Arrhythmogenesis and Contractile Dysfunction in Heart Failure

Roles of Sodium-Calcium Exchange, Inward Rectifier Potassium Current, and Residual β-Adrenergic Responsiveness

Steven M. Pogwizd,* Klaus Schlotthauer,* Li Li, Weilong Yuan, Donald M. Bers

Abstract—Ventricular arrhythmias and contractile dysfunction are the main causes of death in human heart failure (HF). In a rabbit HF model reproducing these same aspects of human HF, we demonstrate that a 2-fold functional upregulation of Na+-Ca2+ exchange (NaCaX) unloads sarcoplasmic reticulum (SR) Ca2+ stores, reducing Ca2+ transients and contractile function. Whereas β-adrenergic receptors (β-ARs) are progressively downregulated in HF, residual β-AR responsiveness at this critical HF stage allows SR Ca2+ load to increase, causing spontaneous SR Ca2+ release and transient inward current carried by NaCaX. A given Ca2+ release produces greater arrhythmogenic inward current in HF (as a result of NaCaX upregulation), and ≈50% less Ca2+ release is required to trigger an action potential in HF. The inward rectifier potassium current (IK1) is reduced by 49% in HF, and this allows greater depolarization for a given NaCaX current. Partially blocking IK1 in control cells with barium mimics the greater depolarization for a given current injection seen in HF. Thus, we present data to support a novel paradigm in which changes in NaCaX and regulatory Ca2+ sensitivity at this critical HF stage allows SR Ca2+ release and arrhythmogenesis. (Circ Res. 2001;88:1159-1167.)

Key Words: heart failure ■ excitation-contraction coupling ■ Na+-Ca2+ exchange ■ Ca2+ transport ■ K+ currents

Heart failure (HF), which affects more than two million Americans, is associated with high mortality as a result of contractile dysfunction (pump failure) or sudden death caused by ventricular arrhythmias.1 The genesis of HF syndromes is complex and multifactorial, but altered cellular Ca2+ regulation may be a final common pathway in both pump failure and arrhythmogenesis.2–5 Decreased Ca2+ transients in HF reduce myofilament activation and depress contractility.2 Although it is unknown why Ca2+ transients are depressed, it is likely due to a decrease in sarcoplasmic reticulum (SR) Ca2+ release or Ca2+ influx via Ca2+ current (ICa_L). Many, although not all, HF studies show that ICa_L is unchanged.3,4,6 Decreased SR Ca2+ release could reflect either reduced SR Ca2+ release channel sensitivity to ICa,L or reduced SR Ca2+ content. Reduced SR Ca2+ load can be caused by decreased SR Ca2+-ATPase (SERCA) and/or increased Na+-Ca2+ exchange (NaCaX), because these transporters compete for [Ca2+], during relaxation and diastole.7 Moreover in HF, data indicate lower SERCA expression8,9 and increased NaCaX expression,6,10,11 but direct assessment of SR Ca2+ content in HF is limited. It is also unclear what role altered NaCaX plays with respect to contractile dysfunction in HF. These issues are addressed here.

Electrical reentry contributes to ventricular tachycardia (VT) in many pathophysiological states, but 3-dimensional mapping studies show that most fatal arrhythmias in HF initiate by a nonreentrant mechanism12–15 such as delayed afterdepolarizations (DADs) and early afterdepolarizations.16–17 This is true for 100% of VTs in human nonischemic cardiomyopathy (and 50% in ischemic cardiomyopathy).18,19

At normal action potential (AP) duration and heart rates, DADs may predominate over early afterdepolarizations. DADs, which are enhanced by β-adrenergic receptor (β-AR) stimulation,16 occur after AP repolarization and are initiated by spontaneous SR Ca2+ release. This leads to activation of a Ca2+-activated transient inward current (Iinward), which has been proposed to be carried by any of the following different Ca2+-activated currents: (1) NaCaX current (INaCaX), (2) Ca2+-activated chloride current (ICl(Ca)), or (3) a non-selective cationic current (Iinward).16,20–22 The inward rectifying K current (IK1) is crucial in stabilizing the resting membrane potential.
membrane potential ($E_m$). Although $I_{K1}$ is reduced in human HF, it is unclear, especially from a quantitative standpoint, how this may destabilize resting $E_m$ and ultimately contribute to the genesis of DADs, triggered APs, and arrhythmogenesis in HF.

