Chapter 2

Cardiac Function in Heart Failure: The Role of Calcium Cycling

Overview

During the cardiac action potential, it is the rise in the level of cytoplasmic calcium as well as the sensitivity of several calcium-sensitive proteins to that released calcium that determines the force of myocardial contraction. Both calcium entry and sensitivity are significantly reduced in heart failure. In this chapter, we discuss how calcium primarily enters the cell through the L-type calcium channel in the plasma membrane. This triggers a large release of calcium primarily through channels (ryanodine receptors) in the sarcoplasmic reticulum. Calcium then binds to several proteins that activate the interaction of actin and myosin in the myofilaments. Finally, this calcium is removed from the cytoplasm back into the sarcoplasmic reticulum and out of the cell through the plasma membrane by several active energy-dependent processes. This calcium removal process is also altered during the development of heart failure. In this chapter, these changes are discussed along with the potential new treatments for heart failure involving changes in calcium entry, exit, and sensitivity.

Introduction

It is the loss of the heart's ability to adequately pump sufficient blood that is the characteristic finding in heart failure. A normal heart can increase its pumping ability to a great extent. Myocardial contractility is primarily controlled by calcium cycling into and out of the cytoplasm of cardiac myocytes as well as calcium sensitivity of various proteins in cardiac myocytes. Calcium initially enters the cell through channels in the plasma membrane, although the major path for calcium entry into the cell cytoplasm is from the sarcoplasmic reticulum. Calcium release channels in the sarcoplasmic reticulum are activated by calcium entry from the plasma membrane. The released cytoplasmic calcium interacts with calcium-sensitive proteins to control the force and rate of contraction. Calcium is then removed from the cytoplasm by several energetic processes, which pump it back into the sarcoplasmic reticulum and

out through the plasma membrane. This calcium cycling of the normal heart is illustrated in Fig. 2.1. Calcium can also enter the mitochondria. All of these processes are altered during the transition to heart failure (HF) [1, 2]. This leads to a loss of contractile reserve. In this chapter, we will first discuss the calcium entry into the cytoplasm both from outside the cell and from the sarcoplasmic reticulum and how this entry is altered in HF. Thereafter calcium sensitivity will be addressed, as well as changes in calcium stores in the sarcoplasmic reticulum. We will also discuss calcium removal and how this parameter is altered in HF. Finally, we will analyze changes in the calcium transients that occur in HF. Some of the changes in calcium cycling that occur in heart failure are presented in Fig. 2.1. It has been proposed that calcium cycling defects may be the final common pathway in the progression to HF [3]. Treatment strategies have been proposed to address the issue of increasing the ability of calcium to ameliorate function in the failing heart [4–7].

Calcium Entry Through the Plasma Membrane

Calcium enters the cardiac myocyte cytoplasm from the extracellular space mainly through L-type Ca^{2+} channels. These channels are one of the main systems in the heart for Ca^{2+} uptake regulation [8, 9]. Their structure has been comprehensively studied and consists of heterotetrameric polypeptide complexes [10, 11]. There are also several accessory subunits of this channel. The L-type Ca^{2+} channels are responsible for the activation of sarcoplasmic reticulum calcium release channels (RyR2) and are controllers of the force of muscle contraction generation in the heart. Thus, the activity of the heart depends on L-type Ca^{2+} channels [8, 12]. The L-type Ca^{2+} channels and the RyR2 receptors are closely linked in the T-tubules of cardiac myocytes [13], and there appears to be a physical connection between these two channels [12]. Phosphorylation of the L-type Ca^{2+} channel-forming subunits by different kinases is one of the most important ways to change the activity of L-type Ca^{2+} channel

