Ca^{2+} waves, accompanied by propagating contractions, have been recorded in trabeculae with focal damage (see sect. IV).

Confocal images of microscopically quiescent trabeculae are illustrated in Figure 3B. Ca^{2+} sparks are readily visible in the full-frame image as spatially localized bright regions and in the line-scan images as localized transient changes in fluorescence in microscopically quiescent muscle (590). In line-scan images, Ca^{2+} waves are apparent as regions of elevated $[Ca^{2+}]_i$ that move at constant velocity. Ca^{2+} sparks are common ($\lesssim$300/s) at body temperature, with ~10% of these being generated from repeatedly firing single sites. The average spacing between Ca^{2+} spark sites is 2 μm or intervals of one SL. In addition to single Ca^{2+} sparks, the line scans showed that Ca^{2+} sparks larger in extent than 2 μm occurred at ~10% of the frequency of the single Ca^{2+} sparks. Ca^{2+} sparks are similar in time course and spatial spread in unstimulated muscle compared with those recorded in single isolated cardiac cells. The fluorescence ratio can be used to calculate the $[Ca^{2+}]_i$ by assuming that the lowest fluorescence at the site of the Ca^{2+} spark represents fluorescence at the normal "resting" $[Ca^{2+}]_i$ (100 nM). The time to rise from 10 to 90% of the peak is 5 ms, and the time to fall from peak to half of peak is 40 ms. The average Ca^{2+} spark is preceded by a rise of the $[Ca^{2+}]_i$, which starts 10 ms before the Ca^{2+} spark. Such an event, which suggests the possibility of triggering of some of the Ca^{2+} sparks by a local rise of $[Ca^{2+}]_i$,

has also been described in isolated cells. After the peak of the Ca^{2+} spark, the width of the region with elevated Ca^{2+} increases with time consistent with diffusion of Ca^{2+} away from the Ca^{2+} spark generating site, as has also been shown in isolated cells (407). Most Ca^{2+} sparks in muscle reach an amplitude of ∼200 nM with a progressive decrease of the number of larger sparks (>400 nM). A similar distribution has been found in single isolated cells. The peak amplitude Ca^{2+} sparks is ∼200 nM, which is below the level at which cross-bridges are activated in intact trabeculae. Although the exact estimate of $[Ca^{2+}]_i$ on the submicrometer scale is problematic due to both the rapid changes of $[Ca^{2+}]$ and the kinetics of buffering by fluorescent indicators, the observation that Ca^{2+} sparks occur in microscopically quiescent muscles is not surprising.

A) Calcium Sparks in Atrial and Purkinje Cells: From ultrastructural analysis, peripheral couplings in cat atrial cells are circular and measure 0.2–0.6 μm This is consistent with the size of the individual Ca^{2+} release events that have been observed in situ (53). In atrial cells from normal hearts, Ca^{2+} sparks are more frequently seen at the periphery (500 sparks·s^{-1}·pl^{-1}) of the cell compared with the center (100 sparks·s^{-1}·pl^{-1}) (232). Central sparks tend to be larger and longer in spatial spread. In fact, release sparks in atrial cells can occur as doublets, triplets, or compound sparks (53, 597) and can span up to 7 μm with spatial distance between these events being variable within different regions of the cell. In rat atrial cells, electrically evoked Ca^{2+} transients are comprised of a set of Ca^{2+} sparks that appear to have a specific spatiotemporal order; that is, at specific peripheral sites, a Ca^{2+} spark always appears first and the activation order of sites for remaining sparks remains consistent with each subsequent paced beat and is not modified by SR load (38, 341). These data suggest that at least for the rat, there may be L-type Ca^{2+} channel SR couplings that show a different sensitivity to CICR.

In normal canine Purkinje cells, spontaneous Ca^{2+} sparks have characteristics similar to those of ventricular cells; however, in the presence of normal $[Ca^{2+}]_o$, there is also a population of wider and larger sparks (513). These compound sparks of Purkinje cells may represent near-synchronous activation of multiple types of Ca^{2+} release channels. For canine Purkinje cells, this could mean a combination of Ca^{2+} releases from both IP_3R and RyR receptor release channels (513).

2. Microscopic Ca^{2+} waves in normal muscle—Slowly traveling Ca^{2+} waves occur rather rarely in trabeculae ($[Ca^{2+}]_o$ = 1 mM; 37°C) and appear comparable to those in single cells (511, 528, 588). They occur commonly several seconds after the twitch. Their average frequency is ∼2.5 Hz/cell, and they transmit less than ∼4 SL. More often than not, waves propagate in only one direction. This suggests that if these waves start at a gap junction, their propagation into one or both cells connected to the gap junction would be dictated by chance. It is striking that Ca^{2+} waves show Ca^{2+} sparks on their leading edge, with an average distance of Ca^{2+} sparks along the edge of ∼1 SL (91). These latter authors concluded that in single cells Ca^{2+} sparks may provide the regenerative mechanism for a Ca^{2+} propagation wave from one terminal cisternae to another. In this case, the trigger for Ca^{2+} spark generation during a propagated wave would consist of Ca^{2+} arriving from an adjacent Ca^{2+} spark generating site (91). If Ca^{2+} release from the site is proportional to the

rate of rise and the absolute $[Ca^{2+}]_i$ reached at the Ca^{2+} spark site, one would anticipate that waves would propagate at a constant velocity, since the same process would repeat itself at each following site. These results may provide an explanation for spontaneous motion observed previously in the form of SLIF in rat papillary muscles. In this regard, it has been reported recently that the frequency of Ca^{2+} sparks recovers after stimulation, similar to that observed for SLIFs (286). If single Ca^{2+} sparks precede the development of Ca^{2+} waves, it is conceivable that SLIF accompanies Ca^{2+} waves and that Ca^{2+} sparks remain undetected by techniques that monitor only sarcomere motion. Nevertheless, small Ca^{2+} waves, if in only a few myocytes, would be unable to cause a depolarization sufficient to trigger an action potential if the myocytes were well coupled to its neighbors.

3. Ca^{2+} waves in intact whole hearts—Minamikawa et al. (368) were the first to demonstrate that traveling Ca^{2+} waves (propagation velocities 60–100 μm/s) occurred in the perfused rat heart. Despite low temporal resolution of their images, they concluded that Ca^{2+} waves play little if any role in pathology, since they were easily abolished by pacing. Improvement of confocal imaging to more "real" time has allowed further investigations into the types of Ca^{2+} waves observed in perfused rat hearts. Hama et al. (190) concluded that Ca^{2+} waves in their normal hearts had limited effects on Ca^{2+} homeostasis of the myocardium. Kaneko et al. (259) extended these studies (also in rat hearts) by describing three types of Ca^{2+} waves in perfused hearts. Interestingly, waves of somewhat similar characteristics occurred in both the quiescent and presumably Ca^{2+}-overloaded hearts. The incidence and velocity of in situ Ca^{2+} waves were related to $[Ca^{2+}]_o$ and presumably the Ca^{2+} load of the SR. More recent studies in normal rat hearts confirm previous work reporting that intercellular Ca^{2+} wave propagation was mostly confined to two or three cells (18). Furthermore, these authors suggested that spatiotemporal summation of changes in transmembrane potential caused by individual Ca^{2+} waves may underlie generation of triggered electrical impulses such as those that occur in trabeculae or aggregates of Purkinje cells from the infarcted heart. Nevertheless, despite the numerous technical limitations of these types of isolated heart experiments (see Ref. 514), Ca^{2+} waves in normal hearts seem of little importance to rhythm in these hearts. On the other hand, Ca^{2+} waves occurring in the regions of nonuniformity of the ablated rat heart may gain importance (532).

C. Regulation of Ca^{2+} Transport

The transient elevation of $[Ca^{2+}]_i$ following the start of the AP can affect ion channel function, impacting on the time profile of the AP during the plateau and repolarization phases on a beat-to-beat basis. Ca^{2+} could do so by directly binding to ion channel proteins or by influencing the activity of other proteins, which could then modulate ion channel behavior. In this section we discuss the effect of $[Ca^{2+}]_i$ on currents involved in the various phases of the AP.

Well known are the effects of Ca^{2+} on depolarizing currents during the AP, yet little is known about the influence of $[Ca^{2+}]_i$ on sodium current (I_{Na}) on a beat-to-beat basis. Recent biochemical evidence suggests that our current thinking that voltage-gated cardiac sodium channels are not directly coupled to Ca^{2+} signaling events may not be true. These data suggest that the Ca^{2+} binding sensor protein CaM binds to the α-subunit of the rat brain type

II Na^+ channel (382). Moreover, COOH-terminal residues bind Ca^{2+}-bound and Ca^{2+}-free CaM, apoCam. The human cardiac sodium channel ($Na_v1.5$) also contains residues within this "IQ" motif that bind Ca^{2+}/CaM (531). In so doing, there is an increase in the proportion of slowly inactivating Na^+ channels. A mutation associated with Brugada syndrome in the COOH-terminal region (A1924T) inhibits the slow inactivation induced by Ca^{2+}/CaM (531). More recent data have shown that residues within the EF hand domain of $Na_v1.5$ bind Ca^{2+} with an affinity within a range known for Ca^{2+} sensors (593). Such Ca^{2+} binding increases Na^+ channel availability by producing a shift in voltage dependence of channel availability. In a recent report studying various sodium channel isoforms, it was suggested that CaM modulation of function is isoform specific (131), and the effect is to modulate the COOH-terminal inactivation of the III-IV linker of $Na_v1.5$ (277).

$[Ca^{2+}]_i$ or current-dependent inactivation of the L-type Ca^{2+} current has been recognized for many years (312, 364). Hallmarks of this process in native cells include the complex time course of current decay and the presence of a dip in the inactivation curve; that is, in tightly buffered cells, whole cell Ca^{2+} currents recorded during the final pulse to a fixed test potential of a three-step inactivation protocol show a minimum current level near 0 mV, but current increases again at conditioning steps positive to 0 mV. Finally, Ca^{2+} current-dependent inactivation is evident in that the decay of I_{CaL} is faster the larger the current amplitude (360) or by Ca^{2+} buffering or use of Ba or Sr as the charge carrier. Both Ca^{2+} released from the SR as well as Ca^{2+} influx through the voltage-activated I_{CaL} contribute to the Ca^{2+}-dependent inactivation (517). In ventricular cells, normal SR Ca^{2+} release can reduce the calculated integrated Ca^{2+} influx by 50%. In fact, local SR Ca^{2+} flux that is sensed by the Ca^{2+} channel peaks within 5 ms and is independent of the amplitude of the release. The mechanism of how influx and subsequent release of Ca^{2+} but not other ions, hasten the Ca^{2+} current decay is unknown. One hypothesis is that Ca^{2+} directly bind to the α-subunit of the L-type Ca^{2+} channel protein. An initial hypothesis was that a consensus Ca^{2+} binding motif (EF hand) is near the inner mouth of the proposed channel and is required for current-induced inactivation of channel activity (124, 390). However, mutagenesis of putative Ca^{2+} binding sites in this region of the channel does not entirely remove Ca^{2+}-dependent inactivation (418, 637). Other data suggest that 40 amino acids located near the COOH terminus of the α-subunit protein of the L-type Ca^{2+} channel are implicated in the process (418, 503, 637).

While the COOH terminus of the L-type Ca^{2+} channel α-subunit contains binding sites for many regulatory proteins, recent data show that CaM can bind to the COOH terminus IQ domain (410, 417, 643) as well as a CaM-binding domain that lies between the EF and IQ regions (385, 410, 447). This suggests that CaM functions as a Ca^{2+} sensor for calcium-dependent inactivation of the channel. In fact, at Ca^{2+} levels of 10–100 nM, a portion of the resting COOH-terminal domain binds CaM acting as its tether (423); that is, CaM is preassociated with the channel. In this latter scenario, the two lobes of a single CaM molecule do not tether to the same site but rather bind to multiple noncontiguous sites. Upon the further elevation of Ca^{2+}, one lobe of CaM binds specific IQ residues while the other lobe remains as a secure anchor for CaM. CaM interaction with IQ residues then allows for quick and efficient inactivation of the L-type Ca^{2+} current. In fact, while one CaM molecule

is sufficient for calcium-dependent inactivation of the channel in an expression system, local CaM concentrations near the Ca^{2+} channel have been estimated to be as great as 2.5 mM (383), much greater than global estimates of CaM (345). Interestingly, residues involved in tethering CaM also appear to be involved in controlling the rate of inactivation of Ba^{2+} currents, which is assumed to inactivate by a voltage-dependent process (423). While the N lobe of CaM has been implicated in Ca^{2+}-dependent inactivation of other Ca^{2+} channel isoforms (323), it is unclear at this time as to its role in $Ca_v1.2$ Ca^{2+}-dependent inactivation. Recent work by Kim et al. (278) suggests that in the presence of both CaM and Ca^{2+} which bind and change the conformation of the COOH terminus, certain residues can interact with now nearby residues of the I-II linker. This combined complex then occludes the pore. Interestingly, another Ca^{2+} sensor, CaBP1, binds to the pore subunit in this way as to prevent $Ca_v1.2$ inactivation (636). The role of CaM in this functional effect is not known.

The influx of Ca^{2+} (estimated to be $\sim 10\ \mu$mol/l cytosol) most likely inactivates L-type Ca^{2+} channel activity, but under some circumstances, a $[Ca^{2+}]_I$-dependent increase or facilitation of the L-type Ca^{2+} current has been described (155, 184, 214). Interestingly, facilitation of L-type Ca^{2+} channels is diminished in the presence of ryanodine and prevented by CaMKII inhibitory agents (11, 605, 620). In fact, dialysis of cells with constitutively active form of CaMKII restores I_{CaL} facilitation (10, 602). Recently Hudmon et al. (227) showed that CaMKII tethers to the Ca^{2+} channel helping to form the macromolecular complex. When Ca^{2+} rises via voltage-dependent entry or its subsequent SR release, it activates CaMKII and thus phosphorylates the channel protein (227), inducing modal gating shifts favoring long channel openings (139). This above apparent cross-talk occurs because CaMKII activity in turn reduces the "gain" of ECC (601). The frequency response of CaMKII is modulated by both the amplitude and duration of Ca^{2+} spikes (123). On the other hand, CaM and its binding to the pore-forming unit of the channel appears to control both inactivation and facilitation of P/Q-type Ca^{2+} channels (126). In this latter scenario, Ca^{2+} binding to the NH_2-terminal lobe of CaM initiates inactivation while the Ca^{2+} sensing portion of the NH_2-terminal lobe initiates Ca^{2+} current facilitation. Some have described a scenario where the time course of Ca-CaM, CaMKII, and two of its phosphorylation sites is one where the time course of Ca-CaM largely follows that of the global Ca^{2+} transient, while that of CaM bound to CaMKII declines more slowly. Thus with repetitive stimuli, CaMKII accumulates in its active state (345).