The goal of this study was to define molecular mechanisms underlying both arrhythmogenesis and contractile dysfunction in HF. Studies were performed in an arrhythmogenic rabbit HF model of combined aortic insufficiency and constriction. This rabbit HF model resembles human nonischemic HF in exhibiting marked left ventricular (LV) dilation, contractile dysfunction in HF (by lowering SR Ca$^{2+}$ plays a central role in mediating both arrhythmogenesis and contractile dysfunction in HF (by lowering SR Ca$^{2+}$ load).

Materials and Methods

Rabbit HF Model and Myocyte Isolation

In New Zealand White rabbits (~3.5 kg), HF was induced by aortic insufficiency and 2 to 4 weeks later by thoracic aortic constriction. In New Zealand White rabbits (~3.5 kg), HF was induced by aortic insufficiency and 2 to 4 weeks later by thoracic aortic constriction, when the LV end-systolic dimension exceeded 1.2 cm. At this stage, intravenous infusion of isoproterenol (1 g/kg per minute) for 3 minutes was performed in conscious control and HF rabbits with monitoring of the surface ECG. Protocols were approved by the University of Illinois at Chicago Animal Studies Committee. Rabbit LV myocytes were isolated as described, with back flow across the incompent aortic valve in HF rabbits blocked by a balloon-tipped catheter inflated in the LV outflow tract.

Contraction [Ca$^{2+}$], and Patch Clamp

Myocyte shortening was measured by video edge detection and [Ca$^{2+}$] was measured by indo-1 and fluo-3 epifluorescence. The normal Tyrod’s (NT) solution contained (in mmol/L) NaCl 140, KCl 4, MgCl$_2$ 1, CaCl$_2$ 2, glucose 10, and HEPES 5 (pH 7.4). Myocytes were studied at 23°C or 37°C.

Some myocytes were field-stimulated in NT (Figure 1B). Perforated patch voltage clamp was done in experiments illustrated in Figures 1C through 1D. This agrees with previous $I_{Ca}$ data in which Ca$^{2+}$ transients were prevented. If the coupling between the L-type Ca$^{2+}$ channel and SR Ca$^{2+}$ release channel were altered in HF, SR Ca$^{2+}$ release would cause less Ca$^{2+}$-dependent $I_{Ca}$ inactivation in HF. However, we found no HF-associated change in time constants of $I_{Ca}$, inactivation ($\tau_{fast}$ or $\tau_{slow}$) or fraction of inactivation in the fast phase (Figure 1F). Ca$^{2+}$ transients and $I_{Ca}$ were increased by exposure to isoproterenol in both control and HF myocytes (Figures 1C and 1D). Whereas the $\beta$-AR stimulation of $I_{Ca}$ in HF was significantly less than in control, the $\Delta$Ca$^{2+}$ response was comparable (65% in HF versus 78% in control). Thus, HF cells exhibit clear residual $\beta$-AR responsiveness, consistent with the progressive but incomplete $\beta$-AR down-regulation seen both in human HF and in this rabbit HF model.
Contractile Dysfunction, Reduced SR Ca\(^{2+}\), and Enhanced NaCaX

Steady-state twitch Ca\(^{2+}\) transients and contractions in non-dialyzed and non-voltage–clamped HF myocytes at 37°C (1 Hz) were reduced by ~40%. This was paralleled by a 40% decrease in SR Ca\(^{2+}\) content (Figure 2A), as assessed by caffeine-induced Ca\(^{2+}\) transients. 26 This lower SR Ca\(^{2+}\) load is sufficient to explain the reduced twitches and \(\left[\text{Ca}^{2+}\right]_i\) in HF. At constant \(I_{Ca}\), the ratio of \(\Delta[\text{Ca}^{2+}]\) for twitch:caffeine is a useful index of fractional SR Ca\(^{2+}\) release and excitation-contraction coupling. This ratio was unchanged in the HF rabbit, in contrast to previous results in failing rat heart. 4 There was also no reason to infer altered myofilament Ca\(^{2+}\) sensitivity, because changes in \(\Delta[\text{Ca}^{2+}]\) paralleled those of contraction. To completely rule out changes in myofilament Ca\(^{2+}\) sensitivity or ryanodine receptor responsiveness, more detailed study is required.