Fig. 2.1 (**a**) Calcium entry and exit from a normal cardiac myocyte. Calcium (■) enters from outside through L-type calcium channels (Ica, L). This triggers Ca^{2+} release from the ryanodine receptors (RyR) in the sarcoplasmic reticulum, called calcium-induced calcium release (CICR). Calcium then activates the myofilaments by binding to troponin C. Calcium is removed from the cytoplasm to the outside of the cell by a sodium–calcium exchanger, which requires an active Na^+/K^+ ATPase. There is also a plasma membrane Ca^{2+} ATPase. Calcium is pumped back into the sarcoplasmic reticulum by a Ca^{2+} ATPase (SERCA) that is controlled by a phospholamban. (**b**) Calcium entry and exit from a failing cardiac myocyte. There is reduced calcium entry through the L-type calcium channels and RyR. This is shown by reduced numbers but may also involve reduced activity. Sodium–calcium exchanger activity may increase, but SERCA function is reduced. There is also more diastolic calcium in the cytoplasm
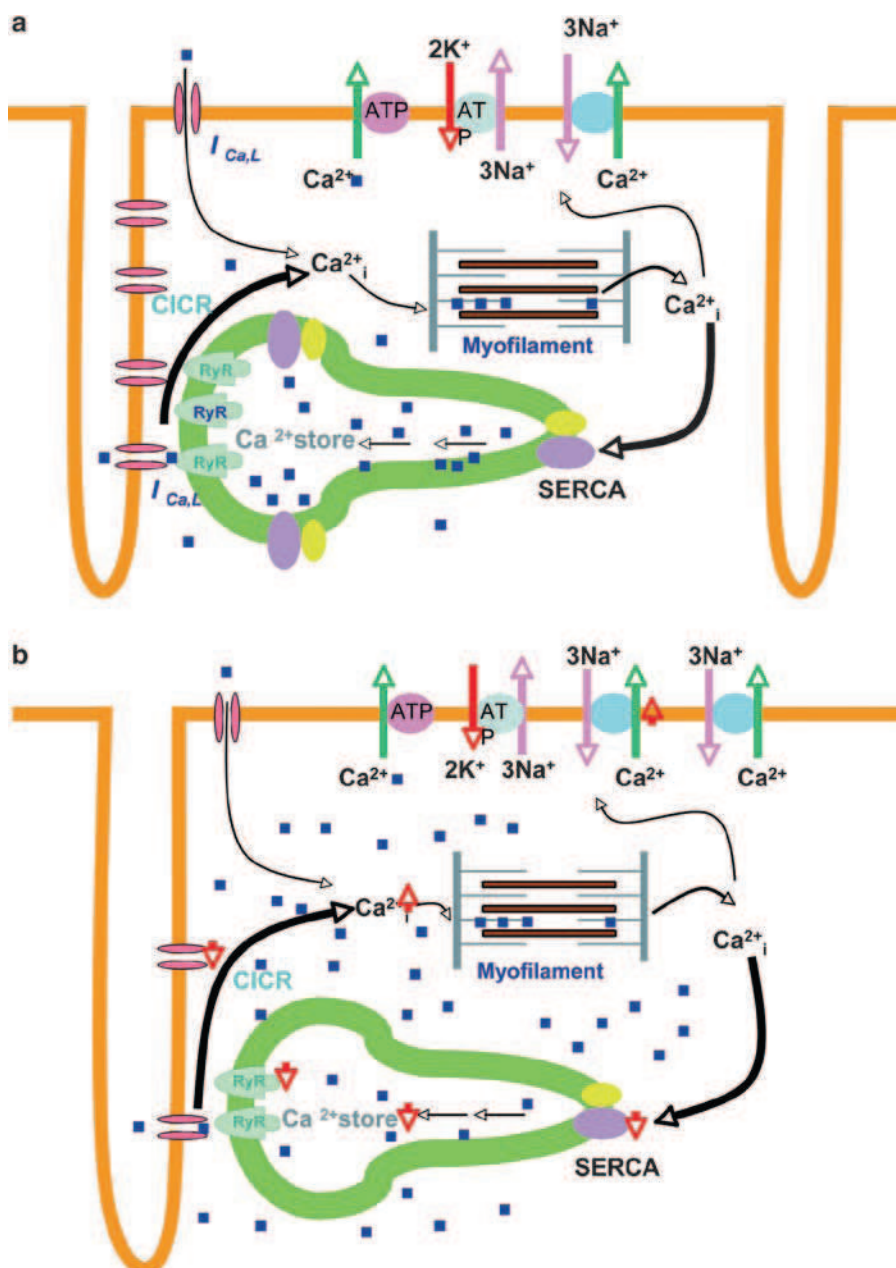
(see Chap. 8). Phosphorylation can either increase or decrease channel activity. Additionally, the activity of L-type Ca^{2+} channels depends on Ca^{2+} concentration in cytoplasm. Other calcium channels may play a minor role in calcium entry into the cardiac myocytes [14]. The Ca^{2+} current entering the cardiac cells through the L-type Ca^{2+} channel facilitate contraction. This entry process is regulated by phosphorylation of L-type Ca^{2+} channels and intracellular Ca^{2+} concentration. Disturbances in cellular Ca^{2+} transport and regulation of L-type Ca^{2+} channels are directly related to HF.