Once an L-type Ca^{2+} channel is activated and inactivated, it follows a predictable time course as it recovers from inactivation, repriming itself for the next stimulus. This recovery process is voltage and Ca_i dependent. Voltage-dependent recovery has a reasonably fast phase and slow (477) or very slow (65, 263) phase. Importantly, recovery from $[Ca^{2+}]_i$-induced inactivation may occur at positive plateau potentials and depends on both SR and Na^+/Ca^{2+} exchanger function (364, 496, 498). Presumably recovery from $[Ca^{2+}]_i$-dependent inactivation allows the L-type Ca^{2+} channels to reopen and provide Ca^{2+} influx during early afterdepolarizations (see sect. IV*B3*A).

Current generated by the Na^+/Ca^{2+} exchanger protein ($I_{Na/Ca}$) depends on $[Ca^{2+}]_i$ (578), due to the contribution of $[Ca^{2+}]_i$ to the diffusion gradient for Ca^{2+} (51) as well as its regulatory role on Na^+/Ca^{2+} exchanger function. Regulatory Ca^{2+} is not transported by the exchanger

protein. Instead, it serves to "activate" the exchanger. In excised patches Ca^{2+} affinity for the regulatory site on the cytoplasmic loop of the Na^+/Ca^{2+} protein is 0.1–0.3 μM (163, 206). It is thought that $[Ca^{2+}]_i$ augments peak outward $I_{Na/Ca}$ by promoting the exchanger's recovery from Na^+-independent inactivation. If the low-affinity Ca^{2+} binding sites remain so in intact cells, then Na^+/Ca^{2+} currents should be modulated via this Ca^{2+} binding on a beat-to-beat basis as Ca^{2+} influx and SR release ensue.

In normal myocytes the time course of decline of inward $I_{Na/Ca}$ that occurs upon membrane repolarization is related to the time course of the spatially averaged $[Ca^{2+}]_i$ transient (16, 141, 578). In myocytes from diseased hearts showing abnormal $[Ca^{2+}]_i$ cycling, $I_{Na/Ca}$ could contribute substantially to both altered outward and inward currents. Therefore, in myocytes from hypertrophied/failed hearts where the relaxation phase of $[Ca^{2+}]_i$ transients may be slowed (e.g., Ref. 50), slowly decaying inward Na^+/Ca^{2+} exchanger currents would exist during diastole. Under conditions of disease where the L-type Ca^{2+} channel function is downregulated [e.g., postcoronary artery occlusion (3, 63)] and perhaps the Na^+/Ca^{2+} exchanger is upregulated (220, 330, 426, 499, 630), a large Ca^{2+} influx seen upon depolarization could be carried by the Na^+/Ca^{2+} exchanger. Currents generated by Na^+/Ca^{2+} exchanger could be both sustained and oscillatory during a maintained depolarization. These currents have been termed the transient inward current, I_{ti} (310).

Currents favoring cardiac repolarization can also be modified by changes in $[Ca^{2+}]_i$. The P_o of the native cardiac delayed rectifier channel (I_{Ks}) is increased with an increase in $[Ca^{2+}]_i$ (472, 542), thereby producing enhanced outward currents with increased $[Ca^{2+}]_i$. Elevation of $[Ca^{2+}]_i$ above 10 nM enhances I_{Ks} without an effect on the current-voltage relationship (265, 572). Noise analysis has shown that $[Ca^{2+}]_i$ increases the P_o of the native I_{Ks} channels without changing their unit amplitude (542). What remains unclear is whether this K^+ channel modulation is due to Ca^{2+} binding directly to a site on the channel protein or due to activation of a Ca^{2+}-dependent signaling molecule. However, recent evidence suggests that CaM-dependent NOS3 activation confers the Ca^{2+} sensitivity on I_{Ks} (24). Furthermore, there is a Ca^{2+} interaction between CaM and a CaM binding pocket on the KCNQ1 COOH terminus that appears critical for I_{Ks} channel assembly (174, 483). Previous studies evaluating the role of Ca^{2+}/CaM in KCNQ function had revealed conflicting results (165, 174, 584, 622). Some long QT mutations in KCNQ1 channels disrupt this CaM interaction preventing functional assembly of channels (174, 483). Finally, CaM also regulates KCNQ1 gating, relieving inactivation in a Ca^{2+}-dependent fashion (174). Thus it appears that Ca^{2+}/CaM affects activation, inactivation of the channel, and interaction with its accessory protein, KCNE1.

The rapid component of the native delayed rectifier current (I_{Kr}) has distinct negatively charged channel residues near a voltage sensor that bind extracellular Ca^{2+} affecting the alignment of the S3-S4 segments (254). Recently reexamined by Fernandez et al. (156), it was shown that specific residues in a pocket between the S2 and S3 segments contribute to these low-affinity binding sites for Ca^{2+}. With Ca^{2+} binding, the process of voltage-dependent activation is modified. Thus modest external Ca^{2+} concentrations have been shown to significantly affect the fraction of HERG channels participating in action potential repolarization (255). Intracellular Ca^{2+} changes would not be expected to cause such effects.

Ca^{2+} influx may also contribute to a "dynamic" rectification of the inward rectifying K^+ current (I_{K1}) since both the probability of opening of the channel in subconductance states and rectification of I_{K1} appear to be $[Ca^{2+}]_i$ dependent (356). An increase in $[Ca^{2+}]_i$ is expected to increase rectification of I_{K1} (234, 352) but not nearly as much as $[Mg^{2+}]_i$ or polyamines. Interestingly, cytochalasin but not colchicine removes this Ca^{2+}-dependent effect, suggesting a role for cytoskeletal actin filaments in rectification of this channel (356). Recent data obtained in intact voltage-clamped cells suggest that $[Ca^{2+}]_i$-dependent I_{K1} rectification contributes to <2% of total rectification (625) and that Ca^{2+}-dependent reduction in I_{K1} contributes to remodeled I_{K1} in cells from failing hearts (154).

Transient outward currents, described in early Purkinje fiber (161, 493) and canine myocyte studies (549), reflect the sum of a K^+ current through a voltage-dependent, $[Ca^{2+}]_i$-independent channel (I_{tol}) and one through a $[Ca^{2+}]_i$-dependent Cl^- conducting channel [I_{to2} also called $I_{Cl(Ca)}$] (161, 216, 645, 646).

Kv4 α-subunit proteins are thought to underlie the voltage-dependent transient outward currents in animal as well as human ventricular cells. The integral components of the native Kv4 channel complex are a group of Ca^{2+} binding proteins called KChIPs (9). KChIPs have some similarities to other calcium-binding proteins (e.g., recoverin, DREAM, calsenilin, GCAPS, and NCS-1) and KChIP2 is predominately expressed in heart. Expression of KChIP2 with Kv4.2 proteins produces increased density of Kv4.2 currents as well as changes in activation and inactivation properties of these currents (hyperpolarizing direction). The effects of KChIP2s on Kv4.3 proteins are specific, since no effect was seen when KChIPs were coexpressed with Kv1.4 or Kv2.1 proteins (9). Interestingly, KChIP1 has similar effects on Kv4.2 and Kv4.3 subunits but opposite effects on Kv4.1 subunits (387). Recent studies using splice variants of human KChIP2 have shown that KChIP effects on Kv4.3 current decay is significantly reduced when intracellular Ca^{2+} is buffered. On the other hand, the effects of KChIP to increase current density and speed recovery are Ca^{2+} independent (130). A minimal KChIP isoform accelerates recovery and slows inactivation kinetics of Kv4.3, and Ca^{2+} binding to KChIP2d relieves KChIP-induced slowing of Kv4.3 inactivation (411). The modulatory effects of KChIP1 on Kv4 currents is eliminated when EF-hand motifs are mutated, suggesting that modulation is Ca^{2+} dependent (9). Recent data suggest that KChIP2 also affects Kv1.5 currents in a Ca^{2+}-dependent way (320).

More important to the voltage-dependent transient outward current in atrial cells may be the proper functioning of the Kv1.4 K^+ channel (8). Unlike Kv4.3 channels, Kv1.4 channels are dephosphorylated by Ca^{2+}-regulated calcineurin and phosphorylated by CaMKII (445). Phosphorylation via CaMKII results in a slowing of current inactivation and acceleration in recovery from inactivation. This is entirely consistent with findings in human atrial cells where CaMKII inhibitors reduce sustained atrial currents restoring native peak I_{to} currents (538).

In normal canine and feline myocytes, the amplitude of I_{to2} is small relative to the voltage-dependent, 4-aminopyridine-sensitive I_{to1} (164, 497, 549). For this reason, I_{to2} is studied in the presence of catecholamines in some studies (549, 645), or high concentrations of strophanthidin (493) (presumably resulting in increased $[Ca^{2+}]_i$). Conversely, Ca^{2+} depletion

of the SR, e.g., by ryanodine, and Cl^- transport blockers, e.g., DIDS, have been shown to block I_{to2} in cardiac cells (269, 549, 645). Despite the importance of this $[Ca^{2+}]_i$-dependent Cl^- channel for normal cardiac repolarization as well as its potential involvement in arrhythmogenesis (193, 217, 268, 559, 644), little is known about its physiology and specific pharmacology. Recently, a low-conductance (1.0–1.3 pS) Ca^{2+}-activated Cl^- channel of high membrane density ($3/\mu m^2$) has been described in canine myocytes (103). Despite the relatively low Ca^{2+} sensitivity of this channel, they can conduct significant current transiently or in a sustained manner depending on $[Ca^{2+}]_i$ and time course of the subplasmalemmal $[Ca^{2+}]_i$ transient (103, 269, 292, 340), suggesting an apparent voltage-dependent Ca^{2+} sensitivity of the channel. This Cl^- current is activated upon depolarization after I_{CaL}-induced Ca^{2+} release from the SR as well as upon caffeine-induced Ca^{2+} release (406). Characteristically I_{to2} decays before the global cellular Ca^{2+} transient has reached its peak (497). However, under strict voltage-clamp conditions with different "clamped" levels of intracellular Ca^{2+}, I_{to2} shows little or no voltage-induced inactivation (269, 644). The specific protein giving rise to the small-conductance Ca^{2+}-activated Cl^- channels (CLCA) in native cardiac cells remain unknown. Tissue expression levels of cloned CLCA subunits (bCLCA1, mCLCA1, hCLCA1, hCLCA2) reveal none is highly expressed in heart. The presence of a $[Ca^{2+}]_i$-dependent Cl^- current in normal human electrophysiology remains controversial (149, 319). For instance, it appears that a caffeine-evoked $[Ca^{2+}]_i$-dependent current is not Cl^- sensitive in human atrial myocytes (289, 319). Rather, human atrial cells express a $[Ca^{2+}]_i$-dependent nonspecific cation channel (168). Finally, the role of this current in beat-to-beat AP will depend on the status of the L-type Ca^{2+} channel and SR load. In acquired disease, the Ca^{2+} currents are often remodeled (for review, see Ref. 422).

Two apparently different Ca^{2+}-dependent cation channels have been identified in adult and neonatal ventricular cells. Ca^{2+} is needed for activation of both channels, and each channel appears to be equally permeable to Na^+, K^+, Li^+, and Cs^+. Activation of the first type of cation channel in neonatal (104) and adult cardiac cells requires $[Ca^{2+}]_i$ to exceed 0.3 μM (142). The P_o of the channel increases with $[Ca^{2+}]_i$ and is insensitive to voltage. The native channel is activated with an intracellular injection of Ca^{2+} (351) or by caffeine-induced Ca^{2+} release from the SR (245). Thus the kinetics of the channel in ventricular (104, 142, 600) and human atrial cells (289) are determined by changes in $[Ca^{2+}]_i$ and not by voltage. In adult guinea pig myocytes, the estimated channel density is $0.04–0.4/\mu m^2$.

A second Ca^{2+}-activated cation channel, observed in bilayer experiments of canine ventricular sarcolemma vesicles, is sensitive to both $[Ca^{2+}]_i$ and voltage (210). In the presence of resting $[Ca^{2+}]_i$ levels (100 nM), a membrane potential more positive than −60 mV causes activation. The probability of opening increases to a maximum with depolarization to 0 mV. It has been estimated that this channel may be expressed at a high density in Purkinje fibers where transient inward currents associated with Ca^{2+} overload conditions (39, 80, 264) are as large as 100 nA.

An alternatively spliced form of the TRP3 protein (transient receptor potential, like protein 3) has been identified in heart (398). When expressed in oocytes, this variant, TRP3sv, encodes a cation-selective channel that is Ca^{2+} activated, but appears unrelated to the family of "capacitative Ca^{2+} entry currents." Such currents were partially blocked by trivalents like

$GdCl_3$ or $LaCl_3$. TRPC4 and TRPC5 channels have been identified in neonatal cardiac cells (482), while in embryonic and neonatal mouse cells, a store-operated Ca^{2+} influx channel has been proposed and persists in RyR2 knockout mice (554). In neonatal rat cells, Ca^{2+} store depletion activates inward currents perhaps due to TRP channels (229). In adult canine ventricle and Purkinje cells, TRPC3, -6, and -7 have been identified (137). A Mg^{2+}-inhibited TRPM6/7-like current has been described biophysically in both voltage-clamped pig and rat cells (185). Activation with diacylglycerol (DAG) appears to activate a Ca^{2+}-activated nonselective channel in rat (180). These authors suggest it is due to TRPM4b channels, similar to findings in human atrial cells (179). Interestingly, TRPV4 channels complex with RyR channels in smooth muscle cells (140), and TRPC6 channels associate with RyR2 proteins in cardiac cells (137).

At high $[Ca^{2+}]_i$, inactivation of the L-type Ca^{2+} current has been described (496) and is presumably due to a Ca^{2+}-induced reduction of the P_o of the channel(124). The site of this inactivation may be Ca^{2+} binding sites on the COOH terminus of the α-subunit of the L-type Ca^{2+} channel protein (see above). Factors influencing the intracellular $[Ca^{2+}]_i$ as well as changes in $[Ca^{2+}]_i$ itself can alter the size of T-type Ca^{2+} currents, especially in canine Purkinje cells (7, 309, 547, 552).

IV. Calcium and Arrhythmogenesis

A. Inherited Mutations That Cause Ca^{2+}-Dependent Arrhythmias

1. RyR2 mutations and arrhythmias—Coumel et al. (109), Swan et al. (520), and Leenhardt et al. (313) recognized catecholaminergic polymorphic ventricular tachycardia (CPVT) as a malignant clinical entity that causes stress-related syncope and sudden death in children, occurs without structural heart disease and can be treated by suitable β-blockers. CPVT is similar to familial polymorphic ventricular tachycardia (FPVT) (299) but occurs without a long QT interval and is not accompanied by the pattern of torsade des pointes arrhythmia. The electrocardiogram (ECG) pattern seen during exercise with induced bidirectional arrhythmias preceding VT is reminiscent of triggered arrhythmias occurring with digitalis intoxication. Genetic analysis by Swan et al. (520), Priori et al. (431), and Laitinen et al. (299) have now shown that these patients exhibit mutations of RyR2 (human ryanodine receptor type 2) that map to chromosome 1q42-q43. More recent genotype-phenotype analysis of patients with CPVT has shown that there are two groups of patients: the predominately male patient with RyR2 CPVT has early symptoms and is at high risk of a cardiac event, and the other group is the nongenotyped CPVT female who shows symptoms later in life (430). The variable expressivities of RyR2 mutations are further illustrated by the fact that 17% of the gene carriers had no phenotype.