Although reduced SR Ca\(^{2+}\) content is the simplest interpretation of the lower Ca\(^{2+}\) transients induced by APs and caffeine, increased cytosolic Ca\(^{2+}\) buffering could also be involved. Figures 2B and 2C show cytosolic Ca\(^{2+}\) buffering measured by the method of Trafford et al. 32 Rapid caffeine-induced Ca\(^{2+}\) release activates Ca\(^{2+}\) extrusion via \(I_{NaCa}\) (Figure 2B, top). The amount of total Ca\(^{2+}\) ([Ca\(^{2+}\)]\(_{Tot}\)) removed is given by the \(I_{NaCa}\) integral, and that Ca\(^{2+}\) removal causes \(\left[\text{Ca}^{2+}\right]_i\) to change (Figure 2C, left). The Ca\(^{2+}\) buffering slope (\(\Delta[\text{Ca}^{2+}]_i/\Delta[\text{Ca}^{2+}]\)) for physiological \([\text{Ca}^{2+}]_i\) is unaltered in HF. Nevertheless, instantaneous inward \(I_{NaCa}\) for any given \([\text{Ca}^{2+}]_i\) was much larger in HF (Figure 2B, bottom), indicating that \(I_{NaCa}\) is functionally upregulated during dynamic Ca\(^{2+}\) transients (confirming our data showing 2-fold increases in NaCaX mRNA, protein, and \(I_{NaCa}\) where [Ca\(^{2+}\)] was clamped). 6 The enhanced inward \(I_{NaCa}\) means that NaCaX must compete better with SERCA during twitch relaxation and diastole and thereby directly explains the reduced SR Ca\(^{2+}\) and contractile dysfunction in HF (even if SERCA was relatively unchanged; see Discussion).

SR Ca\(^{2+}\) Load, Spontaneous SR Ca\(^{2+}\) Release, and Arrhythmogenesis

How might these Ca\(^{2+}\) alterations be involved in arrhythmogenes? Indeed, if SR Ca\(^{2+}\) load is reduced, one may expect less spontaneous SR Ca\(^{2+}\) release and triggered APs in HF. One resolution to this paradox might be that in HF a lower-threshold SR Ca\(^{2+}\) load causes spontaneous SR
Ca\textsuperscript{2+} release and \(I_{t}\). We measured this threshold in voltage-clamped myocytes (Figures 3A and 3B) by driving increasing amounts of Ca\textsuperscript{2+} into the cell and SR by varying the duration of a loading pulse at +50 mV and also by increasing [Ca\textsuperscript{2+}]\textsubscript{o} to 4 mmol/L and adding 1 to 10 \(\mu\)mol/L isoproterenol. On repolarization (\(E_{m}\) = –80 mV), resting cell length (RCL), [Ca\textsuperscript{2+}]\textsubscript{i}, and \(I_{t}\)s were recorded. Rapid application of caffeine (10 mmol/L) released remaining SR Ca\textsuperscript{2+}. Summing \(I_{t}\) and \(I_{Na/Ca}\) integrals indicates SR Ca\textsuperscript{2+} content before \(I_{t}\). Aggressive Ca\textsuperscript{2+} loading conditions were required to induce \(I_{t}\)s (1 to 10 \(\mu\)mol/L isoproterenol and/or [Ca\textsuperscript{2+}]\textsubscript{o}=4 mmol/L). B, Threshold SR Ca\textsuperscript{2+} load for \(I_{t}\) occurrence (average of 4 lowest loads that gave an \(I_{t}\) and 4 highest that did not) were not different in HF and control (n = 93 HF and 100 control). C, Caffeine-activated \(D_{[Ca^{2+}]i}\)-induced current was abolished by blockade of \(I_{Na/Ca}\) (37°C). D, Peak and integrated \(I_{t}\) from experiments as in panel A (n = 34 HF and 56 control). *\(P<0.05\).

Figure 3. SR Ca\textsuperscript{2+} load, spontaneous SR Ca\textsuperscript{2+} release, \(I_{t}\), and \(I_{Na/Ca}\). A, Varying SR Ca\textsuperscript{2+} load in voltage-clamped myocytes by the indicated protocol (23°C). Longer times at +50 mV drive more Ca\textsuperscript{2+} in via \(I_{Na/Ca}\), for a given [Ca\textsuperscript{2+}]\textsubscript{i} transient in HF vs control (n = 10 HF and 7 control). B, \(I_{Na/Ca}\) evoked by caffeine (Caff) application reveals a greater \(I_{Na/Ca}\) for a given [Ca\textsuperscript{2+}]\textsubscript{i} transient in HF vs control (n = 10 HF and 7 control). Slopes are from linear regressions. *\(P<0.05\). C, Cytosolic Ca\textsuperscript{2+} buffering was not different for HF vs control myocytes (n = 10 HF and 7 control), for which buffer power is taken as the slope of the \([Ca^{2+}]_{cyt}/[Ca^{2+}]\) relationship.