Calcium entry into cardiac myocytes is significantly affected by the development of HF. Some of the changes asso-

ciated with HF are related to changes in the phosphorylation state of the L-type Ca^{2+} channels [4]. In mice, overexpression of L-type Ca^{2+} channels leads to HF [15]. The structure of these channels changes during HF, and their remodeling may prove useful in the treatment of the failing heart [10].

It is not clear whether there are changes in total channel density during the development of HF [11]. Some studies have suggested that there may be reduced expression of these calcium channels in the failing heart [6], in which the coupling between the L-type calcium channels and the calcium release channels of the sarcoplasmic reticulum is also reduced [16]. Although, calcium entry into the cell is reduced in HF,

activation of calcium channels has not proved to be useful in the treatment of HF, in which other calcium entry channels may also play a role [14].

Calcium Release from the Sarcoplasmic Reticulum

During the cardiac action potential, Ca^{2+} influx across the cell membrane via L-type Ca^{2+} channels triggers the release of more Ca^{2+} from the sarcoplasmic reticulum, primarily by activating ryanodine receptors (RyR2) in the adjacent sarcoplasmic reticulum membrane [12, 13]. L-type Ca^{2+} channels are located predominantly in the T-tubules, in close proximity to RyR2 channels at the dyad: the junctional region where Ca^{2+} influx from the surface channels triggers sarcoplasmic reticulum Ca^{2+} release [9, 13]. The geometry of this region is of critical importance for proper myocardial function [17]. RyR2 function is regulated by several accessory proteins [18]. Calcium induced calcium release is one of the major controllers of myocardial function [19]. Most of the rise in cytoplasmic calcium that occurs during the cardiac action potential is related to calcium released from the sarcoplasmic reticulum by the RyR2.

Local release of calcium from the RyR2 channels leads to calcium sparks [20] and the rise of intracellular Ca^{2+} activates the contractile proteins. The systolic Ca^{2+} transient is the spatial and temporal sum of such local calcium releases (calcium sparks). The fraction of the total sarcoplasmic reticulum Ca^{2+} content that is released during any given action potential depends on the sarcoplasmic reticulum Ca^{2+} content, the various accessory proteins and the size of the Ca^{2+} trigger [18, 19, 21].

The calcium release channels in the sarcoplasmic reticulum become dysfunctional during the development of HF [5, 19, 22, 23], in which there is evidence for a significant change in the phosphorylation state of these RyR2 channels [4, 12, 24]. However, expression levels of the RyR2 channels may not change significantly [25]. Furthermore, there are slowed calcium transients related to activation of this channel [22, 23].

The structural relationship between the RyR2 channels and the L-type calcium channels is significantly altered with the development of HF [16], in which the physical coupling between these channels is reduced. Moreover, RyR2 channels become leaky during HF [24, 26], although whether this increased leakiness of the RyR2 channels is a cause or an effect of the failing heart is not clear. Fixing this leakiness may prove to be a good therapeutic strategy in the treatment of HF [24]; and this is supported by recent observations suggesting that in HF, RyR2 channels may be useful therapeutic targets [18, 27]. Interestingly, several mutations of the RyR2 channel that affect channel activity have been associated

with the development of human heart failure [22]. These changes in RyR2 and L-type calcium channels lead to reduced calcium transients in failing hearts.