Tiso et al. (541) reported that one of the (at least 6) forms of arrhythmogenic right ventricular dysplasia, ARVD type 2, a catecholamine-sensitive autosomal dominant cardiomyopathy, is also caused by mutations in the hRyR2 (human ryanodine receptor type 2) (29, 438, 520).

A) Functional Implications: The 60 missense mutations (Fig. 5B) reported so far (see updated information at http://www.fsm.it/cardmoc/) occur in domains of RyR2 that may be

involved in regulation of the P_o of RyR channels by the phosphorylation-dependent binding protein FKBP12.6 or direct alteration in gating (23, 30, 95, 197, 299, 300, 430, 431, 539, 541). In fact, the properties of the hRyR2 mutation R4497C as it is expressed in HEK cells are altered compared with wild-type; there is an enhanced basal activity of the RyR channel that is accompanied by augmented spontaneous Ca^{2+} release (250). In other studies (315), only PKA activation of mutant RyR2 proteins produces a significant gain-of-function defect consistent with enhanced Ca^{2+} leak. These findings suggest that abnormal Ca^{2+} cycling based on dysfunction of SR Ca^{2+} release channels are involved in potentially lethal and genetically transmitted human cardiac arrhythmias.

Most studies have characterized the properties of mutant RyR2 channels in expressed cell systems but recently mice with knock-in RyR2 mutations have been produced (87, 262). Cells from both knock-in mice show a gain-in-function represented by presence of delayed after-depolarizations (DADs) and/or $[Ca^{2+}]_i$ oscillations. Functional characteristics of these mutants compared with wild-type have ranged from enhanced sensitivity to Ca^{2+} (251, 252) to increased "leak." The mechanisms of the increased leak under these circumstances appear to fall into a few general categories. First is the interdomain hypothesis (235, 609), which states that under normal conditions, the NH_2-terminal of the RyR channel folds over in such a way as to interact with certain residues of the central domain of the same channel protein. With this interdomain interaction, the channel is in a stable closed state. "Leak" arises in mutant channels when this interdomain interaction is weakened. A second hypothesis is that the "leak" is due to faulty protein-protein interactions owing to PKA-mediated hyperphosphorylation of RyR2. The latter is assumed to cause dissociation of the FKBP12.6 protein to result in abnormal Ca^{2+} channel activity (580). Recent data suggest that the R2474S mutation of RyR2, which causes the "unzipping" of the inter-domains, is still able to interact with FKBP12.6 but, now, PKA phosphorylation of RyR2 has a greater effect on its dissociation (397). Finally, it has been proposed that RyR2 mutations associated with CPVT/ARVD2 (251) exhibit a lower threshold for store-overload-induced Ca^{2+} release. Whether these mechanisms of RyR dysfunction occur in native cells and lead to spontaneous Ca^{2+} release and arrhythmias is not as yet known.

2. CASQ mutations and arrhythmias—In four families CPVT has been associated with homozygous and heterozygous missense mutations in the calsquesterin2 gene (CASQ2) (296, 428).

A) Functional Implications: Calsequestrin is the most abundant Ca^{2+} binding protein in the cardiac SR. It contains up to 50 Ca^{2+} binding sites. Original work on cardiac CASQ showed a K_d of 400–600 μM (369), while recent data using a Ca^{2+} overlay procedure (133) suggest that the K_d of wild-type CASQ2 is ~2.2 mM (133). The folding and stabilization of CASQ depends on the concentration of Ca^{2+} (576). COOH-terminal residues of CASQ and triadin interact within the SR lumen (489), while the NH_2-terminal residues appear neither to interact with triadin nor junctin (576). It is not entirely clear how these conformational changes in CASQ affect the response of RyR to luminal Ca^{2+}. However, the addition of CASQ to RyRs with triadin and junction inhibits RyR channel activity even at low luminal Ca^{2+} levels (186). In fact, CASQ remains associated with the junctional membrane when

Ca^{2+} is 1–2 mM but is removed when Ca^{2+} luminal is >4 mM. As such, CASQ increases relative P_o of RyRs when Ca^{2+} luminal concentration is >1.5 mM (32).

The identified missense mutation in patients with CPVT changes the charge of the CASQ protein in such a way as to alter Ca^{2+} binding and thus the conformational changes. Because CASQ plays an important role in SR Ca^{2+} release (537), cells with mutated CASQ would have reduced SR storage capacity. In fact, Viatchenko-Karpinski et al. (562) showed that when rat cells were infected with the CASQ mutant D307H, the Ca^{2+} storage capacity of the SR is reduced (and/or the CASQ/RyR2 interaction is disrupted). This in turn reduces Ca^{2+} transients and spark amplitudes. By reducing the effective buffering of the SR, cells become more prone to abnormal Ca^{2+} release in the presence of adrenergic stimulation presumably by promoting the generation of Ca^{2+} waves (291). One study has shown that a point mutation of CASQ altered Ca^{2+}-dependent binding of the mutant CASQ to both triadin-1 and junctin (536). Recent data on new CASQ2 mutations in patients with CPVT suggest that while some mutations can lead to altered binding to Ca^{2+} to CASQ2, others lead directly to altered regulation of RyR2 (133). Finally, as yet, no atrial arrhythmias have been genetically linked to RyR2 or CASQ2 genes.

3. Ca^{2+} channel mutations and arrhythmias—Timothy's syndrome is a multiorgan disorder that can cause atrioventricular (AV) block, T-wave alternans, and ventricular tachyarrhythmias. In one large family where the inheritance pattern was clear, affected individuals had prolonged QT intervals and spontaneous arrhythmias (507). No mutations were found in known long QT syndrome genes. However, an analysis of one $Ca_v1.2$ splice variant (exon 8a) revealed a missense mutation in residues of the COOH terminus end of the S6 segment of Domain 1. Another two individuals also had severe polymorphic ventricular tachycardias and a severe variant of this syndrome (506). Again de novo mutations were found in exon 8 of $Ca_v1.2$. Biophysical studies revealed that these mutations produce sustained Ca^{2+} currents that lacked voltage-dependent inactivation. One mutation, G436R, in the rabbit $Ca_v1.2$ gene produces spontaneous mode 2 gating that depends on CaMKII-dependent protein phosphorylation (147). As such, it is predicted that these mutated $Ca_v1.2$ Ca^{2+} currents will persist during the action potentials of cardiac cells. Simulations showed that such a change in Ca^{2+} influx leads to abnormal Ca^{2+} dynamics and DADs. Presumably then, the arrhythmias in these individuals would be sensitive to Ca^{2+} channel blockers.

4. Ankyrin B mutations and arrhythmias—Congenital long QT syndrome has been associated with mutations in ion channels and recently in a large French family with mutations in the adaptor ankyrin B protein (381, 475). Affected family members show severe bradycardia and atrial fibrillation (475). Ankyrin B proteins are critical for anchoring other proteins to a specific cell location. For example, ankyrin B places Na^+-K^+ pumps, Na^+/Ca^{2+} proteins, and IP_3R proteins at t-tubule SR sites (379, 381). In mice where ankyrin B has been knocked down, some cardiac ion channels remain normal, but altered Ca^{2+} transients occur and with adrenergic stress action potentials with either early afterdepolarizations (EADs) or DADs occur (381). The human mutation of ankyrin B blocks the interaction of ankyrin B to its target effectors and would most likely lead to altered Ca^{2+} homeostasis and Ca^{2+}-dependent arrhythmias.

Mutations of ankyrin G are associated with one form of the Brugada syndrome (380); however, arrhythmias have not as yet been linked to dysfunction of Ca^{2+}.

5. Long QT syndromes and Ca^{2+}-dependent arrhythmias—Long QT syndrome is a cardiac syndrome that is characterized by prolongation of the QT interval of the ECG. This prolongation is presumably due to APD prolongation of at least some of the ventricular cells. Patients with long QT can have specific ventricular arrhythmias such as torsade de pointes and ventricular fibrillation (VF). Genes associated with long QT syndrome in patients are KCNQ1, KCNH2, SCN5A, ankyrin B, KCNE1, and KCNE2. For the genes that encode ion channels, both gain-in-function and loss-in-function mutations have been described (444). It is thought that "triggers" that lead to the arrhythmias in these patients are due to disturbances of impulse initiation/conduction or both. Clearly from basic electrophysiological studies, it is known that just by prolonging the APD of a cardiac cell, one could set up conditions for reentry as well as increase the likelihood of EADs or DADs (110). But, are abnormal Ca^{2+} releases critically involved in the triggers of long QT-associated arrhythmias? Unfortunately, there are no Ca^{2+} data on cells from patients with these gene-based arrhythmias. Information so far has been from mouse models of long QT.

DeltaKPQ SCN5A causes a gain in Na^+ channel function, and cells isolated from DeltaKPQ SCN5A knock-in mice generate EADs and cardiac arrhythmias particularly at rapid rates (394). No DADs were reported, and no Ca^{2+} imaging was performed to determine the role of intracellular Ca^{2+} in these EAD-generating cells. A more severe phenotype has been described in mice with a N1325S mutation of SCN5A (540). Again, these mice show the expected long QT, arrhythmias, and persistent Na^+ currents. Cells from these mice showed EADs and late EADs (phase 3 EADs which could be due to Ca^{2+} waves) particularly at short pacing cycle lengths. Again, no DADs were observed in these cells, and Ca^{2+} was not imaged. However, if no other adaptive mechanisms exist in these mutant mice, then the prolonged APD secondary to persistent Na^+ entry could in fact lead to increased Ca^{2+} influx, which in turn would increase SR stores and increase the likelihood of spontaneous intracellular Ca^{2+} releases, Ca^{2+} waves, and DADs.

B. Automaticity

1. Normal automaticity—Phasic nondriven rhythmic electrical activity occurs in various regions of the normal heart. The term *normal automaticity* refers to nondriven electrical activity of the sinoatrial nodal (SAN) cells, latent atrial pacemaker cells, and Purkinje fibers. Recent data combining voltage clamp with Ca^{2+}-imaging techniques have implicated a role for Ca^{2+} in modulating the slope of phase 4 depolarization and thus automatic firing rates of the following cell types.

A) SAN Cells: In SAN cells, Ca^{2+} release channels are distributed in the cytoplasm as regular bands, localized to Z lines with some near to the sarcolemma (440). A highly localized subsarcolemmal Ca^{2+} release from the SR occurs concurrently with phase 4 depolarization (55, 231) and spreads in a wavelike manner by CICR (55). Ryanodine, which reduces conductance of the Ca^{2+} release channel in cardiac cells (459), slows the final phase of depolarization and thus pacemaker activity of cat, guinea pig, and rabbit SAN cells (55,

321, 440, 441). Furthermore, a compound used to chelate intracellular $[Ca^{2+}]_i$ (BAPTA-AM) reduces Ca^{2+} transients and slows the firing rate of the SAN cell (321). Ryanodine also significantly reduces the positive chronotropic effect of β-adrenergic stimulation (304, 440) consistent with the idea that β-adrenergic stimulation modulates RyR Ca^{2+} release to augment sinus node firing rates (564), and that high basal cAMP levels of SAN cells are linked to this SR Ca^{2+} cycling (563). However, this finding is controversial (223), and fundamental work to show how the local Ca^{2+} releases lead to the global SAN Ca^{2+} transient has not been done. In fact, there is no information at this time on the fundamental basis of the SAN local Ca^{2+} release. Whether ryanodine reduces the contribution of Ca^{2+}-dependent Na^+/Ca^{2+} exchanger current (55), Ca^{2+}-dependent T-type Ca^{2+} currents, or Ca^{2+}-dependent I_{Ks} to phase 4 depolarization in SAN cells remains controversial at this time. Nevertheless, such evidence suggests that intracellular Ca^{2+} at least modulates SAN activity.

B) Atrial Pacemaker Cells: In cells from the pacemaker region of normal cat right atria, a late diastolic component of nondriven rhythmic activity depends on SR Ca^{2+} release (231, 461). In one study, a slow SR leak of Ca^{2+} during diastole provides persistent Ca^{2+} extrusion via the Na^+/Ca^{2+} exchanger, which in turn generates inward current and atrial cell depolarization (461, 638). In normal cat atrial and ventricular myocytes, the rate of spontaneous Ca^{2+} leak from the SR is very low and thus no diastolic depolarization occurs (28). Interestingly, SAN cells do not show this diastolic Ca^{2+} efflux (28). In a combined confocal and voltage-clamp study of latent atrial pacemaker cells, the local release of Ca^{2+} from the SR occurring during late-phase diastolic depolarization is nickel sensitive, suggesting a role for the voltage-activated T-type Ca^{2+} channels in modulating latent pacemaker function (231). Agonists such as endothelin-1 increase the rate of spontaneous Ca^{2+} release as well as nondriven electrical events (342), suggesting that endothelin increases IP_3 production, which subsequently sensitizes RyRs to release Ca^{2+} spontaneously. Spatially altered properties of the subcellular Ca^{2+} release also underlie arrhythmogenic events, such as Ca^{2+} waves, in cat atrial cells (283).

C) AV Nodal Cells: Morphologically, normal spontaneously active AV nodal cells show action potentials preceding large Ca^{2+} transients. After it peaks, the Ca^{2+} declines slowly, occurring even during the pacemaker depolarization. Ryanodine completely blocks AV node Ca^{2+} transients and presumably also abolishes the pacemaker activity (194). Thus the slow decline of Ca^{2+} during depolarization and subsequent pacemaker depolarization may activate Na^+/Ca^{2+} exchanger in these cells (194).

D) Normal Purkinje Fibers: Data from several laboratories (76, 443) have clearly shown that the normally polarized individual canine Purkinje cell is quiescent and lacks normal automaticity in the absence as well as in the presence of catecholamines (443) despite the fact that I_f has been identified in this cell type (76). This is quite unlike adult SAN cells where the individual cell shows normal automaticity, and under voltage-clamp, I_f is prominent (240). Moreover, it appears that the minimal element needed for automaticity is a “dense pack” aggregate of Purkinje cells. In fact, in Purkinje cell aggregates from normal canine hearts, focally arising Ca^{2+} waves occur in the absence of electrical stimulation (64). These spontaneous Ca^{2+} waves appear to originate at cell borders similar to those in

ventricular trabeculae (see below), can propagate the full extent of an aggregate, and often initiate membrane depolarization. In some cases, these depolarizations are accompanied by nondriven electrical activity of the well-polarized Purkinje cell (61). Thus spontaneous Ca^{2+} release clearly modulates normal Purkinje cell pacemaker function.