As such, the \(I_{Na/Ca}\) (including \(I_{t}\)) in Figure 3A can be integrated to evaluate the SR Ca\textsuperscript{2+} load that was present at the moment the first spontaneous \(I_{t}\) occurred. Although \(I_{t}\)s in Figures 3A and 3B were seen only with isoproterenol, for a given depolarizing pulse, \(I_{t}\)s were more readily induced in HF than control (8 of 10 versus 3 of 9; \(P<0.05\); for 10 \(\mu\)mol/L isoproterenol, [Ca\textsuperscript{2+}]\textsubscript{i}=2 mmol/L). We attribute this to the upregulated NaCaX and greater Ca\textsuperscript{2+} influx while holding at +50 mV.
However, the crucial result is that the threshold SR Ca$^{2+}$ load for $I_t$ induction was unchanged in HF (Figure 3B).

A typical $I_t$ removes 15 to 20 μmol Ca$^{2+}$/L cytosol from the cell (and SR). Thus, in cells in which SR Ca$^{2+}$ was driven to the highest levels (as in Figure 3A), two or more $I_t$s were reproducibly observed and the second $I_t$ brought the SR Ca$^{2+}$ load below threshold. At more modest SR Ca$^{2+}$ load (eg, ∞115 μmol/L cytosol), a single $I_t$ was sufficient to bring SR Ca$^{2+}$ load below threshold.

If SR Ca$^{2+}$ load is low in HF myocyte and threshold SR Ca$^{2+}$ load for triggering an $I_t$ is unaltered, how does it increase to produce $I_t$s? This paradox can be explained by sympathetic bursts, which stimulate the SERCA, raising SR Ca$^{2+}$ load above threshold. This is supported by our findings above that β-AR activation significantly enhanced aftercontractions (in 100% of HF cells) and $I_N$s (in 80% of HF cells) by increasing SR Ca$^{2+}$ (Figures 1B, 3A, and 3B) and also induced ventricular arrhythmias including nonsustained VT in 3 of 3 intact HF rabbits (versus 0 of 3 controls). This may also explain why sudden arrhythmic deaths are more common in 3 of 3 intact HF rabbits (versus 0 of 3 controls). This may also explain why sudden arrhythmic deaths are more common in 3 of 3 intact HF rabbits (versus 0 of 3 controls). This may also explain why sudden arrhythmic deaths are more common in 3 of 3 intact HF rabbits (versus 0 of 3 controls). This may also explain why sudden arrhythmic deaths are more common in 3 of 3 intact HF rabbits (versus 0 of 3 controls).

**Δ[Ca$^{2+}$] Required to Trigger an AP**

If the threshold SR Ca$^{2+}$ for release is unchanged, perhaps the increased propensity for triggered arrhythmias in HF reflects the way the cell responds to a given SR Ca$^{2+}$ release. Indeed, in HF peak $I_{NaCa}$, during spontaneous $I_N$s was larger, even for a comparable amount of net charge moved (integrated $I_v$, Figure 3D). This higher peak $I_t$ agrees with greater inward $I_{NaCa}$ versus [Ca$^{2+}$], during caffeine-induced contractions (Figure 2B). This is expected to cause greater depolarization (∆$E_m$) in HF for a given ∆[Ca$^{2+}$], bringing $E_m$ closer to threshold to fire an AP.

We tested this quantitatively by measuring $E_m$ in current-clamped myocytes and applying caffeine to produce controlled ∆[Ca$^{2+}$]. Figures 4A and 4B show APs, twitch ∆[Ca$^{2+}$], and subsequent caffeine-induced Ca$^{2+}$ transients, and the associated caffeine-induced afterdepolarizations (or cDADs). In HF, the AP duration was 19% longer and the AP and twitch [Ca$^{2+}$] were comparable (Figures 4B). This is expected to cause greater depolarization (∆$E_m$) in HF for a given ∆[Ca$^{2+}$], bringing $E_m$ closer to threshold to fire an AP.