While RyR2 Ca^{2+} release channels have received significant attention, the role of a second pathway for internal Ca^{2+}-release has largely been ignored. The cellular role for inositol 1,4,5-trisphosphate receptors (IP_3R) has remained elusive. However, there is great and growing interest in cardiac IP_3 signaling due to the known importance of several IP_3-inducing agonists (e.g., endothelin, angiotensin II, and norepinephrine) in both hypertrophy and HF [28]. While agonist-induced IP_3-dependent Ca^{2+} release is readily observed in most tissues, the role of IP_3Rs in cardiac tissue is less clear. The role played by IP_3Rs has yet to be convincingly demonstrated in the normal heart. However, there are suggestions that it may lead to amplification of Ca^{2+} signals from the RyR2 or be independently activated through several diverse pathways that lead to the generation of IP_3 [29]. This second calcium release channel in the sarcoplasmic reticulum may play a role in normal excitation–contraction coupling. There are also suggestions that the importance of IP_3Rs can change significantly during normal aging [30]. This implies that these other calcium release channels may have an increased importance during the development of HF.

Calcium Sensitivity

Myocardial contraction is initiated when Ca^{2+} binds to a specific site on cardiac troponin C [31]. This 12-residue EF-hand loop contains six residues that coordinate Ca^{2+} binding and six residues that do not appear to influence Ca^{2+} binding directly [32]. Structural changes in troponin C affect its calcium sensitivity [32]. Ca^{2+} binding affinity controls contractile force and changes in many types of diseases. Troponin C is part of a troponin complex that together with tropomyosin affects the interaction between actin and myosin leading to the development of myocardial contraction [33, 34]. The interaction between troponin C and calcium is the critical final step of calcium induced control of myocardial contractility. Stretch also affects calcium sensitivity and force development [35]. This is part of the explanation for the Frank–Starling mechanism [36], which may be affected by stretch activated calcium channels. In addition to troponin C, there are several other calcium binding proteins that affect myocardial contractility [37], including calpains and calcium dependent protein kinases [38–41]. These various calcium binding proteins regulate the force of myocardial contraction in the normal heart.

Mutations in troponin C have been associated with the development of HF [34], and changes in calcium sensitivity of troponin may be a potentially useful treatment for HF [42, 43]. As the heart progresses into failure significant reductions in calcium sensitivity occur [33, 44]. Furthermore,

decreased phosphorylation level of troponin C occurs in HF [45], and this may be contributory to the decreased contractile function observed in the failing heart [33]. Agents that stabilize troponin C may prove useful.

Several reports have claimed that the increased sensitivity of troponin to calcium observed in the failing heart is due to changes in phosphorylation of troponin I [46]. Several mutations in troponin isoforms have been associated with HF [34]. The ability of the heart to respond to wall stress is also depressed [3]. Other myocardial calcium-binding proteins may also be useful targets for gene therapy in HF [37, 41].

Sarcoplasmic Reticulum Calcium Stores

The major site of internal cellular calcium storage is the sarcoplasmic reticulum (SR). The amount of calcium released by the RyR2 receptors depends, in part, on the amount of calcium in the SR [21]. The calcium content of the SR depends on the balance between calcium uptake by the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) and efflux of calcium through RyR2 channels [47]. Calsequestrin is by far the most abundant Ca^{2+}-binding protein in the SR of cardiac muscle [48]. There is a physical link between calsequestrin and RyR2, which allows some control of calcium release during the action potential. This link controls the release of calcium through the RyR2 [49]. Calsequestrin is not the only binding calcium protein in the SR, since calsequestrin null mice are viable suggesting that other protein can also regulate calcium storage in the SR [50]. Other calcium binding proteins including sarcalumenin, calumenin, etc. [51, 52], may also play an important role in calcium storage in the SR.