2. Abnormal automaticity—Fibers that become chronically depolarized show nondriven electrical activity that does not depend on an initiating beat. Diseased Purkinje as well as diseased human atrial fibers both show such abnormal automaticity. In one study, rates of firing of the abnormal foci were strongly modulated by agents that affect SR function (60, 148). Recent studies in atrial cells from both patients with and without atrial fibrillation (AF) as well as in cells from the rapid pacing model of AF have an increase in Ca^{2+} spark and Ca^{2+} wave frequency (225), as well as RyR2 channel dysfunction (561). Dysfunction of RyR2 in AF in the absence of adrenergic stimulation leads to an increase in the probability of opening of release channels (561). It is not clear whether such dysfunction in Ca^{2+} is accompanied by DADs and/or abnormal atrial cell automaticity. On the other hand, recent fluorescence data provide conclusive evidence that an increased frequency of micro Ca^{2+} transients in diseased Purkinje cell aggregates contribute to the abnormally automatic arrhythmias originating in the Purkinje network of the postmyocardial infarction heart (Fig. 6) (61). These frequent micro Ca^{2+} transients are sensitive to ryanodine, suggesting that in this model of acquired disease, spontaneous Ca^{2+} release is the fundamental abnormality leading to arrhythmias.

3. Triggered activity

A) Role of Calcium in EADS: While the role of propagating Ca^{2+} waves in membrane DADs is reasonably well accepted (see below), EADs in ventricular myocytes appear not to be due to a spontaneous regional increase in $[Ca^{2+}]_i$ or propagating Ca^{2+} waves. Rather, during EADs, fluorescence transients show synchronous changes of $[Ca^{2+}]_i$ throughout the myocyte lacking distinct high peaks (121, 373, 374, 567). These findings are consistent with the idea that a change in membrane potential primarily causes the observed increases in $[Ca^{2+}]_i$ during an EAD. Evidence supporting a role for the L-type Ca^{2+} window current in the BAY K 8644-induced EADs in sheep Purkinje cells has been the demonstration of the appropriate voltage- and time-dependent properties of the whole cell L-type Ca^{2+} current as well as of its single-channel events (215, 247). In rabbit Purkinje cells, isoproterenol induces large EADs (20–30 mV) during which spatially uniform, circumferential rise in subsarcolemmal Ca^{2+} is observed (105). β-Adrenergic stimulation of canine ventricular cells produces EADs that are thought to be accompanied by spontaneous Ca^{2+} release (566). Early Ca^{2+} "aftertransients" or aftercontractions rise earlier than upstroke of change in membrane voltage of the EAD, suggesting that spontaneous Ca^{2+} release and nickel-sensitive inward Na^+/Ca^{2+} exchanger current underlie the EADs (565). Simultaneous voltage and Ca^{2+} mapping data of rabbit hearts with experimental long QT syndrome suggest that during EADs in the epicardium, a rise of $[Ca^{2+}]_i$ precedes the voltage rise by ~20 ms in one focus while within millimeters the signals are synchronous (94). The actual amplitude of the Ca^{2+} signal that precedes the voltage signal is not known, and therefore, it is difficult to assess whether this "initiating" Ca^{2+} pulse is secondary to spontaneous Ca^{2+} release.

In other models, EADs have been shown to depend on Ca^{2+} loading and Na^+/Ca^{2+} exchange current (412, 413) and/or CaMKII activity (12, 603). In the latter studies, action potential prolongation preceding EAD generation increases both L-type Ca^{2+} current and $[Ca^{2+}]_i$ transient, while transient inward currents were associated with elevated $[Ca^{2+}]_i$. Although it is known that elevated $[Ca^{2+}]_i$ can inactivate L-type Ca^{2+} current, its predominant effect is to further enhance Ca^{2+} currents through activation of CaMKII (12). In fact, recent experimental data suggest that CaMKII inhibitors suppress clofilium-induced EADs in the isolated heart and the appearance of I_{ti} in rabbit myocytes (12, 603).

EADs occurring at potentials more negative than that of activation of L-type Ca^{2+} current have been called high membrane potential or phase 3 EADs (114, 413) and can be elicited after spontaneous termination of rapid pacing in isolated atrial preparations (73). Subcellular Ca^{2+} dynamics most probably underlie these depolarizations since they are augmented by an increased SR Ca^{2+} load. In fact, in two-dimensional simulations of LQT2 with increased sympathetic tone, spontaneous Ca^{2+} release in a region of the tissue generated an EAD which propagated, and due to the inhomogeneity of the substrate, initiated more nondriven electrical activity (228). Whether these Ca^{2+} abnormalities are in the form of spontaneous Ca^{2+} release and traveling Ca^{2+} waves is unknown at this time.

B) Arrhythmias, DADS, and Calcium Waves in Myocardium: Like in any arrhythmia, triggered arrhythmias both result from the previous impulse and lead to subsequent impulse generation. It has been shown that DADs are based on a spontaneous increase in $[Ca^{2+}]_i$ leading to a transient inward current on the one hand and to activation of the contractile filaments on the other hand (158, 264). Kass et al. (264) proposed that a small $[Ca^{2+}]_i$ transient, assumed to be due to “spontaneous” Ca^{2+} release from the SR, leads to a transient inward current. Hence, a sufficiently large Ca^{2+} load of the SR would create an unstable state where the spontaneous Ca^{2+} release could become so large that the resulting transient inward current would depolarize the cells sufficiently to trigger a new action potential, which would perpetuate itself as a triggered arrhythmia. Spontaneous Ca^{2+} release in individual cells in tissue has been shown to lead to DADs which are determined in amplitude by the amplitude of the local $[Ca^{2+}]_i$ transient and by the spatial extent of this transient. Large and extensive Ca^{2+} transients are likely to generate a large I_{ti} which may overcome the electrotonic drain of adjacent cells and generate a DAD of sufficient amplitude to trigger an ectopic beat.

I) Myocytes: Spontaneous Ca^{2+} release from the SR at submicrometer scale has been well-documented in both isolated dispersed cells and cardiac trabeculae using confocal microscopy. Regional Ca^{2+} waves occur after an action potential-induced synchronous Ca^{2+} transient in a myocyte accompanied by an aftercontraction and a DAD. Typically, the interval between the last stimulation and the onset of the first Ca^{2+} wave shortens and the probability of multiple foci of Ca^{2+} waves increases when the stimulus frequency or $[Ca^{2+}]_o$ is increased (82). These observations are consistent with the concept that the increase in $[Ca^{2+}]_i$ causes a transient net inward current and resulting in a DAD. Any of the $[Ca^{2+}]_i$-dependent currents described above might be involved in the generation of net inward current and most probably depends on the cell type.

Ca^{2+} waves usually start at one end of a myocyte, where one might envisage gap junctions. When a Ca^{2+} wave begins in a focus within a myocyte, it spreads at equal velocity in all directions (528). Sometimes Ca^{2+} waves emerge, as a domelike region of spontaneously elevated $[Ca^{2+}]_i$ (300 nM) ~20 μm in diameter, and propagate as a localized 10-μm-wide band of elevated $[Ca^{2+}]_i$ (528, 592). Amplitude and width of Ca^{2+} waves are fairly constant during propagation (242, 528), and their velocity of propagation is typically ~100 μm/s in quiescent cells (242, 302, 327, 510, 528, 587, 588, 592).

Ca^{2+} waves in isolated myocytes occur randomly with a frequency that may vary from <0.1 to ~5 Hz, although remarkably stable intervals between spontaneous Ca^{2+} waves can be observed (241). In an individual cell, the frequency of Ca^{2+} waves increases monotonically with increased SR Ca^{2+} loading as does the number of foci (82). When Ca^{2+} waves start from two or more foci within a myocyte, the waves appear to collide without augmentation of $[Ca^{2+}]_i$. After the collision, $[Ca^{2+}]_i$ declines without evidence of further wave propagation, demonstrating refractoriness of the propagation mechanism (39, 242). Thus Ca^{2+} waves are the consequence of a process with a "refractory period." If an action potential is elicited during the propagation of a Ca^{2+} wave, the amplitude of the global Ca^{2+} transient and the accompanying twitch induced by that action potential are reduced by the preceding Ca^{2+} wave. The decrease of the Ca^{2+} transient of the action potential is more pronounced if the interval with the preceding Ca^{2+} wave transient is short (375). It appears that resultant twitch of the myocyte recovers with a time course similar to that of the mechanical restitution curve. This is indirect evidence that the spontaneous transient and twitch generation share the same mechanisms involved in intracellular Ca^{2+} cycling (83).

Traveling Ca^{2+} waves and membrane depolarizations occur in normal canine Purkinje cell aggregates (64) as well as in Purkinje cells that have survived in the border zone of an infarcted heart (61). In this latter study, the spatial extent, number, and duration of the spontaneously occurring Ca^{2+} waves present in the aggregate at any one time dictate the amplitude and duration of the membrane depolarization that occurs and thus the likelihood of triggering a nondriven electrical event (61). In rabbit Purkinje cells, transient inward current (I_{ti}) underlying DADs was recorded both in the absence of spontaneous Ca^{2+} release and in the presence of variable spontaneous release (105). In an experimental model of disordered Ca^{2+} dynamics in left atrial preparations, Chou et al. (96) have shown that after rapid rates of pacing of the pulmonary vein (PV) sleeve area, spontaneous Ca^{2+} release, presumably from myocardial cells, precedes the depolarization of the PV cells. This leads to nondriven triggered activity in these cells which perpetuates the arrhythmic period (96). The mechanism of this focal spontaneous Ca^{2+} release is unknown, but presumably it is related to the rapid pacing-induced Ca^{2+} accumulation in the SR of PV cells. With the use of high-resolution calcium and voltage mapping (219), DADs and spontaneous Ca^{2+} release have now been mapped to the origin of the autonomically enhanced PV ectopy of the canine pulmonary veins.

To control SR Ca^{2+} release, Schlotthauer and Bers (474) applied a rapid caffeine superfusion to normal rabbit ventricle cells. The amplitude of the caffeine-induced membrane depolarization (cDADs) doubled for every 88 nM change in $[Ca^{2+}]_i$. Furthermore, if a cDAD voltage change of 12.5 mV occurred (~424 nM Ca^{2+} change), an

action potential was elicited. The cDAD-induced action potential threshold was altered if the membrane voltage change occurred faster (474). DADs are relatively easily induced in ventricular hypertrophy secondary to renal hypertension (17), to isoproterenol infusion (365), and in failing ventricular trabeculae (120, 560). In some cases, a role for I_{ti} has been shown as the ionic mechanism and elevated $[Ca^{2+}]_i$ has been implicated (365, 558). But traveling Ca^{2+} waves have only been illustrated in isoproterenol-stimulated cells (121) and trabeculae from the failing rat heart (120).

II) Cardiac muscle: ter Keurs and collaborators (115) discovered that only when cardiac muscle is damaged locally, such as by microelectrode impalement or dissection procedures, Ca^{2+} waves start near the damaged region and propagate in a coordinated fashion into adjacent tissue. These aftercontractions in multicellular preparations occur as the combined result of the mechanical effects and elevated cellular Ca^{2+} levels owing to the regional damage and thus may give rise to premature beats as well as triggered arrhythmias. These aftercontractions appear to be initiated by stretch and release of the damaged region during the regular twitch, and they propagate into neighboring myocardium, hence, the term *triggered propagated contractions* (TPCs). Damage-induced TPCs may, therefore, serve as the mechanism that couples regional damage with the initiation of premature beats and arrhythmias in the adjacent myocardium. The displacement of the TPC, or the Ca^{2+} wave that causes the TPC, occurs at a velocity of propagation (V_{prop}) along the long axis of the muscle which varies at room temperature from 0.1 to 15 mm/s (372, 386) and is correlated tightly with the amplitude of the twitch preceding the TPC, suggesting that the Ca^{2+} load of the SR dictates V_{prop}. In contrast, sarcomere stretch, which increases twitch force for any level of loading of the SR, does not increase V_{prop} of the TPC (118). Studies of the effects of interventions such as varied $[Ca^{2+}]_o$, Ca^{2+} channel agonists, and antagonists also support the idea that the Ca^{2+} load of the SR is the main determinant of V_{prop} (117). On the other hand, interventions that cause a leak of Ca^{2+} from the SR (caffeine and ryanodine) increase V_{prop}, suggesting that V_{prop} also depends on the diastolic cytosolic Ca^{2+} level (372). Finally, the rate of initiation of TPCs is tightly correlated with V_{prop} when the Ca^{2+} load of the SR is modulated, suggesting that the triggering process and the propagation process share closely related mechanisms.

III) Mechanisms underlying propagated Ca^{2+} waves

A) Initiation of Ca^{2+} waves in myocytes: Fabiato's work (152) on the properties of cardiac SR has provided a potential explanation for spontaneous Ca^{2+} release in isolated myocytes. He observed that in mechanically skinned cells in which the SR was intact, excessive Ca^{2+} loading of the SR caused spontaneous Ca^{2+} release (152). The mechanism for increased probability of opening of the SR-Ca^{2+} channel when the SR is heavily loaded with Ca^{2+} is still uncertain but suggests that the channel is directly or indirectly sensitive to the luminal $[Ca^{2+}]$ of the SR. The localization of a Ca^{2+} sensor in the transmembrane domain of the RyR channel would make it suitable as a sensor of both luminal and cytosolic $[Ca^{2+}]$. Intact cells with a high SR-Ca^{2+} load show similar phenomena (82, 287). Hence, the oscillatory character of a triggered arrhythmia in myocardium with a high cellular Ca^{2+} load may be due to further increase of Ca^{2+} entry into the cells during the action potentials of the arrhythmia causing even more Ca^{2+} loading of the SR. Consequently, as soon as the release

process has recovered after an electrically induced Ca^{2+} release, the overloaded SR again releases a fraction of its Ca^{2+}. The requirement that the Ca^{2+} release mechanism must recover first would explain the presence of a delay between aftercontractions and afterdepolarizations to the preceding beat.