![Figure 4. cDADs. A. Last steady-state (SS) AP and twitch [Ca$^{2+}$] (1 to 4 Hz), and caffeine-induced SR Ca$^{2+}$ release. B. Frequency dependence of AP duration at 95% repolarization (APD$_{95}$) and twitch ∆[Ca$^{2+}$] (n=8 HF and 11 control). C. Blocking NaCaX in Na-free, Ca$^{2+}$-free solution (0Na/0Ca; with lithium replacing sodium, n=12) abolished cDADs despite similar ∆[Ca$^{2+}$], whereas blocking $I_{NaCa}$ with 50 μmol/L niflu-mate did not prevent cDADs (mean ∆$E_m$, n=10). *P<0.01.](image)
Altered Potassium Currents: Ca\textsuperscript{2+}-Independent Changes

Figures 5B and 5C show that in HF rabbits, transient outward and inward rectifier potassium currents (\(I_{\text{to}}\) and \(I_{K1}\)) were reduced significantly (by 34% and 49%, respectively), as has been reported in human HF.\textsuperscript{23} Notably, the 49% reduction in \(I_{K1}\) in HF would be quantitatively sufficient to explain the Ca\textsuperscript{2+}-independent shifts seen in Figure 6A, we partially blocked \(I_{K1}\) in control cells (IC\textsubscript{50} ~5 \textmu mol/L, left) and in a representative cell (right) shifts \(\Delta E_m,\) vs pseudo-\(I_{to}\) as in HF.

\(\Delta E_m\) doubles for each 59 versus 105 nmol/L \(\Delta [\text{Ca}^{2+}]_i\) for subthreshold cDADs (curves and small points). In HF, the mean \(\Delta [\text{Ca}^{2+}]_i\), threshold for a triggered AP is also reduced by nearly 50% (280 versus 515 nmol/L, large squares). Although the stimulation frequencies at which caffeine triggered APs were comparable for HF and controls (\(\approx 1.5\) to 2 Hz), this may merely reflect a lower-baseline SR Ca\textsuperscript{2+} load in HF coincidently offset by the decreased level of \(\Delta [\text{Ca}^{2+}]_i\), necessary to trigger an AP. The crucial result is that lower \(\Delta [\text{Ca}^{2+}]_i\) is required for a cDAD to trigger an AP in HF (as expected from the increased \(I_{\text{NaCa}}\)). However, \(E_{m}\) (\(\Delta E_m\) doubles for each 59 versus 105 nmol/L \(\Delta [\text{Ca}^{2+}]_i\)) for subthreshold cDADs (curves and small points). In HF, the mean \(\Delta [\text{Ca}^{2+}]_i\), threshold for a triggered AP is also reduced by nearly 50% (280 versus 515 nmol/L, large squares). Although the stimulation frequencies at which caffeine triggered APs were comparable for HF and controls (\(\approx 1.5\) to 2 Hz), this may merely reflect a lower-baseline SR Ca\textsuperscript{2+} load in HF coincidently offset by the decreased level of \(\Delta [\text{Ca}^{2+}]_i\), necessary to trigger an AP. The crucial result is that lower \(\Delta [\text{Ca}^{2+}]_i\) is required for a cDAD to trigger an AP in HF (as expected from the increased \(I_{\text{NaCa}}\)). However, \(E_{m}\) might also respond differently to a given \(I_{\text{NaCa}}\) in HF (eg, as a result of other currents).

In HF, \(I_{\text{to}}\) was observed at all \(E_m\) values and would tend to destabilize the resting \(E_m\) (Figure 5C, inset). Thus, a given \(I_{\text{to}}\) might produce greater depolarization in the face of reduced \(I_{K1}\).

Figure 6A tests this expectation quantitatively using current injections of varying amplitude, with time courses that simulate real \(I_{\text{to}}\)s (but without changing \([\text{Ca}^{2+}]_i\), or Ca\textsuperscript{2+}-activated currents). Increasing the amplitude of these pseudo-\(I_{\text{to}}\)s results in larger depolarization,\textsuperscript{22} and with sufficient injected charge (ie, threshold charge) an AP is triggered. In HF, any given pseudo-\(I_{\text{to}}\) produces greater depolarization (small points and curves in Figure 6A). More importantly, the threshold current integral (or charge) to trigger an AP is \(\approx 25\%\) smaller in HF (large squares; \(P<0.05\)).