There are significant alterations in the calsequestrin and SR calcium loads in HF [5]. This may contribute to the increased diastolic calcium levels observed in cardiac myocytes during diastole in HF [49]. Furthermore, calsequestrin loss may also contribute to the development of cardiac hypertrophy [50]. Other calcium binding proteins in the SR may also be affected in the failing heart [51]. Initially, the SR calcium stores may be increased during the early stages of heart failure [53]. However, calcium levels significantly decrease in the SR as the degree of heart failure progresses [37]. Some of these changes are related to increased leakiness from the SR [24, 26]. It is possible that improving calcium storage or its control in the SR may prove a useful target for the treatment of HF.

Calcium Removal

The Na^+/Ca^{2+} exchanger is the major plasma membrane transport protein that can cause calcium to exit from the cardiac myocyte [54]. The direction and amplitude of the Na^+/Ca^{2+} exchanger current depend on the membrane potential and on the internal and external Na^+ and Ca^{2+} levels. The Na^+/Ca^{2+} exchanger is the main pathway for Ca^{2+} extrusion from ventricular myocytes [54]. This exchanger is regulated by a variety of accessory proteins such as phospholemman [55, 56]. However, the full extent of its control is controversial [57].

Protein phosphorylation is a major regulator of the Na^+/Ca^{2+} exchanger [57]. Under some circumstances, the Na^+/Ca^{2+} exchanger can operate in the reverse mode and allow calcium entry into the cardiac cell. This exchanger depends in large measure on the activity of the Na^+/K^+ ATPase, which keeps the internal sodium levels low. A plasma membrane calcium ATPase can also aid in the removal of cytoplasmic calcium to the outside [58]. During each heart beat, Ca^{2+} balance is preserved by Ca^{2+} entry via L-type Ca^{2+} channels and Ca^{2+} exit predominantly via the Na^+/Ca^{2+} exchanger.

The importance of the Na^+/Ca^{2+} exchanger in controlling myocardial contractility actually increases during HF [59]. This suggests downregulation of other important calcium handling proteins in the failing heart. Blockade of the Na^+/Ca^{2+} exchanger has been suggested as a possible beneficial therapeutic intervention in heart failure [60]. Classic ways of increasing inotropic activity in failing hearts primarily rely on activation of Na^+/Ca^{2+} exchanger by blocking the Na^+/K^+ ATPase in the plasma membrane. Cardiac glycosides such as digitalis and a variety of agents have been used to block Na^+/K^+ ATPase and increase calcium retention in the cytoplasm of failing myocytes [7, 61], which increases the inotropic capacity of the failing cardiac myocytes.

Much of the calcium in the cytoplasm at the end of a cardiac action potential is returned to the SR. The cardiac isoform of the SR calcium ATPase (SERCA2a) is a calcium ion pump powered by ATP hydrolysis [62]. SERCA2a transfers Ca^{2+} from the cytosol of the cardiac myocyte to the lumen of the SR during muscle relaxation. This transporter has a key role in cardiac myocyte calcium regulation [9].

Phospholamban acts as a major control of SERCA [63]. Phospholamban reduces the activity of SERCA, thus reducing calcium reentry into the SR [64]. When phospholamban becomes phosphorylated, inhibition of SERCA2a is reduced. A number of kinases can phosphorylate phospholamban [65–67], that speeds the re-uptake of calcium into the sarcoplasmic reticulum. There are also calcium binding proteins within the SR that help regulate SERCA activity [51, 52, 63]. In addition, there is a calcium ATPase in the plasma membrane that can also remove calcium during normal myocardial functioning although this is a relatively minor pathway for calcium removal from the cytoplasm [1, 5, 6, 58].