B) Initiation of TPCs in multicellular preparations: TPCs arise invariably in damaged regions of cardiac muscle. Spontaneous activity in the damaged zone is usually random; hence, the accompanying Ca^{2+} transients are small and do not propagate through the muscle, but can cause Ca^{2+} overload and spontaneous activity in the border zone. This process continues until the [Ca^{2+}] gradient between cells is minimal or until gap junctions close (302). The existence of spontaneous SR Ca^{2+} release activity and contractions increases resting tension and decreases twitch force (287, 511). Thus twitch force of the damaged cells and cells of the border zone is less than that of the central region of the trabeculae. During an electrically evoked twitch, contraction of the central region of the normal trabeculae stretches the damaged region. During the rapid relaxation phase of the twitch, the stretched damaged region shortens suddenly. Stretch or quick release of damaged ends of trabeculae during the electrically driven twitch trigger TPCs (118) and may provide an explanation for the triggering mechanism. TPCs always start shortly after rapid shortening of damaged areas, suggesting that it is actually the shortening during relaxation that initiates a TPC. The observation (5, 6, 21, 224) that rapid shortening of a contracting muscle causes release of Ca^{2+} from the myofilaments provides a candidate mechanism for initiation of TPCs. In fact, Ca^{2+} that dissociate from the contractile filaments due to the quick release of the damaged areas during relaxation accelerate the initiation of a TPC and Ca^{2+} wave if CICR has recovered sufficiently to allow amplification of the initial Ca^{2+} transient in the damaged region and/or the border zone (571). Reduction of the afterload to <20% of twitch amplitude eliminates TPCs completely; this effect can be immediately reversed by forcing the muscle to contract again against a high afterload. At the same time, it is clear that as long as a TPC is observed, V_{prop} is not influenced by the manipulation of the afterload. So, apparently the probability of triggering a TPC depends on the force supported by the damaged area and the border zone and hence on the degree of stretch of these areas during the twitch. The TPC appeared to be initiated when force declined rapidly while the stretched areas shortened during the relaxation phase of the twitch. Studies of the contributing factors (nonuniform ECC vs. force decline in the stretched area vs. stretch of that area) suggest that rapid decline of force in the stretched area is responsible for rapid dissociation of Ca^{2+} from the contractile filaments, which initiates the Ca^{2+} waves (534, 570). These authors suggest that the rate of Ca^{2+} dissociation depends on force development and is significantly accelerated during a rapid reduction of force; elimination of force by externally unloading the muscle would eliminate accelerated Ca^{2+} dissociation from the myofilaments and hence eliminate the initiating event of the Ca^{2+} waves and TPCs (534, 570).

C) Propagation of Ca^{2+} waves: The fact that Ca^{2+} waves travel at a constant velocity and with constant amplitude through an isolated myocyte and/or a multicellular preparation provides an important clue about the mechanism of wave propagation. Diffusion of Ca^{2+} alone would clearly be too slow and would be accompanied by a decline of the observed wave amplitude. Propagation of electrical activity is much faster (1 m/s for the action

potential in ventricular myocardium), and thus electrotonic conduction is too fast (~0.1 m/s) to be compatible with the observed values of V_{prop} in trabeculae. A mechanism of Ca^{2+} wave propagation in cells has been proposed that consists of diffusion of Ca^{2+} due to the local increase of $[Ca^{2+}]_i$ and subsequent CICR from adjacent SR, similar to the waves propagated by Ca^{2+} sparks. The transition from nonpropagating sparks to propagating sparks and a Ca^{2+} wave is possibly caused by an increase in Ca^{2+} sensitivity of the SR Ca^{2+} release channel as a consequence of greater SR Ca^{2+} loading (92).

Propagation with a constant velocity is consistent with a model of CICR propagated by Ca^{2+} diffusion along its concentration gradient to adjacent sarcomeres and adjacent cells (82, 118, 285, 386) and is supported by work on saponin-skinned muscle fibers which also exhibit propagating local contractions, suggesting the cell membrane is not essential for the phenomenon (115). The observation that neither initiation of TPCs nor their propagation is affected by gadolinium ions suggests that stretch-activated channels play little or no role in the initiation or propagation of damage-induced TPCs (632). As was shown by the lack of effects of varied afterload and varied sarcomere length on V_{prop}, it is unlikely that stretch of the myofibrils is essential to the propagation process.

The characteristics of Ca^{2+} waves and TPCs in trabeculae are quite similar. In addition, neither spontaneous activity in single myocytes nor TPCs in trabeculae require an intact sarcolemma, and both are abolished by agents that interfere with SR Ca^{2+} loading or release. On the other hand, at first glance, a striking difference between them is the propagation velocity. The velocity of Ca^{2+} waves in unstimulated cells is about 10 times lower than V_{prop}. However, TPCs are generated in cardiac muscle preparations at short intervals after the twitch such that their properties are affected by residual binding of Ca^{2+} to intracellular ligands (see sect. II*C*). This is in contrast to the situation in myocytes where the moment of appearance of a Ca^{2+} wave following the twitch is both random and usually later. Hence, elimination of Ca^{2+} from the ligands during late diastole, after the Ca^{2+} extrusion processes have done their work, should reduce V_{prop} in muscle (386).

V_{prop} has been shown to vary experimentally from 0.1 to 6 mm/s, and maximal values of 15 mm/s have been observed. This speed is stunning if one realizes that only movement of a Ca^{2+} transient at speed lower than 0.03 mm/s can be explained by diffusion of Ca^{2+} based on the concentration gradient and the diffusion constant in an aqueous medium. The speed should be lower in the cytosol, since the effective diffusion constant is lower than in water owing to Ca^{2+} binding to, and dissociation from, ligands. Backx et al. (20) investigated which parameters of Ca^{2+} diffusion and CICR are required for the high V_{prop} in muscles by modeling the behavior of a myofibril accompanied by its SR during a sudden focal Ca^{2+} release. From the model we learned that Ca^{2+} transients propagate through the cytosol at a rate modified by binding to troponin and calmodulin and sequestration by the SR, as well as by the rate of Ca^{2+} release from adjacent release sites of the SR. V_{prop} increased indeed in the model from 0.1 to 15 mm/s if the "model cell" was loaded with Ca^{2+}, which resulted in both a rise of the diastolic $[Ca^{2+}]_i$ and the Ca^{2+} load of the SR. The former led to increased occupancy of the intracellular ligands with Ca^{2+} and, hence, an increase in the effective diffusion constant for Ca^{2+}; the latter led to an increase of the amount of Ca^{2+} released by the SR and, assumedly, an increase of the rate of Ca^{2+} release (20). This combination would

be expected to result from loading of cardiac cells with Ca^{2+} during repetitive stimulation as well as due to exposure to high $[Ca^{2+}]_o$ or Ca^{2+} agonists (372, 386). An important conclusion on the basis of the model is that the observed range of V_{prop} could be achieved without postulating conduction of electrical or mechanical signals (20).

Although these observations have provided a reasonable framework for explanation of propagated Ca^{2+} waves, the model is still only a working model and many questions remain unanswered. For example, the mechanism of propagation of a Ca^{2+} wave from one cardiac cell to another has received little attention. It has been reported that there is apparently continuous propagation of a Ca^{2+} wave from one cell to another with no delay or change of velocity at the cell-to-cell junction (527). On the other hand, it has been noted that in myocytes without Ca^{2+} overload a local increase in $[Ca^{2+}]_i$ using caged Ca^{2+} does not propagate (395) and that a Ca^{2+} wave induced by local application of caffeine decreases in both amplitude and velocity as it propagates along the cell (545). The high V_{prop} suggests that the barrier for Ca^{2+} diffusion imposed by gap junctions between cells is minor compared with the other parameters in the model such as Ca^{2+} binding to ligands in the cell and Ca^{2+} extrusion and sequestration processes. Zhang et al. (631) tested the importance of gap junctions to the properties of the TPCs in experiments where the trabeculae were exposed to the gap junction blockers heptanol and octanol. Although these compounds like many drugs have probably numerous side effects, their main effect is assumed to be a reduction of the open frequency of gap junctions. Exposure of the muscles to these alcohols decreased both the rate of initiation and V_{prop} dramatically with only a small decrease in twitch force (631). This suggests that closure of gap junctions reduces the rate of initiation and V_{prop} by reducing the effective rate of Ca^{2+} diffusion from cell to cell.

Second, since mitochondria are located in close proximity to RyR (436), it has been suggested that Ca^{2+} uptake via the mitochondrial uniporter may contribute to a local control of Ca^{2+} wave propagation (479).

IV) Propagated Ca^{2+} release elicits DADs: Whenever a TPC arises, it is accompanied by a depolarization similar to a DAD. It appears that the duration of the depolarization correlates exactly with the time during which the TPC travels through the trabeculae. The amplitude of the afterdepolarization also correlates exactly with the amplitude of the TPC (115). The tight correspondence between the time course of TPCs and those of the depolarizations suggests that the depolarization is elicited by a Ca^{2+}-dependent current, which exists as long as the $[Ca^{2+}]_i$ transient (wave) persists, as has been proposed by Kass et al. (264). In the small trabeculae used for TPC studies, this depolarization can be recorded over a distance of a few millimeters without much decrement due to electrotonic conduction. This assumption was verified experimentally by interrupting the propagation process of the TPC by locally heating the muscle. Local heating of the muscle caused the TPC to stop at the site of heating. In contrast, the concomitant depolarization could still be measured at a distance of ∼1 mm distal of the heating site (115) again as a result of electrotonic conduction of the DAD for which the current generators are located in the region with elevated $[Ca^{2+}]_i$. This observation clearly indicates that the depolarization cannot be the source of the TPC but must be induced by the TPC. The effect of local heating makes it also unlikely that TPCs are induced as a result of a linear gradient of Ca^{2+} overload along the muscle from a maximum

in the damaged region to a minimum at the other end of the muscle. Such a gradient could potentially cause apparent propagation of a contraction if Ca^{2+} overload-induced Ca^{2+} release would occur along the muscle at a latency that is small in the damaged region and increases linearly toward the other end of the muscle.

A TPC accompanied by a DAD can become sufficiently large to elicit an action potential with twitch. The action potential triggered by the first TPC may add so much Ca^{2+} to the cell that a triggered arrhythmia starts. Triggered arrhythmias indeed occur in the damaged muscle when the Ca^{2+} load of the SR is large. At room temperature triggered arrhythmias occur during the first hour after damage to the muscle has occurred. In such a case, the full-blown arrhythmia is usually preceded by the repeated occurrence of single premature beats. At 37°C, the time span over which these damage-related events occur in human trabecula is much shorter, and the TPCs, which cause the premature beats, disappear in 10 min or less (116). Under those conditions it is likely that their occurrence is limited by rapid closure of gap junctions as a result of persistently elevated Ca^{2+} levels in the damaged cells. In addition, the pH in these cells may be low due to the enormous metabolic load resulting from intense ion movement across their membranes or across membranes of adjacent cells. The lowered pH may promote gap junction closure.

In the intact canine wedge preparation under conditions of enhanced Ca^{2+} influx, simultaneous voltage/Ca^{2+} imaging studies have shown that multiple, simultaneous spontaneous Ca^{2+} release events can occur, and when they occur, the calcium release starts from a group of cells and then propagates outward but within a 3- to 4-mm region (267) (Fig. 7). The amplitude and occurrence of these spontaneous Ca^{2+} release events are related to the region of the ventricle (endocardial cells more prone than epicardium) as well as to the region with the greatest accumulation of diastolic Ca^{2+} in this preparation. Presumably this is due to the slower uptake (less SERCA2a) of Ca^{2+} in endocardial cells (573). In an ischemia/reperfusion model in the isolated guinea pig heart, monomorphic VTs and VF have been associated with spontaneous Ca^{2+} release. In 17% of the cases, the onset of spontaneous Ca^{2+} release preceded epicardial depolarizations by 2–15 ms (305), implying reverse ECC and arrhythmogenesis. Such Ca^{2+} changes appeared confined to a local region (1.8×1.8 mm^2) of these hearts.

Additional studies have suggested a similar coupling between the mechanical events during the twitch calcium and membrane electrophysiology. Studies of both skeletal and cardiac muscle have shown that a quick release of the muscle during contraction causes rapid release of Ca^{2+} from contractile filaments (224). Lab et al. (293) provided a link between these observations by showing that quick releases can induce a $[Ca^{2+}]_i$ transient accompanied by a DAD. Cardiac disease leads invariably to mechanical nonuniformity of myocardium. While the role of electrical nonuniformity of the myocardium in re-entry arrhythmias is well established, it is less well known to what extent nonuniform myocardial stress and strain distributions and nonuniform ECC may play a role in the initiation of extrasystoles that start arrhythmias. It is well known that tens of micromoles (per liter cell volume) of Ca^{2+} shuttle during the cardiac cycle between the SR and the cytosol where TnC is the dominant ligand. Hence, it is conceivable that nonuniformity of myocardium may lead to extrasystoles by several mechanisms including both abnormal SR Ca^{2+} transport

following damage and abnormal mechanical events in nonuniform myocardium, which cause dissociation of Ca^{2+} from TnC. It has been discussed how "spontaneous" SR Ca^{2+} release causes both transient inward currents and arrhythmogenic DADs as well as aftercontractions (see sect. IV*B3*). A sufficiently large SR Ca^{2+} load in cells at the rim of a damaged region could create an unstable state where spontaneous SR Ca^{2+} release may become so large that the resulting I_{ti} depolarizes the cells enough to trigger a new action potential, which perpetuates itself as a triggered arrhythmia (110). Alternatively, events that result from the tug of war between normal myocardium and weak cells in the ischemic zone could trigger the Ca^{2+} release and lead to arrhythmias. This tug of war may play a role in Ca^{2+} release, triggered in damaged regions of isolated rat ventricular and human atrial trabeculae, resulting in Ca^{2+} release that appears to be initiated after stretch of the damaged region during the regular twitch and propagates into neighboring myocardium by the combination of Ca^{2+} diffusion and Ca^{2+}-induced SR Ca^{2+} release.

Experimentally, a mechanical discontinuity along the trabeculae has been created by exposing the preparation to a small constant flow of solution with a composition that reduces ECC in myocytes only within that segment (570) (Fig. 8). Force, sarcomere length, as well as $[Ca^{2+}]_i$ were measured regionally. When the jet contained caffeine, butane-dione-monoxime (BDM), or low $[Ca^{2+}]$, muscle-twitch force decreased and the sarcomeres in the exposed segment were stretched by the shortening of the normal regions outside the jet. During relaxation the sarcomeres in the exposed segment shortened rapidly. Short trains of stimulation at 2.5 Hz reproducibly caused Ca^{2+} waves to rise from the borders exposed to the jet. Interestingly, these Ca^{2+} waves started during force relaxation of the last stimulated twitch and propagated into segments both inside and outside of the jet. Arrhythmias, in the form of nondriven rhythmic activity, were triggered when the amplitude of the Ca^{2+} wave increased by raising $[Ca^{2+}]_o$. The arrhythmias disappeared when the muscle uniformity was restored by turning the jet off (570). The authors have used the four-state model of the cardiac cross-bridge (Xb) with feedback of force development to Ca^{2+} binding by TnC and observed that the force-Ca^{2+} relationship as well as the force-sarcomere length relationship and the time course of the force and Ca^{2+} transients in cardiac muscle can be reproduced faithfully by a single effect of force on deformation of the TnC-Ca^{2+} complex and thereby on the dissociation rate of Ca^{2+}. Importantly, this feedback predicts that rapid decline of force in the activated sarcomere causes release of Ca^{2+} from TnC-Ca^{2+}, which is sufficient to initiate arrhythmogenic Ca^{2+} release from the SR. These results show that nonuniform contraction can cause Ca^{2+} waves underlying TPCs and suggest that Ca^{2+} dissociated from myofilaments plays an important role in the initiation of arrhythmogenic Ca^{2+} waves (534, 570).