To test whether the reduction in \(I_{K1}\) in HF would be quantitatively sufficient to explain the Ca\textsuperscript{2+}-independent shifts seen in Figure 6A, we partially blocked \(I_{K1}\) in control cells (Figure 6B) to see whether that could mimic the shift seen in HF. Barium blocked \(I_{K1}\) with an IC\textsubscript{50} of 5 to 15 \textmu mol/L (depending slightly on \(E_m\)). Subthreshold pseudo-\(I_{\text{to}}\)s in a representative control cell are shown in the absence and
presence of 3 μmol/L barium. Barium shifted the relation just as seen in HF. Mean barium effects were to shift doubling charge from 0.45±0.06 to 0.21±0.03 C/F at 3 μmol/L barium and to 0.157±0.013 C/F at 5 μmol/L barium (n=14, 4, and 4, P<0.05). Therefore, the 49% I_{K1} reduction in HF is sufficient to completely and quantitatively explain the greater depolarization for a given current injection in HF (Figure 6A).

**Discussion**

We conclude (Figure 7) that three major factors conspire to greatly enhance the propensity for arrhythmogenesis in HF: (1) increased NaCaX (providing more arrhythmogenic I_{K1} for any given SR Ca^{2+} release), (2) reduced I_{K1} (allowing greater depolarization for any given I_{K1}), and (3) residual β-AR responsiveness (required to raise the low SR Ca^{2+} load in HF to the point at which more spontaneous SR Ca^{2+} release occurs).

The current(s) responsible for DADs has been controversial, but we have shown that I_{NaCaX} is the current that underlies I_{D} and DAD in myocytes from HF rabbits at 37°C (similar to I_{D} data at 20°C in human HF). Although other Ca^{2+}-activated currents may occur, particularly in other species or cell types in the heart, they do not contribute quantitatively to I_{D} or DADs under physiological conditions in ventricular myocytes from rabbits (and likely, humans) with HF. Moreover, the 2-fold upregulation of NaCaX in rabbit and human HF indicates that larger I_{NaCaX} and DADs would be expected for a given Δ[Ca^{2+}], (and we have demonstrated this quantitatively for I_{NaCaX} and cDADs).

I_{K1} was decreased by 49% in HF rabbit myocytes (similar to human HF). No quantitative functional link has previously been developed for I_{K1} as a cause of arrhythmogenesis in HF. We show that the reduction of I_{K1} is quantitatively sufficient to explain the greater depolarization seen for a given inward current (Ca^{2+}-independent pseudo-I_{K}) in HF. Thus, reduced I_{K1} in HF is of paramount importance in lowering the threshold for an I_{K}-triggered AP. Although I_{NaCaX} is almost entirely responsible for I_{Ca} (in control and HF), reduced I_{K1} in HF allows that I_{NaCaX} to produce greater depolarization. Based on the HF shifts in Figures 5A and 6A and computer models (J.L. Puglisi and D.M. Bers, unpublished observations, 2000), the increased I_{NaCaX} and reduced I_{K1} contribute about equally to the altered Δ[Ca^{2+}] threshold and propensity for triggered arrhythmias.

The role of SR Ca^{2+} load in arrhythmogenesis has been unclear, especially because of the paradoxical lower SR Ca^{2+} load in HF versus high SR Ca^{2+} required to cause spontaneous SR Ca^{2+} release. Here we resolve this paradox by demonstrating directly that HF cells can be readily driven to high SR Ca^{2+} load and spontaneous SR Ca^{2+} release (which causes arrhythmias initiated by DADs). This is where residual β-AR responsiveness in our paradigm is critical. Indeed, we found that 100% of HF cells exhibit spontaneous SR Ca^{2+} release and aftercontractions after isoproterenol (although an IC_{50} for isoproterenol was not determined). Moreover, in very-late-stage human HF, there are fewer sudden arrhythmic deaths, and this corresponds to the time when there is more complete loss of β-AR responsiveness. At this stage as pump failure continues, arrhythmias may be less likely because the SR Ca^{2+} load never gets high enough for spontaneous SR Ca^{2+} release (although elevated NaCaX and reduced I_{K1} may persist).