The expression of SERCA2a is significantly decreased in HF, which leads to abnormal Ca^{2+} handling and a deficient contractile state [6, 25, 62]. This also leads to reduced

calcium removal from the cytoplasm. Following numerous studies in isolated cardiac myocytes and small and large animal models, a clinical trial is underway to restore SERCA2a expression in HF patients by use of adeno-associated virus type 1. Beyond its role in contractile abnormalities in HF, SERCA2a overexpression has beneficial effects in a host of other cardiovascular diseases, and is considered an important target for gene therapy in HF [37, 68].

It is clear that changes in SERCA2a and phospholamban play an important role in the development of HF [5], and preventing the action of phospholamban on SERCA2a may play a beneficial role [69]. Since changes in phospholamban and SERCA2a lead to prolonged calcium transients in failing cardiac myocytes [6, 62, 70], treatment to improve the actions of phospholamban and SERCA2a are currently the major focus of treatment strategies to improve calcium handling during HF.

Changes in Calcium Transients

Calcium transients are involved in regulating electrical signaling and contraction in the heart [1]. The calcium transient that occurs during the action potential in a cardiac myocyte is regulated via ion currents and exchangers, the regulation of other channels or exchangers, and the action potential shape. This is critical for excitation–contraction coupling. When the heart begins to fail, there are alterations in this calcium transient due to the changes discussed above. Since baseline cytosolic diastolic calcium levels are elevated, this may contribute to cardiac diastolic dysfunction [71], that may be partially related to calcium leak from the SR [26].

The rise of the calcium transient is also slowed and diminished in HF. This is related to changes in the L-type calcium channel and the RyR2 channels in the SR [4–6, 19, 22]. The fall in the calcium transient is also slowed in the failing heart. This change is related to reduced calcium removal primarily back into the SR through changes in phospholamban and SERCA2a [6, 62, 70]. Restoring the calcium transient toward its normal functioning may provide several useful targets for the development of novel therapy in the treatment of heart failure.

Conclusions

Ca^{2+} cycling defects in HF are characterized by reduced calcium entry, impaired sarcoplasmic Ca^{2+} release and an associated Ca^{2+} leak, reduced SR Ca^{2+} reuptake, and reduced Ca^{2+} transients. Molecular targeting approaches to correct these abnormalities hold promise as a new therapeutic modality in the advanced end-stage heart failure patient. These patients have reduced calcium transients and impaired cardiac contractility. Further progress in understanding of Ca^{2+} cycling defects with relevant application in the clinical setting would be useful [72].

Despite remarkable pharmacological advances in the treatment of patients with HF, the rate of development of new therapies, particularly for patients with moderate to severe HF, appears to have slowed. A number of very promising targets have been suggested involving the Ca^{2+} cycling pathway, for selective manipulation using gene transfer approaches. This may provide new treatment approaches for patients with HF.

Summary

- Calcium enters cardiac myocytes primarily through L-type calcium channels.
- Calcium entry is reduced in heart failure.
- Calcium entry triggers activation of ryanodine receptors to release calcium from the sarcoplasmic reticulum.
- Ryanodine receptors release less calcium, more slowly and become leaky during heart failure. Changes in IP_3 receptors may also play a role in heart failure.
- Calcium binds to calcium sensitive proteins, primarily troponin C, to cause myofilament activation.
- Calcium sensitivity is depressed in heart failure.
- A large amount of calcium is stored in the sarcoplasmic reticulum and this storage is reduced in heart failure.
- The Na^+/Ca^{2+} exchanger is the major mechanism to remove calcium from the cytoplasm to the outside of the cell. It requires an active Na^+/K^+ ATPase for its functioning. There is also a plasma membrane Ca^{2+} ATPase.
- The Na^+/Ca^{2+} exchanger may become more prominent in heart failure.
- Calcium is pumped back into the sarcoplasmic reticulum by a Ca^{2+} ATPase (SERCA2a). This ATPase is primarily controlled by phospholamban.
- SERCA2a activity is reduced in heart failure.
- In heart failure, the diastolic cytoplasmic level is higher and the calcium transients are reduced and slowed.
- Improvements in calcium cycling or sensitivity may prove useful targets for the treatment of heart failure.

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