Arrhythmogenic Ca^{2+} waves underlying triggered propagated contractions arise from Ca^{2+}-overloaded regions near damaged areas in the cardiac muscle. Ca^{2+} waves can also be induced in undamaged muscle, in regions with nonuniform ECC by the cycle of stretch and release in the border zone (BZ) between the damaged and intact regions. The same authors studied the hypothesis that rapid shortening of sarcomeres in BZ during relaxation causes Ca^{2+} release from TnC on thin filaments and initiates Ca^{2+} waves and went on to test whether elimination of this shortening will inhibit the initiation of Ca^{2+} waves, while SR

Ca^{2+} overload will enhance the waves. In this study, increase of $[Ca^{2+}]_i$ during TPCs was observed only after quick release of the muscle that followed a short (~200 ms) stretch during twitch. This observation confirmed our hypothesis that Ca^{2+} dissociated from TnC plays an important role in the acceleration of Ca^{2+} waves underlying TPCs (571). When a small jet of HEPES solution with 10 mM $[Ca^{2+}]$, or $[Ca^{2+}]_o$ containing BDM, was used to weaken a small muscle segment (10% of muscle length), the high $[Ca^{2+}]_o$ jet induced spontaneous diastolic sarcomere contractions in the jet region while attenuating the twitch sarcomere shortening outside the jet-stretched region. Stimulus trains induced Ca^{2+} waves inside the high $[Ca^{2+}]_o$ jet region upon twitch relaxation by 60%; Ca^{2+} waves started in the border zone of the BDM jet. The initial local $[Ca^{2+}]_i$ rise of the waves by high $[Ca^{2+}]_o$ was twice that by BDM. And arrhythmias occurred frequently (40%) in trabeculae after exposure to the high-$[Ca^{2+}]_o$ jet. Exponential stretches (10% muscle length) early during relaxation reduced sarcomere shortening in the weakened segment of the muscles and decreased force of a triggered propagating contraction (F_{TPC}) by 50%, and both delayed and reduced V_{prop} commensurate with the reduction F_{TPC}. The results are consistent with the hypothesis that Ca^{2+} release from TnC initiates arrhythmogenic propagating Ca^{2+} release in mechanically nonuniform myocardium. Prevention of sarcomere shortening reduces the Ca^{2+} dissociation from TnC, and initiation and propagation of these Ca^{2+} waves would be potentiated by high SR-Ca^{2+} overload.

C. Re-entrant Excitation

1. Ca^{2+} and impulse propagation—Important components of reentrant excitation are impulse propagation and unidirectional block. Both theoretical and experimental models (257, 338, 446, 486) suggest that under some circumstances the L-type Ca^{2+} current and $[Ca^{2+}]_i$ can affect cardiac impulse propagation. In neuronal tissues activity-dependent modulation of action potentials occurs as Ca^{2+} accumulates in the cell. Action potential propagation is slowed with a sudden flash-induced increase of $[Ca^{2+}]_i$ (338). Ca^{2+} accumulation during action potential propagation impedes propagation probably due to $[Ca^{2+}]_i$-dependent inactivation of the L-type Ca^{2+} current in settings where the Ca^{2+} currents of neuronal action potentials are reduced and improves conduction at sites of impedance mismatch (338). Similar studies have now been completed in patterned growth cultures of neonatal myocytes (446) and adult cell pair preparations (257). Importantly, these latter studies emphasize that the L-type Ca^{2+} current of the myocyte at the region of a current-to-load mismatch can become essential for impulse propagation (or block) (446). Reversal of such block can be accomplished by using BAY K 8644, an agonist of the L-type Ca^{2+} current. In an experimental cell model of action potential conduction, discontinuous action potential propagation increases the peak Ca^{2+} current of cells while also causing a brief increase in the cellular Ca^{2+} transient (569).

The critical relationship between altered $[Ca^{2+}]_i$ to discontinuities of conduction in arrhythmogenic substrates such as those of acute ischemia or those during the healing/healed phase postmyocardial infarction is not clear at this time. However, the mechanism of "pseudo-block" during reentrant arrhythmias in the healing infarcted heart may depend not only on the cell surface redistribution of gap junction proteins, but also on the loss of function of the L-type Ca^{2+} channels and its subsequent impact of intracellular Ca^{2+} cycling

(19). In mapping studies of reentrant excitation in ventricles postmyocardial infarction, an L-type Ca^{2+} current agonist is antiarrhythmic (75), presumably due to its effect to increase the amplitude of the remodeled L-type Ca^{2+} currents and $[Ca^{2+}]_i$ in the border zone myocytes that form the substrate of these reentrant arrhythmias (433).

If altered Ca^{2+} can initiate arrhythmias, how does elevated $[Ca^{2+}]_i$ contribute to perpetuation of a re-entrant arrhythmia? Two types of studies have been completed in an attempt to address this question. First, simulations of spiral waves have shown that they destabilize when $[Ca^{2+}]_i$ transient nonuniformities are allowed to occur (98). The result is a fibrillatory pattern of excitation. However, when both $[Ca^{2+}]_i$ and voltage were measured experimentally during VF in the nonremodeled heart, there appears to be a loss of association of phasic $[Ca^{2+}]_i$ transients with fibrillatory waves (400, 598), suggesting that $[Ca^{2+}]_i$ is not essential for VF maintenance.

2. Ca^{2+} and gap junction permeability—Intercellular electrical transmission occurs via a set of ion channel proteins and specialized membrane structures called gap junctions. Each channel is formed by close apposition of two hemichannels each of which is in an opposing cell (618). Gap junctions can provide passage of many molecules (cAMP, Ca^{2+}, IP_3, ATP) up to 1 kDa in size (56, 462, 470). In cardiac cells, gap junctional conductance can be regulated acutely by pH, Ca^{2+}, cAMP, and cGMP (449). Therefore, Ca^{2+} can be both flowing through gap junctions as well inhibiting their conductance. In the first case, Ca^{2+} released upon RyR activation can travel as a wave across a cell (631) and propagate to adjoining cells via gap junctions (513). In cells transfected with both connexin43 and RyR receptors propagation of Ca^{2+} waves between cells is sensitive to octanol (544). Furthermore, in this experimental cell model, both Ca^{2+} wave propagation and gap junctional conductance between a pair of cardiac cells are related to the state of tyrosine phosphorylation of connexin43 (543). How the Ca^{2+} wave crosses the gap junction is unknown, but extracellular disulfide bonds of the connexin43 proteins between the adjoining cells appear critical for wave propagation (544).

D. Nonuniform ECC and Electromechanical Alternans

T-wave alternans as well as QT alternans are ECG descriptors that are characterized by beat-to-beat changes in T-wave morphology as well as the QT interval. Both measures are positive prognostic indicators of arrhythmic events (451, 452, 501, 546). Although both observations have been linked to spatial and temporal heterogeneity of repolarization of action potentials in the heart (408, 409), spatial and temporal changes in intracellular Ca^{2+} within myocytes have also been implicated (432). Several recent reviews discuss the nomenclature and current understanding of the relationship between Ca^{2+} and voltage in alternans (143, 150, 450, 471, 583). In fact, in the nonremodeled guinea pig heart, alternans of both APD and $[Ca^{2+}]_i$ occur preferentially at the base of the heart (432). These latter data imply that the normal spatial heterogeneity of Ca^{2+} transients (a base to apex gradient) is potentially a cellular mechanism of Ca^{2+} alternans (93, 266, 573). Mechanical alternans accompanies $[Ca^{2+}]_i$ transient alternans (218, 273, 294, 460), and both are sensitive to agents that affect SR function (e.g., ryanodine). In atrial cells Ca^{2+} transient alternans can be seen where there was failure of Ca^{2+} wave propagation from the periphery to the cell's

center every other stimulated beat (233). In fact, cellular Ca^{2+} alternans has been related to the amount of Ca^{2+} released from the SR, which is determined by the trigger (L-type Ca^{2+} current), the SR load, and the metabolic and phosphorylation state of the RyR. Some have also suggested that diastolic fluctuations of SR Ca^{2+} occur during alternans, and this leads to Ca^{2+} transient alternans. This has recently been examined directly (421), and these results suggest that factors other than SR load are critical for frequency-related Ca^{2+} alternans in a single cell.

Mechanical alternans would be expected on the basis of APD alternans in a model of ECC as described in Reference 195. The model predicts two types of alternans, i.e., the alternans in which APD and force increase and decrease together, i.e., “in-phase” alternans, or the changes in APD occur “out of phase” with those of force. The amount of Ca^{2+} released during any beat depends on the Ca^{2+} influx during the preceding action potential. This is true for myocytes with a robust SR function; in cells with a diminished SR Ca^{2+} storage ability, APD determines concomitant Ca^{2+} release directly. Acute changes in $[Ca^{2+}]_i$ affect the membrane currents (see above) and thus provide a feedback mechanism that controls APD of the concurrent beat. Furthermore, at high heart rates (at which alternans is usually found), relaxation may be incomplete. As a result of the elevated $[Ca^{2+}]_i$, ligands in the cytosol including the SR Ca^{2+} pumps would be occupied and the effect of variation of Ca^{2+} influx would be more pronounced. Alternans also occurs in metabolically compromised muscle. Hence, the force of each contraction may influence the cytosolic phosphate level; the latter will reduce force of the next contraction (271). Force of contraction increases the sensitivity of TnC for Ca^{2+}. As a consequence, elevated cytosolic phosphate levels will reduce the binding of released Ca^{2+} to the contractile filaments. Perhaps this is related to the Ca^{2+} transient alternans of ischemia (434).

Triggered propagated contractions could be also involved in the generation of a mechanical alternans. Here a strong contraction would trigger a substantial Ca^{2+} release that propagates as TPC. The strong TPC would reduce the Ca^{2+} release during the next electrically driven beat. This beat would be weak and followed by a small TPC. The subsequent beat would be strong again. If the $[Ca^{2+}]_i$ feedback mechanism to membrane currents described above is operational, one would expect an “out of phase” alternans with evidence of DADs of varying amplitude. Elimination of SR function would eliminate this alternans. Recent data regarding alternans produced by small depolarizing steps may reflect this, since alternans in this case was due to large Ca^{2+} transients resulting from intracellular wave propagation (134).

In a recent study discordant electrical alternans was described when membrane repolarization alternated with the opposite phase between groups of neighboring cells (408). This type of alternans was directly linked to the formation of unidirectional lines of block and reentrant ventricular fibrillation. Whether mechanical alternans accompanies or causes these arrhythmogenic beats remains unknown at this time. While some believe that heterogeneities in electrical restitution properties are central to the basis for discordant alternans, we still underappreciate the role of nonuniform ECC and/or the intrinsic variability of the Ca^{2+} transient across the ventricular wall (266). In fact, when normal cells which show APD/Ca^{2+} transient alternans are voltage clamped with an action potential

waveform of fixed duration, Ca^{2+} transient alternans persist (98, 177). Studies combining optical voltage and Ca^{2+} fluorescence measures indicate that the shapes of the Ca^{2+} transients recorded from cells within 1.1 mm in the intact heart are similar but differ significantly from alternans observed with acute ischemia (101, 434, 435). Furthermore, recent evidence points to a role of Ca^{2+} cycling rather than electrical restitution in T-wave alternans in normal hearts (93, 432).

V. Summary

Ca^{2+} play a key role in both the short- and long-term properties of cardiac cells and are thus involved in the development of arrhythmias. The nature of the many mechanisms via which Ca^{2+} exerts its effects is by no means fully understood. The notion that these ions do play a key role in the development of arrhythmias is not surprising. The structure of cardiac cells enables rapid electrical conduction as well as rapid activation of the contractile system even though diffusion of Ca^{2+} is slow. Nature has, therefore, provided amplification stations between the sarcolemma and the myofibrils so that both the delivery and the removal of Ca^{2+} is accelerated. Simultaneously, the Ca^{2+} sensitivity of many proteins in the cardiac cell is so high such that activation of contractile proteins occurs at $[Ca^{2+}]_i$ only slightly above the diastolic level. Furthermore, $[Ca^{2+}]_i$ affects the electrical processes at the surface membrane profoundly. It is therefore plausible that instability of the Ca^{2+} transport systems is involved in the mechanisms that lead to overall instability of the tissue during arrhythmias. In addition, Ca^{2+} plays an important role in the long-term life of the cardiac cell by affecting both the composition and cellular distribution of proteins which dictate the phenotype of the cell. Turnover of these proteins is so fast that it is likely that the very factors which determine the initiation of an arrhythmia may themselves change the cardiac cell phenotype and thus alter the cell's future response to the same factors. Solving the nature of these intricate and dynamic interactions promises to be an important area of research for a better recognition and understanding of the nature of Ca^{2+} and arrhythmias. In so doing, our solutions will provide a more complete understanding of the molecular basis for the targeted control of cellular calcium in the treatment and prevention of such.

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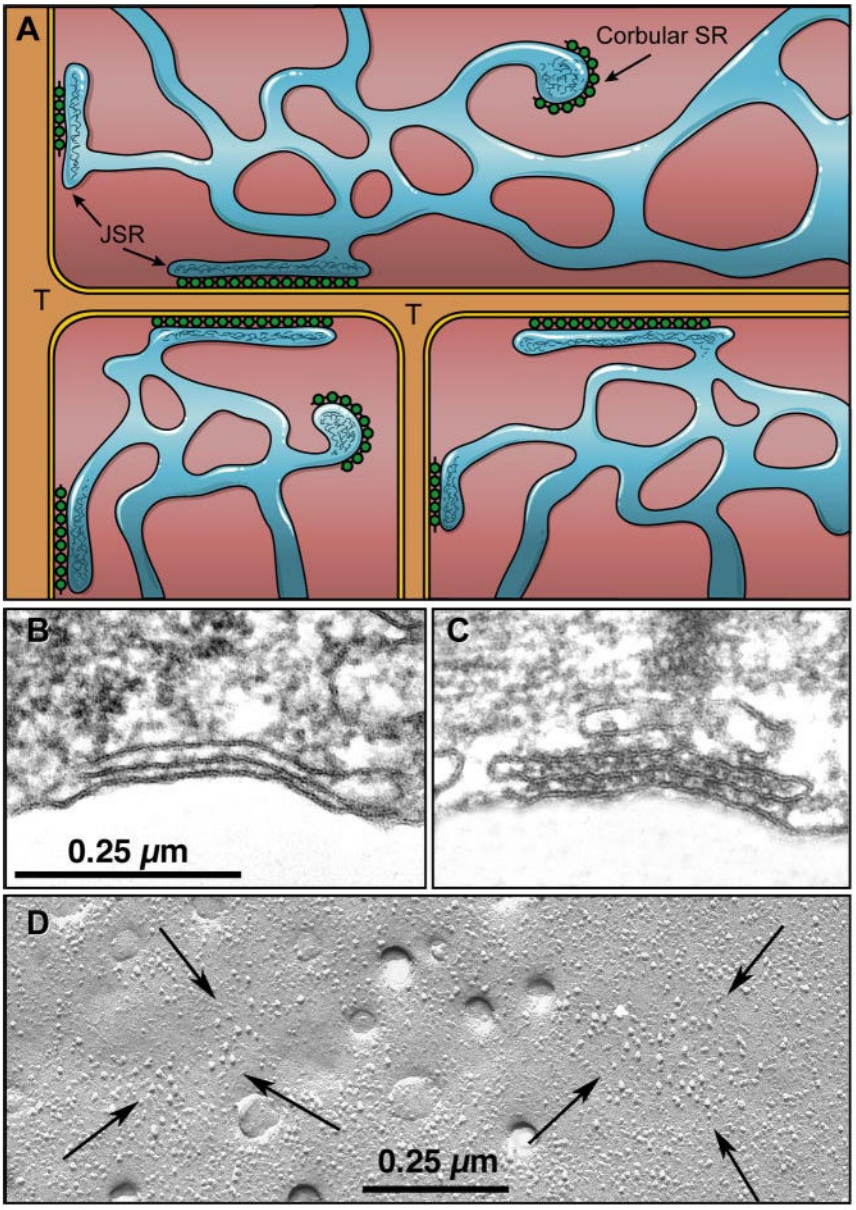

Fig. 1.