The higher NaCaX in HF also contributes to contractile dysfunction by competing with the SERCA and unloading the SR. In this rabbit HF model, we had not detected alteration in SERCA on Northern or Western blots, but function in HF myocytes appeared to be decreased by up to 24%. This minimal SERCA alteration (compared with some HF models) illustrates that the large increase in NaCaX alone may be sufficient to unload the SR and hence cause contractile dysfunction. Of course, any reduction in SERCA versus NaCaX would further shift this balance and lower the SR Ca^{2+} load more severely. This demonstrates a novel dual role for elevated NaCaX as a central causative factor in both arrhythmogenesis and contractile dysfunction. This also relates to human HF, in which Hasenfuss et al found that 44% of failing human hearts (their group I, with preserved diastolic function) had ≈2-fold increase in NaCaX protein expression and ≈25% decrease in SERCA, which is very similar to our HF rabbits. Additional reduction of SERCA seen in HF...
patients with diastolic dysfunction slows twitch relaxation and further decreases SR Ca\(^{2+}\) load and systolic function.\(^{11}\) Although increased NaCaX expression in HF could enhance Ca\(^{2+}\) entry (via outward I\(_{\text{SR}}\)),\(^{36,37}\) this seems likely only for very prolonged APs in HF. This effect was not seen here.

This work and novel paradigm (Figure 7) raise the issue of molecular targets for therapeutics in HF. Inhibiting NaCaX might improve contractile function and acutely limit arrhythmias but is dangerous because of the crucial role of NaCaX in removing the Ca\(^{2+}\), which enters at each beat via I\(_{\text{Na}}\). Partially blocking NaCaX could worsen cellular Ca\(^{2+}\) overload, ultimately causing spontaneous SR Ca\(^{2+}\) release and arrhythmia (as seen with Na/K-ATPase inhibition in digitalis toxicity).

Such spontaneous SR Ca\(^{2+}\) release can seriously exacerbate contractile dysfunction by desynchronizing contractions in cells, which are in series with each other,\(^{7}\) even if arrhythmogenic I\(_{\text{SR}}\) was less. Increasing SERCA (eg, by gene transfer or phospholamban inhibition)\(^{38,39}\) would help the SERCA compete better with NaCaX to maintain more normal SR Ca\(^{2+}\) load and improve contractile function, but it may increase the propensity for Ca\(^{2+}\) overload and DADs. SR Ca\(^{2+}\)/pump stimulation could be the reason why phosphodiesterase inhibitor inotropes (which increase cAMP) are proarrhythmic and increase mortality.\(^{40}\) Blocking \(\beta\)-ARs could prevent spontaneous SR Ca\(^{2+}\) release by reducing the increment in SR Ca\(^{2+}\) load (induced by adrenergic surges). This would account for the effectiveness of \(\beta\)-AR blockers in reducing sudden death in HF.\(^{41}\) Enhancing I\(_{\text{Kp}}\) to stabilize resting E\(_{\text{m}}\) could also be beneficial but could also reduce excitability, propagation rate, and AP duration. Overall, a balance must be sought to enhance SERCA function without increasing arrhythmogenesis.

HF and its etiologies are extremely complex, but altered myocyte Ca\(^{2+}\) regulation and ion channels appear to be crucial in the final common pathways of sudden death and pump failure. The data here support a novel paradigm of three crucial in the final common pathways of sudden death and HF. The increased NaCaX is unique in contributing to both contractile dysfunction (reducing SR Ca\(^{2+}\) load) and arrhythmogenesis. This novel paradigm provides both a framework and a challenge for further understanding and therapeutic development.

**Acknowledgments**

Financial support was provided by NIH Grants HL-46929 (to S.M.P.) and HL-30077 and HL-64724 (to D.M.B.). We appreciate the technical contributions of S. Scaglione and L. Leach.

**References**


Arrhythmogenesis and Contractile Dysfunction in Heart Failure: Roles of Sodium-Calcium Exchange, Inward Rectifier Potassium Current, and Residual β-Adrenergic Responsiveness

Steven M. Pogwizd, Klaus Schlotthauer, Li Li, Weilong Yuan and Donald M. Bers

Circ Res. 2001;88:1159-1167; originally published online May 24, 2001; doi: 10.1161/hh1101.091193

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/88/11/1159

Data Supplement (unedited) at:
http://circres.ahajournals.org/content/suppl/2001/05/18/hh1101.091193.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/