A: Ca^{2+} release units in cardiac muscle (chick myocardium). Dyads are formed by junctional sarcoplasmic reticulum (SR) with feet on their cytosolic surface and containing calsequestrin (CSQ), associating with the surface membrane or the membrane of t tubules (T). Corbular SR contains the same components but does not associate with the cell membrane. *B* and *C*: peripheral couplings; docked, but not yet fully differentiated (embryo 2.5 days). *D*: freeze fracture of cell membrane arrows surrounding junctional domains containing dihydropyridine receptor (DHPR) particles. [From Franzini-Armstrong et al. (162).]

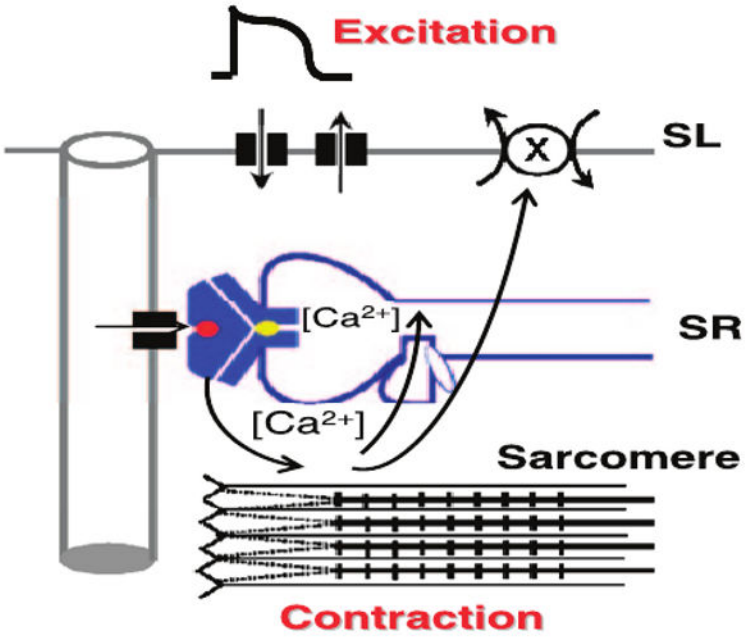

Fig. 2.

Diagram of the excitation-contraction coupling system in the cardiac cell. During the action potential Ca^{2+} enters the cells as a rapid influx followed by a maintained component of the slow inward current. Ca^{2+} entry does not lead directly to force development as the Ca^{2+} that enter are rapidly bound to binding sites on the SR that envelops the myofibrils. The rapid influx of Ca^{2+} via the t tubules is thought to induce release of Ca^{2+} from a release compartment in the SR, by triggering opening of Ca^{2+} channels in the terminal cisternae, thus activating the contractile filaments to contract. Relaxation follows because the cytosolic Ca^{2+} is sequestered again in an uptake compartment of the SR and partly extruded through the cell membrane by the Na^{+}/Ca^{2+} exchanger and by the low-capacity high-affinity Ca^{2+} pump. The force of contraction is thus determined by the circulation of Ca^{2+} from the SR to the myofilaments and back to the SR, and by the amount of Ca^{2+} that has entered during the preceding action potential. The relaxation rate of the twitch depends on the rate of Ca^{2+} dissociation from the myofilaments and on the rates of Ca^{2+} sequestration and extrusion. It is important to note that the process of Na^{+}/Ca^{2+} exchange is electrogenic so that Ca^{2+} extrusion through the exchanger leads to a depolarizing current.

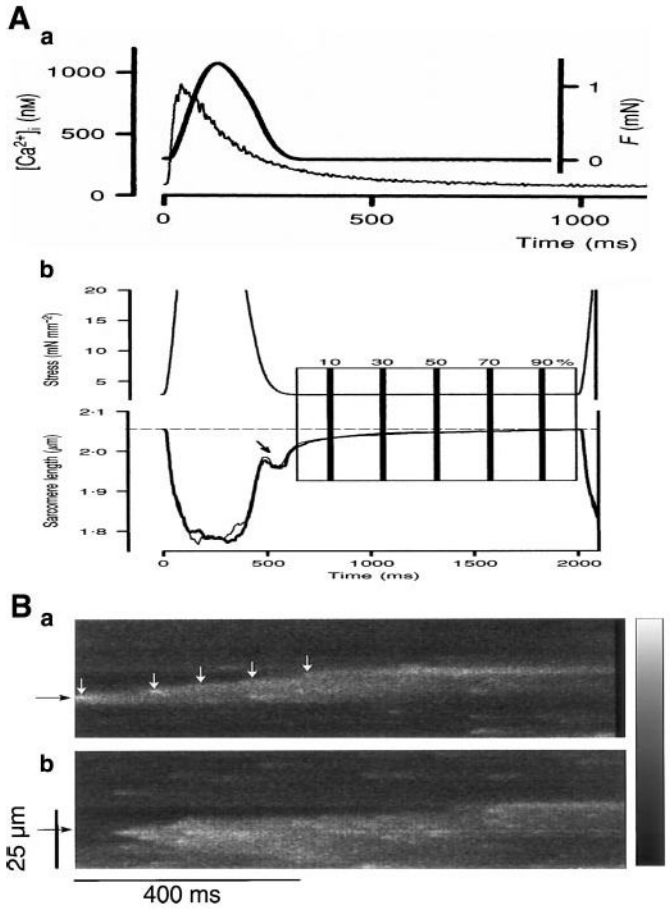

Fig. 3.

A, a superimposed tracings are force (thick black line) and intracellular calcium (Ca_i) transient (thin black line) recordings of the electrically stimulated trabecula. Bottom tracing illustrates the slow change in Ca_i occurring in normal muscle during the diastolic period (between vertical dotted lines). *A, b*: force at increased gain and sarcomere length during the twitch and subsequent diastolic pause. Note that no sarcomere length fluctuations (>1.3 nm) occur (535). *B*: enlarged confocal image depicting the characteristics of line scans during propagation of one microscopic Ca^{2+} wave (*top panel a*) and during initiation and propagation of another (*bottom panel b*) in normal muscle. In *Ba*, the Ca^{2+} wave has an asymmetric appearance, as if it encounters a border or failed to propagate in one direction. In *Bb*, the wave begins as a "V," indicating equal propagation in both directions; however, this wave stops propagating. The black arrows in both panels mark the same position in the two scans, indicating that the two waves started at the same place. The white arrows indicate the position of sparks at the leading edge of the wave in *A*. [From Wier et al. (590).]

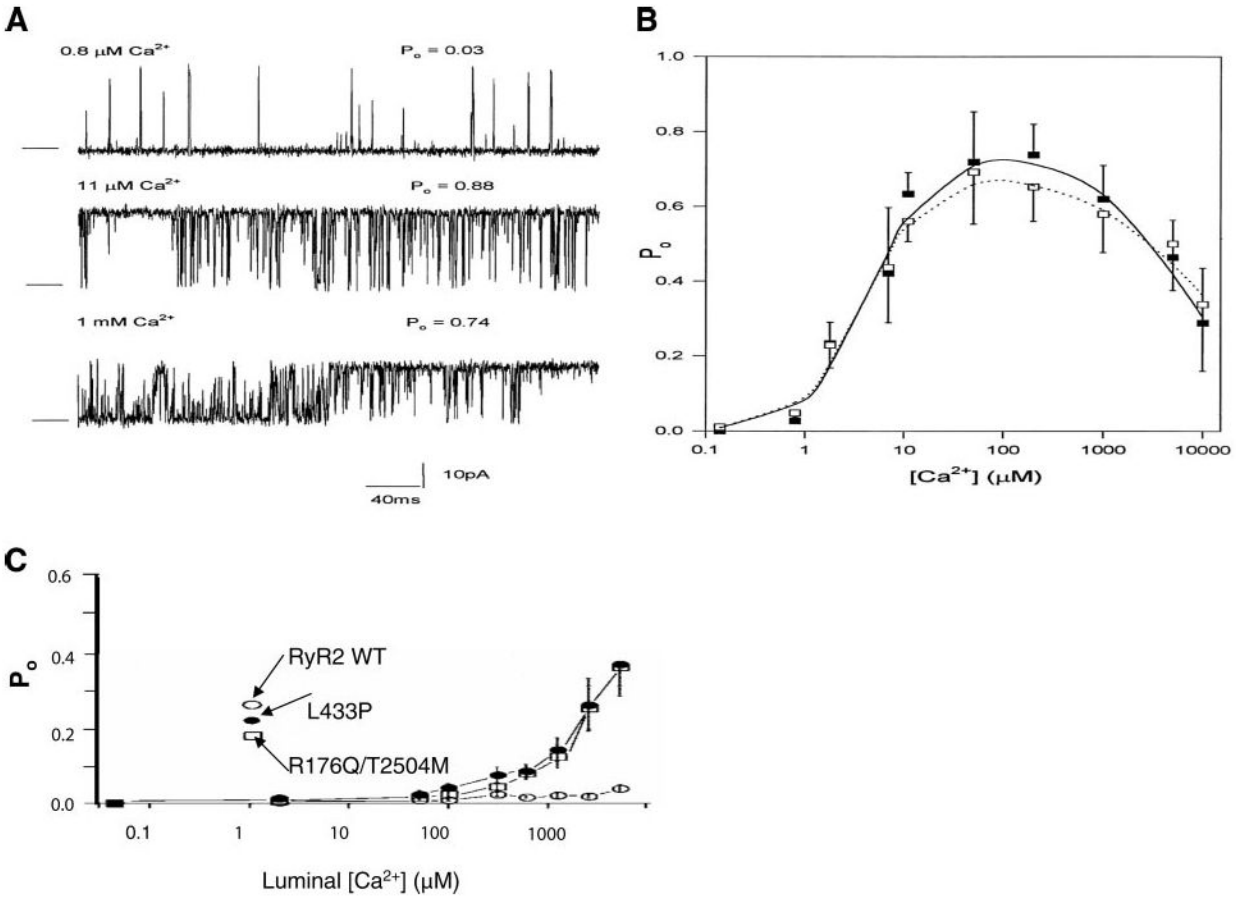

Fig. 4.

Dependence of ryanodine receptor (RyR) single-channel activities on cytosolic Ca^{2+} and SR-luminal Ca^{2+}. *A*: original current traces from cardiac Ca^{2+} release channels at three differing Ca^{2+} levels. Upward deflections indicate openings from closed state (small bar at *left*). *B*: average single-channel open probability (P_o) values determined as in *A* at +35 mV (closed symbol) and −35 mV (open symbol). See Ref. 606 for more information. *C*: P_o-luminal $[Ca^{2+}]$ relationship of wild-type RyR2 expressed in HEK293 cells compared with the P_o-luminal $[Ca^{2+}]$ relationship of RYR2 channels with mutations linked to VT (L433P and R176Q/T2504M). These mutations displayed a leftward shift of the P_o-luminal $[Ca^{2+}]$ relationship without a change in the sensitivity to cytosol $[Ca^{2+}]$. See Ref. 251 for details.

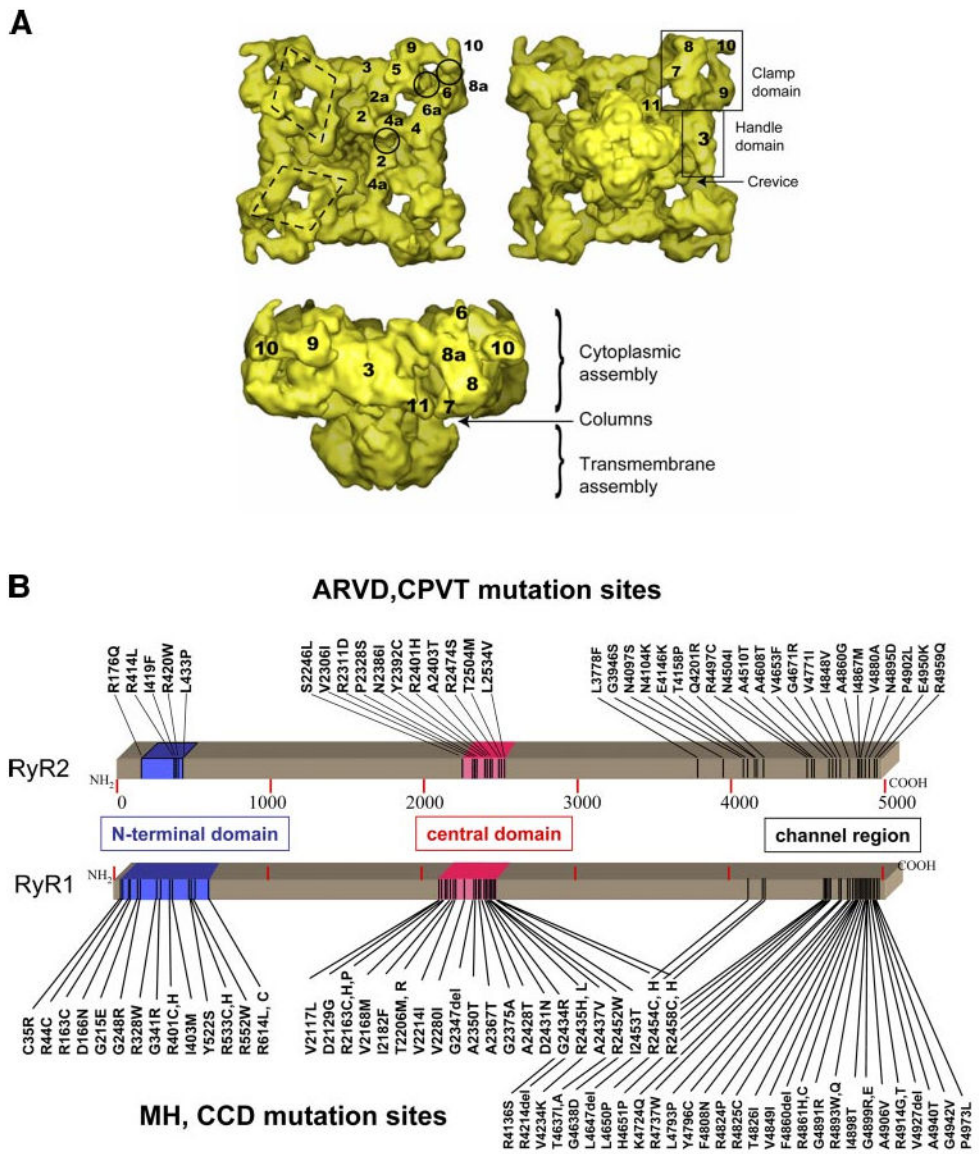

Fig. 5.

A: ultrastructure of RyR1 at 9.5 Å resolution. The receptor is composed of a cytosolic assembly linked to a transmembrane assembly (TMA) through a neck region which conveys columns that form the vestibule of the TMA and the Ca^{2+} channel in the center of the TMA to the regulatory elements in the clamps and handle domain of the cytosolic assembly (see text for further details). [From Samso et al. (468).] *B*: schematic diagram of the reported mutation sites of RyR1 and RyR2. NH_2 terminus, central domain, and transmembrane (channel) regions are denoted. For more information, see text and http://pc4.fsm.it:81/cardmoc/. [From Yano et al. (617).]

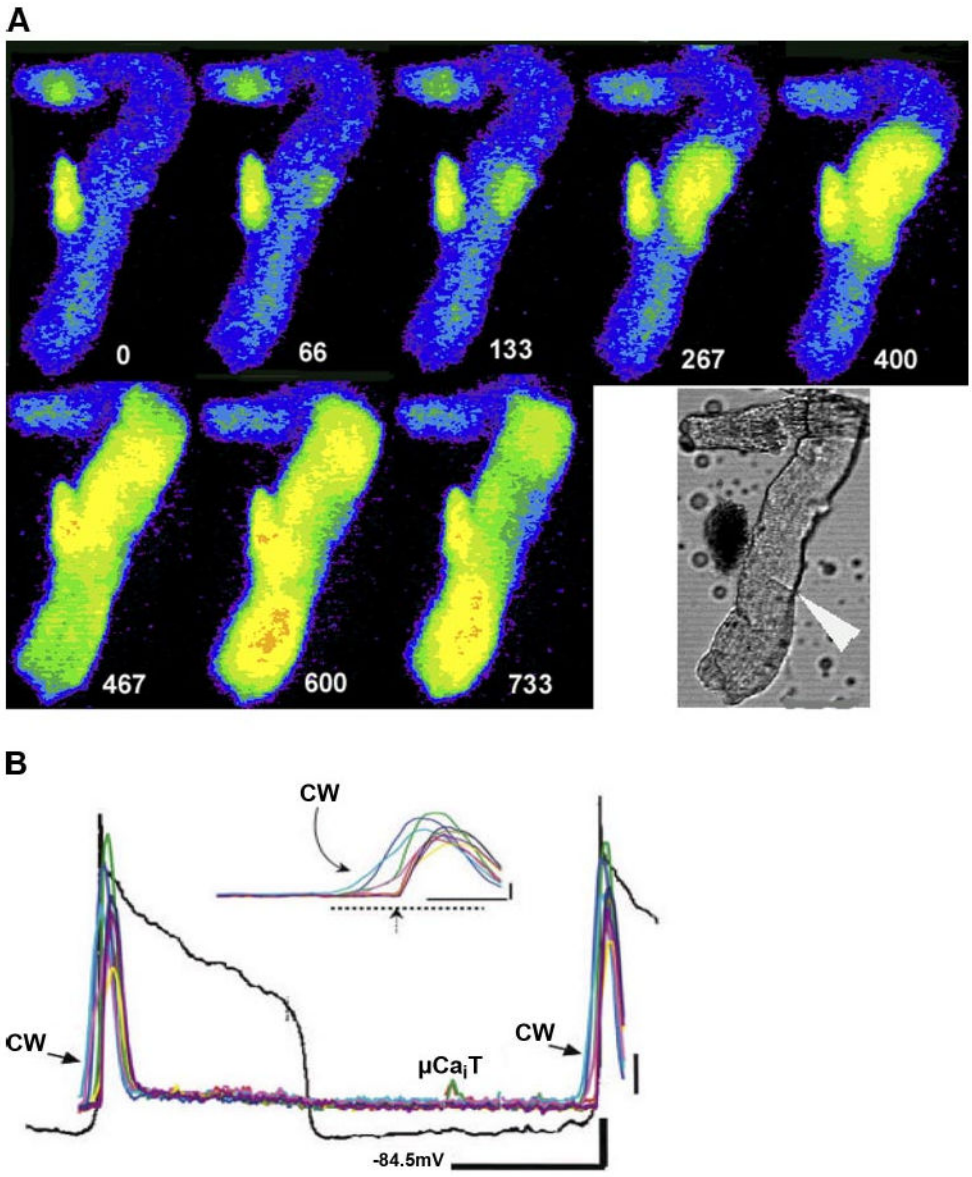

Fig. 6.

Large cell wide (CW) Ca^{2+} waves can lead to sufficient membrane depolarization to elicit an action potential (AP). *A*: selected image frames of Ca^{2+} from an IZPC (Purkinje cell aggregate from the infarcted heart) during the Ca^{2+}-induced electrical activity. Time relative to *t*=0 of first frame is depicted by white numbers. Lower white light image is of aggregate during experiment. Large white arrowhead indicates probable cell border. *B*: transmembrane potential (black line) and Ca^{2+} (multicolored lines) changes of this aggregate during the CW wave induced electrical activity. μCaiT represents a small micro Ca^{2+} wavelet that occurred during the recording but that is not shown in these epifluorescent images (see Ref. 61 for more details).

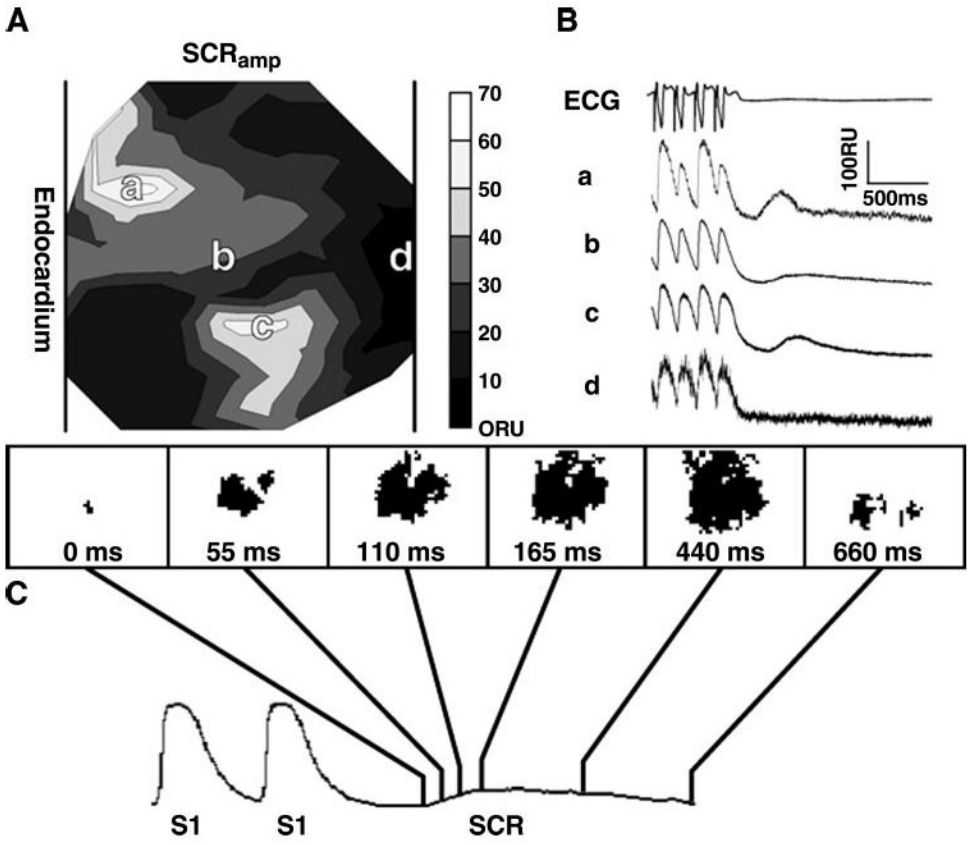

Fig. 7.

Multiple simultaneous spontaneous Ca^{2+} release events in the isolated canine wedge preparation under Ca^{2+}-loaded conditions. *A*: representative transmural map (endocardium to the *left*, epicardium to the *right*) depicting activity of imaged Ca^{2+}. Imaged area is 14 mm × 14 mm. SCR_{amp} means spontaneous calcium release amplitude as determined from recordings such as those shown in *B*. Relative fluorescent ratio units (ORU) are depicted by the various shades of gray in the bar. Note this map reveals that there are two "hot" spots of relatively high-amplitude SCR (denoted by *a, c*). Corresponding local Ca^{2+} transients during this time are seen in *B*. Note that while there is SCR near endocardium (*site a*) and midmyocardium (*site c*), there is no release at *site d* (epicardium). The SCRs are depicted as delayed after Ca^{2+} transients in *B*. [From Katra and Laurita (267).] *C*: one local Ca^{2+} transient in another preparation with selected images (0 to +660 ms) above showing the isochrones of Ca^{2+} levels during the inscription of the after Ca^{2+} transient. Note that SCR starts at one focus (~1.2 mm^2) and then during the course of the global transient propagates outward at ~26 mm/s. At its maximum this SCR covers ~35 mm^2. (From Laurita laboratory, unpublished data.)

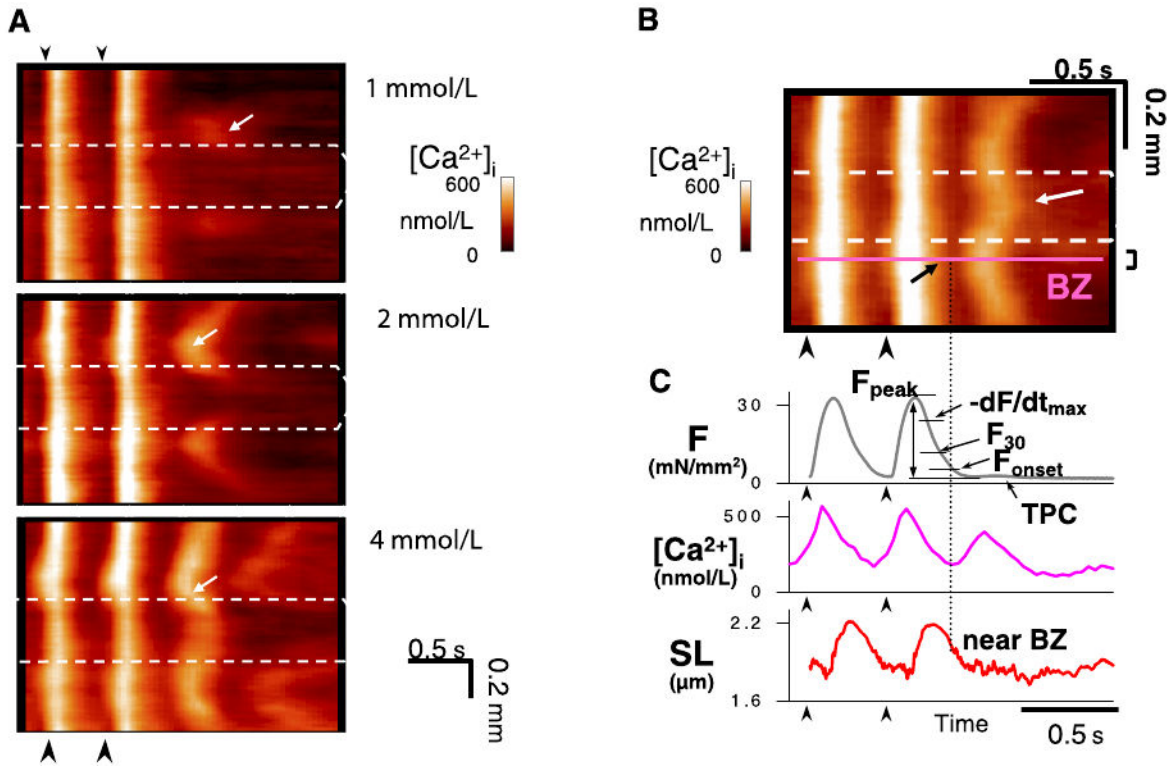

Fig. 8.

Initiation of Ca^{2+} waves in experimental multicellular preparation of nonuniform excitation-contraction coupling. *A*: Ca^{2+} waves induced by a local BDM exposure at various Ca^{2+} concentrations (1, 2, and 4 mM). BDM is delivered to the trabecula via a jet system that superfuses the region denoted by the dotted lines. Note that increasing Ca^{2+} led to the initiation of Ca^{2+} waves that propagate into the segment inside the jet and into the normal muscle. Both the amplitude of the initial and propagating Ca^{2+} transient as well as propagation velocity increased with increase in Ca^{2+}. Arrows indicate initiation sites. *B*: collision of Ca^{2+} waves in the jet region (white arrow). *C*: Ca^{2+} traces, F records, and SL (sarcomere records) from average profiles indicated by the square bracket in *B*. Note that the onset of the initial Ca^{2+} rise of the wave in *B* (denoted by the black arrow in *B*) corresponds with the time at which the twitch had relaxed to 10% (F onset) and late during relaxation. [From Wakayama et al. (570).]

Table 1

Ca^{2+} binding to troponin C and calmodulin in the cardiac cell

Parameter	Value	Source
Troponin Ca^{2+} specific binding sites		
Concentration ($trop^T$)	60 μM	Lee and Allen et al. (311)
Ca^{2+} on-rate (K_{on}^{T})	39 $\mu M^{-1}\cdot s^{-1}$	Robertson et al. (442)
Ca^{2+} off-rate (K_{off}^{T})	19.6 s^{-1}	Robertson et al. (442)
Troponin Ca^{2+} -Mg^{2+} binding sites		
Concentration ($trop^T$)	60 μM	Lee and Allen (311)
Ca^{2+} on-rate (K_{on}^{TC})	60 $\mu M^{-1}\cdot s^{-1}$	Wang et al. (575)
Ca^{2+} off-rate (K_{off}^{TC})	2.4 s^{-1}	Wang et al. (575)
Mg^{2+} on-rate (K_{on}^{TM})	0.04 $\mu M^{-1}\cdot s^{-1}$	Wang et al. (575)
Mg^{2+} off-rate (K_{off}^{TM})	20 s^{-1}	Wang et al. (575)
Calmodulin binding sites		
Concentration	25 μM	Wier and Yue (591)
Ca^{2+} on-rate (K_{on}^{C})	9.2 $\mu M^{-1}\cdot s^{-1}$	Wang et al. (575)
Ca^{2+} off-rate (K_{off}^{C})	7.3 s^{-1}	Wang et al. (575)
Free $[Mg^{2+}]_i$	0.72 ± 0.06 mM	Gao et al. (172)
Diastolic free $[Ca^{2+}]_i$	0.07–0.25 μM	Stuyvers et al. (515)